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AUSTRALIAN PHARMACEUTICAL FORMULARY AND HANDBOOK 21ST EDITION

THE EVERYDAY GUIDE TO PHARMACY PRACTICE

Pharmaceutical Society of Australia

Pharmaceutical Society of Australia

Australian Pharmaceutical Formulary and Handbook

21st Edition

The everyday guide to pharmacy practice

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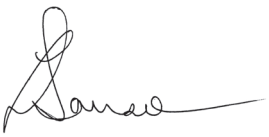
Preface

It is with great pleasure that I bring you the 21st edition of the Australian Pharmaceutical Formulary and Handbook (APF). First published in 1902, the APF is now in its 107th year. During this time, its purpose and intent have changed considerably. Originally a small formulary, it has evolved into a substantial clinical handbook valuable in many aspects of pharmacy practice and academia, both in Australia and overseas. This evolution has occurred primarily to meet the growing needs of pharmacists as a result of changing practice and practice environment and increasing consumer education. After 107 years, and with governments around the world focusing on preventative health strategies and promotion of consumer self-care, the shift in the primary nature of the pharmacist's role from compounder to counsellor has never been more important. With scientific research producing an ever-growing body of evidence-based medicine, consumers and other health professionals look to pharmacists to provide accurate, reliable and timely clinical advice. Ranked amongst the top five most trusted professionals in a 2008 consumer survey, pharmacists are well positioned to fulfil their current and future professional responsibilities with the support of reputable texts such as the APF.

Building upon previous editions, this edition brings together the past, present and future of pharmacy practice and teaching. The content incorporates both theory and best practice, and has been rigorously developed and reviewed by a range of experts, and industry stakeholders have also been consulted. This edition sees the APF adopt a new contemporary style that is easy to read and navigate, and it now comes standard as a book and CD-ROM package. The content has also been re-organised to further enhance readability. Some of the many changes to content in the 21st edition include the addition of new medicines in all relevant sections, a new 'OTC Counselling guides' section and the addition of new extemporaneous formulae.

In keeping with the APF's intent as the everyday guide to pharmacy practice, this edition provides valuable information for students and pharmacists in all settings, be they in community, hospital or academia. Readers are advised to refer to the APF website (www.psa.org.au/apf) on a regular basis for updates and general information. The 21st edition of the APF supersedes and replaces all previous editions.

Finally, I commend the Pharmaceutical Society of Australia and its staff for producing another quality edition of the APF.



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Section A

Dispensing and advice to consumers

Counselling and cautionary advisory labels for medicines

Counselling

Pharmacists must offer counselling to the patient at every opportunity. Appropriate counselling ensures that medication has the desired therapeutic effect and that the incidence of preventable adverse effects is minimised. It is the pharmacist's responsibility to promote the quality use of medicines by ensuring that the patient receives the required information. Counselling involves the communication of information that would encourage this outcome.

Counselling should be reinforced with written instructions, including labels attached to the immediate container of dispensed medicines (where practical), as well as Consumer Medicine Information. Written instructions do not, however, replace verbal counselling.

Counselling for repeat prescriptions is also important as it enables the pharmacist to determine by appropriate questioning and information exchange whether a patient is experiencing adverse reactions or has other concerns relating to their medicine.

Whenever possible, oral medications should be taken with a glass of water while the patient is in an upright position.

Cautionary advisory labels

The most common issues requiring written reinforcement of counselling are incorporated in the cautionary advisory labels (CALs) as either 'Ancillary labels' or 'Additional instructions'. Samples of each CAL are included in this section to assist with identification of the correct label to be used. These CALs were approved by the APF Editorial Board and, while there may be other appropriate supplementary labels in use, they are not approved by the Editorial Board. A full set of specifications suitable for printing companies can be obtained by contacting the PSA directly on 02 6283 4777.

Pharmacists should note that changes to CALs from the previous edition are marked using  . These changes may represent a therapeutic protocol change or a clarification recommended by the CAL Working Group to assist consumers.

To avoid confusion, previous versions of CALs should not be used.

Medicines requiring labels

Table A.1 lists medicines for which CALs are required. Medicines are considered for inclusion in the list by the CAL Working Group of the APF Editorial Board if they meet at least three of the following criteria:

- They are medicines in clinical use in Australia.
- They are medicines registered in Australia since the previous edition of the *Australian Pharmaceutical Formulary and Handbook*.
- They are taken orally or routinely self-administered by injection—excluding those administered within a health care facility.
- The medicine is considered by the CAL Working Group to warrant additional information to achieve quality use of medicines principles—e.g. transdermal products.

Medicines that may not be currently registered in Australia but that are likely to be available in the near future are also included.

In Table A.1 pharmacists should refer to both individual medicines listed for combination products.

Labelling considerations

The CALs for each medicine are determined by considering:

- evidence from the published literature—including the approved Product Information and Consumer Medicine Information
- statutory requirements included in Appendix K of the Standard for Uniform Scheduling of Drugs and Poisons (SUSDP) by the National Drugs and Poisons Schedule Committee of the Therapeutic Goods Administration.

It may be appropriate for pharmacists to add the designated label(s) to non-prescription products if such information is not provided on the immediate container, package label, or Product Information in the package.

In general, pharmacists may use their knowledge and professional discretion in deciding whether to omit one or more ancillary labels. The exception is medicines for which laws require that certain advisory labels be attached—that is, namely labels 1 and 1a for medicines listed in Appendix K of the SUSDP.[a] The prescriber may recommend that a CAL not be used, but in this

a. The Australian Pharmaceutical Formulary and Handbook does not include those drugs listed in Appendix K that are no longer available in Australia or are administered only by a health professional.

circumstance the prescription should specify the exact requirements regarding patient counselling.

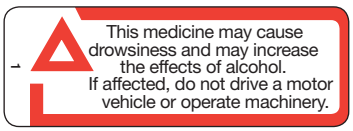
> Pharmacists should be aware that specific state and territory legislation regarding labelling of medical products may have requirements in addition to what is specified in this section.

Ancillary labels

Ancillary labels are to be attached to the immediate container of the dispensed medicine whenever possible. They fall into two categories:

- those that warn against undesirable effects—including interactions with other medications or foods
- those that are designed to optimise efficacy in the use of the medication.

Label 1

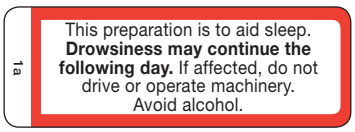


Label 1 is used for medicines whose primary or secondary effect is sedation. Ethanol, which is also a central nervous system depressant, may cause an additive sedative effect.

If alcohol is contraindicated, label 2 should also be used.

Consider providing the PSA Pharmacy Self Care Fact Card *Medicines and Driving*.

Label 1a



If the medicine is intended for use as an aid to sleep and to be taken as a single bedtime or nightly dose, label 1a replaces label 1.

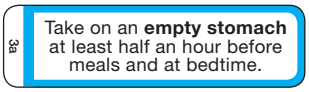
Counselling may be necessary to establish whether sleep induction is a primary or secondary effect and whether or not alcohol is absolutely contraindicated.

Label 2

Label 2 is used for medicines that have been reported to interfere with the metabolism of ethanol, yielding adverse effects, or with which ethanol ingestion may be contraindicated.

For example, female patients taking acitretin should not drink alcohol-containing beverages during and for two months after stopping therapy. Alcohol is a major factor in inducing the conversion of acitretin to etretinate, which has prolonged effects (e.g. teratogenicity).

Label 3a

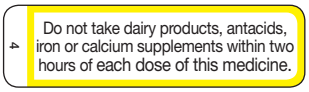


Label 3a is used for medicines administered four times a day and for which ingestion with food causes a significant reduction in bioavailability. For medicines administered less than four times a day, label 3b or additional instruction C (see Additional instructions) should be used in place of this label.

Alternatively, the pharmacist may recommend actual times of dosing that are compatible with the patient's lifestyle, ensuring that at least half an hour has elapsed before ingestion of food.

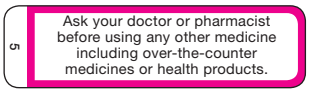
Label 3b

Label 4



Label 4 is used for tetracyclines, bisphosphonates, fluoroquinolone antibiotics and other medicines that can form poorly soluble complexes with metal ions, resulting in reduced bioavailability. The reference to dairy products is to be deleted for minocycline and doxycycline, where absorption is not significantly affected by co-administration with dairy products. The label is also used for medicines such as ketoconazole whose dissolution is adversely affected by antacids.

Label 5



Interactions between medicines can lead to therapeutic failure or adverse effects. These interactions may be pharmacodynamic in nature or caused by alterations in the absorption or the clearance of the medicine. The clinical significance of the interaction is likely to be greater for those medicines with narrow therapeutic indices (see 'Clinically important drug interactions', Section D). Label 5 is used for medicines that are known to be involved in multiple interactions, usually via the inhibition of the metabolic clearance of a range of medicines. Certain complementary medicines (the term 'health products' is used here to encompass all products bought in pharmacies, supermarkets and health food outlets) can interact with other medications, and patients must be warned of this possibility when taking these products (see 'Complementary medicines', Section C).

Pharmacists are advised to consult the *Australian Medicines Handbook* or the approved Product Information for more details.

Previously, this label was used to warn patients taking non-selective monoamine oxidase inhibitors about the dangers of ingesting certain foods: this warning is now included as additional instruction I (see 'Additional instructions').

Label 6

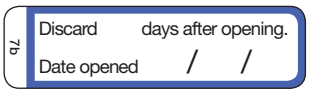
Certain medicinal products require storage at temperatures between 2 °C and 8 °C to minimise decomposition. This can be achieved by storing in a household refrigerator.

Note that for insulins the vial or cartridge in current use does not need to be stored under refrigeration. See also Label 7b.

Label 7a

or

Label 7b

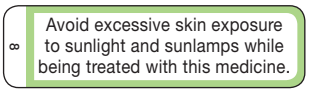


Some products have a limited shelf life due to chemical decomposition or the possibility of bacterial contamination. For example, the shelf life for eye preparations is 28 days after opening, unless a shorter time is dictated by instability or other considerations. For some products, the 'in use' shelf life can be greater than 28 days. Pharmacists should refer to the Product Information.

In use insulin vials or cartridges can be kept at room temperature (25 °C) for 28 days.

For individual extemporaneous products see 'General formulary', Section A.

Label 8



Some medicines can cause a phototoxic or photo-allergic reaction in some patients exposed to sunlight or sunlamps. Patients receiving these medicines should be encouraged to minimise exposure to sunlight or sunlamps and should be counselled to use 30+ sunscreen agents and/or protective clothing to minimise potential problems of this type. Some cytotoxic medicines and immunosuppressive agents increase the incidence of some skin cancers, and patients prescribed these medicines should therefore avoid excessive sunlight or sunlamp exposure.

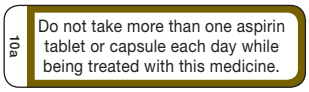
Label 9

The abrupt cessation of prolonged therapy with certain medicines has the potential to cause serious consequences: e.g. adverse effects following abrupt cessation of benzodiazepines, long-term oral corticosteroids and beta-blockers have been reported. Increased frequency and severity of seizures have been recorded following sudden withdrawal of anticonvulsant therapy.

Patients should be advised that this label does not override the need to consult the prescriber if adverse effects occur during treatment.

Pharmacists should not use this label where it clearly conflicts with the directions—e.g. prednisolone 25 mg, once daily for four days.

Label 10a



Label 10a is used to reduce the risk of hypoglycaemia in people with diabetes and should be used on all antidiabetic drugs, including insulin. High doses of aspirin may cause hypoglycaemia and influence control of diabetes. Doses used for antiplatelet effect (less than 300 mg/day) are unlikely to have this effect.

This label may also be useful when NSAIDs are taken concurrently with aspirin. There is an increased risk of gastrointestinal adverse effects, including bleeding, when NSAIDs (including COX-2 inhibitors) are combined with aspirin. In some people the benefit of reduced cardiovascular risk from aspirin may be considered to outweigh this risk.

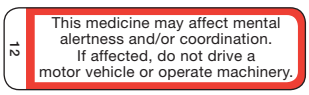
Label 10b

Label 10b should be used when oral anticoagulants (e.g. warfarin) are dispensed. Aspirin at any dose interferes with platelet aggregation and is not recommended for patients receiving oral anticoagulants such as warfarin unless low-dose aspirin is intentionally prescribed.

Label 11

Label 11 is to be used for potassium-sparing diuretics, ACE inhibitors and angiotensin II receptor antagonists. Cases of serious hyperkalaemia have been reported with these combinations. Pharmacists should ensure that if such a combination is used by a patient the medical practitioner is aware of the potential risk of hyperkalaemia.

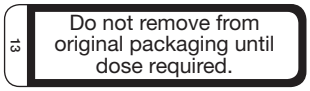
Label 12



Some medicines cause symptoms of central nervous system disturbances including—CNS over-excitation, dizziness, light-headedness and fatigue—and may impair motor coordination. These symptoms frequently disappear on continued therapy. However, some patients, especially older ones, may be affected and, in the interest of safety, this label should be used for such medicines.

Note that label 12 sometimes applies only to initial therapy or when the dose is increased.

Label 13



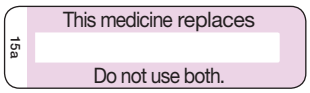
Many medicines are supplied in child-resistant or strip packaging. Patients should be discouraged from transferring the product to another container. Some medicinal products are presented in specific packaging to maintain their stability (e.g. amoxycillin with clavulanic acid, aspirin, sodium valproate) and removal from the packaging can cause chemical and/or physical deterioration.

Notwithstanding this, all medicines should generally not be removed from the original containers until a dose is required, since the shelf life of the product is determined in the container/packaging approved for marketing. Removal for inclusion in dose-administration aids should be restricted to short periods unless evidence of stability of the product in the device is known.

Label 14

Inhaled steroids increase the risk of oral fungal infections. Rinsing the mouth after use reduces the incidence of this problem. Patients should be advised to expectorate after rinsing.

Label 15a



or

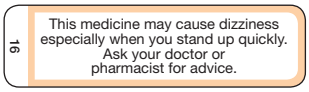
Label 15b

Labels 15a or 15b will be used when one brand of a medicine is replaced by another. They should also be used when one medicine in a particular therapeutic class is replaced by another medicine in the same class, and it is not intended that the patient take both products. A patient's knowledge of the name of the active ingredient will help reduce the chance of inadvertent dose duplication due to brand substitution.

There is evidence of patient confusion about the availability of numerous generic brands of the same medicine. It is recommended that in chronic therapy, brand consistency is maintained where appropriate. Where a generic substitution occurs, the pharmacist should ensure that the product brand can be identified at the time of the next dispencing. In addition, the patient should be counselled regarding the substitution.

Under the conditions for which the sponsor of a generic product has gained Pharmaceutical Benefits Scheme approval, a generic product must be available from all wholesalers.

Label 16

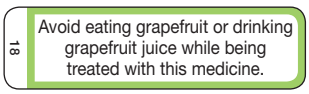


Label 16 is to be used for medicines that are likely to cause orthostatic hypotension, especially in the elderly. The falls that can result are a major cause of bone fractures and other morbidity in older patients. Pharmacists should ensure that they provide adequate verbal and written counselling. Consider providing the PSA Pharmacy Self Care Fact Card *Preventing Falls*.

Label 17

Label 17 has been replaced by label 5.

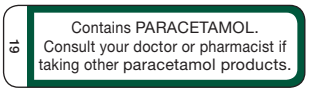
Label 18



Various components of grapefruit have been shown to inhibit the metabolising enzymes of several important medicines, thereby increasing the bio-availability of these medicines and the incidence of adverse effects.

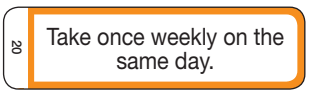
The effect of grapefruit is unpredictable and is likely to vary greatly between patients. Since no recommendation can be made on the quantities that may be safely consumed, patients should be advised to avoid ingestion of grapefruit while undergoing treatment with this medicine.

Label 19



Label 19 is necessary for all products containing paracetamol because of the diversity of combination products whose brand names do not signify the presence of the medicine. The label is also appropriate for use on over-the-counter combination products containing paracetamol. The usual recommended adult total daily dose of paracetamol is 4 g.

Label 20

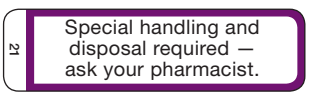


For some inflammatory conditions—including rheumatoid arthritis and psoriasis—anti-inflammatory agents (e.g. methotrexate) are used in low-dose, once-a-week regimens. Serious adverse outcomes (including death) have been known to occur following excessive dosing. Pharmacists must confirm the dose is appropriate and stress the reason for the once-a-week dose and the need for constant monitoring.

Some bisphosphonates and antimalarials are also administered once a week.

The pharmacist is to encourage the taking of these medicines on the same day each week.

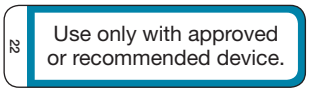
Label 21



Label 21 is to be used for all cytotoxic agents. Pharmacists may also refer to The Society of Hospital Pharmacists of Australia Standards of Practice for the Safe Handling of Cytotoxic Drugs in Pharmacy Departments.

Use label 21 also for transdermal patches (such as fentanyl, nicotine, nitrate and hormone replacement) that may contain residual amounts of potentially harmful medication after normal therapeutic use.

Label 22



Label 22 is to be used for capsules intended for inhalation rather than oral administration—e.g. tiotropium capsules. Instances of these being swallowed have occurred.

Additional instructions

Additional instructions are to be attached to the immediate container or incorporated in the main label. The decision on where to place the instructions should fall to the pharmacist, based on their professional judgment.

A

Add the words 'swallow whole' for preparations such as enteric-coated and modified-release products whose release characteristics depend on the product being swallowed whole, or where breaking or crushing products may cause an excessive dose to be released, with the possibility of toxicity. Some tablets can be broken into dosage sections but the portions should not be chewed or crushed. Some capsules may be opened if the pellets they contain are not broken (see 'Modification of oral formulations', Section A).

B

Add the words 'take with or soon after food'. For some medicines, gastrointestinal adverse effects can be reduced by administration with food. For some oral hypoglycaemic agents, it is important that food is taken with the drug to minimise the risk of hypoglycaemic episodes. The extent of absorption of ketoconazole is enhanced when administered with food because of a reduced stomach-emptying rate and greater dissolution in the acidic environment of the stomach. The absorption of griseofulvin is enhanced when administered with food because of greater dissolution caused by the stimulated flow of bile.

C

Add the words 'take at least half an hour before food'.

D

Add the words 'until all used' or 'until all taken'. The completion of a recommended course of therapy with antibiotics or antibacterial agents can reduce the incidence of relapse and minimise the emergence of resistant strains. This label may not be appropriate with paediatric dosage forms where the total number of doses in the preparation is greater than needed to define an adequate course of therapy. For example, antibiotics are commonly given for a five to seven day course only. Patients should be advised that this instruction does not override the need to consult the prescriber if adverse effects occur.

E

Add the words 'continue for 14 days after symptoms cease'. This instruction is to be used for topical antifungal preparations. It cannot be inferred from the disappearance of symptoms of a dermal fungal infection that the causal organism has been eradicated.

F

Add the words 'take immediately before food'.

G

Add the words 'take in the morning. Drink plenty of water'. Cyclophosphamide can cause severe cystitis. Ample fluid intake and frequent voiding may reduce the incidence of this adverse effect. This can be achieved by administration of the drug in the morning and advising the patient to drink plenty of water during the day.

H

Add the words 'store frozen.'

I

Add the words 'certain foods should be avoided'. This additional instruction is for use with the non-selective monoamine oxidase inhibitors (e.g. phenelzine) and should be accompanied by appropriate counselling and the provision of the monoamine oxidase inhibitors advice card (see next page).

J

Add the words 'shake well before each use'.

K

Add the words 'for external use only'.

L

Add the words 'caution not to be taken'.

M

Add the words 'do not swallow'.

N

Add the words 'contains peanut oil'.

Figure A.1 The monoamine oxidase inhibitors advice card

PATIENT

MEDICINES

Unless otherwise advised, the following foods and medicines should be avoided while taking this medication and for at least two weeks after ceasing therapy:

FOODS

The medicine that has been prescribed for you reacts with tyramine, which is found in a variety of foods, some of which you will need to avoid. It is important to eat food that is as FRESH as possible. DO NOT use leftover foods. This rule applies particularly to protein foods, such as meat, fish, game and offal (liver, heart, brains, sweetbreads, tripe, kidney). Avoid any food that has caused you unpleasant reactions in the past.

Avoid at all times

Matured cheeses

Beers and chianti

Yeast extract products (Marmite, Bovril, Vegemite, Promite, Bonox, vitamin products)

Salted or pickled herrings

Fermented or 'aged' foods (e.g. some game, salami, dried sausage, pâté)

These foods may be consumed in amounts not greater than listed

Bananas (not overripe)—2 medium per day

Avocado—1 medium per day

Wines (other than chianti)—1 glass per day

Spirits—1 measure per day

MEDICINES

Consult your pharmacist or doctor before using any other medicine including complementary medicines. If you are to receive an anaesthetic for surgical or other purposes, advise the doctor or dentist that you are taking this medicine.

Avoid using

Nasal drops/sprays containing ephedrine, phenylephrine.

Cough mixtures or cold or hay fever preparations containing ephedrine, pseudoephedrine, phenylephrine or dextromethorphan.

Table A.1 Medicines requiring cautionary advisory labels

Medicine	Ancillary label (number) and/or additional instruction (letter)
Abacavir	12
Abatacept	6
Acamprosate	2, A, B
Acarbose	B
Acetazolamide	10a, B
Aciclovir (oral)	D
Acitretin	2 (women), 5, 8, B
Adalimumab	6
Adefovir	9
Alendronate	20 (certain dosage forms), A, C
Allopurinol	12†, B
Alprazolam	1, 9
Alprostadil	6 (reconstituted)
Amantadine	9, 12, 16, B
Amiloride	11, 12†, 16
Aminoglutethimide	1†, 16
Aminophylline	5, B
Amiodarone	5, 8, 18
Amisulpride	1, 12, 16
Amitriptyline	1, 9, 13, 16
Amlodipine	9, 12†
Amoxycillin	D
Amoxycillin suspension	6, 7a, D
Amoxycillin with clavulanic acid	13, D, F
Amoxycillin with clavulanic acid suspension	6, 7a, D, F
Amphotericin B	D
Ampicillin	3b, D
Anagrelide	1, 16
Anakinra	6
Anastrozole	12
Aprepitant	5
Aripiprazole	1, 16†
Artemether with lumefantrine	12, A, B
Aspirin	13, A*, B
Atazanavir	5, B
Atenolol	9, 12†
Atomoxetine	5, 12†
Atorvastatin	18
Atovaquone	B, D
Auranofin	B
Azathioprine	8, 21, A*, B
Azithromycin	D (multiple dosing)
Baclofen	1, 9, B
Balsalazide	A, B
Beclomethasone oral inhalers	14
Benzhexol	1, 9 (long-term regular therapy)
Benztropine	1, 9 (long-term regular therapy)
Betahistine	1, 16

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Antacids will decrease the absorption of many medicines. Unless specifically indicated to the contrary, the administration of antacids should be separated by a period of about 2 hours from other orally administered medicines whenever possible. Similar separation of the dosing of cholestyramine, colestipol, lanthanum and sevelamer from other medicines is also recommended.

Table A.1 Medicines requiring cautionary advisory labels (continued)

Medicine	Ancillary label (number) and/or additional instruction (letter)
Bethanechol	3a or C
Bicalutamide	16, B
Bifonazole	E
Biperiden	1, 9 (long-term regular therapy)
Bisoprolol	9, 12, A (not chewed)
Bosentan	1, 5, 16
Bromazepam	1, 3b, 9
Bromocriptine	5, 12, 16, B
Brompheniramine	1, 13
Budesonide oral capsules	9, A, F
Budesonide oral inhaler with nebuliser solution	14
Bumetanide	16
Buprenorphine	1, 21 (patches)
Bupropion	5, 12†, 16†, A
Buspirone	1, 18
Busulfan	21
Butoconazole	D
Cabergoline	12†, B
Calcitriol	5
Calcium folinate	3b
Candesartan	11, 12†, 16†
Capecitabine	12†, 21, B
Captopril	3b (dose less than 50 mg), 7a (solution), 11, 12, 16†
Carbamazepine	5, 9, 12†, 13, 18, A*, B
Carvedilol	9, 12†, 13, 16
Cefaclor	A*, D
Cefaclor suspension	6, 7a, D
Cefuroxime (oral)	B, D
Celecoxib	10a, 12†
Cephalexin	D
Cephalexin suspension	6, 7a, D
Cetirizine	1, 13
Chloral hydrate	1a, 2, 12
Chlorambucil	6, 12†, 21
Chloramphenicol	7b
Chloroquine	13, B
Chlorpheniramine	1, 13
Chlorpromazine	1, 8, 9 (long-term regular therapy), 16
Chlorthalidone	16, B
Cholecalciferol	5
Ciclesonide	14
Cimetidine	5
Cinacalcet	5, B
Ciprofloxacin (oral)	3b, 4, 8, 12, D
Citalopram	5, 9, 12
Clarithromycin	5, D
Clindamycin	D
Clobazam	1, 9

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Antacids will decrease the absorption of many medicines. Unless specifically indicated to the contrary, the administration of antacids should be separated by a period of about 2 hours from other orally administered medicines whenever possible. Similar separation of the dosing of cholestyramine, colestipol, lanthanum and sevelamer from other medicines is also recommended.

Table A.1 Medicines requiring cautionary advisory labels (continued)

Medicine	Ancillary label (number) and/or additional instruction (letter)
Clodronate	3b, (1 hour before or 2 hours after) 4 , A
Clofazimine	8, 12, B
Clomiphene	12
Clomipramine	1, 9, 13, 16
Clonazepam	1, 9
Clonidine	1, 9, 16
Clopidogrel	9, 10a
Clotrimazole	E (dermal)
Clozapine	1, 9, 12, 16
Codeine	1 (greater than 20 mg dose)
Colchicine	5
Cortisone	9, B
Cromoglycate (capsules for inhalation)	22
Cyclophosphamide	8, 21, G
Cyclosporin	5, 8, 18
Cyclosporin (oral solution)	5, 7a, 8, 18
Cyproheptadine	1, 13
Cyproterone	12, B
Dacarbazine	8, 21
Danazol	5, 8
Dantrolene	1, 8
Dapsone	B
Darbepoetin	6
Darunavir	5, B
Dasatinib	4 (antacids), 5, 12, A
Deferasirox	3b, 13
Deferiprone	13
Delavirdine	5
Demeclocycline	3b, 4, 8, D
Desmopressin	5, 13
Desvenlafaxine	9, 12, A
Dexamethasone (oral)	9 (except short courses), B
Dexchlorpheniramine	1, 13, A*
Dextropropoxyphene	1
Diazepam	1 or 1a, 9
Diazoxide	16
Diclofenac	10a, 12†, A*, B
Dicloxacillin	3a, D
Didanosine	3b, A*
Didanosine suspension	3b, 6, 7a
Digoxin	5
Dihydrocodeine	1 (greater than 20 mg dose)
Dihydroergotamine	5, 18
Diltiazem	9, 12†, A*
Dimenhydrinate	1, 13
Diphenhydramine	1, 13
Diphenoxylate	1, 13
Dipyridamole	16, A*

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Antacids will decrease the absorption of many medicines. Unless specifically indicated to the contrary, the administration of antacids should be separated by a period of about 2 hours from other orally administered medicines whenever possible. Similar separation of the dosing of cholestyramine, colestipol, lanthanum and sevelamer from other medicines is also recommended.

Table A.1 Medicines requiring cautionary advisory labels (continued)

Medicine	Ancillary label (number) and/or additional instruction (letter)
Disopyramide	9, A
Disulfiram	2, 5
Domperidone	C
Donepezil	12, 16
Dornase alfa	6
Dothiepin	1, 9, 13, 16
Doxepin	1, 9, 13, 16
Doxycycline	4 (delete dairy products), 8, B, D
Doxylamine	1, 13
Droperidol	1
Duloxetine	5, 9, 12, A
Econazole	D*, E (dermal)
Efavirenz	3b, 5, 12
Eformoterol (capsules for inhalation)	22
Emtricitabine	12, A
Enalapril	11, 12†, 16†
Enfuvirtide	12
Entacapone	4 (delete milk, antacids, calcium), 5, 9, 12, 16
Entecavir	3b
Eplerenone	5, 11, 12, 18
Epoetin alfa	6
Epoetin beta	6
Eprosartan	11, 12†, 16†
Erlotinib	3b, 5
Erythromycin	5, A, C, D
Erythromycin ethyl succinate	5, D
Erythromycin ethyl succinate suspension	5, 6, 7a, D
Escitalopram	5, 9, 12
Esomeprazole	A* (can be dispersed in non-carbonated water)
Etanercept	6, 16
Ethacrynic acid	16, B
Ethosuximide	1, 9
Etidronate	4, A, C (2 hours)
Etoposide	18, 21, C
Everolimus	5, 8, 18, A*
Exemestane	B
Exenatide	6, 7b
Ezetimibe	5
Famciclovir	D
Felodipine	9, 12†, 18, A
Fenofibrate	8, A
Fentanyl	1, 21 (patch and lozenge)
Ferrous fumarate	13, B*
Ferrous gluconate	4 (delete dairy products), 13, C
Ferrous sulfate	4 (delete dairy products), 13, A*, C
Flecainide	9, 12, 13
Flucloxacillin	C or 3b, D
Flucloxacillin suspension	C or 3b, 6, 7a, D

† Most appropriate during initial treatment or when dosage is increased.

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Antacids will decrease the absorption of many medicines. Unless specifically indicated to the contrary, the administration of antacids should be separated by a period of about 2 hours from other orally administered medicines whenever possible. Similar separation of the dosing of cholestyramine, colestipol, lanthanum and sevelamer from other medicines is also recommended.

Table A.1 Medicines requiring cautionary advisory labels (continued)

Medicine	Ancillary label (number) and/or additional instruction (letter)
Fluconazole	5, D
Fludarabine	12, A*
Fludrocortisone	9, B
Flunitrazepam	1 or 1a, 9
Fluorouracil	8, 21
Fluoxetine	5, 9, 12
Flupenthixol	1, 16
Fluphenazine	1, 8, 9 (long-term regular therapy), 16
Flutamide	8
Fluticasone (oral inhalation)	14
Fluvoxamine	5, 9, 12, A*
Fosamprenavir	5
Fosamprenavir liquid	3a, 5
Fosinopril	11, 12†, 16†
Frusemide	16
Gabapentin	1, 9
Galantamine	5, 12, A*, B
Gatifloxacin	4 (delete dairy products, calcium), 12†, D
Gefitinib	5, 12†
Gemfibrozil	3b
Glatiramer	6
Glibenclamide	10a, B
Gliclazide	10a, A*, B
Glimepiride	10a, F (or add 'with a meal')
Glipizide	10a, B
Glyceryl trinitrate	13 (patches), 16, 21 (patches)
Glyceryl trinitrate (tablets)	7b, 13, 16
Granisetron	12
Griseofulvin	2, 8, 12, B, D
Haloperidol	1, 16
Hydralazine	12, 16
Hydrochlorothiazide	16
Hydromorphone	1, A*
Hydroxychloroquine	8 (delete skin), 13, B
Hydroxyurea	21, B
Hyoscine	12
Hyoscyamine	12
Ibandronate	A*, C
Ibuprofen	10a, 12†, B
Idarubicin	21, A*, B
Iloprost	12†, 22
Imatinib	B
Imipramine	1, 9, 13, 16
Imiquimod	8, K
Indapamide	16
Indinavir	3b, 5, 12
Indomethacin	10a, 12†, A*, B
Infliximab	6

† Most appropriate during initial treatment or when dosage is increased.

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Antacids will decrease the absorption of many medicines. Unless specifically indicated to the contrary, the administration of antacids should be separated by a period of about 2 hours from other orally administered medicines whenever possible. Similar separation of the dosing of cholestyramine, colestipol, lanthanum and sevelamer from other medicines is also recommended.

Table A.1 Medicines requiring cautionary advisory labels (continued)

Medicine	Ancillary label (number) and/or additional instruction (letter)
Insulins	6 (except vial or cartridge in use), 7b, 10a
Interferon alfa	6, 12
Irbesartan	11, 12†, 16†
Isoniazid	3b
Isosorbide dinitrate	16
Isosorbide mononitrate	16, A*
Isotretinoin	8, B, D
Itraconazole	5, B, D
Itraconazole solution	5, C (one hour), D
Ivabradine	5, 13, 18, B
Ketoconazole	4 (delete iron and calcium), 5, B, D, E (dermal)
Ketoprofen	10a, 12†, A*, B
Ketorolac	10a, 12†, A*, B
Labetalol	9, 12†, 16
Lamivudine	12
Lamotrigine	1, 9
Lansoprazole	A*
Lanreotide	6
Lanthanum	5, B
Lapatinib	3b, 5, 12, 18
Latanoprost	7b
Leflunomide	A
Lenalidomide	12, A
Lercanidipine	9, 12†, 18, C
Letrozole	12
Levamisole	2, 12
Levetiracetam	1, 9
Levocabastine	1
Levodopa with decarboxylase inhibitor	9, 16
Linezolid	D, I
Lisinopril	11, 12†, 16†
Lithium carbonate	5, 13, B
Lomustine	2, 3b, 21
Lopinavir with ritonavir	5, 6, B
Lorazepam	1 or 1a, 9
Losartan	11, 12†, 16†
Maraviroc	5, 16
Medroxyprogesterone	12†
Mefenamic acid	10a,12†, B
Mefloquine	12
Megestrol	12
Meloxicam	10a,12†, A*, B
Melphalan	3b, 6, 21
Memantine	12†
Mepyramine	1, 13
Mercaptopurine	3b, 8, 21
Mesalazine (oral)	3b*, 13, A*
Metformin	10a, A*, B

† Most appropriate during initial treatment or when dosage is increased.

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Table A.1 Medicines requiring cautionary advisory labels (continued)

Medicine	Ancillary label (number) and/or additional instruction (letter)
Methadone	1
Methotrexate	8, 10a, 20, 21
Methoxsalen	8
Methyldopa	12†, 16
Methylnaltrexone	16
Methylphenidate	12, 13, A*
Methysergide	B
Metoclopramide	12
Metoprolol	9, 12†, A*
Metronidazole	2, 5, B, D
Metronidazole suspension	2, 3b, D
Mexiletine	12, 13
Mianserin	1, 9, 13, 16
Miconazole	D, E (dermal)
Midazolam	1 or 1a
Minocycline	4 (delete dairy products), 8, 12, B, D
Minoxidil	16
Mirtazapine	1, 9, A (not chewed)
Misoprostol	B
Moclobemide	9, 12, B
Modafinil	12
Morphine and salts	1, A*
Moxifloxacin	4 (delete dairy products and calcium), 12†, D
Moxonidine	9, 12
Mycophenolate/mycophenolic acid	8, 9, A
Naltrexone	12
Naproxen	10a, 12†, A*, B
Naratriptan	12
Nelfinavir	5, B
Nevirapine	5
Nicorandil	9, 12
Nicotine patch	21
Nicotinic acid	B
Nifedipine	9, 12†, 18, A*
Nilotinib	4, 5, 18, A
Nilutamide	2, 12
Nitrazepam	1 or 1a, 9
Nitrofurantoin	12, B, D
Norfloxacin	3b, 4, 8, 12, D
Nortriptyline	1, 9, 13, 16
Nystatin	B*, D, E (dermal)
Octreotide	6
Olanzapine	1, 8, 16
Olmesartan	11, 12†, 16†
Olsalazine	B
Omeprazole	13, A*
Opium	1
Orlistat	B

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Antacids will decrease the absorption of many medicines. Unless specifically indicated to the contrary, the administration of antacids should be separated by a period of about 2 hours from other orally administered medicines whenever possible. Similar separation of the dosing of cholestyramine, colestipol, lanthanum and sevelamer from other medicines is also recommended.

Table A.1 Medicines requiring cautionary advisory labels (continued)

Medicine	Ancillary label (number) and/or additional instruction (letter)
Orphenadrine	1, 13
Oseltamivir	A*, D
Oxazepam	1 or 1a, 9 (long-term regular therapy)
Oxcarbazepine	5, 9, 12, 13
Oxpentifylline	A, B
Oxprenolol	9, 12†, A
Oxybutynin	12
Oxycodone	1, A*
Paliperidone	1, 16, A
Pancreatin	A*, B
Pancrelipase	F
Pantoprazole	A
Paracetamol (and products containing paracetamol)	13, 19, A*
Paricalcitol	5, 12
Paroxetine	5, 9, 12, B
Penicillamine	3a, 4
Peppermint oil	3b, A
Pergolide	9, 12†, 16†, B
Perhexiline	5, 12†
Pericyazine	1, 9 (long-term regular therapy), 16
Perindopril	11, 12†, 16†
Pethidine	1
Phenelzine	1, 5, 6, 13, 16, I
Phenindione	10b
Pheniramine	1, 13
Phenobarbitone	1, 5, 9
Phenoxybenzamine	12, 16
Phenoxymethylpenicillin	3a or 3b, D
Phentermine	12, A
Phenytoin	5, 9, 12†, 13
Pholcodine	1
Pimozide	1, 16
Pindolol	9, 12†
Pioglitazone	10a
Piperazine oestrone sulfate	12†, 16
Piroxicam	10a, 12†, B
Pizotifen	1
Posaconazole	5, 12, B, J
Potassium chloride	A*, B
Pramipexole	1, 9, 12, 16
Praziquantel	12, B
Prazosin	12†, 16
Prednisolone (oral)	9 (except short courses), B
Prednisone (oral)	9 (except short courses), B
Pregabalin	1, 9
Primaquine	B
Primidone	1, 5, 9
Probenecid	10a, B

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Antacids will decrease the absorption of many medicines. Unless specifically indicated to the contrary, the administration of antacids should be separated by a period of about 2 hours from other orally administered medicines whenever possible. Similar separation of the dosing of cholestyramine, colestipol, lanthanum and sevelamer from other medicines is also recommended.

Table A.1 Medicines requiring cautionary advisory labels (continued)

Medicine	Ancillary label (number) and/or additional instruction (letter)
Procarbazine	2, 5, 21, I
Prochlorperazine	1, 16
Proguanil	4 (delete milk, iron and calcium), B
Promethazine	1
Propantheline	9, 12
Propranolol	9, 12†
Quetiapine	1, 9, 12†, 16†
Quinapril	11, 12†, 16†
Quinidine	13, A*
Rabeprazole	A
Raltegravir	12
Ramipril	11, 12†, 16†
Reboxetine	9, 12†, 16
Repaglinide	13
Rifabutin	5, D
Rifampicin	3b, 5, D
Riluzole	12
Risedronate	20 (certain forms), A, C
Risperidone	1, 16
Ritonavir	5, B
Rivastigmine	12, B
Ropinirole	12
Rosiglitazone	10a, A
Rotigotine	1, 9, 12, 13, 16
Roxithromycin	3b, D
Salbutamol	22 (capsules and nebules), 7b (foil wrapping)
Salcatonin	6
Saquinavir	5, 18, B
Selegiline	5, 12, B
Sertraline	5, 9, 12
Sevelamer	13, A, B
Sibutramine	5, 12
Sildenafil	5, 16
Simvastatin	18
Sirolimus	5, 6 (solution), 7b (solution), 8, 18
Sitaxentan	5
Sodium fusidate	A*, B, D
Somatropin	6
Sorafenib	3b, 5
Sotalol	4 (delete antacids and iron) 9, 12†, C (1–2 hours)
Spironolactone	11, 12†, 16
Strontium ranelate	4
Sucralfate	3b, 5
Sulfadoxine with pyrimethamine	8, B
Sulfasalazine	A*, B
Sulindac	10a, 12†, B
Sulthiame	9
Sumatriptan	12

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Table A.1 Medicines requiring cautionary advisory labels (continued)

Medicine	Ancillary label (number) and/or additional instruction (letter)
Sunitinib	5, 12
Tacrolimus	3b, 5, 8, 12, 13, 18
Tadalafil	5, 16
Tamoxifen	12†
Tamsulosin	12, 16, A,
Telbivudine	12
Telmisartan	11, 12†, 16†
Temazepam	1 or 1a, 9 (long-term regular therapy)
Temozolomide	21, C (1 hour)
Tenofovir	12†
Terazosin	12†, 16
Terbinafine	D
Teriparatide	6, 7b
Tetrabenazine	1
Thalidomide	1, 16
Theophylline	5, A*, B
Thioguanine	8, 21
Thioridazine	1, 8, 9 (long-term regular therapy), 16
Thyroxine	3b, 4, 6
Tiagabine	1, 9, B
Tiaprofenic acid	10a, 12†, B
Ticlopidine	10b, A, B
Tiludronate	4, A, C (2 hours)
Tinidazole	2, B, D (multiple dosing)
Tiotropium	22 (capsules for inhalation)
Tipranavir	5
Tolterodine	12, 16
Topiramate	1, 9, 12, A*
Tramadol	1, 5, A*
Trandolapril	11, 12†, 16†
Tretinoin (oral)	8, B
Triamterene	11, B
Triazolam	1 or 1a, 9 (long-term regular therapy), 18
Trifluoperazine	1, 8, 9 (long-term regular therapy), 16
Trimeprazine	1, 13
Trimethoprim	D
Trimethoprim Sulfamethoxazole	8, B, D
Trimipramine	1, 9, 13, 16
Triprolidine	1, 13
Tropisetron	12, C (1 hour)
Valaciclovir	D
Valganciclovir	12†,13, 21, A, B
Valproate	9, 10a, 12†, 13, A*, B
Vancomycin	D
Vardenafil	5, 16
Varenicline	12, 13, A, B
Venlafaxine	5, 9, 12, B
Verapamil	9, 12, 13, 18, A*, B*

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Table A.1 Medicines requiring cautionary advisory labels (continued)

Medicine	Ancillary label (number) and/or additional instruction (letter)
Vigabatrin	9, 12†
Voriconazole	5, 8, 12, C, D
Warfarin	5, 10b
Zafirlukast	3b
Zalcitabine	12†
Zanamivir	D
Zidovudine	12
Zinc sulfate	B
Ziprasidone hydrochloride	1, 12, 16, B
Zolmitriptan	12
Zolpidem	1 or 1a, A*
Zonisamide	1, 5, 9
Zopiclone	1 or 1a
Zuclopenthixol	1, 8, 13, 16
Groups of compounds	
Angiotensin converting enzyme inhibitors	11, 12†, 16†
Angiotensin II receptor antagonists	11, 12†, 16†
Antibiotics	D
Anticoagulants	10b
Anticonvulsants	9
Antidepressants—tricyclic and tetracyclic	1, 9, 13, 16
Antidepressants—SSRI	9, 12
Antifungals (oral and vaginal)	D
Antifungals (topical)	E
Antihistamines (except desloratadine and loratadine)	1
Beta-blockers	9, 12†
Benzodiazepines	1 or 1a, 9 (long-term regular therapy)
Calcium channel blockers	12
Corticosteroids (oral)	9 (except short courses), B
Cytotoxics	8, 21
Diuretics	16
Eye preparations (28 days unless specified or authorised otherwise)	7b
Hypnotics	1a
Hypoglycaemic agents	10a, B
Immunosuppressants	8
Insulins	6 (except vial/cartridge in use), 7b, 10a
Medicines packed in child-resistant or strip packaging	13
Monoamine oxidase inhibitors, non-selective	1, 13, 16, I
Nitrates	16
Nonsteroidal anti-inflammatory agents	10a, 12†, B
Phenothiazines (as antipsychotics)	1, 8, 9 (long-term regular therapy), 16
Quinolone antibacterials (except topical)	3b, 4, 8, 12, D
Tetracyclines	4, 8, D
Vaccines	6

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Further information

Consumer Medicine Information and the Pharmacist January 2007. Available to PSA members at www.psa.org.au/site.php?id=38.

Latin abbreviations used in prescription writing

One of the major causes of medication errors is the ongoing use of potentially dangerous abbreviations and dose expressions. Latin was once the language of health care and its use made medical literature universally readable among educated people. Today English is the predominant language of medical literature yet, despite this, many health professionals continue to use Latin abbreviations.

Most of the abbreviations in the list below are provided for historical interest and teaching purposes only, as they are no longer used in prescription writing. However, some of them are still in common use. The New South Wales Therapeutic Advisory Group (TAG) has produced a document entitled *Recommendations for Terminology, Abbreviations and Symbols used in the Prescribing and Administration of Medicines* that strongly recommends the use of plain English and the avoidance of abbreviations, including Latin abbreviations.[1] However, in recognition of the fact that certain abbreviations are still in use, it includes a list of the terms and abbreviations that are commonly used and understood and therefore considered acceptable for use. These appear in bold script in the table below.

Abbreviation	Latin	English
aa	ana	of each
ac	ante cibum	before food
ad		make up to
ad part dolent	partes dolentes	to the painful parts
ah	alternis horis	every other hour
altern d	alterno die	every other day
altern hor	alterno hora or alternis horis	every other hour
ap	ante prandium	before dinner
applic	applicandus	to be applied
	applicatio	an application
	applicetur, applicentur	let it, let them, be applied
aq	aqua	water
aq bull	aqua bulliens	boiling water
aq calid	aqua calida	warm or hot water
aq dest	aqua destillata	distilled water
aq ferv	aqua fervens	boiling water
aq gel	aqua gelida	cold water
aq pluv	aqua pluvialis	rain water
aur	auris	the ear
aur dextr (laev)	auris dextrae (laevae)	to right (left) ear
aurist	auristillae	ear drops
bid	bis in die	twice a day
bd	bis die	twice a day
brev	brevis	short
bull	bulliens	boiling
c	cum	with
calid	calidus	warm or hot
cap	capiat	let him take
cc	cum cibis	with food
cib	cibus	food
co	compositus	compound
coch	cochleare	spoonful
collut	collutorium	a mouthwash
collyr	collyrium	an eye lotion

Abbreviation	Latin	English
conspers	conspersus	a dusting powder
cort	cortex	bark
crem	cremor	a cream
cyath	cyathus	glass
d	dies	a day
deglut	deglutiatur	let it be swallowed
dest	destillatus	distilled
dexter		right
dieb altern	diebus alternis	every other day
d in p aeq	divide in partes aequales	divide into equal parts
dol urg	dolore urgente	when the pain is severe
dolent part	dolenti parti	to the afflicted part
dp	directione propria	with proper direction
dulc	dulcis	sweet
dup	duplex	double
dur	durus	hard
dur dol	durante dolore	while the pain lasts
emp	emplastrum	a plaster
enem	enema	an enema
ex aq	ex aqua	with water
ext	extractum	an extract
f or ft	fiat (fiant)	let it (them) be made
flav	flavus	yellow
fort	fortis	strong
frigid	frigidus	cold
fusc	fuscus	brown
garg	gargarisma	a gargle
gtt	guttae	drops
guttur	appl gutturi applicandus	to be applied to the throat
hab	habeat	let him have (or take)
hac noct	hac nocte	tonight
haust	haustus	a draught
hd	hora decubitus	at bedtime
hs	hora somni	at bedtime
ic	inter cibos	between meals

Abbreviation	Latin	English
IM (or IMI)		intramuscular (injection)
inf	infusum	an infusion
infric	infricetur	let it be rubbed in
	infricandus	to be rubbed in
inj	injectio	an injection
in p aeq	in partes aequales	in equal parts
insuff	insufflatio	an insufflation
irrig	irrigatio	an irrigation
IV		intravenous
lac		milk
laev	laevus	left
lat	lateri dolenti	to the affected side
liq	liquor	a solution
lot	lotio	a lotion
m	**mane**	in the morning
m	mitte	send
m	misce	mix
md	more dicto	as directed
mdu	more dicto utendus	to be used as directed
m et n	mane et nocte	morning and night
mist	mistura	a mixture
mitt	mitte	send
moll	mollis	soft
n	nocte	at night
narist	naristillae	nasal drops
neb	nebula	mist
n et m or n mque	nocte maneque	night and morning
nig	niger	black
nov	novus	new
o	octarius	a pint
o alt hor	omni alternis horis	every other hour
ocul	oculo	to (for) the eye
oculent	oculentum	an eye ointment
oh	omni hora	every hour
om	omni mane	every morning
on	omni nocte	every night
paa	parti affectae applicandus	to be applied to the affected part
p aeq	partes aequales	equal parts
part effect	parti affectae	to the affected area
part dolent	parti dolenti	to the painful part
pc	post cibum	after food
pess	pessus	a pessary
pig	pigmentum	a paint
po	per os	by mouth
pond	ponderosus	heavy

Abbreviation	Latin	English
prn	pro re nata	when necessary
pulv	pulvis	a powder
qd	quaque die	every day
qid	quater in die	four times a day
q	quaque	every
qqh	quaque quarta hora	every four hours
q6h	quaque sex hora	every six hours
qs	quantum sufficiat, quantitas sufficiens, or quantum satis	sufficient
quat	quater	four times
quot	quotidie	daily
Rx		prescription
s	sumendus	to be taken
sem ind die	semel in die	once a day
semih	semihora	half an hour
sig	signa	label
sinist	sinister	left
sos	si opus sit	if necessary
sp	spiritus	spirit
ss	semisse	half
stat	statim	immediately
sum	sumendus	to be taken
sumend	sumendus	to be taken
supp	suppositorium	a suppository
SVM	spiritus vini methylatus	methylated spirit
SVR	spiritus vini rectificatus	rectified spirit
syr	syrupus	syrup
tab	tabletta	a tablet
tdd	ter de die	three times a day
tds	ter die sumendus	to be taken three times a day
tid	ter in die	three times a day
tinct or tr	tinctura	a tincture
troch	trochiscus	a lozenge
tuss	tussis	a cough
tuss urg	tussi urgente	when the cough is troublesome
u	utendus	to be used
UEA	ung emulsif aquos	aqueous cream
ung	unguentum	an ointment
ut dict	ut dictum	as directed
ut direct	ut directum	as directed
utend	utendus	to be used
vap	vapor	an inhalation

References

1. New South Wales Therapeutic Advisory Group Inc. Recommendations for terminology, abbreviations and symbols used in the prescribing and administration of medicines. October 2006. At: www.ciap.health.nsw.gov.au/nswtag/publications/guidelines/TERMINOLOGY1206.pdf.

Medical abbreviations

Abbreviations are commonly used in health-related documents. New ways to truncate, abbreviate or express terminology and complex terms are continually being developed. Many identical abbreviations may mean something completely different depending on which health professional is using them. An example is MMR, which can mean medication management review; measles, mumps rubella vaccine; monthly morbidity reports or multimedia resources. Use abbreviations cautiously and avoid abbreviations where the interpretation may be ambiguous. The following table shows some of the more common abbreviations.

Abbreviation	Expanded form
AAA	abdominal aortic aneurysm
ABG	arterial blood gases
ACA	adenocarcinoma; anticardiolipin antibody; anterior cerebral artery
ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ACR	albumin–creatinine ratio
ACS	acute coronary syndrome
ACT	activated clotting time
ACTH	adrenocorticotrophic hormone
AD	Alzheimer's disease
ADHD	attention deficit hyperactivity disorder
ADP	adenosine diphosphate
ADT	adult diphtheria and tetanus vaccine
AE	air entry; adverse effect; atrial ectopics; above elbow
AF	atrial flutter/fibrillation
AIDS	acquired immune deficiency/immunodeficiency syndrome
AKA	above knee amputation
ALL	acute lymphoblastic leukaemia; acute lymphocytic leukaemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMD	age-related macular degeneration
AMI	acute myocardial infarction
AMSE	abbreviated mental state examination
ANA	antinuclear antibodies
ANCA	antineutrophil cytoplasmic antibodies
anti-CPP	antibodies to cyclic citrullinated peptides
anti-HCV	hepatitis C antibody
APC	argon plasma coagulation
APTT (aPTT)	activated partial thromboplastin time
ARA	acute respiratory acidosis
ARF	acute renal failure; acute respiratory failure
ARMD	age-related macular degeneration
AS	ankylosing spondylitis; aortic stenosis

Abbreviation	Expanded form
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
AT1	angiotensin type 1 receptor
AT1RA	angiotensin type 1 receptor antagonists
AT2	angiotensin type 2 receptor
AV	aortic valve
AXR	abdominal x-ray
BCC	basal cell carcinoma
BG	blood gases
BGL	blood glucose level
Bili	bilirubin
BKA	below knee amputation
BMD	bone mineral density
BMI	body mass index
BNO	bladder neck obstruction; bowels not open
BNP	B-type natriuretic peptide
BO	bowels open
BP	blood pressure; British Pharmacopoeia
BPD	bipolar disease/disorder
BPH	benign prostatic hypertrophy/hyperplasia
BS	bowel sounds; breath sounds
BSA	body surface area
BSL	blood sugar level
BUN	blood urea nitrogen
Bx	biopsy
CA	carcinoma
CAB	coronary artery bypass
CABG	coronary artery bypass graft
CAD	coronary artery disease
CAL	chronic airflow limitation
C-ANCA	anti-neutrophil cytoplasmic antibody test
CAP	community-acquired pneumonia
CAPD	continual ambulatory peritoneal dialysis
CAT	computerised axial tomography
CBC	complete blood count

Abbreviation	Expanded form
CBD	common bile duct
CBE	clinical breast examination; complete blood examination
CBP	complete blood picture/profile
CCB	calcium channel blocker
CCF	congestive cardiac failure; chronic cardiac failure
CDT	combined diphtheria and tetanus vaccine
CEA	carotid endarterectomy; carcinogenic embryonic antigen
CF	cystic fibrosis; children's formula
CFU	colony-forming units
CHF	chronic heart failure; congestive heart failure
CI	confidence interval
CK	creatine kinase
CK-MB	creatine kinase—MB isoenzyme
Cl_{cr}	creatinine clearance
CLL	chronic lymphocytic leukaemia
CMI	Consumer Medicine Information
CML	chronic myelocytic/myeloid leukaemia
CNS	central nervous system
COAD	chronic obstructive airways disease
COBH	change of bowel habit
COLD	chronic obstructive lung disease
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CREST	calcinosis, Raynaud's phenomenon, (o)esophageal dysfunction, sclerodactyly, telangiectasia
CRF	chronic renal failure; chronic respiratory failure
CRP	C-reactive protein
CSF	colony stimulating factor; cerebrospinal fluid
CSU	catheter specimen urine
CT	computerised axial tomography
CTD	connective tissue disease
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CVA	cerebrovascular accident
CVD	cerebrovascular disease
CXR	chest x-ray
D&C	dilation and curettage
DAT	dementia Alzheimer's type; diet as tolerated
DBP	diastolic blood pressure
DDx	differential diagnosis
DM	dermatomyositis
DMARD	disease-modifying antirheumatic drugs
DMMR	domiciliary medication management review
DPI	dry powder inhaler
DRE	digital rectal examination
DSI	digital subtraction angiography
DU	duodenal ulcer
DUE	drug usage evaluation
DVT	deep vein thrombosis
Dx	diagnosis
EAR	estimated average requirement
EBV	Epstein Barr virus
ECC	emergency cardiac care; external cardiac compression
ECG	electrocardiogram; electrocardiograph
ECT	electroconvulsive therapy
EF	ejection fraction
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EN	enteral nutrition
ENA	extractable nuclear antigens
EOM	external otitis media
ESR	erythrocyte sedimentation rate
EUC	electrolytes, urea and creatinine
FAB	frontal assessment battery
FBC	full blood count
FBG	fasting blood glucose
FEF	forced expiratory flow
FEV	forced expiratory volume
FEV_1	forced expiratory volume in one second
FH	family history
FSH	follicle stimulating hormone
FUO	fever of unknown origin
FVC	forced vital capacity
GCA	giant cell arteritis
GERD	gastro-(o)esophageal reflux disease
GFR	glomerular filtration rate
GGT	gamma glutamyltransferase
GI	gastrointestinal
GM-CSF	granulocyte macrophage colony-stimulating factor
GORD	gastro-oesophageal reflux disease
GP	glycoprotein
GTT	glucose tolerance test
GU	gastric ulcer; genitourinary
HA	headache
HAV	hepatitis A virus
Hb	haemoglobin

Abbreviation	Expanded form
HbA_{1C}	glycosylated haemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	haematocrit
HCV	hepatitis C virus
HD	haemodialysis
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency/immunosuppressive virus
HMR	home medicines review
HR	heart rate
HSA	human serum albumin
HSV	herpes simplex virus
HT	hypertension
Hx	history
IA	intra-arterial
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICH	intracranial haemorrhage
ICLE	intracapsular lens extraction
IDDM	insulin dependent diabetes mellitus
Ig	immunoglobulin
IgM anti-HAV	hepatitis A immunoglobulin M antibody
IL-1	interleukin-1
IL-1Ra	interleukin-1 receptor antagonist
IM	intramuscular
INR	international normalised ratio
IOL	induction of labour; insertion of lens; intraocular lens
IOP	intraocular pressure
ISQ	in status quo
ITP	idiopathic thrombocytopenic purpura
IU	international unit
IV	intravenous
Ix	investigation
JVP	jugular venous pressure/pulse
JVPNE	jugular venous pressure not elevated
JVPNR	jugular venous pressure not raised
LA	left atrium; local anaesthetic
LAA	left atrial appendage
LAC	lupus anticoagulant
LAP	laparoscopy; laparotomy; left atrial pressure; leucocyte alkaline phosphatase; lower abdominal pain
LBO	lower bowel obstruction

Abbreviation	Expanded form
LD50	lethal dose in 50% of the test population
LDH	lactate dehydrogenase; lactic acid dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test, lung function tests
LH	luteinising hormone
LHF	left heart failure
LMWH	low molecular weight heparin
LOA	loss of appetite
LOC	loss of consciousness
LVEF	left ventricular ejection fraction
LVF	left ventricular failure
LVH	left ventricular hypertrophy
MAOI	monoamine oxidase inhibitor
MBA	multiple blood/biochemical analysis
MCTD	mixed connective tissue disease
MCU	microculture of urine
MCV	mean cell volume; mean corpuscular volume
MDI	metered dose inhaler
MDP	manic depressive psychosis
MI	myocardial infarction
MIC	minimum inhibitory concentration
MMR	measles, mumps, rubella vaccine; medication management review
MMSE	mini-mental state examination
MODM	mature onset diabetes mellitus
MRI	magnetic resonance imaging
MRR	medication regimen review
MRSA	methicillin/multiple resistant staphylococcus aureus
MS	multiple sclerosis
MSE	mental state examination
MSSU	mid-stream specimen of urine
MSU	mid-stream urine
MVA	motor vehicle accident
MVD	mitral valve disease
NAD	no abnormality detected
NBM	nil by mouth; no bowel movement; normal bowel movement
NBS	normal bowel sounds
NFI	not for investigation
NFO	no further orders
NFR	not for resuscitation
NGT	nasogastric tube
NIDDM	non–insulin dependent diabetes mellitus
NHL	non-Hodgkin's lymphoma

Abbreviation	Expanded form
NOF	neck of femur
NQMI	non-Q-wave myocardial infarction
NSA	no significant abnormality
NSAID	non-steroidal anti-inflammatory drug
NSR	normal sinus rhythm
NSTEACS	non-ST elevation acute coronary syndrome
NSTEMI	non-ST elevation myocardial infarction
NVD	nausea, vomiting and diarrhoea; normal vaginal delivery
OA	osteoarthritis; on admission
OCD	obsessive compulsive disorder
OE	on examination
OTC	over-the-counter
PCI	percutaneous intervention
PCV	packed cell volume
PE	pulmonary embolus; premature ejaculation; pre-eclampsia
PEG	percutaneous enterogastric tube
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
PERL	pupils equal, reacting to light
PERLA	pupils equal, reacting to light and accommodating
PET	positron emission tomography
PFT	pulmonary function tests
PI	Product Information
PIC	percutaneous intravascular catheter
PLT	platelets
PM	polymyositis; post mortem
PMH	past medical history
PMR	polymyalgia rheumatica
PMS	premenstrual syndrome
PMT	premenstrual tension
PN	parenteral nutrition
PO	per-oral; pulmonary oedema
PPAR	peroxisome proliferator activated receptor
PPI	proton pump inhibitor
PPM	permanent pacemaker
PPs	peripheral pulses
PR	per rectum; pulse rate
PSA	prostate-specific antigen
PSS	progressive systemic sclerosis
PTA	percutaneous transluminal angioplasty
PTCA	percutaneous transluminal coronary angioplasty
PTH	parathyroid hormone
PTSD	post-traumatic stress disorder
PU	peptic ulcer
PUD	peptic ulcer disease
PUO	pyrexia of unknown origin
PV	per vagina
PVD	peripheral vascular disease
PVR	post-void residual
QMI	Q-wave myocardial infarction
RA	rheumatoid arthritis; right atrium
RAS	renal artery stenosis; renin angiotensin system
RBC	red blood count; red blood cell
RCC	red cell count
RCV	red cell volume
RDS	respiratory distress syndrome
REM	rapid eye movement
RF	renal failure; rheumatic fever; rheumatoid factor
RFT	respiratory function test; renal function tests
RHF	right heart failure
RMMR	residential medication management review
RPR	rapid plasma reagin test
RSV	respiratory syncytial virus
RVF	right ventricular failure
Rx	prescription
SA	sinoatrial node
SAARD	slow-acting antirheumatic drug
SAE	serious adverse event
SBE	subacute bacterial endocarditis
SBO	small bowel obstruction
SC	subcutaneous
SCS	spinal canal stenosis
SD	senile dementia; standard deviation; sudden death
SH	social history
SIADH	syndrome of inappropriate antidiuretic hormone
SLE	systemic lupus erythematosus; slit lamp examination
SOA	swelling of ankles
SOB	short of breath
SOBOE	shortness of breath on exertion
SPPS	stable plasma protein solution
SPR	see previous result
SS	Sjögren's syndrome; systemic sclerosis
SSG	split skin graft
SSRI	selective serotonin reuptake inhibitor

Abbreviation	Expanded form
ST	sinus tachycardia
STD	sexually transmitted disease
STEMI	ST elevation myocardial infarction
STI	sexually transmitted infection
SV	stroke volume
SVT	supraventricular tachycardia
Sx	signs; symptoms
T_3	liothyronine/triiodothyronine
T_4	thyroxine
TA	temporal arteritis
TCA	tricyclic antidepressant
TCD	transcranial Doppler
TDM	therapeutic drug monitoring
TENS	transcutaneous electrical nerve stimulation
TFT	thyroid function tests
THR	total hip replacement
TIA	transient ischaemic attack
TIBC	total iron-binding capacity
TKR	total knee replacement
TMJ	temporomandibular joint
TNF	tumour necrosis factor
TOE	trans-oesophageal echocardiogram
TOV	trial of voiding
TPMT	thiopurine methyltransferase
TPN	total parenteral nutrition
TRUS	transrectal ultrasound
TSE	transmissible spongiform encephalopathy
TSH	thyroid stimulating hormone
TURP	transurethral resection of prostate
Tx	therapy; treatment
TZD	thiazolidinediones
U&E	urea and electrolytes

Abbreviation	Expanded form
UA	unstable angina
UEC	urea, electrolytes, creatinine
UFH	unfractionated heparin
URTI	upper respiratory tract infection
US	ultrasound
UTI	urinary tract infection
VaD	vascular dementia
VC	vital capacity
VEGF	vasoendothelial growth factor
VF	ventricular fibrillation
VIP	vasoactive intestinal peptide
VSD	ventricular septal defect
VT	ventricular tachycardia
WBC	white blood cell
WCC	white cell count
WNL	within normal limits
#	fracture
+	present; noted
+/-	uncertain/equivocal; plus or minus
++	present significantly
+++	present in excess
0	not present; no abnormality
1/7	one day
1/24	one hour
1/52	one week
1/12	one month
4/24	every four hours
5/7	five days
4/52	four weeks
3/12	three months
6/12	six months
12/12	one year

Further information

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Modification of oral formulations

Many people have difficulty swallowing solid dose forms, such as capsules and tablets, and altering these forms (e.g. crushing tablets or opening capsules) can make administration easier. However, it is important to ensure that the alteration of dosage forms does not result in reduced medicine effectiveness, a greater risk of toxicity or an unacceptable presentation in terms of taste or texture. Pharmacists should note that, once a marketed product has been altered (e.g. crushed), it is no longer being used in accordance with the manufacturer's 'Product Information' and may be considered an 'off-label' product.

These guidelines provide a step-by-step approach to:

- the assessment of swallowing ability
- deciding which medications and dose forms can be altered and which cannot
- the processes of alteration and administration
- ongoing monitoring and assessment of therapy
- documenting the key elements of the processes.

Six-step process to ensure desired therapeutic response[1]

1. Assessment of swallowing ability

There are several reasons why orally administered dose forms of some medicines may need to be altered, including a physical inability to swallow whole foods or medications as a result of a disease state or trauma; dysphagia after stroke; a psychological inability to swallow medication; and a refusal, due to deteriorating cognitive state, to take medication. Any of these reasons may lead to a decision to alter solid oral medications for ease of administration. There are complex issues involved in a person refusing or being unable to take medication, and they should be carefully considered and dealt with on an individual basis.

An inability to swallow solid medications may be a transient or episodic disability and, when clinical circumstances change, renewed attempts to encourage taking unaltered dosage forms should be made. The ability of some people to swallow may vary during the day so that, when clinically acceptable, changing to alternative dosing times may reduce the need for product alteration.

A comprehensive consultation by a speech pathologist is commonly used to provide a detailed assessment of a person's ability to swallow, especially in the hospital or aged care facility setting. This has important implications for a person's medicines, diet and risk of aspiration.

2. Review of the medication regimen

Difficulties experienced in swallowing medications should always provide a stimulus for a review of the medication profile with a view to changing to different formulations (e.g. oral liquid, transdermal patch, dispersible tablet, sublingual tablet) of the same medicine, changing to an alternative medicine or stopping medicines that are no longer necessary. The reviewer should differentiate between those oral preparations that need to be swallowed and those that need to be retained in the mouth for optimal effect (e.g. sublingual glyceryl trinitrate tablets and amphotericin lozenges). People who are alert but unable to swallow may be able to manage the latter groups of products.

In many cases, alternative preparations of the required medication may be available. For example, dispersible tablets or sustained-release capsules containing pelletised units which can be opened and dispersed on food. Immediate release dose formulations can usually be crushed without any major concerns. If a liquid formulation of the required medicine is available, be aware that a dose given as a liquid is likely to be absorbed more quickly than the same dose given as a modified-release solid preparation. Smaller doses of the liquid formulation given more frequently may be required to achieve the same total daily dose. A drug given as a liquid dosage form may have a different bioavailability compared with when it is administered as a solid dose form, leading to different pharmacological effects. Pharmacists should refer to the Product Information to establish the equivalency of dose forms. Excipients such as ethanol, sorbitol or sucrose, which are commonly found in liquid dose forms, may also influence choice of formulation.

3. Which formulations should not be altered?

The 'Clinical monographs' in Section B provide information on some specific medicines which should not be altered or crushed (e.g. solid dose forms that are dispersible in water). Pharmacists should regularly consult approved Product Information for updated information on specific dose forms or new formulations.

Some formulations should not be altered in any way because of:

- *Alteration in absorption characteristics.* This is of particular concern with controlled/sustained release medications, which are formulated to release the drug in a controlled manner over a defined dosing period, usually 12 or 24 hours. Wording such as 'controlled release' (CR), 'sustained release' (SR), 'modified release' (MR), 'controlled delivery' (CD), or 'enteric coated' (EC) implies that the dose form has altered release characteristics. Crushing these formulations will compromise the release characteristics and may result in an unintended large bolus dose with unwanted or exaggerated therapeutic effect (e.g. alteration of sustained release verapamil tablets results in an increased risk of hypotension and bradycardia) or, in the case of an enteric coated dose form, a drug being degraded in gastric acid, rendering it less effective.

  Although sustained release products cannot be crushed, some can be halved—e.g. *Imdur* 60 mg (but **not** 120 mg).

  It is acceptable to open capsules containing medication formulated into small pellets where the release properties are built into the pellet and not the capsule casing—e.g. *Kapanol* capsules. The pellets may be mixed into water, juice or milk or sprinkled onto a small amount of soft food. The pellets must not be chewed or crushed and the mouth should be rinsed to ensure that all pellets have been swallowed.
- *Alteration in stability*. For example, nifedipine is extremely susceptible to light. Omeprazole is degraded by exposure to gastric acid; crushing the tablet will expose the medicine to gastric acid in the stomach before the medicine reaches its site of absorption in the upper small intestine.
- *Alteration in desired effect due to failure to reach the site of action*. Some products are formulated to release medicine at a defined site in the gastrointestinal tract. For example, some mesalazine formulations, such as a resin-coated tablet, are designed to release the medicine in the lower small intestine (Pentasa) or colon (Salofalk, Mesasal).

Some formulations may be altered if clinically indicated, however the following factors should be considered:

- Alteration may increase the risk of local irritant effect. Some medicines irritate the oesophagus and/or stomach (upper gastrointestinal tract)—e.g. aspirin. In the event that potentially irritant medications do need to be crushed, medication administration should be accompanied by sufficient liquid to ensure that no medication residue is left in contact with the oesophagus. Some irritant medicines (e.g. alendronate) should not be crushed due to their potential to cause severe upper gastrointestinal irritation and ulceration.
- The medication may have an unacceptable or undisguisable taste (e.g. hydroxychloroquine tablets are coated to disguise the exceptionally bitter taste). In these cases, crushing will not alter the effectiveness but may compromise patient adherence.

Some formulations may be altered if precautions are observed:

- Film coatings may be used to mask taste, odour or protect from light or moisture. Alternative methods of disguise may be necessary when breaking or crushing film coated tablets. Medicines altered in this way should be administered immediately.
- Some medicines may be altered to make administration easier if occupational health and safety precautions are observed—e.g. cytotoxic medicines, isotretinoin (a teratogen), chlorpromazine (can cause contact dermatitis). For example, women who are or may potentially be pregnant, should not handle crushed or broken tablets of finasteride (or handle tablets with wet hands) due to the possibility of absorption and the potential risk to a male fetus.[2]

4. Suitable techniques for crushing

Pharmacists should refer to the 'Extemporaneous dispensing', Section A.

A variety of equipment is suitable for alteration of solid oral medication dose forms. There are three principles to follow when deciding which equipment to use:

- Equipment should permit essentially complete and reproducible recovery of powdered material.
- Equipment used for more than one person's medication should be washed with detergent and thoroughly dried after each use to minimise contamination from residue of other medications or excipients.
- For cytotoxic medications, a dedicated set of equipment must be used for each person, and procedures implemented to avoid exposure of powdered material to the pharmacist or between patients (seek specialist advice on suitable procedures).

Crushing more than one tablet together can make it easier to both crush and retrieve mixed medicines from the device used for crushing. In most cases the potential for chemical interaction between medicines that are crushed and mixed together is not great, but in order to minimise the possibility of an interaction the medication should be administered as soon as possible after crushing and/or mixing together.

There are some medications that should not be crushed together because, when administered, one medicine will cause reduced absorption of the other (e.g. calcium reduces the absorption of fluoroquinolone antibiotics, tetracylines and bisphosphonates).

When tablets and capsules are to be given together, crush the tablets first. Then open the capsule and add the contents to the crushed tablets. This will avoid crushing sustained release or enteric coated pellets contained within the capsule.

A consistent crushing technique will avoid significant alterations in the amount of medicine administered with each dose.

5. Administration of altered medications

The altered formulation may be mixed with a small amount of semi-solid food such as jam, fruit puree or yoghurt to disguise unpleasant taste or texture and aid compliance. In some cases dairy products such as yoghurt should not be used. (see Table A.1, Section A for Medicines requiring label 4). Crushed tablets or capsule contents should not be sprinkled on to meals because portions of the meal may be left uneaten.

Crushed tablets or capsule contents should be taken as soon as possible after altering and mixing with any food or liquid. This will minimise both the risk of medicine degradation and inadvertent administration to the wrong person. Wherever possible, the person receiving the medication should be upright, or as close as practicable to upright, when taking oral medications.[3]

Always ensure that any solid medications, whether altered or not, are taken with sufficient water or other suitable liquid to minimise the risk of oesophageal irritation.

6. Monitoring and assessment

Good clinical practice dictates that monitoring and assessing therapeutic response is required whenever medications are administered. This is especially important when alteration of a dosage form is required. Lack of expected effect and/or adverse effects may indicate altered absorption as a result of product alteration, and a further medication review may be required.

All relevant aspects of the six-step process must be documented. The records should be retained and be available to all relevant members of the healthcare team.

References

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Extemporaneous dispensing

Extemporaneous dispensing (compounding)

Extemporaneous dispensing (compounding) is the preparation and supply of a single 'unit of issue' of product which is intended for immediate use by a specific patient.

Extemporaneous preparations for individual patients can be dispensed or compounded by pharmacists in premises that are not accredited under the Code of Good Manufacturing Practice requirements but meet professional standards and comply with the requirements outlined in this section. Pharmacists have a duty to ensure dispensed products are safe and efficacious. Furthermore, equipment, premises and raw materials must be of an acceptable standard for compounding purposes. The use of sound pharmaceutical techniques is essential to ensure that a product of adequate quality is produced. Any formulation that is dispensed or compounded must be based on sound pharmacological, clinical and pharmaceutical principles. See also 'Compounding' in the 'Professional Practice Standards'.

Extemporaneous products are required for various reasons, including liquid formulations needed for paediatric and geriatric patients; a registered product being discontinued or unavailable; patient-specific requirements; products that must be freshly made.[1,2] Pharmacists should consider the use of a listed or registered commercial product that can be efficaciously and safely used for the intended purpose in place of an extemporaneously prepared product.

The APF includes formulae that are not available commercially, with some exceptions. These have been included predominantly for teaching purposes.

The designation CF (children's formula), is used to identify a formulation that is intended for use in children. The designation BP refers to the current edition of the *British Pharmacopoeia*.

Extemporaneous manufacturing, which is the production of a batch of a product, resulting in a number of units of use intended for supply over a period of time, should not be performed unless in premises approved, certified or exempted for such purposes and where the product has documented stability data. Pharmacists who engage in extemporaneous manufacturing have an obligation to be aware of and comply with the requirements of the Code of Good Manufacturing Practice, which can be found at www.tga.gov.au/docs/html/gmpcodau.htm.

Pharmacists practising extemporaneous manufacturing must ensure that products are labelled according to the requirements of Therapeutic Goods Order No. 69, which can be found at www.tga.gov.au/docs/pdf/tgo/tgo69.pdf or www.tga.gov.au/docs/html/tgo/tgo69_1.htm.

Personnel

Precautions should be taken to minimise the risk of contamination of products or personnel. Eating or drinking is not to be permitted in preparation areas, and hands should be washed and dried before any compounding activity occurs. Staff should wear protective clothing (e.g. laboratory coat, disposable gloves and hair covering) during any procedures. Additional precautions (e.g. eye protection, dust mask and powder-containment systems) may be appropriate when compounding potent substances such as hormones. Staff should refer to the Material Safety Data Sheet for each substance—it is available from the supplier of compounding ingredients—for handling and storage requirements.

In respect of MSDS and labels, employers and self-employed persons must:

- obtain an MSDS of a hazardous substance from the supplier
- keep a register containing a list of all hazardous substances used at the workplace and put a copy of any MSDS obtained in the register
- take reasonable steps to ensure the MSDS is not changed other than by the manufacturer or importer
- keep the MSDS close to where the substance is being used
- ensure a label is fixed to a hazardous substance container
- ensure warnings are given about enclosed systems containing hazardous substances.

Equipment and premises

Pharmacists should not compound preparations for which they do not have the appropriate facilities or equipment. To avoid the risk of contamination, all manipulations should be conducted in dedicated dispensing areas. All working surfaces should be in good condition, hygienic and covered with impervious washable materials. Work surfaces should be thoroughly cleaned before and after compounding activities.

All equipment must be in good working order and be maintained and stored in a manner which protects it

from damage and contamination. It must be thoroughly cleaned after and immediately before each use. Balances and measures should be regularly checked at specified intervals and the appropriate records maintained. The sensitivity of balances must be appropriate for the quantities being weighed.

Certain manipulations (e.g. aseptic transfer, sterilisation, handling of cytotoxic agents and biological modifiers) require specialised equipment and facilities and should be undertaken only at adequately designed and equipped premises by trained and experienced personnel.

Procedures

Preparation of some products requires specialised training and ongoing experience to maintain special skills. Products with specific formulation requirements (e.g. extended, sustained, modified or delayed release) should only be prepared where there is evidence of compliance with the appropriate pharmacopoeial standard.

All excipients and ingredients employed by pharmacists in the preparation of these products must be of the highest pharmaceutical grade, be suitable for administration to humans, and comply with the requirements of pharmacopoeial standards (e.g. British Pharmacopoeia, European Pharmacopoeia, US Pharmacopoeia, National Formulary, International Pharmacopoeia) or other standards appropriate for their use. This involves obtaining ingredients from reputable suppliers who can supply a certificate of analysis. Materials must be stored under recommended conditions and be labelled with a validated expiry date and batch number.

Water used in the preparation of non-sterile extemporaneous products should be Purified Water BP which has been freshly boiled and cooled or Water for Irrigation BP. Water used in the preparation of sterile extemporaneous products should be Water for Injections BP.

Microwave ovens

A microwave oven specifically designated for compounding purposes can be used as an alternative means of heating when preparing creams and lotions. It should never be used for dissolving ingredients in preparations—particularly ointments in which the ingredients are present at concentrations above their solubility. When heating oils, care should be taken to avoid super-heating. Appropriate containers must also be used.

Sterilisation methods

The conditions for sterilisation laid down in this handbook reflect those given in the current edition of the British Pharmacopoeia. Where heating in an autoclave is specified, sterilisation by filtration may be used as an alternative—provided the nature of the preparation permits this. Heating with a bactericide is not considered a satisfactory alternative.

Liquid medications

Many drugs are not formulated commercially in dosage forms suitable for paediatric use. It may be necessary to prepare liquid oral formulations by reformulating commercially available products, including injections or tablets or capsules. It is preferable to get a dose that is a fraction of a tablet or capsule—e.g. quarter of a tablet that can be cut—if this is appropriate for the age/size of the patient. This requires consultation with the prescriber. In these exceptional cases, consideration must be given to the stability of the drug in the vehicle. When dispersing tablets in water and taking an aliquot of the dispersion, it is necessary to know whether the medication becomes soluble or the dispersion achieves an adequate suspension to measure an accurate dose. Pharmacists are advised to contact a hospital pharmacy department for advice. See also 'Modification of oral formulations', Section A.

When using tablets or capsules, the highest strength available should be used wherever possible to minimise the amount of other ingredients. Some brands may contain excipients which render them unsuitable for use in the preparation of liquid formulations. Check the Product Information and the Consumer Medicine Information (CMI).

Unless otherwise stated sustained-release or enteric-coated products should not be reformulated as the resulting product is likely to have poor stability.

If tablets are used they should be crushed and the powder triturated with a small amount of the vehicle before making to volume (see 'Modifications of oral formulations', Section A).

In these types of preparations, which are likely to contain undissolved active ingredients, suspending agents may be required (see 'Mixtures').

Formulae for liquid preparations for internal use included in the handbook are adjusted to a dose volume of either 5 or 10 mL. However, dose ranges are included in most of these formulae to permit the prescribing of larger doses when required. The metric dose in millilitres should be stated on the preparation's label and the patient instructed on how to use a correctly calibrated medicinal measure/syringe. *Use of domestic spoons should be discouraged.* It is important to unambiguously state the strength of a product (i.e. mg/mL or mg/5 mL). Confusion can arise with products that are available in multiple strengths, especially if instructions are 'x' mL per dose.

For more information on liquid medications, see the 13th edition of the Royal Children's Hospital Melbourne Paediatric Pharmacopoeia.

Storage and expiry dates

The following standard storage instructions have been adopted in Australia for labelling of therapeutic goods:

- Store below –18 °C (Deep freeze)
- Store below –5 °C (Freeze)
- Store at 2–8 °C (Refrigerate. Do not freeze)
- Store below 8 °C (Refrigerate)
- Store below 25 °C
- Store below 30 °C

The shelf life of a product is dependent on the conditions of storage. A product may fail to meet official standards if it is kept for any prolonged period outside the labelled temperature range, when the expiry date marked on it has been passed, or when repackaged.

Products that must be stored below –18 °C, below –5 °C, below 8 °C or below 25 °C should be kept below the prescribed temperature at all times. Storage below –5 °C will generally be attainable in the freezing compartment of a domestic refrigerator. Storage below 8 °C will generally be attainable in the main storage compartment of a domestic refrigerator. Storage below 25 °C will be attainable by standard air conditioning in places where the ambient temperature exceeds 25 °C. Products that must be stored at below 25 °C or below 30 °C should be kept below the nominated temperature for at least 95% of the time and should never be stored at temperatures exceeding 40 °C.

Formulations in this handbook are intended primarily for extemporaneous dispensing by pharmacists. An expiry date of 28 days or less should be assigned unless otherwise specified. When a product must be freshly prepared it should be issued within 24 hours of preparation. When a product must have been prepared recently this indicates that deterioration is likely if the product is stored for longer than four weeks. It is therefore desirable for the product to be issued within seven days of preparation.

Documentation of extemporaneous dispensing

A record must be kept of all extemporaneous dispensing to enable the full history of a product to be determined. Clear and unambiguous documentation of all compounding activities is a quality assurance requirement, reduces the risk of error, and facilitates the maintenance of product quality. This record should be retained for two years from the date of dispensing of the preparation or as required by state law. The following page shows an example of an extemporaneous dispensing form.

Weights and measures

Weights should be stated in multiples or fractions of a gram, milligram or microgram. Fluid measures should be stated in multiples or fractions of a millilitre. The following abbreviations may be used:

- g – gram
- mg – milligram
- mL – millilitre.

In order to avoid confusion, the word ‘microgram’ should be written in full, not abbreviated.

Containers and labelling

The containers used should be appropriate for the use of the product and stability of the ingredients. Child resistant closures should be used if possible. Reference should be made to the Therapeutic Goods Order No. 80 as applicable.

Extemporaneously prepared products should be labelled in accordance with state law and should also include the approved pharmacopoeial or Australian Pharmaceutical Formulary name (or the amount or concentration of all active ingredients and preservatives if not a pharmacopoeial or APF formulation), the expiry date, directions for use, required ancillary labels and storage conditions.

Quality control

The pharmacist is responsible for ensuring the quality of an extemporaneously prepared product. He or she should verify that the product has been prepared according to the documented procedures and meets product specifications before authorising release for dispensing to a patient.

Complaints and recalls

Errors, defects and complaints about extemporaneous products should be investigated and steps taken to remedy any problems. A recall procedure should be documented in the event that a dispensed product must be recovered.

Self-inspection

There should be a systematic approach to improvement of the compounding activities in a pharmacy and to ensuring conformity with the requirements of this section and professional practice standards. Self-inspections should be conducted at regular intervals to identify areas for improvement and the resulting actions taken should be documented.

Extemporaneous dispensing form

Pharmacy name

Patient's name

Contact details

Prescriber name

Contact details

Prescription

Formula source (if applicable)

Date of preparation

Product prepared by

Working formula

Ingredient	Manufacturer	Batch number	Expiry date	Measured quantity	Measured by	Checked by

Methods and notes

Container description and size

Additional labels

Attach copy of label used on product

Expiry date

Product released by
(name and signature)

General formulary

Applications

Applications are liquid or semi-solid preparations for external use.

Containers and storage: Store at less than 25 °C unless otherwise specified. Dispense in amber, fluted poison bottles.

Labelling: Label K: FOR EXTERNAL USE ONLY. Shake the bottle (if applicable).

Expiry: 28 days from the date of preparation unless otherwise specified.

benzyl benzoate application

Applic. Benzyl. Benz.; benzyl benzoate lotion

benzyl benzoate ..... 25 g
emulsifying wax ..... 2 g
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains 25% of benzyl benzoate (limits 22.5 to 27.5% w/v of $C_{14}H_{12}O_2$).

Method: Melt the emulsifying wax (see 'Emulsifying ointment', Section A). Add the benzyl benzoate and mix. Add this mixture to 70 mL of purified water previously heated to about 70 °C. Stir until cold and adjust to volume with purified water.

Use: For the treatment of scabies. After a bath apply with a brush to the whole of the body except the face and head; leave on for 24 hours without bathing; application should be repeated in five to 10 days.

Capsules

Capsules prepared extemporaneously consist of powders enclosed in a hard gelatin or cellulose capsule for individual dosages. Capsules of medication are generally available commercially. However, on occasions a small quantity of medicine may be required that is not available in that form. The capacity of capsules depends on the actual powder density of the ingredients. Hard empty gelatin capsules are available in the following codes and the approximate amount that each will hold of lactose (most common diluent):

No. 00: ..... 930 mg
No. 0: ..... 650 mg
No. 1: ..... 490 mg
No. 2: ..... 360 mg
No. 3: ..... 290 mg

Method: Appropriate attenuation (dry dilution) of the medicine in a diluent is carried out with a mortar and pestle. The final attenuation containing the correct amount of medicament is weighed into the empty capsule or the final powder is spread in a layer about 5 mm thick, and the empty capsule is punched into the powder until it is filled while continually checking for correct weight on a tared balance.

Containers and storage: If any of the constituents are deliquescent or volatile, the capsule should be stored and supplied in airtight containers.

boric acid vaginal capsule

boric acid ..... 600 mg

Method: As for preparation of capsules (just described) using No. 0 or 00 capsules.

Use: For Candida glabrata.

Label: Label L: CAUTION: NOT TO BE TAKEN.

Creams

Creams are semi-solid preparations, usually emulsions, which are intended for application to the skin. They may be watermiscible (oil-in-water emulsions)—described in this formulary as aqueous creams—or oilmiscible (water-in-oil emulsions)—described as oily creams.

Containers and storage: Creams should be stored and supplied in well-closed containers which prevent evaporation and be kept below 25 °C. Collapsible tubes of metal or suitable plastics should be used whenever possible.

Expiry: The expiry date is 28 days from the date of preparation unless otherwise specified.

Labelling: If the product is for topical use, the container should be labelled FOR EXTERNAL USE ONLY. If the product is for nasal, otic, vaginal or rectal use, the container should be labelled CAUTION: NOT TO BE TAKEN.

Creams should be labelled to include the name and percentage of any preservative agent used.

When chlorocresol is used as the preservative, it should be dissolved using warm water in a closed container.

Oily creams

Oily creams are protective and emollient in nature. Oily cream, cold cream and oily glycerol cream are bases of this type. Such bases are not suitable for the presentation of water-soluble antiseptics. They may be used for local protectives (e.g. calamine, zinc oxide) and for the application of some oil-soluble medicaments (e.g. camphor, menthol, methyl salicylate).

Aqueous creams

Aqueous creams can effectively deliver medicaments to body surfaces. Creams may become concentrated through loss of water, so caution must be exercised in relation to the strengths of caustic medicines used with them. Creams are watermiscible and readily removed by washing.

Aqueous creams may be used for water-soluble antiseptics (e.g. chlorhexidine), water-soluble local anaesthetics and most other dermatological agents.

In the use of aqueous creams, it must be recognised that the water present may reduce the stability of many medicaments and encourage the growth of micro-organisms unless suitable preservatives are included. The preservatives specified in aqueous creams may be replaced by suitable alternative antimicrobial preservative agents provided the name and concentration of the alternative agent used are stated on the label.

Care must be taken to avoid contamination during preparation. The apparatus used in the preparation of creams, and the final containers, should be thoroughly cleansed, rinsed in freshly boiled and cooled water, and dried. Purified water used in the preparation of creams should be freshly boiled and cooled before use.

Aqueous creams may be classified according to the chemical type of the emulgent used.

Anionic creams

Anionic creams contain emulgents which yield large anions and therefore are potentially incompatible with cationic drugs. An ion-pair is likely to be formed between the anionic emulgent and the cationic drug, and this may reduce either the efficacy of the emulgent or the activity of the drug (see 'Emulsifiers and stabilisers', Section A). Aqueous cream is a cream of this type.

Cationic creams

Cationic creams contain emulgents which yield large cations and therefore are potentially incompatible with anionic drugs. An ion-pair is likely to be formed between the cationic emulgent and the anionic drug, and this may reduce either the efficacy of the emulgent or the activity of the drug (see 'Emulsifiers and stabilisers', Section A). Cetrimide cream aqueous is a cream of this type.

Non-ionic creams

Non-ionic creams contain emulgents which yield virtually no ions. The emulgents are often polyoxyethylene esters or ethers. These creams are usually compatible with both anionic and cationic drugs. Cetomacrogol cream aqueous is a cream of this type.

aluminium acetate cream oily

Burrow's cream

aluminium acetate solution ..... 5 mL
zinc oxide ..... 20 g
wool fat ..... 25 g
arachis oil ..... 25 mL
purified water, freshly boiled and cooled ..... 27 mL

These quantities make 100 g of cream.

Method: Melt the wool fat with the arachis oil with the aid of gentle heat. Triturate the zinc oxide with this mixture until smooth and allow to cool. Mix the aluminium acetate solution and the purified water and incorporate into the oil phase.

Use: Mild antipruritic in subacute dermatitis.

Label: Label N: CONTAINS PEANUT OIL.

aqueous cream

simple cream; Hydrous emulsifying ointment; Ung. Emulsif. Aquos. (UEA)

emulsifying ointment ..... 30 g
glycerol ..... 5 mL
phenoxyethanol ..... 1 g
purified water, freshly boiled and cooled ..... to 100 g

When this product is ordered with cationic drugs (see 'Emulsifiers and stabilisers', Section A), it should be replaced by cetomacrogol cream or aqueous cetrimide cream.

Method: Melt the emulsifying ointment and mix with 5 mL of glycerol and 60 mL of purified water heated to approximately 70 °C. Stir until a semi-solid cream forms, then add the phenoxyethanol and adjust to 100 g with the purified water. Mix thoroughly.

Use: Anionic base, emollient. May be a useful vehicle for incorporating drugs such as sulfur, salicylic acid, phenol and coal tar.

buffered cream aqueous

sodium phosphate ..... 2.5 g
citric acid monohydrate ..... 0.5 g
chlorocresol ..... 0.1 g
emulsifying ointment ..... 30 g
purified water, freshly boiled and cooled ..... to 100 g

Method: Add the solids to a warmed 200 mL container then add 65 mL of just-boiled purified water (>80 °C), close the container and shake to dissolve. Mix with the melted emulsifying ointment and stir until a semi-solid cream forms. Adjust to 100 g with purified water and mix thoroughly.

Note: This cream has a pH of approximately 6.

Use: Anionic base, emollient. May be a useful vehicle for incorporating drugs such as sulfur, salicylic acid, phenol and coal tar.

calamine cream aqueous

calamine ..... 4 g
zinc oxide ..... 3 g
cetomacrogol emulsifying wax ..... 6 g
arachis oil ..... 30 g
chlorocresol ..... 0.1 g
purified water, freshly boiled and cooled ..... to 100 g

Strength: Contains 4% of calamine and 3% of zinc oxide (limits 4.3 to 5.3% w/w, calculated as Zn).

Method: Melt the cetomacrogol emulsifying wax (see 'Cetomacrogol cream aqueous', this page) in the arachis oil at 70 °C. Add the chlorocresol to a warmed 200 mL container, then 55 mL of just-boiled purified water (>80 °C), close the container and shake to dissolve. Mix the two phases and stir until a semi-solid cream forms. Adjust to 93 g with purified water and mix thoroughly. Triturate the calamine and zinc oxide with a small portion of the cream, then incorporate in the remainder.

Use: Antipruritic.

Label: Label N: CONTAINS PEANUT OIL.

calamine cream oily

calamine ..... 32 g
oleic acid ..... 0.5 mL
phenoxyethanol ..... 1 mL
arachis oil ..... 21.5 mL
wool fat ..... 17.5 g
calcium hydroxide solution ..... 29.5 mL

The above quantities make 100 g of cream.

Strength: Contains 32% of calamine (limits 16.5 to 20.1% w/w, calculated as Zn).

Method: Melt the wool fat in the arachis oil and the oleic acid. Add the phenoxyethanol, triturate the calamine with this mixture in a mortar until smooth and incorporate the calcium hydroxide solution.

Use: Protective, antipruritic.

Label: Label N: CONTAINS PEANUT OIL.

cetomacrogol cream aqueous

non-ionic cream; sorbolene cream

cetomacrogol emulsifying wax* ..... 15 g
liquid paraffin ..... 10 g
white soft paraffin ..... 10 g
chlorocresol ..... 0.1 g
propylene glycol ..... 5 mL
purified water, freshly boiled and cooled ..... to 100 g

*Cetomacrogol emulsifying wax consists of cetomacrogol 1,000 (20%) and cetostearyl alcohol (80%).

Method: Melt the cetomacrogol emulsifying wax in the paraffins at about 70 °C. Add the chlorocresol to a warmed 200 mL container, then 60 mL of just-boiled purified water (>80 °C), close the container and shake to dissolve. Immediately add the propylene glycol to the aqueous phase, then mix both phases and stir until a semi-solid cream forms. Adjust to 100 g with purified water and mix thoroughly.

Use: Non-ionic base, emollient. This non-ionic cream base may be used for incorporating cationic, non-ionic and anionic substances.

cetrimide cream aqueous

Crem. Cetrimid. Aquos.

cetrimide ..... 0.5 g
chlorocresol ..... 0.1 g
cetostearyl alcohol ..... 7.5 g
liquid paraffin ..... 50 g
purified water, freshly boiled and cooled ..... to 100 g

Strength: Contains 0.5% of cetrimide (limits 0.44 to 0.53% w/w of $C_{17}H_{38}BrN$).

Method: Melt the cetostearyl alcohol in the liquid paraffin at 60 °C. Add the cetrimide and the chlorocresol to a warmed 200 mL container, then approximately 40 mL of just-boiled purified water (>80 °C), close the container and shake to dissolve. Mix the two phases and stir until a semi-solid cream forms, then adjust to 100 g with purified water and mix thoroughly.

Use: Cationic base, emollient antiseptic. This cream base may be used for incorporating cationic substances such as chlorhexidine, aminacrine, acriflavine and ichthammol.

chlorhexidine cream aqueous

chlorhexidine gluconate solution ..... 5 mL
cetomacrogol emulsifying wax ..... 25 g
liquid paraffin ..... 10 g
purified water, freshly boiled and cooled ..... to 100 g

Strength: Contains 1% of chlorhexidine gluconate (limits 0.9 to 1.1% w/w of $C_{22}H_{30}Cl_2N_{10}.2C_6H_{12}O_7$).

Method: Melt the cetomacrogol emulsifying wax (see 'Cetomacrogol cream aqueous', previous page) in the liquid paraffin and mix with 50 mL of purified water heated to approximately 70 °C. Stir until a semi-solid cream forms. Mix the chlorhexidine gluconate solution with the remaining 10 mL of purified water and stir through the cream in three separate 5 mL portions. Adjust to 100 g if necessary.

Note: Chlorhexidine gluconate solution BP is an aqueous solution containing 19 to 21% w/v of chlorhexidine gluconate.

Use: Antiseptic preparation for furunculosis or folliculitis.

coal tar and zinc cream oily

coal tar ..... 1 g
castor oil ..... 1 g
zinc cream oily ..... 98 g

Strength: Contains about 31% of zinc oxide (limits 29.2 to 33.6% w/w of ZnO).

Method: Triturate the coal tar with the castor oil and mix with the zinc cream.

Use: Antipruritic, protective.

Label: Label N: CONTAINS PEANUT OIL.

cold cream

Ceratum Hydrosum; Crem. Refrig. Oleos.; Ung. Refrig.

white beeswax ..... 17 g
liquid paraffin ..... 45 g
borax ..... 1 g
purified water, freshly boiled and cooled ..... 37 mL

Method: Melt the white beeswax in the liquid paraffin. Warm the purified water to about 70 °C and use it to dissolve the borax. Mix the two phases and stir until cool.

Note: The proportions of white beeswax and liquid paraffin may be varied to suit the prevailing temperature.

Use: Water-repellent cream.

dimethicone cream aqueous

silicone cream

dimethicone 350 ..... 10 g
liquid paraffin ..... 40 g
cetostearyl alcohol ..... 5 g
cetrimide ..... 0.5 g
chlorocresol ..... 0.1 g
purified water, freshly boiled and cooled ..... to 100 g

Method: Melt the cetostearyl alcohol in the dimethicone 350 and liquid paraffin. Add the cetrimide and chlorocresol to a warmed 200 mL container, then add approximately 40 mL of just-boiled purified water (>80 °C), close the container and shake to dissolve. Mix the two phases and stir until a semi-solid cream forms, then adjust to 100 g with warm purified water and mix thoroughly. Stir until cool.

Use: Water-repellent cream.

glycerol cream aqueous

Crem. Glycer. Aquos.

glycerol ..... 15 g
cetomacrogol emulsifying wax ..... 15 g
liquid paraffin ..... 10 g
white soft paraffin ..... 10 g
chlorocresol ..... 0.1 g
purified water, freshly boiled and cooled ..... to 100 g

Method: Melt the cetomacrogol emulsifying wax (see 'Cetomacrogol cream aqueous', previous page) and white soft paraffin in the liquid paraffin. Add the chlorocresol to a warmed 200 mL container, then approximately 45 mL of just-boiled purified water (>80 °C), close the container and shake to dissolve. Add the glycerol to the aqueous phase then mix both phases, and stir until a semi-solid cream forms. Adjust to 100 g with purified water and mix thoroughly.

Use: Emollient.

glycerol cream oily

Crem. Glycer. Oleos.; oily glycerin cream

glycerol ..... 20 g
calcium hydroxide solution ..... 32 mL
arachis oil ..... 22 g
wool fat ..... 26 g

Method: Melt the wool fat in the arachis oil. Triturate this mixture with small portions of the calcium hydroxide solution. Add the glycerol (also in small portions) and mix.

Use: Traditional emollient.

Label: Label N: CONTAINS PEANUT OIL.

ichthammol and zinc cream oily

oily ichthammol cream

ichthammol ..... 5 g
wool fat ..... 15 g
zinc cream oily ..... 80 g

Strength: Contains 25.6% of zinc oxide (limits 23.1 to 29.1% w/w of ZnO).

Method: Triturate the wool fat (may need to be melted with the aid of gentle heat) with the oily zinc cream until smooth. Incorporate the ichthammol.

Use: Traditional application for inflammatory and eczematous disorders.

Label: Label N: CONTAINS PEANUT OIL.

methyl salicylate compound cream

Crem. Meth. Sal. Co.

methyl salicylate ..... 25 mL
eucalyptus oil ..... 10 mL
menthol ..... 4 g
cetomacrogol emulsifying wax ..... 20 g
purified water, freshly boiled and cooled ..... to 100 g

Method: Melt the cetomacrogol emulsifying wax (see 'Cetomacrogol cream aqueous', p. 37) to about 60 °C. Dissolve the menthol in the eucalyptus oil and add, together with the methyl salicylate, to the melted wax. Warm 38 mL of purified water and add to the mixture with stirring. Adjust to weight with purified water and stir until cool.

Note: The product will thicken over time, although this can be accelerated by cooling to 2–8 °C.

Use: Topical analgesic, rubefacient.

oily cream

hydrous ointment; wool alcohols cream

wool alcohols ointment ..... 50 g
phenoxyethanol ..... 1 g
dried magnesium sulfate ..... 0.5 g
purified water, freshly boiled and cooled ..... to 100 g

Method: Melt the wool alcohols ointment at a temperature below 65 °C. Warm 45 mL of purified water to about the same temperature and use it to dissolve the magnesium sulfate and phenoxyethanol. Mix the two phases and adjust to weight with water. Stir until cool.

Note: The phenoxyethanol may be replaced by benzyl alcohol or a suitable concentration of another effective preservative, provided the patient has not developed a sensitivity to the alternative preservative.

Use: Dermatological oily base.

propylene glycol cream

propylene glycol ..... 15 g
cetomacrogol emulsifying wax ..... 15 g
white soft paraffin ..... 10 g
liquid paraffin ..... 10 g
chlorocresol ..... 0.1 g
purified water, freshly boiled and cooled ..... to 100 g

Method: Melt the cetomacrogol emulsifying wax (see 'Cetomacrogol cream aqueous', p. 37) in the paraffins at about 70 °C. Add the chlorocresol to a warmed 200 mL container, then approximately 45 mL of just-boiled purified water (>80 °C), close the container and shake to dissolve. Immediately add the propylene glycol to the aqueous phase, then mix both phases and stir until a semi-solid cream forms. Adjust to 100 g with purified water and mix thoroughly.

Use: Emollient.

salicylic acid and sulfur cream aqueous

Crem. Acid. Salicyl. et Sulfur.

salicylic acid ..... 2 g
sulfur ..... 2 g
aqueous cream ..... 96 g

Strength: Contains 2% of salicylic acid (limits 1.8 to 2.2% w/w of $C_7H_6O_3$) and 2% of sulfur (limits 1.8 to 2.2% w/w of S).

Method: Triturate the salicylic acid and sulfur along with a small amount of aqueous cream to make a smooth paste. Gradually incorporate the remaining aqueous cream to make 100 g.

Note: Avoid contact with metals.

Use: Seborrhoeic dermatitis of the scalp.

zinc cream oily

zinc cream; Crem. Zinc. Oleos.

zinc oxide ..... 32 g
oleic acid ..... 0.5 mL
arachis oil ..... 21.5 mL
wool fat ..... 17.5 g
calcium hydroxide solution ..... 30.5 mL

These quantities make 100 g of cream.

Strength: Contains 32% of zinc oxide (limits 30 to 34% w/w of ZnO).

Method: Melt the wool fat in the arachis oil and the oleic acid with the aid of gentle heat. Triturate the zinc oxide with the mixture until smooth. Allow to cool slowly. Incorporate the calcium hydroxide solution in

several portions. Best prepared in a mortar using the method of doubling.

Use: Protective sunscreen agent.

Label: Label N: CONTAINS PEANUT OIL.

Ear drops

Ear drops are solutions or suspensions[3] of medicaments in water, glycerol, propylene glycol or diluted ethanol. Propylene glycol should not be used if the eardrum is perforated: ototoxicity has been reported. It may be appropriate to filter ear drops if particulate matter is present in the solution.

Containers and storage: Ear drops should be dispensed in bottles with a dropper, or in a suitable plastic container. Store at below 25 °C unless otherwise specified.

Labelling: The container should be labelled CAUTION: NOT TO BE TAKEN. The name and concentration of any preservative agent used should also be shown.

Expiry: The expiry date is 28 days from the date of preparation unless otherwise specified.

Instructions for use to be provided to patients

- Clean and dry external ear canal thoroughly, making sure no trace of soap remains.
- Lie down with affected ear pointing upwards.
- Hold bottle in clenched hand for a few minutes to warm drops.
- Instil drops and remain in position for a few minutes.
- If a gauze 'wick' is used it must be kept moist with the drops and replaced after 24 hours.

acetic acid ear drops

acetic acid (33% w/w) ..... 3 mL
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains about 1% w/v of acetic acid (limits 0.91 to 1.12% w/v of $C_2H_4O_2$).

Use: Otitis externa.

aluminium acetate ear drops
Aurist. Alumin. Acet.

aluminium acetate solution ..... 60 mL
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains about 8% of aluminium acetate (limits 0.9 to 1.2% w/v, calculated as Al).

Note: The aluminium acetate ear drops of the British Pharmacopoeia consist of undiluted aluminium acetate solution.

Use: Otitis externa.

chlorhexidine ear drops

chlorhexidine acetate ..... 0.05 g
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains 0.05% w/v (1 in 2,000) of chlorhexidine acetate.

Note: These ear drops must not be used if the eardrum is perforated.

Use: Otitis externa.

hydrocortisone ear drops

hydrocortisone ..... 0.5 g
glycerol ..... to 100 mL

Strength: Contains 0.5% of hydrocortisone (limits 0.45 to 0.55% w/v of $C_{21}H_{30}O_5$).

Note: These ear drops should be protected from light.

Use: Anti-inflammatory.

hydrogen peroxide ear drops

hydrogen peroxide solution (6%) ..... 25 mL
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains 1.12 to 1.83% w/v of H_2O_2 (corresponds to about five times its volume of available oxygen).

Note: These ear drops should be freshly prepared and protected from light.

Use: Otitis externa, removal of ear wax.[3,4]

salicylic acid ear drops
Aurist. Acid. Salicyl.

salicylic acid ..... 2 g
ethanol (90%) ..... 50 mL
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains 2% of salicylic acid (limits 1.8 to 2.2% w/v of $C_7H_6O_3$).

Method: Dissolve the salicylic acid in ethanol and make to volume with purified water.

Use: Otitis externa.[4]

sodium bicarbonate ear drops
Aurist. Sod. Bicarb.

sodium bicarbonate ..... 5 g
glycerol ..... 30 mL
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains 5% of sodium bicarbonate (limits 4.7 to 5.3% of $NaHCO_3$).

Method: Dissolve the sodium bicarbonate in 60 mL of purified water without the aid of heat, add the glycerol and make to volume with purified water.

Note: These ear drops should be recently prepared.

Use: Removal of ear wax.

spirit ear drops
Aurist. Spirit.

ethanol (90%) ..... 50 mL
purified water, freshly boiled and cooled ..... to 100 mL

Use: Drying agent.

Elixirs

Elixirs are aromatic liquid preparations that are a convenient means of administering potent or potentially nauseating medicaments in a palatable form in small dose-volumes. The solvent frequently contains a high proportion of ethanol and/or syrup, but other solvents such as glycerol are sometimes used.

Containers and storage: Well-sealed containers. Store at less than 25 °C unless otherwise specified.

Expiry: 28 days after preparation.

Eye drops

Eye drops are aqueous or oily solutions or suspensions for instillation into the eye. They must be sterile and be prepared under conditions validated as appropriate for the preparation of sterile products.

Sterilisation: The procedure recommended for sterilisation is stated in each formula. The methods stated, such as 'sterilise by heating in an autoclave' or 'sterilise by filtration', are those specified in the British Pharmacopoeia.

Vehicle: For aqueous solutions, water for injections BP should be used; this may be replaced by freshly distilled water whenever the eye drops are sterilised immediately. Eye drops should be prepared in a vehicle which is bactericidal and fungicidal. The eye drops described in this handbook should be clarified, where practicable, by filtration through a membrane filter. Wherever possible they have been formulated to be approximately isotonic with lachrymal secretion (equivalent to 0.9% w/v sodium chloride), using sodium chloride or another suitable adjusting substance (see 'Isosmotic and isotonic solutions', Section G).

Prescribing: The strengths of eye drops in this handbook are those commonly used in ophthalmic practice. If a variation in the proportion of active ingredient is desired, the prescriber should state the required strength, and any required adjustment to the vehicle will be made by the pharmacist.

Buffered vehicles for eye drops may be required: suitable formulae are set out in 'Buffer solutions', Section G. It should be recognised that such vehicles may reduce the time and temperature stability of certain medicaments; modified methods of preparation and sterilisation may be required.

Should a thickened vehicle be required, 0.3% w/v of hypromellose 4,500 may be added.

Following repeated application of eye drops at short intervals or over a long period, the user may develop a sensitivity to certain preservatives included in the formulation. Should this occur, a different preservative may be substituted, having due regard to compatibility.

Containers and storage: Eye drops should be dispensed in containers capable of being closed so as to exclude micro-organisms. Dropper bottles are suitable, but the user must be cautioned about avoiding contamination during use. Containers made of materials other than glass and the rubber teats used on droppers should be impregnated with any bactericide or preservative included in the eye drops. Containers made of materials other than glass may be permeable to oxygen and be unsuitable for formulations which undergo oxidation; they may also release unwanted substances (e.g. plasticisers). The volume of solution dispensed in each container should be limited so as to discourage prolonged storage. For drops containing antibiotics, cocaine or corticosteroids, the volume should generally be limited to 5 mL. Store at less than 25 °C unless specified otherwise.

Labelling: The label on the container must bear the name and the strength of the preservative used and the date of preparation. The container should be labelled CAUTION: NOT TO BE TAKEN.

Expiry: The patient should be advised to discard unused eye drops 28 days after opening the container (unless a shorter or longer period is directed).

Note: The benzalkonium chloride solution used in some of the eye drops described in this handbook is

a British Pharmacopoeia formula containing 50% of benzalkonium chloride.

Instructions for use to be provided to patients

- Wash hands thoroughly.
- Open the eye, tilt head back and look upwards.
- Gently pull down the lower lid to form a pouch.
- Approach the eye from the side and hold the dropper or bottle dropper near the lid, but do not touch the eyelids or lashes.
- Drop one drop into the pouch.
- Close the eyes (do not rub them) and try not to blink for a short time.
- Apply gentle pressure for a few minutes with a finger to the bridge of the nose to prevent the medication being drained from the eye.
- Blot excess solution around the eye with a tissue.
- Do not use solution if it is discoloured or has changed in any way since being purchased.
- If possible, have another person administer the eye drops.
- Discard within the specified time, usually 14–28 days.
- If instilling more than one drop in an eye (of the same or different preparations), separate each installation by several minutes to avoid washing drops out of the eye.

adrenaline eye drops strong

adrenaline ..... 1 g
boric acid ..... 0.5 g
sodium metabisulfite ..... 0.1 g
disodium edetate ..... 0.1 g
benzalkonium chloride solution BP ..... 0.02 mL
water for injections BP ..... to 100 mL

Strength: Contains 1% of adrenaline (limits 0.9 to 1.1% w/v of $C_9H_{13}NO_3$).

Method: Sterilise by filtration.

Note: These eye drops contain 1% of adrenaline.

Use: Treatment of wide-angle glaucoma.

If vasoconstrictor adrenaline eye drops are required, zinc and adrenaline eye drops may be suitable. The eye drops should be recently prepared and be protected from light.

cocaine eye drops strong

cocaine hydrochloride ..... 5 g
chlorhexidine acetate ..... 0.01 g
water for injections BP ..... to 100 mL

Strength: Contains 5% of cocaine hydrochloride (limits 4.75 to 5.25% w/v of $C_{17}H_{21}NO_4$.HCl).

Method: Sterilise by heating in an autoclave.

Note: Cocaine eye drops should not be prescribed or dispensed in volumes exceeding 5 mL.

Use: Anaesthetic.

homatropine and cocaine eye drops

Gutt. Homatrop. et Cocain.

homatropine hydrobromide ..... 2 g
cocaine hydrochloride ..... 2 g
boric acid ..... 0.5 g
chlorhexidine acetate ..... 0.01 g
water for injections BP ..... to 100 mL

Strength: Contains 2% of homatropine hydrobromide (limits 1.8 to 2.2% w/v) and 2% of cocaine hydrochloride (limits 1.9 to 2.1% of cocaine hydrochloride, $C_{17}H_{21}NO_4$.HCl).

Method: Sterilise by heating in an autoclave.

Note: These eye drops should not be prescribed or dispensed in volumes exceeding 5 mL.

Use: Mydriatic anaesthetic.

physostigmine eye drops

Gutt. Physostig.; eserine eye drops

physostigmine sulfate ..... 0.5 g
sodium metabisulfite ..... 0.1 g
sodium chloride ..... 0.8 g
benzalkonium chloride solution BP ..... 0.02 mL
disodium edetate ..... 0.05 g
water for injections BP ..... to 100 mL

Strength: Contains 0.5% of physostigmine sulfate [limits 0.45 to 0.55% w/v $(C_{15}H_{21}N_3O_2)_2.H_2SO_4$].

Method: Sterilise by filtration.

Note: These eye drops should be protected from light.

zinc and adrenaline eye drops

BZA eye drops

zinc sulfate ..... 0.25 g
adrenaline solution BP ..... 10 mL
boric acid ..... 1.5 g
sodium metabisulfite ..... 0.05 g
chlorbutol ..... 0.5 g
glycerol ..... 1 mL
water for injections BP ..... to 100 mL

Strength: Contains 0.25% of zinc sulfate (limits 0.22 to 0.28% w/v of $ZnSO_4.7H_2O$).

Method: Sterilise by heating in an autoclave.

Note: These eye drops should be protected from light. Adrenaline solution BP contains 0.1% w/v adrenaline as adrenaline acid tartrate.

Use: Astringent.

Eye lotions

Eye lotions are sterile aqueous solutions that are used in large volume. They are intended for use on one occasion only. Preservatives are added only if prescribed. They should be prepared under conditions appropriate for the preparation of sterile products.

Containers and storage: Fluted bottles. Store at less than 25 °C (unless specified otherwise).

Eye lotions for firstaid should be in bottles with an outlet that permits the lotion to be poured straight out of the container into the eye. Plastic squeeze-bottles with a nozzle stopper permitting air entry and with the outlet covered by a removable cap are suitable.

Labelling: The container should be labelled CAUTION: NOT TO BE TAKEN. In addition, directions should be given that any portion of the solution not used after the seal is first broken should be discarded—e.g. CONTAINS NO PRESERVATIVE. USE ONCE AND DISCARD ANY RESIDUE.

disodium edetate eye lotion

disodium edetate ..... 0.4 g
water for injections BP ..... to 100 mL

Method: Sterilise by heating in an autoclave.

Use: For removing calcium deposits in the cornea.

sodium bicarbonate eye lotion
Collyr. Sod. Bicarb.; alkaline eye lotion

sodium bicarbonate ..... 3.5 g
water for injections BP ..... to 100 mL

Method: Place the solution in the final container and pass carbon dioxide through it for at least one minute. Seal the container so as to be gas-tight and sterilise by heating in an autoclave. The container must not be opened until at least two hours after the solution has cooled to room temperature.

Use: To be applied undiluted for removing mucous from the eye.

Gels

Gels are oil-free, water-miscible, viscous preparations that are used for the application of water-soluble medicaments to body surfaces. Tragacanth gels (glycanths) or methylcellulose gels are used (see 'Mucilages', p. 48). They have the advantage over aqueous solutions of maintaining contact with skin and mucous membranes for longer periods. Methylcellulose provides a more durable adhesive film compared with other gelling agents. These gels are compatible with anionic and most cationic substances. They may be sterilised by autoclaving.

Containers and storage: Gels should be stored and supplied in well-sealed containers that prevent evaporation. Store below 25 °C unless specified otherwise.

Expiry: Gels containing tragacanth are prone to bacterial contamination and should be discarded 28 days after manufacture unless a shorter period is indicated.

chlorhexidine gel

chlorhexidine gluconate solution BP ..... 2.5 mL
tragacanth ..... 2.5 g
glycerol ..... 25 mL
purified water, freshly boiled and cooled ..... to 100 g

Strength: Contains 0.5% of chlorhexidine gluconate (limits 0.42 to 0.58% w/w of $C_{22}H_{30}Cl_2N_{10}.2C_6H_{12}O_7$).

Method: Mix the tragacanth with the glycerol and add most of the purified water. Heat to boiling, cool, add the chlorhexidine gluconate solution, adjust to weight, and mix.

Note: If the gel is to be applied to broken skin or used for surgical procedures, it should be produced as a sterile product in single-use units. This preparation should be protected from light.

Chlorhexidine gluconate solution BP is an aqueous solution containing 19 to 21% w/v of chlorhexidine gluconate.

Use: Antiseptic lubricant.

glyco-gelatin gel
glyco-gelatin base

gelatin ..... 25 g
glycerol (by weight) ..... 40 g
purified water, freshly boiled and cooled ..... to 100 g

Method: Soak the gelatin in 80 g of purified water in a tared dish. Add the glycerol and heat in a water bath, stirring occasionally, until the gelatin has dissolved.

Continue the heating until the product weighs 100 g. When used as a pessary base, heat at 100 °C for one hour before incorporating the medicament.

Note: This product should not be confused with glycerol suppositories, where glycerol is the medicament.

Use: As a suppository or pessary base for the incorporation of other drugs.

Inhalations

Inhalations are liquid preparations containing volatile substances that, on vaporisation, are intended to be brought into contact with the respiratory tract. Used as nasal decongestants.

Containers and storage: Inhalations should be dispensed in fluted bottles.

Method: The following inhalations should be prepared without the aid of heat.

Labelling: Containers should be labelled CAUTION: NOT TO BE TAKEN.

Instructions for use to be provided to patients:

- Add 5 mL to approximately 500 mL of hot (not boiling) water.
- Inhale the vapours for five to 10 minutes.

benzoin and menthol inhalation

menthol ..... 1 g
compound benzoin tincture ..... to 50 mL

menthol inhalation

menthol ..... 1 g
ethanol (90%) ..... to 50 mL

menthol and pine inhalation
compound menthol inhalation

menthol ..... 1 g
pumilio pine oil* ..... 2.5 mL
ethanol (90%) ..... to 50 mL

**Melaleuca alternifolia* oil (tea-tree oil) may be substituted.*

Insufflations

Insufflations are powders intended for introduction into the ear, nose, throat, body cavities or wounds.

Containers and storage: Well-sealed containers should be used, and storage should be at temperatures below 25 °C unless specified otherwise.

iodine insufflation

iodine ..... 0.8 g
potassium iodide ..... 0.4 g
anaesthetic ether ..... 10 mL
lactose, in fine powder ..... 98.8 g

Method: Dissolve the iodine and potassium iodide in the anaesthetic ether in a glass mortar. Add the lactose and mix quickly. Allow ether to evaporate. Protect from heat or iodine will volatilise.

Note: The preparation may be introduced into the ear via a tube (e.g. a straw).

Caution: Ether is extremely flammable.

Use: Antiseptic.

Irrigations

The following sterile solutions are intended for use as bladder irrigations.

Containers and storage: Impervious containers with a seal should be used. Storage should be at temperatures less than 25 °C unless specified otherwise.

Labelling: The label should state the date of manufacture and bear the message CAUTION: NOT TO BE TAKEN. There should be a label indicating that any portion of the solution not used after the seal is first broken should be discarded—e.g. USE ONCE AND DISCARD ANY RESIDUE.

acetic acid irrigation

acetic acid (33% w/w) ..... 6 mL
water for injections BP ..... to 100 mL

Strength: Contains about 2% w/v of acetic acid (limits 1.88 to 2.15% w/v of $C_2H_4O_2$).

Method: Sterilise by heating in an autoclave.

Use: Antibacterial.

chlorhexidine irrigation

chlorhexidine gluconate solution BP ..... 0.1 mL
water for injections BP ..... to 100 mL

Strength: Contains 0.02% w/v (1 in 5,000) of $C_{22}H_{30}C_{12}N_{10}.2C_6H_{12}O_7$.

Method: Sterilise by heating in an autoclave.

Note: Chlorhexidine gluconate solution BP is an aqueous solution containing 19 to 21% w/v of chlorhexidine gluconate. Protect from light.[3]

Use: Antibacterial.

sodium citrate irrigation

sodium citrate .....4 g
water for injections BP ..... to 100 mL

Strength: Contains 4% of sodium citrate (limits 3.7 to 4.3% w/v of $C_6H_5Na_3O_7.2H_2O$).

Method: Sterilise by heating in an autoclave.

Use: Alkalinising irrigation.

Linctuses

Linctuses are viscous liquid preparations having demulcent, expectorant or sedative properties. They are given in doses of small volume to be swallowed slowly without the addition of water, usually for the relief of cough.

Containers and storage: Linctuses should be stored in well-sealed containers at temperatures of less than 25 °C unless specified otherwise.

Expiry: The expiry date is 28 days from the date of preparation unless otherwise specified.

codeine linctus
Linct. Codein

codeine phosphate ..... 500 mg
purified water..... 10 mL
glycerol ..... 20 mL
methyl hydroxybenzoate solution ..... 1 mL
syrup*..... to 100 mL

*If commercially available syrup containing a hydroxybenzoate is used, the amount of methyl hydroxybenzoate added should be adjusted.

Strength: Contains 0.5% of codeine phosphate (limits 0.45 to 0.55% w/v of $C_{18}H_{21}NO_3H_3PO_4.½H_2O$).

Dose: 5 mL.

Note: Protect from light.

Use: Antitussive.

Label: Label 1: This medicine may cause drowsiness and may increase the effects of alcohol. If affected, do not drive a motor vehicle or operate machinery.

simple linctus

citric acid monohydrate .....2.5 g
concentrated anise water ..... 1 mL
methyl hydroxybenzoate solution ..... 1 mL
syrup*..... to 100 mL

*If commercially available syrup containing a hydroxybenzoate is used, the amount of methyl hydroxybenzoate added should be adjusted.

Dose: 5 to 10 mL.

Use: Linctus base.

Liniments

Liniments are usually liquid or semi-liquid preparations which are intended for external application with friction[5] and may contain substances possessing analgesic, rubefacient, soothing or stimulating properties. They should be applied only to intact skin.

Containers: Liniments should generally be dispensed in fluted poison bottles.

Labelling: The containers should be labelled FOR EXTERNAL USE ONLY.

methyl salicylate liniment
Lin. Methyl. Salicyl.

methyl salicylate ..... 25 mL
arachis oil ..... to 100 mL

Strength: Contains 25% of methyl salicylate (limits 23.0 to 2 6.5% v/v of $C_8H_8O_3$).

Method: Prepare by dissolution into final calibrated bottle; avoid contact with water.

Use: Counter-irritant, analgesic.

Label: Label N: CONTAINS PEANUT OIL.

methyl salicylate compound liniment
Lin. Methyl. Salicyl. Co.

menthol ..... 4 g
eucalyptus oil ..... 10 mL
methyl salicylate ..... 25 mL
arachis oil ..... to 100 mL

Strength: Contains 25% of methyl salicylate (limits 23.0 to 26.5% v/v of $C_8H_8O_3$).

Method: Prepare by dissolution into final calibrated bottle; avoid contact with water. If crushing menthol crystals, use a glass mortar.

Use: Counter-irritant, analgesic.

Label: Label N: CONTAINS PEANUT OIL.

Lotions

Lotions are liquid preparations intended for application to the skin. They may contain aqueous, ethanolic or emulsified vehicles and are usually applied without friction.

Containers: They should generally be dispensed in fluted poison bottles.

Expiry: The expiry date is 28 days from the date of preparation unless otherwise specified.

Labelling: The containers should be labelled FOR EXTERNAL USE ONLY and SHAKE THE BOTTLE.

aluminium acetate lotion aqueous
Burrow's lotion

aluminium acetate solution ..... 5 mL
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains 0.7% of aluminium acetate (limits 0.07 to 0.1% w/v, calculated as Al).

Note: The lotion should be freshly prepared and used within seven days, taking care to limit the possibility of microbial contamination.

When aluminium acetate lotion is prescribed, aqueous aluminium acetate lotion should be dispensed.

Use: Wet dressings in acute weeping dermatoses.

calamine lotion
Lot. Calam.

calamine ..... 15 g
zinc oxide ..... 5 g
bentonite, sterilised ..... 3 g
sodium citrate ..... 0.5 g
liquefied phenol ..... 0.5 mL
glycerol ..... 5 mL
purified water, freshly boiled and cooled ..... to 100 mL

Method: Sterilise the bentonite by heating at not less than 160 °C for at least two hours. Dissolve the sodium citrate in about 70 mL of purified water. Triturate the zinc oxide with the glycerol then add the calamine, bentonite and sodium citrate solution. Triturate until smooth, then add the liquefied phenol, adjust to volume with purified water, and mix. Usually prepared in a mortar using the method of doubling.

Caution: Liquefied phenol is very caustic.

Use: Soothing and protective agent, antipruritic.[4]

calamine lotion oily
Lot. Calam. Oleos.

calamine ..... 5 g
wool fat ..... 1 g
arachis oil ..... 50 mL
oleic acid ..... 0.5 mL
calcium hydroxide solution ..... to 100 mL

Strength: Contains 5% of calamine (limits 2.52 to 3.35% w/w, calculated as Zn).

Method: Melt the wool fat, arachis oil and oleic acid together, then triturate the calamine with this liquid. Incorporate 47 mL of calcium hydroxide solution into the oil phase. Usually prepared in a mortar using the method of doubling.

Use: Antipruritic.

Label: Label N: CONTAINS PEANUT OIL.

cetomacrogol lotion
cleansing lotion

cetomacrogol emulsifying wax ..... 3 g
liquid paraffin ..... 10 mL
glycerol ..... 10 mL
chlorhexidine gluconate solution BP ..... 0.1 mL
purified water, freshly boiled and cooled ..... to 100 mL

Method: Melt the cetomacrogol emulsifying wax (see 'Cetomacrogol cream aqueous', p. 37) in the liquid paraffin and mix with 50 mL of purified water heated

to approximately 70 °C. Stir until a semi-solid cream forms. Mix the chlorhexidine gluconate solution with the glycerol and 25 mL of purified water, then incorporate this in portions into the cream. Adjust to volume and mix.

Note: Chlorhexidine gluconate solution BP is an aqueous solution containing 19 to 21% w/v of chlorhexidine gluconate.

Use: Cleansing lotion.

formaldehyde lotion
formalin lotion

formaldehyde solution BP ..... 3 mL
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains 1% of formaldehyde (limits 0.95 to 1.25% w/v of CH_2O).

Note: This lotion should be freshly prepared.

Note: Handle formaldehyde with care—use appropriate precautions.

Use: Plantar warts, especially in patients with associated hyperhidrosis. Sensitisation may occur.

salicylic acid and coal tar lotion

salicylic acid .....2 g
coal tar solution ..... 5 mL
castor oil ..... 1 mL
spike lavender oil ..... 0.1 mL
ethanol (90%) ..... to 100 mL

Method: Dissolution.

Use: Psoriasis of the scalp.

Mixtures

Mixtures are liquid preparations intended for oral administration and in which the medicaments are dissolved or suspended in an essentially aqueous vehicle. They are not formulated to keep for long periods. In some cases it is essential that the mixture be freshly prepared.

Insoluble and indiffusible substances are suspended by the use of various colloidal substances of high viscosity so that, when the mixture is shaken, the insoluble materials remain in suspension long enough for a dose to be measured. Usual proportions of suspending agents are:

- compound tragacanth powder—2 to 3%
- tragacanth mucilage—10 to 20%
- acacia mucilage—25 to 50%
- methylcellulose mucilage—50%
- carboxymethylcellulose suspension—20 to 40%
- sodium alginate—0.5 to 2%.

Containers and storage: All containers are to be provided with an adequate seal. Store at less than 25°C unless otherwise specified.

Labelling: Containers should be labelled SHAKE THE BOTTLE to ensure even distribution of the content before the dose is given.

Expiry: The patient should be advised to discard any remaining mixture 28 days after the date of preparation unless otherwise specified.

ferrous sulfate mixture

ferrous sulfate .....3 g
ascorbic acid ..... 100 mg
orange syrup ..... 5 mL
benzoic acid solution ..... 2 mL
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains 3% of ferrous sulfate (limits 2.7 to 3.3% w/v of $FeSO_4.7H_2O$).

Dose: 10 mL well diluted with water. May be taken up to three times daily via a straw to reduce staining of the teeth.

Method: Dissolve ferrous sulfate in 50 mL of purified water, add ascorbic acid, orange syrup and benzoic acid solution. Mix until dissolved and make up to volume with purified water.

Note: Should be recently prepared.

Use: Iron replacement therapy.

Containers and storage: Protect from light.

gentian mixture alkaline
Mist. Gent. Alk.

concentrated compound gentian infusion..... 10 mL
sodium bicarbonate .....5 g
compound hydroxybenzoate solution ..... 1 mL
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains 5% of sodium bicarbonate (limits 4.7 to 5.3% w/v of $NaHCO_3$).

Dose: 10 to 20 mL three times daily in water before meals.

Note: Should be recently prepared.

Use: Loss of appetite.

potassium citrate mixture
Mist. Pot. Cit.

potassium citrate ..... 20 g
citric acid monohydrate ..... 4 g
lemon syrup ..... 10 mL
methyl hydroxybenzoate solution ..... 1 mL
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains 20% of potassium citrate (limits 18.5 to 21.5% w/v of $C_6H_5K_3O_7.H_2O$).

Dose: 10 to 20 mL well diluted with water.

Note: Each 10 mL contains approximately 19 mmol of potassium.

Use: Urinary alkaliniser.

potassium citrate and sodium bicarbonate mixture

potassium citrate ..... 10 g
sodium bicarbonate ..... 7.5 g
orange syrup ..... 10 mL
methyl hydroxybenzoate solution ..... 1 mL
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains 10% of potassium citrate (limits 9.2 to 10.8% w/v of $C_6H_5K_3O_7.H_2O$).

Dose: 10 to 20 mL well diluted with water.

Note: Each 10 mL contains approximately 9 mmol of both potassium and of sodium.

Use: Urinary alkaliniser.

senega and ammonia mixture
Mist. Seneg. et Ammon.

ammonium bicarbonate ..... 2.5 g
compound camphor spirit ..... 10 mL
liquorice liquid extract ..... 5 mL
concentrated senega infusion ..... 5 mL
compound hydroxybenzoate solution ..... 1 mL
purified water, freshly boiled and cooled ..... to 100 mL

Dose: 10 to 20 mL up to four times daily.

Use: Expectorant, decongestant.

sodium citrate mixture
Mist. Sod. Cit.

sodium citrate ..... 20 g
citric acid monohydrate ..... 4 g
lemon syrup ..... 10 mL
methyl hydroxybenzoate solution ..... 1 mL
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains 20% of sodium citrate (limits 18.5 to 21.5% w/v of $C_6H_5Na_3O_7.2H_2O$).

Dose: 10 to 20 mL well diluted with water.

Use: Urinary alkaliniser.

Mucilages

Mucilages are thick, viscous aqueous solutions of gums. They may be used for suspending insoluble substances in mixtures.

Containers and storage: Store at 2–8 °C in an adequately sealed wide-mouthed container.

Expiry: These products have a shelf life of 28 days from the date of manufacture.

carboxymethylcellulose mucilage

carboxymethylcellulose sodium ..... 1.5 g
ethanol (90%) ..... 5 mL
compound hydroxybenzoate solution ..... 1 mL
purified water, freshly boiled and cooled ..... to 100 mL

Method: Mix the carboxymethylcellulose sodium with the ethanol in a dry calibrated bottle. As quickly as possible, add most of the purified water and shake vigorously. Add the compound hydroxybenzoate solution, shake, then adjust to volume.

Note: Anionic mucilage.[5]

methylcellulose mucilage
Mucil. Methylcellulos.

methylcellulose (400–1,500 cps) ..... 2 g
compound hydroxybenzoate solution ..... 1 mL
purified water, freshly boiled and cooled ..... to 100 mL

Method: Add the methylcellulose to 20 mL of purified water previously heated to about 95 °C. When the powder is moistened, chill quickly, add compound hydroxybenzoate solution and cold purified water to produce 100 mL, and mix.

Note: Various grades of methylcellulose are available with the apparent viscosity of a 2% w/w solution at 20 °C indicated by an appended number.

tragacanth mucilage

tragacanth, finely powdered ..... 1.25 g
ethanol (90%) ..... 2 mL
benzoic acid solution ..... 2 mL
compound hydroxybenzoate solution ..... 1 mL
purified water, freshly boiled and cooled ..... to 100 mL

Method: Mix the tragacanth with the ethanol in a dry calibrated bottle. As quickly as possible, add most of the purified water and shake vigorously. Add the benzoic acid solution and the compound hydroxybenzoate solution, shake, then adjust to volume.

There is often confusion between tragacanth powder and tragacanth powder compound. The latter is not appropriate for this formula.

Nasal instillations

Nasal instillations are liquid preparations of drops or sprays used in the nasal passages. Viscosity, tonicity and pH of nasal instillations should approximate those of nasal secretions to avoid adversely affecting ciliary action.

Oily solutions should not be used: the oil retards the ciliary action of the nasal mucosa, and drops of oil may enter the trachea and cause aspiration pneumonitis.

Containers and storage: Bottles with a dropper should be used or suitable plastic containers. Nasal sprays should be dispensed in containers allowing the delivery of a reproducible dose of the preparation in a fine spray. Store at below 25 °C unless otherwise specified.

Expiry: The expiry date is 28 days from the date of preparation unless otherwise specified.

Labelling: Containers should be labelled CAUTION: NOT TO BE TAKEN.

Instructions for use to be provided to patients: nasal sprays

- Clear nose by gently blowing. Shake container before each use. Insert spray nozzle into nostril.
- Block other nostril and, while sniffing gently, spray once with head and canister vertical and once with head tilted forward and canister vertical.
- Repeat for other nostril.
- Do not use spray more often than directed.

Instructions for use to be provided to patients: nasal drops

- Clear nose by gently blowing.
- Lie down with the head lower than the shoulders. Insert the appropriate number of drops.
- Remain in the same position for several minutes to allow drops to penetrate.
- Dropper should be used by one person only and should be rinsed after each use.
- Do not use drops more often than directed.

ephedrine instillation

ephedrine nasal drops; ephedrine nasal spray

ephedrine hydrochloride ..... 1 g
chlorbutol ..... 0.5 g
sodium chloride ..... 0.5 g
propylene glycol ..... 5 mL
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains 1% of ephedrine hydrochloride (limits 0.9 to 1.1% w/v of $C_{10}H_{13}NO.HCl$).

Note: If 0.5% of ephedrine is prescribed the amount of sodium chloride does not need adjustment. Continual use may lead to rebound congestion.

Use: Decongestant.

phenylephrine instillation

phenylephrine nasal drops; phenylephrine nasal spray

phenylephrine hydrochloride ..... 0.25 g
sodium metabisulfite ..... 0.1 g
sodium chloride ..... 0.6 g
chlorbutol ..... 0.5 g
propylene glycol ..... 5 mL
purified water, freshly boiled and cooled ..... to 100 mL

Note: This solution should be stored in small, well-filled airtight containers protected from light. Continued use may lead to rebound congestion.

Use: Decongestant.

alkaline nasal douche

powder for saline instillation

sodium bicarbonate ..... 50 g
sodium chloride ..... 50 g

Use: 2 g dissolved in 100 mL of warm water as a nasal douche.

Ointments

Ointments are semi-solid preparations which may contain a medicament or mixture of medicaments dissolved or dispersed in a suitable base. They are used as emollients, as protective preparations on the skin, or for the local application of medicaments.

Emollient and protective ointments may contain vegetable oils, synthetic esters of fatty acids or wool fat, together with unreactive substances such as soft paraffin. They may consist of water-miscible bases such as macrogols, as well as emulsifiable bases which render the base miscible with tissue exudates and are more readily removed from the skin by washing.

Storage: Below 25 °C.

Labelling: FOR EXTERNAL USE ONLY. If the product is for nasal or otic use, the container should be labelled CAUTION: NOT TO BE TAKEN.

Expiry: 28 days from date of preparation unless otherwise specified.

benzoic acid ointment compound

Ung. Acid Benz. Co.; Whitfield's ointment

benzoic acid, in fine powder ..... 6 g
salicylic acid, in fine powder ..... 3 g
emulsifying ointment ..... 91 g

Strength: Contains 6% of benzoic acid (limits 5.7 to 6.3% w/w of $C_7H_6O_2$) and 3% of salicylic acid (limits 2.7 to 3.3% w/w of $C_7H_6O_3$).

Method: Triturate the benzoic acid and the salicylic acid with a small amount of emulsifying ointment until smooth. Gradually incorporate the remainder of the base using the method of doubling.

Use: Chronic dry-scaling tinea.

Label: Label E: CONTINUE FOR 14 DAYS AFTER SYMPTOMS CEASE.

dithranol ointment

dithranol in fine powder ..... 0.1 g
white soft paraffin ..... 99.9 g

Method: Triturate the dithranol with a small amount of the paraffin until smooth. Gradually incorporate the remainder of the base using the method of doubling. Avoid the use of metal spatulas.

Note: The concentration of dithranol may be cautiously increased to a maximum of 1%. Concentrations greater than 1% may be applied for very short exposure periods of 20–30 minutes, being then removed from the skin.

This ointment stains skin, fair hair and clothing. Contact with the eyes must be avoided. The ointment also darkens on exposure to light and should be stored and supplied in an opaque container.

Use: Psoriasis.

dithranol and salicylic acid ointment

dithranol, in fine powder ..... 0.1 g
salicylic acid ..... 0.5 g
liquid paraffin ..... 20 g
emulsifying ointment ..... 79.4 g

Method: Triturate the dithranol and the salicylic acid separately with small amounts of liquid paraffin, mix together, and gradually incorporate in the emulsifying ointment using the method of doubling. Avoid the use of metal spatulas.

Note: The concentration of dithranol may be cautiously increased to a maximum of 0.5%. Concentrations higher than 1% may be applied for very short exposure periods of 20–30 minutes, being then removed from the skin.

This ointment is intended for application to the scalp and is readily removed with warm water. the ointment stains skin, fair hair and clothing. Contact with the eyes must be avoided.

The ointment also darkens on exposure to light and should be stored and supplied in an opaque container.

Use: Psoriasis.

emulsifying ointment

emulsifying wax* ..... 30 g
white soft paraffin ..... 50 g
liquid paraffin ..... 20 g

* Emulsifying wax is prepared from 1 part of sodium lauryl sulfate and 9 parts of cetostearyl alcohol.

Method: Melt together and stir until cool.

Note: This formula complies with the requirements of the British Pharmacopoeia.

Use: Anionic base capable of absorbing considerable amounts of water or aqueous fluids.

lignocaine and adrenaline ointment

lignocaine hydrochloride ..... 1 g
purified water, freshly boiled and cooled ..... 4 mL
adrenaline solution BP ..... 10 mL
wool fat ..... 15 g
liquid paraffin ..... 20 g
white soft paraffin ..... 50 g

Strength: Contains 1% of lignocaine hydrochloride (limits 0.9 to 1.1% w/w $C_{14}H_{22}N_2O.HCl.H_2O$).

Method: Melt the wool fat and soft paraffin in the liquid paraffin using gentle heat. Stir until just solidified. Dissolve the lignocaine hydrochloride in the purified water and mix with the adrenaline solution. Incorporate the aqueous solution in the oil phase.

Note: Adrenaline solution BP contains 0.1% w/v adrenaline as adrenaline acid tartrate.

Use: Topical anaesthetic.

Containers and storage: Protect from light.

macrogol ointment
polyethylene glycol ointment

macrogol 4000 ..... 35 g
macrogol 400 ..... 65 g

Method: Melt the macrogols together at 60 °C and cool to room temperature

Note: The proportion of the macrogols may be varied to change the consistency to suit the prevailing temperature.

Use: An unreactive, non-greasy water-miscible ointment base which does not ionise in the presence of water and is therefore compatible with both anionic and cationic drugs.

salicylic acid ointment

salicylic acid ..... 2 g
wool alcohols ointment..... 98 g

Strength: Contains 2% of salicylic acid (limits 1.9 to 2.1% w/w of $C_7H_6O_3$).

Method: Triturate the salicylic acid with a small amount of the wool alcohols ointment until smooth and gradually incorporate the remainder of the base using the method of doubling.

Use: Keratolytic.

salicylic acid and coal tar ointment

salicylic acid ..... 3 g
coal tar solution ..... 6 mL
white soft paraffin..... 50 g
emulsifying ointment ..... 44 g

Method: Melt white soft paraffin and emulsifying ointment and stir until cold. Triturate salicylic acid and coal tar solution with a small amount of the base until smooth, then gradually incorporate the remainder of the base using the method of doubling.

Use: Psoriasis.

simple ointment white

wool fat ..... 5 g
hard paraffin ..... 5 g
cetostearyl alcohol..... 5 g
white soft paraffin..... 85 g

Method: Melt together and stir until cold.

Use: Greasy base.

wool alcohols ointment

wool alcohols ..... 6 g
hard paraffin ..... 17 g
white soft paraffin..... 17 g
liquid paraffin..... 60 g

Method: Melt together at a temperature not exceeding 65 °C and stir until cold.

Use: Greasy base capable of absorbing considerable amounts of water or aqueous fluids.

zinc and castor oil ointment

zinc oxide ..... 7.5 g
castor oil..... 50 g
cetostearyl alcohol..... 2 g
white beeswax ..... 10 g
arachis oil ..... 30.5 g

Strength: Contains 7.5% of zinc oxide (limits 7.0 to 8.0% w/w of ZnO).

Method: Triturate the zinc oxide with a small amount of the castor oil until smooth. Add the mixture to the remainder of the ingredients, which have previously been melted together, and stir until cold.

Use: Protective, emollient.

Label: Label N: CONTAINS PEANUT OIL.

zinc and coal tar ointment
Ung. Zinc et Pic.

zinc oxide..... 20 g
coal tar ..... 5 g
castor oil ..... 3 g
white soft paraffin ..... 72 g

Strength: Contains 20% of zinc oxide (limits 18.5 to 21.0% w/w of ZnO).

Method: Mix the coal tar with the castor oil. Triturate the zinc oxide and a small amount of the paraffin. Mix the two together and gradually incorporate the remainder of the base.

Use: Antipruritic, protective.

zinc oxide ointment
zinc ointment

zinc oxide..... 15 g
simple ointment white ..... 85 g

Strength: Contains 15% of zinc oxide (limits 14 to 16% w/w of ZnO).

Method: Triturate the zinc oxide with a small amount of the white simple ointment until smooth and gradually incorporate the remainder of the base.

Use: Protective, sunscreen agent.

Paints

Paints are liquid preparations for application in limited amounts to the skin or mucous surfaces.

Containers and storage: Fluted, airtight bottles should be used. Store at below 25 °C.

Expiry: The expiry date is 28 days from the date of preparation unless otherwise specified.

Labelling: The containers should be labelled FOR EXTERNAL USE ONLY if they are to be applied to skin or CAUTION: NOT TO BE TAKEN if they are to be applied to mucous membranes.

cetrimide and chlorhexidine paint

cetrimide ..... 0.5 g
chlorhexidine gluconate solution BP ..... 2.5 mL
ethanol (90%) ..... 75 mL
purified water, freshly boiled and cooled ..... to 100 mL

Method: Dissolve the cetrimide in the ethanol. Add the chlorhexidine gluconate solution and make to volume with purified water.

Note: Chlorhexidine gluconate solution BP is an aqueous solution containing 19 to 21% w/v of chlorhexidine gluconate.

Use: Antibacterial skin cleanser.

coal tar paint

coal tar ..... 10 g
acetone ..... to 100 mL

Method: Dissolve and filter if necessary.

Note: This preparation is flammable: keep it away from naked flame.

Use: For thick, scaling plaques of psoriasis or chronic dermatitis.

formaldehyde and salicylic acid paint

formaldehyde solution ..... 10 mL
salicylic acid ..... 10 g
acetone ..... 40 mL
ethanol (90%) ..... to 100 mL

Method: Dissolve the salicylic acid in 40 mL of ethanol, add formaldehyde solution and acetone and make to volume with ethanol.

Use: Treatment of warts.

lactic acid and salicylic acid paint

lactic acid ..... 20 mL
salicylic acid ..... 20 g
flexible collodion ..... to 100 mL

Note: This paint should not be applied to the face.

Use: Treatment of warts.

salicylic acid paint
salicylic acid collodion; corn paint

salicylic acid ..... 10 g
flexible collodion ..... to 100 mL

Strength: Contains 10% w/v of salicylic acid (limits 9 to 11% w/w of $C_7H_6O_3$).

Use: Treatment of warts.

Pastes

Pastes are semi-solid preparations with protective properties. They are also used for delivery of medicaments intended for external application.

Containers and storage: Pastes should be stored and supplied in well-sealed containers.

Labelling: The containers should be labelled FOR EXTERNAL USE ONLY if they are to be applied to skin or CAUTION: NOT TO BE TAKEN if they are to be applied to mucous membranes.

coal tar and zinc paste
coal tar paste

coal tar ..... 1 g
castor oil ..... 1 g
compound zinc paste ..... 98 g

Method: Triturate the coal tar with the castor oil and mix with the compound zinc paste.

Use: Psoriasis.

cocaine and adrenaline paste—10%

cocaine hydrochloride ..... 10 g
adrenaline acid tartrate ..... 0.18 g
chlorbutol ..... 1 g
liquid paraffin ..... 45 g
white soft paraffin ..... 44 g

Method: Melt the white soft paraffin in the liquid paraffin and dissolve the chlorbutol in this base. Triturate the adrenaline acid tartrate and cocaine hydrochloride with the base until smooth.

Use: Nasal anaesthetic.

cocaine and adrenaline paste—25%

cocaine hydrochloride ..... 25 g
adrenaline acid tartrate ..... 0.18 g
chlorbutol ..... 1 g
liquid paraffin ..... 45 g
white soft paraffin ..... 29 g

Method: Melt the white soft paraffin in the liquid paraffin and dissolve the chlorbutol in this base. Triturate the adrenaline acid tartrate and cocaine hydrochloride with the base until smooth.

Use: Nasal anaesthetic.

dithranol paste
dithranol and zinc paste

dithranol ..... 0.1 g
zinc and salicylic acid paste ..... 99.9 g

Method: Dispersion of dithranol throughout the paste may be facilitated by prior solution in chloroform.

Note: Avoid the use of metal spatulas. The concentration of dithranol may be cautiously increased to a maximum of 2%. The paste can be removed from the skin using liquid paraffin.

This paste stains skin, fair hair and clothing. It discolours on exposure to light, and should be stored and supplied in an opaque container. Contact with eyes must be avoided.

Expiry: 6 months from date of preparation.

Use: Psoriasis.

trichloracetic acid paste
Upton's paste

trichloracetic acid ..... 10 g
salicylic acid ..... 60 g
glycerol* ..... 20 g

*Or sufficient quantity to make a stiff paste.

Method: Triturate.

Use: Caustic.

zinc paste
zinc paste compound

zinc oxide ..... 25 g
starch ..... 25 g
white soft paraffin ..... 50 g

Strength: Contains 25% of zinc oxide (limits 23.5 to 26.5% w/w of ZnO).

Method: Triturate the zinc oxide with the starch and add to melted white soft paraffin. Mix until cool.

Use: Protective.

zinc and salicylic acid paste
Lassar's paste

salicylic acid ..... 2 g
liquid paraffin ..... 2 g
zinc paste ..... 96 g

Strength: Contains 2% of salicylic acid (limits 1.9 to 2.1% w/w of $C_7H_6O_3$) and 24% of zinc oxide (limits 22.5 to 25.5% w/w of ZnO).

Method: Triturate the salicylic acid with liquid paraffin until smooth and gradually incorporate the zinc paste.

Use: Protective, mild astringent.

Powders

Powders are usually mixtures of two or more powdered medicaments intended for oral administration. The medicaments are usually non-potent and accurate measurement of the dose by the patient is not critical. If, however, potent medicaments are prescribed undiluted, they should be supplied, suitably wrapped, as single doses.

Containers and storage: If any of the constituents are deliquescent or volatile, the powder should be stored and supplied in airtight containers. When supplied as single doses, the powder should be double-wrapped, the inner wrapper being waxed paper.

Some powders are used as pharmaceutical adjuncts.

tragacanth powder compound

tragacanth, finely powdered ..... 15 g
acacia, finely powdered ..... 20 g
starch, finely powdered ..... 20 g
sucrose, finely powdered..... 45 g

Use: As a suspending agent for internal use in concentrations of 2 to 3%.

Shampoos

Containers and storage: Store in well-sealed bottles at below 25 °C.

Labelling: FOR EXTERNAL USE ONLY.

cetrimide shampoo

cetrimide ..... 40 g
ethanol (90%)..... 30 mL
purified water, freshly boiled and cooled ..... 30 mL

Method: Dissolve the cetrimide in the ethanol and slowly add the purified water. Avoid vigorous shaking during preparation.

Note: KEEP OUT OF REACH OF CHILDREN: EXTREMELY TOXIC TO CHILDREN.

Use: Seborrhoea. Dilute 1 part in 20 parts of water before use.

Solutions

aluminium acetate solution
Burrow's solution

aluminium sulfate..... 22.5 g
calcium carbonate ..... 10 g
tartaric acid ..... 4.5 g
acetic acid 33% w/w ..... 25 mL
purified water, freshly boiled and cooled ..... 75 mL

Strength: Contains about 13% of aluminium acetate (limits 1.7 to 1.9% w/v of Al).

Method: Dissolve the aluminium sulfate in 60 mL of the purified water, add the acetic acid and then the calcium carbonate mixed with the remainder of the purified water. Allow to stand for not less than 24 hours in a cool place, stirring occasionally. Filter. Add the tartaric acid to the filtered solution and mix.

benzoic acid solution

benzoic acid..... 5 g
propylene glycol ..... 75 mL
purified water, freshly boiled and cooled ..... to 100 mL

Use: A convenient source of benzoic acid for use as a preservative (dilute to 1 in 50 or 1 in 100).

calcium hydroxide solution
lime water

calcium hydroxide..... 1 g
purified water, freshly boiled and cooled ..... to 100 mL

Method: Shake together until a saturated solution has been achieved and allow to stand. Decant the clear supernatant solution as required.

Use: Used to form calcium soaps of fatty acids in water-in-oil emulsions.

coal tar solution
Liq. Picis. Carb.

coal tar ..... 20 g
polysorbate 80 ..... 5 g
ethanol (90%) ..... to 100 mL

Method: Macerate the coal tar and the polysorbate 80 with 80 mL of ethanol (90%) for seven days in a closed vessel, with occasional agitation. Filter and pass through the filter sufficient ethanol (90%) to produce 100 mL.

compound hydroxybenzoate solution

methyl hydroxybenzoate ..... 8 g
propyl hydroxybenzoate..... 2 g
propylene glycol ..... to 100 mL

Use: Preservative (diluted 1 in 100).

iodine solution aqueous
Lugol's solution

iodine ..... 5 g
potassium iodide ..... 10 g
purified water, freshly boiled and cooled ..... to 100 mL

Strength: Contains 5% iodine (limits 4.75 to 5.25% w/v) and 10% potassium iodide (limits 9.5 to 10.5% w/v KI).

Method: Dissolve the iodine and potassium iodide in 10 mL of water and adjust to volume.

Dose: 1 mL well diluted with water, milk or juice, daily in divided doses for the pre-operative treatment of thyrotoxicosis.

methyl hydroxybenzoate solution

methyl hydroxybenzoate ..... 5 g
propylene glycol ..... to 100 mL

Use: Preservative (diluted 1 in 50 or 1 in 100).

soap solution alcoholic
spirit shampoo

soft soap ..... 50 g
ethanol (90%) ..... to 100 mL

Note: Medicaments such as thymol 0.5% or coal tar solution 5% may be added to this shampoo.

tolu solution

tolu balsam ..... 5 g
ethanol (90%) ..... 30 mL
sucrose ..... 50 g
purified water, freshly boiled and cooled ..... to 100 mL

Method: Dissolve the tolu balsam in 20 mL of ethanol (90%), add 10 g of sterilised purified talc and 35 mL of water heated to 70 °C. Shake vigorously, allow to stand for 24 hours, and filter. Dissolve the sucrose in the filtrate, add the remainder of the ethanol (90%) and adjust to volume with purified water.

Spirits

camphor spirit compound

camphor ..... 0.3 g
benzoic acid ..... 0.5 g
anise oil ..... 0.3 mL
ethanol (60%) ..... to 100 mL

lemon spirit

terpeneless lemon oil ..... 10 mL
ethanol (96%) ..... to 100 mL

Suppositories

Suppositories are solid dose forms shaped for rectal administration and usually containing medicaments that are intended for local or systemic delivery. They are usually made with a suitable fatty base, provided the melting point of the suppositories is not higher than 37 °C. Moulds with a capacity equivalent to 1 g of fatty base are used unless otherwise specified. If a water-miscible base is required, a macrogol base may be used. A suitable macrogol base is 20% w/w macrogol 400 with 80% macrogol 4,000.

When an amount as a dose (as distinct from a percentage) of medicament is prescribed, it is necessary to make an allowance for the volume occupied by the medicament in each suppository. To facilitate this procedure, displacement values (densities of medicament relative to fatty bases) are listed here. These values are guidelines only: displacement values will vary with powder density. A displacement value of 1 is generally used for liquids. If a medicament has a displacement value of 2, then 2 g occupy the same volume as, and therefore displace, 1 g of fatty base, 1.2 g of glyco-gelatin base or 1.2 g of macrogol base.

medicament displacement value

Aminophylline 1.1
Aspirin 1.3
Cinchocaine hydrochloride 1.3
Hydrocortisone 1.6
Hydrocortisone acetate 1.6
Metronidazole 1.7
Morphine hydrochloride or sulfate 1.5
Paracetamol 1.5
Phenobarbitone 1.2
Theophylline 1.5

Containers and storage: Store in well-sealed containers at 2–8 °C.

Expiry: 28 days from date of preparation unless otherwise specified.

Labelling: CAUTION: NOT TO BE TAKEN.

Syrups

Syrups are aqueous solutions with high concentrations of sucrose or other sugars used as sweetened, flavoured vehicles.

Containers and storage: Store in well-sealed containers.

Expiry: 28 days from date of preparation unless otherwise specified.

syrup

sucrose ..... 66.7 g
purified water, freshly boiled and cooled ..... to 100 g

Method: Heat together until dissolved and adjust to weight.

aromatic syrup
Syr. Aromat.

orange tincture..... 5 mL
lemon spirit ..... 0.5 mL
syrup..... to 100 mL

codeine syrup

codeine phosphate ..... 500 mg
purified water, freshly boiled and cooled ..... 1.5 mL
syrup..... to 100 mL

Strength: Contains 0.5% of codeine phosphate (limits 0.45 to 0.55% w/v of $C_{18}H_{21}NO_3H_3PO_4.½H_2O$). Codeine syrup contains 50 mg of codeine phosphate in each 10 mL.

Method: Dissolve the codeine phosphate in the purified water, add sufficient syrup to produce the required volume and mix.

Dose: 2 to 10 mL.

Use: Antitussive.

Label: Label 1: This medicine may cause drowsiness and may increase the effects of alcohol. If affected, do not drive a motor vehicle or operate machinery.

lemon syrup

lemon spirit ..... 0.5 mL
citric acid monohydrate ..... 2.5 g
syrup ..... to 100 mL

lemon syrup neutral

lemon spirit ..... 0.5 mL
syrup ..... to 100 mL

orange syrup

orange tincture..... 6 mL
syrup ..... to 100 mL

tolu syrup

tolu solution ..... 10 mL
syrup ..... to 100 mL

Waters

Aromatic waters may be prepared by diluting the concentrated water with 39 times its volume of freshly boiled and cooled purified water

anise water concentrated

anise oil ..... 2 mL
ethanol (90%)..... 70 mL
purified water..... to 100 mL

Method: Dissolve the anise oil in the ethanol and add sufficient purified water, in successive small portions, to produce the required volume, shaking vigorously after each addition. Add 5 g of sterilised, purified talc, shake occasionally during a few hours, and filter.

Children's formulary

baclofen suspension CF—5 mg/mL

baclofen* ..... 500 mg
glycerin ..... 4 mL
methylcellulose mucilage APF ..... 25 mL
compound hydroxybenzoate solution APF ..... 0.8 mL
syrup APF ..... to 100 mL

*Use baclofen tablets.

Method: Crush the baclofen tablets in a porcelain mortar to a fine powder. Triturate with the glycerin and the methylcellulose mucilage. Add the hydroxybenzoate solution then add the syrup to volume.

Note: Store at 2–8 °C (use ancillary label 6). Shake well before use.

Expiry: 28 days from date of preparation.

dexamethasone suspension CF—1 mg/mL

dexamethasone* ..... 100 mg
ethanol 90% ..... 15 mL
glycerol ..... 40 mL
compound hydroxybenzoate solution APF ..... 2 mL
methylcellulose mucilage APF ..... to 100 mL

*Dexamethasone tablets can be used.

Method: Crush the dexamethasone tablets in a dry glass mortar until finely powdered. Wet the powder with the ethanol and add the glycerol and the compound hydroxybenzoate solution. Add the methylcellulose mucilage to volume.

Note: Store at 2–8 °C (use ancillary label 6).

Expiry: Seven days from date of preparation.

folic acid solution CF—1 mg/mL

folic acid* ..... 100 mg
sodium hydroxide solution (1 molar) ..... qs to pH of 8
compound hydroxybenzoate solution APF ..... 1 mL
purified water ..... to 100 mL

*Folic acid tablets or injection may be used.

Method: If using tablets, crush the tablets to a fine powder, add the hydroxybenzoate solution and triturate with 25 mL of the purified water. Add 70 mL of the purified water and adjust the pH to 8 using the sodium hydroxide solution. Make to volume with purified water.

Note: Store at 2–8 °C (use ancillary label 6). Protect from light. Shake well before use.

Expiry: 28 days from date of preparation.

omeprazole dispersion CF—2 mg/mL

omeprazole* ..... 200 mg
sodium bicarbonate ..... 8 g
compound hydroxybenzoate solution ..... 1 mL
purified water ..... to 100 mL

*Use omeprazole 20 mg capsules.

Method: Dissolve the sodium bicarbonate in the purified water. Empty the capsule contents into a container, add the sodium bicarbonate solution and shake vigorously until a white dispersion forms. The pellets may take many hours to fully disperse.

Note: Store at 2–8 °C (use ancillary label 6). Protect from light. Shake well before use.

Note: The sodium bicarbonate load may cause problems, especially in those with renal impairment and the very young. Check electrolyte and acid–base status of infants below 6 months of age and anyone with renal impairment.

Note: The bioavailability of this product is approximately 50% of the capsules.

Note: As an alternative, omeprazole tablets may be dispersed in water, orange juice or yoghurt and given orally within 30 minutes. The resulting pellets must not be chewed or crushed. Omeprazole degrades rapidly under acidic conditions.

Expiry: 28 days from date of preparation.

pantoprazole dispersion CF—2 mg/mL

pantoprazole* ..... 200 mg
sodium bicarbonate ..... 8.4 g
compound hydroxybenzoate solution ..... 1 mL
purified water ..... to 100 mL

*Use pantoprazole tablets.

Method: Dissolve the sodium bicarbonate in the purified water. Crush the pantoprazole tablets in a mortar and triturate with the sodium bicarbonate solution, transferring to the final container. Shake vigorously for 10 minutes to obtain a uniform dispersion.

Note: Store at 2–8 °C (use ancillary label 6). Protect from light. Shake well before use.

Note: See note under 'Omeprazole dispersion' (above) for use and electrolyte monitoring.

Note: The bioavailability of this product is approximately 75% of the intact tablets.

Expiry: 28 days from date of preparation.

potassium citrate mixture CF

potassium citrate ..... 20 g
citric acid monohyd rate ..... 4 g
lemon syrup ..... 20 mL
methylhydroxybenzoate solution ..... 1 mL
purified water ..... to 100 mL

Strength: Contains 20% of potassium citrate (limits 18.5 to 21.5% w/v of $C_6H_5K_3O_7.H_2O$).

Dose: Dose to be tailored to electrolyte requirements. Give diluted with water.

Note: Store below 25 °C. Compound hydroxybenzoate solution can be substituted for methylhydroxybenzoate solution.

Expiry: 28 days from date of preparation.

propranolol mixture CF—5 mg/mL

propranolol hydrochloride* ..... 500 mg
citric acid monohydrate ..... 1 g
sodium benzoate ..... 100 mg
syrup ..... 40 mL
purified water ..... to 100 mL

*Propranolol hydrochloride tablets may be used.

Method: Crush tablets and solid ingredients in a mortar and add syrup to form an even paste. Slowly add portions of water. Shake the final product before measuring dose.

Note: Do not use brands of propranolol tablets containing calcium carbonate as an excipient.

Note: Store at 2–8 °C (use ancillary label 6). Protect from light. Shake well before use.

Expiry: 28 days from date of preparation.

sodium citrate mixture CF

sodium citrate ..... 20 g
citric acid monohydrate ..... 4 g
lemon syrup ..... 20 mL
methylhydroxybenzoate solution ..... 1 mL
purified water ..... to 100 mL

Strength: Contains 20% of sodium citrate (limits 18.5 to 21.5% w/v of $C_6H_5Na_3O_7.2H_2O$).

Dose: Dose to be tailored to electrolyte requirements. Give diluted with water.

Note: Store below 25 °C. Compound hydroxybenzoate solution can be substituted for methylhydroxybenzoate solution.

Expiry: 28 days from date of preparation.

spironolactone mixture CF—1 mg/mL

spironolactone* ..... 100 mg
carboxymethylcellulose mucilage ..... 20 mL
syrup ..... 40 mL
purified water ..... to 100 mL

*Spironolactone tablets may be used.

Method: Crush tablets in a mortar and add syrup to form an even paste. Slowly add portions of water. Shake the final product before measuring dose.

Note: Store at 2–8 °C (use ancillary label 6). Protect from light. Shake well before use.

Expiry: 28 days from date of preparation.

trimethoprim mixture CF—10 mg/mL

trimethoprim* ..... 1 g
syrup ..... to 100 mL

*Trimethoprim tablets may be used.

Method: Crush tablets in a mortar and add syrup to form an even paste. Shake the final product before measuring dose.

Note: Store at 2–8 °C (use ancillary label 6). Protect from light. Shake well before use.

Expiry: 28 days from date of preparation.

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Emulsifiers and stabilisers

Multiphase drug delivery systems such as emulsions, creams and suspensions have to be stabilised against unwanted cracking, aggregation, creaming or sedimentation if they are to have a useful shelf life. This stabilisation can be achieved either by the adsorption of a surface-active agent at the interface of immiscible phases, thereby modifying the properties of the interface, or by changing the properties of the bulk continuous phase.

Emulsifying agents can be classified according to their dominant mechanism of action and include surface-active agents (surfactants), finely divided solids and viscosity-modifying agents.

Surfactants can be grouped according to the charge on the species that orients at the interface, and as such are classified as:

- anionic surfactants—e.g. sodium lauryl sulfate
- cationic surfactants—e.g. cetrimide
- non-ionic surfactants—e.g. polyoxyethylene sorbitan esters (polysorbates).

In addition to the physicochemical properties of surfactants, consideration should be given to taste, odour and toxicity, depending on the route of administration of the emulsion.[1]

For further information on using emulsifying agents, see the 'General formulary', Section A.

Liquid–liquid dispersions

Emulsifying agents (emulgents) stabilise the dispersion of two immiscible liquids by adsorbing at the interface between the two phases. The continuous phase will be the phase in which the emulsifying agent has the greater solubility. The solubility of a particular emulsifying agent is influenced by temperature. Pharmaceutical properties such as viscosity and elasticity, creaming, sedimentation, cracking rate, physical appearance, and rate of drug release from the product will all be influenced by the amount and type of emulgent used.

The most stable dispersions are produced by selection of a combination of emulgents to match the phases to be dispersed. One such method of selection of surfactant combinations is the Hydrophile–Lipophile Balance System, which uses numerical values to indicate the balance between hydrophilic and lipophilic properties of emulsifying agents.

Preparations for internal use that are usually oil-in-water emulsions have traditionally used gums such as acacia. More modern formulations use synthetic non-ionic emulgents and cellulose derivatives such as methylcellulose or carboxymethylcellulose (carmellose) sodium.

Topical preparations are formulated as oil-in-water or water-in-oil, depending on their intended application. Generally, oil-in-water preparations are non-occlusive and are suitable for application to weeping areas. Water-in-oil preparations are occlusive.

For water-in-oil dispersions, oil-soluble emulgents such as calcium oleate, wool fat and wool alcohols have been traditionally used. Synthetic non-ionic emulsifying agents such as sorbitan esters are now more widely used, without the variability associated with natural products.

For oil-in-water dispersions there is a very wide choice of emulgent. The choice will often be based on the chemical compatibility of the emulsifying agent with the active ingredient. Thus anionic surfactants would be used with active ingredients with large anions, and cationic surfactants would be used with active ingredients with large cations. Non-ionic surfactants are more widely compatible; however, they commonly contain ethylene oxide chains that can also bind drugs and preservatives.

Types of emulgents

Emulgents commonly used to stabilise water-in-oil dispersions are:

- *Soaps*. Soaps of calcium, zinc or aluminium.
- *Wool fat*. Use 5–10%, preferably in conjunction with some fixed oil, which increases the emulsifying power of the wool fat.
- *Wool alcohols*. Use 3–5%, preferably in conjunction with some fixed oil, which increases the emulsifying power of the wool alcohols.
- *Sorbitan esters*. Use 0.1–5%.

Emulgent systems and emulgents commonly used to stabilise oil-in-water dispersions are:

- *Self-emulsifying glyceryl monostearate (anionic)*. Use 3–5% for lotions, 10–15% for creams.
- *Emulsifying wax (anionic)*. Use 1–3% for lotions, 10–15% for creams.
- *Cetomacrogol emulsifying wax (non-ionic)*. Use 1–3% for lotions, 10–15% for creams. Cetomacrogol is an example of a non-ionic macrogol ether.

- *Cetrimide (1 part) (cationic) with cetostearyl alcohol (9 parts)*. Use a total of 1–3% for lotions, a total of 10–15% for creams.
- *Other non-ionic materials* used are ethoxylated macrogol esters, poloxamers (which are a series of polyoxyethylene–polyoxypropylene copolymers) and sorbitan fatty acid ester derivatives which, if ethoxylated, are water soluble (polysorbates) and, if unethoxylated, are oil soluble.[2]

Solid–liquid dispersions

Dispersed solids will tend to aggregate, settle or cream during storage. Dose forms containing dispersed solids must therefore be shaken to ensure uniformity before a portion is removed for use.

If the shelf life of the suspension is short and the proportion of solids low, discrete deflocculated particles can be used. Provided the particles are kept discrete by an appropriate procedure, they will sediment at a rate only dependent on the viscosity of the dispersing liquid, the size of the particles, and the difference in density between the particles and the liquid. However, when these particles do settle, they commonly cake irreversibly on the bottom of the container. Traditionally, tragacanth-based suspending agents were used in such systems to increase the viscosity of the dispersing liquid by making it a 'structured vehicle'.

For longer shelf lives and for more concentrated suspensions, some extent of controlled polymeric flocculation is used. Although the larger aggregates of floccules settle more quickly due to increased particle size, caking is not such a problem and redispersion of the solids can be achieved by normal shaking. A uniform dispersion can be poured from the container since the floccules and vehicle structure take time to reform.

Macromolecular suspending agents have both polymeric flocculation and viscosity-increasing properties. These properties, however, can be markedly influenced by ionic strength and solvent composition.

Unless the stated grade of such agents is used, a variable product results. Common agents used to suspend insoluble drugs are:

- aluminium magnesium silicate, 0.5–2.5%
- carbomer, 0.1–0.4%
- cellulose derivatives (the amount to be used depends on the grade): carboxymethylcellulose (carmellose) sodium, carboxymethylcellulose (carmellose) calcium, hydroxyethylcellulose, hypromellose, methylcellulose
- colloidal silicon dioxide, 1–10%
- povidone (polyvinylpyrrolidone), up to 10%, depending on grade
- sodium alginate, 0.5–2%
- tragacanth products
  - compound tragacanth powder, 2–3%
  - tragacanth mucilage, 10–20%.

Gels

A gel is formed when polymer chains interact to form a three-dimensional system and solvent is trapped within this polymer network. Most extemporaneously prepared gels are semi-solid only below a certain gelling temperature. Other ingredients in the product, particularly electrolytes and co-solvents, influence this temperature. Large quantities of electrolytes may cause precipitation of polymers.[2] Gels may contract on standing and squeeze some of the solvent out. If the solvent comes out of a swollen gel, it is said to exhibit syneresis, or to 'bleed'.[3]

A number of common macromolecular materials are used to form gels. The amount needed is dependent on both the grade of the material and the formulation. The following figures are only a general guide:

- aluminium magnesium silicate, up to 10%
- gelatin, 5–10%
- pectin, 0.5–3%
- tragacanth, 2–3%
- carbomer, 0.5–5%
- cellulose derivatives (hypromellose and methylcellulose), 2–30%
- povidone, 10–40%.

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Opioid substitution therapy

Harm minimisation in pharmacy

The aim of the Australian Government's harm minimisation strategy[1] is to reduce the adverse consequences of drug use for both the individual and society. It involves a balance between three basic concepts:

1. reducing demand for drugs
2. reducing the supplies of drugs available
3. reducing the harm caused by drug use.

Pharmacists have a legal and ethical/moral responsibility to be aware of the potential harm to the individual and to society associated with illicit substance use and to do all they can to ameliorate that harm.

There are many areas in which pharmacists can make an important contribution to harm minimisation, including:

- taking part in health-promotion activities that target the use of all non-medicinal drugs, including nicotine and alcohol
- providing information to drug users about
  - the dangers associated with drug use
  - treatment options available
  - safer methods of drug use
- restricting the supply of over-the-counter pharmaceutical products that have the potential to be abused (e.g. sedating antihistamines, codeine) or may be used in the manufacture of illicit drugs of abuse (e.g. pseudoephedrine)
- monitoring and reporting 'prescription shopping' for potential drugs of abuse, including opioids and benzodiazepines
- supplying clean syringes, needles and clean injecting equipment. Consider providing the PSA Pharmacy Self Care Fact Card *Safer Injecting Practices*
- offering opioid substitution pharmacotherapy (methadone and buprenorphine) programs. In all Australian jurisdictions pharmacies are able to participate in providing opioid substitution therapies after appropriate authorisation by state or territory health authorities.

Harm minimisation does not imply support for illegal or risky behaviour. Rather, it acknowledges that when they occur there is a responsibility to develop, implement and promote measures designed to minimise the harm that such behaviour can cause.

Opioid substitution therapy

Methadone liquid dose forms and buprenorphine sublingual tablets are funded by the Australian Government to manage opiate dependence. They are supplied through pharmacies and clinics in accordance with the laws of the relevant state or territory.

Pharmacists involved in providing methadone or buprenorphine should ensure that they follow documented procedures (state-specific documents issued by the health department or the Pharmaceutical Society of Australia provide detailed guidance) and that they comply with relevant legislation in the provision of these services.

Methadone and buprenorphine are potent opioid drugs. Regular users quickly develop tolerance and may become complacent about the safety of their dosage regimen. On the other hand, a non-tolerant person is likely to experience serious effects with a comparatively small dose. The state and territory regulations are designed to minimise the diversion of these drugs into illicit supply, where they may cause serious harm, particularly in a non-tolerant individual.

Dispensing and dosing

All dispensing of prescriptions and dosing must be carried out in accordance with relevant legislation for each state and territory.

Each pharmacy should have a documented procedure that is adhered to by all staff, including locums and casual staff, each time a dose is dispensed. A documented dosing procedure will ensure that the right person gets the right drug and that the procedure is followed.

Following is a sample dosing procedure. Each step should be double-checked to eliminate potential dispensing errors.

1. Identify the client.
2. Talk to the client to establish that they are not alcohol or drug affected.
3. Confirm the client's ID and prescription details (the client's prescription should be referred to each time they are dosed and/or when take-away doses are dispensed or handed out).
4. Confirm the pharmacotherapy prescribed and the dose, that the prescription is current, and that the client is eligible for a dose on the day (confirm the date of the last dose or take-away).

5. Record the dose to be measured in the dispensing records (book or computer).
6. Measure the dose and place in a suitable clean cup or glass and/or prepare take-away doses.
7. Refer to the dispensing records and confirm client and dose are correct.
8. The pharmacist should personally supervise the client taking the dose.
9. Talk to the client after they have taken the dose to ensure the dose has been swallowed (methadone) or dissolved (buprenorphine).

Supervised dosing

Dosing supervision is an important part of methadone and buprenorphine programs. It aims to ensure that the correct dose is administered completely and diversion or abuse is prevented. Most jurisdictions require that most or all doses are properly supervised. Pharmacists must maintain a consistent approach and:

- dose only one person at a time
- for methadone, ensure the client has swallowed the dose
- for buprenorphine, administer tablets and observe the client for sufficient time to ensure tablets have dissolved (for more information, see below).

Dispensing of take-away doses

When non-supervised doses of methadone or buprenorphine are provided, there is an increased risk of misuse of the drug, with the potential for harmful consequences. This can include:

- intentional overdose (accumulating doses and taking several at once)
- accidental overdose (possibly by an opioid-naive person)
- injection of the drug with the risk of venous damage and increased risk of overdose
- involvement in drug dealing, with potential legal implications.

Lost, stolen or broken take-away doses supplied to a client must not be replaced without specific authorisation from the prescriber.

Documentation

Ensure that the records pertaining to all methadone and buprenorphine clients can be easily located and interpreted by locum staff. This should include some form of identification, preferably a photo, the most recent prescription, a record of dispensed doses (including take-away doses), contact details for the prescriber and any observations about the client which may be relevant.

Legal requirements

As buprenorphine and methadone are controlled drugs (Schedule 8), all the normal legal requirements in terms of prescribing, dispensing, storage and recording must be fulfilled, as well as any state or territory restrictions pertaining to opioid addiction treatment programs.

Intoxication

When methadone or buprenorphine are implicated in fatal overdoses, it is common for other drugs (often alcohol, benzodiazepines or other opioids) to be involved. If clients are noticeably under the influence of drugs, dosing should be refused and the prescriber contacted. The most important and obvious signs of intoxication are sedation, ataxia, disinhibition, slurred speech, a smell of alcohol and pin-point pupils.

Liaising with the prescriber

The pharmacist should maintain regular contact with the prescriber in order to provide any relevant information concerning the progress or, in particular, erratic attendance of their client. If the client has missed the number of consecutive doses defined in legislation, withhold dosing and contact the prescriber.

Methadone for treatment of opioid addiction

The doses of methadone commonly used to treat opioid addiction are considerably larger than those commonly used in analgesia. For methadone, daily doses are usually in the range 30 mg to 80 mg but sometimes exceed 100 mg. Methadone is usually given as a single daily dose. Methadone doses should always be quoted as milligrams of methadone (not millilitres of syrup). Quoting doses in terms of volume is a common source of confusion and error.

Supply of take-away doses

Some state and territory authorities mandate the dilution of methadone take-away doses to reduce the chance of accidental overdose and to discourage injection. Legislation across the different states and territories varies with respect to the requirement for dilution of take-away doses. The volume of dilution required and the diluent used also vary (e.g. in Victoria, doses are recommended to be diluted to 200 ml with fruit juice or other particulate matter such as cordial).

Pharmacists must follow relevant state or territory legislation with respect to the dilution of methadone doses.

In some states, pregnant and other clients who experience difficulties with nausea or vomiting may be given undiluted methadone liquid when authorised by their prescriber. Clients experiencing severe consequences because of a medical condition may also be exempted from dilution (or a recommendation made to dilute with water only) following discussions with the prescriber.

Where local legislation allows, a suggested diluent is:

methadone diluent APF

sodium benzoate.....0.1 g
citric acid .....0.2 g
purified water..... to 100 mL

Packaging: Methadone take-away doses should be packed in a separate childproof non-breakable container for each day's dose.

Labelling: Take-away doses must be labelled appropriately, as shown below.

METHADONE LIQUID – KEEP OUT OF REACH OF CHILDREN

This bottle contains ... mg of methadone
Take the contents of this bottle in a single dose
On [date to be consumed]
[Name of patient]

The label must include the name, address and telephone number of the dispensing pharmacy, the date of dispensing and prescription number, and Ancillary Label 1 and any other appropriate or legislated ancillary labels (see ancillary labels in 'Counselling and cautionary advisory labels for medicines', Section A).

An additional label, as shown below, is also recommended.

To be taken only by mouth by the patient named on the label on the day stated on the label

- Do not inject
- May cause death or serious injury if taken by another person or injected

The aim of this labelling and packaging is to reduce the possibility of accidental ingestion of a take-away dose that may prove fatal to a non-tolerant person or the injection of undiluted methadone liquid, with resultant lactic acidosis causing serious injury or death.

Storage: Take-away doses should be stored in a cool place, secure from children or other individuals.

Buprenorphine for treatment of opioid addiction

Buprenorphine is a partial opioid agonist and antagonist—unlike methadone and heroin, which are full agonists. Buprenorphine can be used in either long-term maintenance treatment or in short-term heroin withdrawal ('detox') programs. In maintenance treatment, buprenorphine is long-acting, allowing dosing every second or third day for some clients.

Buprenorphine is available as tablets (0.4 mg, 2 mg and 8 mg); it must be used sublingually to avoid the significant first-pass metabolism of the drug rendering it less effective. Daily doses generally vary from 2 mg to 32 mg depending on response, but a typical daily dose is about 10–14 mg. The maximum dose is 32 mg daily, unless the prescriber can justify higher doses on the basis of patient history. This should happen in consultation with the pharmacist. Alternate-day or three-times-weekly dosing is suitable for some clients, but the maximum dose given at any one time should not exceed 32 mg.

Important considerations for treatment with buprenorphine

- Buprenorphine can antagonise the effects of other opioids, blocking the effects of heroin or precipitating withdrawal in those already affected by opioids. Clients starting buprenorphine should be advised of the potential consequences.
- Clients should be discouraged from taking buprenorphine if they have used heroin in the previous six hours or for at least 24 hours since last methadone use (a longer period may be recommended for some clients). Ideally, clients should experience some withdrawal symptoms before commencing buprenorphine.
- Precipitated withdrawal can be moderately unpleasant, which can be unhelpful to client stabilisation and undermine client confidence in the treatment.
- Buprenorphine is likely to be safer in overdose than methadone (although it can still be toxic when injected or combined with other central nervous system depressants).
- Withdrawal effects from buprenorphine are sometimes milder than those from heroin or methadone.

Supervised dosing

As with methadone programs, strict supervision is a vital element in the success of buprenorphine treatment. To prevent diversion, the responsible pharmacist must

make sure that each supervised dose is used correctly. This will entail either:

- administering whole tablets and keeping the client under observation until the tablets have dissolved (which can be up to 10 minutes)
- administering tablets roughly crushed. The crushed particles should be placed on a clean spoon or similar, and the pharmacist should check that they are placed correctly under the tongue.

In most circumstances administering crushed tablets will be the most practical option, although this does not remove the need for supervision (it merely reduces the dissolution time moderately and reduces the resale appeal and value of spat out doses). When crushed doses are spat-out and diverted for injection, there are significant risks of infection from bacterial flora that reside in the oral cavity.

Irrespective of the mode of administration, the client must be kept under observation until the tablets have dissolved.

Supply of take-away doses

Unsupervised (take-away) doses of buprenorphine are allowed in certain circumstances in some jurisdictions.

Packaging: Tablets should be dispensed in the original foil packaging and placed in a childproof container.

Labelling: This container should be labelled appropriately, with the drug strength and quantity, complete instructions (including dose and date on which dose is to be taken) plus the information outlined above for methadone take-away doses.

Storage: Take-away doses should be stored in a cool place, secure from children or other individuals.

Buprenorphine–naloxone combination product

The sublingual tablet combination of buprenorphine and naloxone is now being increasingly used in Australia. The formulation can be first choice for some people in the maintenance phase of therapy—in particular, when unsupervised dosing is likely to be a major part of an individual program. The presence of naloxone (an opioid antagonist that is not absorbed sublingually) negates the effect of buprenorphine if the combination is injected. This reduces the diversion value of the formulation. However, diversion for sublingual use has been reported and all standards in pharmacy-supervised dosing protocols should still be observed. Other considerations relevant for this combination are similar to those listed for buprenorphine-only preparations.

References

1. Ministerial Council on Drug Strategy. The National Drug Strategy: Australia's integrated framework 2004–2009. Canberra: Commonwealth of Australia, 2004. Available at: www.nationaldrugstrategy.gov.au/internet/drugstrategy/publishing.nsf/Content/978CCA3285B6CA42CA25717D000297A4/$File/framework0409.pdf.

Further information

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Lintzeris N, Clark N, Winstock A, Dunlop A, Muhleisen P, Gowing L et al. National clinical guidelines and procedures for the use of buprenorphine in the treatment of opioid dependence. Canberra: Commonwealth of Australia, 2006. Available at: www.nationaldrugstrategy.gov.au/internet/drugstrategy/publishing.nsf/Content/15B5C4ED2E7A5F75CA25717E000A39CC/$File/buprenorphine_guide.pdf.

For more information on opioid substitution therapy programs, contact the relevant regulatory authorities in your state or territory.

Section B

Clinical monographs

Clinical monographs

Scope and purpose of this section

This following section provides an A to Z listing of some medicines commonly dispensed or supplied through community pharmacies in Australia. The listings are not comprehensive drug monographs but provide a quick reference for some individual medicines. Pharmacists are referred to other information sources such as the *Australian Medicines Handbook* (AMH) or *Australian Drug Information for the Health Care Professional* (AusDI) if a comprehensive monograph is required.

The medicine-specific information provided here pertains to:

- **Modification of oral formulations**.
- **Cautionary advisory labels** relevant to dispensed medicines. A full listing of ancillary labels and additional instructions can be found in 'Counselling and cautionary advisory labels for medicines', Section A. Note that not all medicines with additional labels are included in this section.
- **Notes** include key information to assist counselling. Some information may assist particularly in the context of a medication review.
- **Special considerations** such as those relating to the elderly, changes to faeces or the urinary system, and renal and/or hepatic impairment.
- **Pregnancy and breastfeeding**. See 'Pregnancy', information below regarding medicines use associated with pregnancy and breastfeeding.
- **Common adult and paediatric dosage ranges**. These are not comprehensive but provide general guidance for medicines commonly prescribed in a community setting. Doses for chemotherapy can vary according to specialist protocols. More detailed dosage information is contained in the AusDI, the AMH or approved Product Information. See below for further information on this, including additional notes on paediatric dosing.

Additional information can also be found in the following sections:

- 'Medication review', Section D.
- 'Medicines and older people', Section D.
- 'Medicines and urinary incontinence', Section D.
- 'Medicines causing discolouration of urine and faeces', Section D.
- 'Modification of oral formulations', Section A.
- 'Optimal medicine concentration ranges', Section D.
- Instructions for patients on the use of specific types of formulations, e.g. ear drops, eye drops and nasal sprays—see 'General formulary', Section A.
- Abbreviations used in this section are explained in 'Medical abbreviations', Section A.

Currency of information

Information published here is current at the time of publication. Pharmacists will appreciate the changing nature of medicines information. Vigilance needs to be exercised in sourcing the most up to date information and using professional judgment for individual cases.

Information on new drugs, or new/revised information on existing drugs, may be available from the National Prescribing Service through its publication *Rational Assessment of Drugs and Research* (RADAR). Each edition publishes a summary of key changes including a list of new and deleted drug monographs. Current and archived editions can be found at www.npsradar.org.au.

Information on product recalls can be obtained from www.tga.gov.au/recalls or www.recalls.gov.au (follow the link to 'Therapeutic Goods').

Pregnancy

Each medicine is assigned a category of risk of use in pregnancy by the Australian Drug Evaluation Committee. For pharmaceutical products containing two or more active ingredients, the categorisation of the combination is based on the component for which the categorisation is most restrictive. The pregnancy risk categories are as follows:

- *Category A*. Drugs which have been taken by a large number of pregnant women and women of child-bearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
- *Category B*. Drugs which have been taken by only a limited number of pregnant women of child-bearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been

observed. As experience of effects of drugs in this category in humans is limited, results of toxicological studies to date (including reproduction studies in animals) are indicated by allocation to one of three subgroups:

  - *Group B1*. Studies in animals have not shown evidence of an increased occurrence of fetal damage.
  - *Group B2*. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
  - *Group B3*. Studies in animals show evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

    For drugs in the B1, B2 and B3 categories, human data are lacking or inadequate and subcategorisation is therefore based on available animal data. The allocation of a B category does not imply greater safety than the C category.

- *Category C*. Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Texts should be consulted for further details.
- *Category D*. Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Texts should be consulted for further details.

  Drugs in category D are not absolutely contraindicated in pregnancy (e.g. anticonvulsants). Moreover, in some cases the D category has been assigned on the basis of 'suspicion'.
- *Category X*. Drugs that have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

The general recommendations provided in this section have been drawn from:

- *Drugs and Pregnancy* (Royal Women's Hospital, 2006)
- *Australian Medicines Handbook* (2008)
- approved Product Information for the drug.

Due to legal considerations, sponsor companies have in some cases applied a more restrictive category than can be justified on the available data. When considering the use of any medicine for a woman who is pregnant, the pharmacist should always consider alternative options, the risks associated with not treating a condition, whether dose adjustments are required, potential adverse effects to the fetus, and any monitoring that may be required.

Breastfeeding

The benefits of breastfeeding, for both mother and infant, are well recognised. Therefore, when the mother requires medication, discontinuing breastfeeding should not be the first choice.

When considering the use of any medication in a woman who is breastfeeding, the pharmacist should first determine:

- whether the drug is necessary—e.g. Are there safer alternatives? Can the treatment be delayed? What are the risks of not treating the condition?
- how the drug is processed by the mother—e.g. To what extent is the drug absorbed systemically by the mother? To what extent is the drug (and any metabolites) excreted in breast milk? What is the half-life of the drug? At what point after a dose will drug milk levels peak?
- how the drug is processed by the infant—e.g. How will the drug (and any metabolites) be absorbed, metabolised and excreted? What are the potential adverse effects? This may differ depending on whether the infant is premature, a neonate or a toddler and whether they have any medical conditions.

The general recommendations provided in this section have been drawn from:

- *Drugs and Breastfeeding* (Royal Women's Hospital, 2006)
- *Australian Medicines Handbook* (2008)
- approved Product Information for the drug.

Breastfeeding safety information is not always included—e.g. where there is no published information available and/or the drug is unlikely to be used by lactating women. In these circumstances, caution would dictate that the drug be avoided in lactation if possible.

Common dosage ranges

Adult and paediatric dosage information is included in this section and is presented as doses or dosage ranges for uses and indications that are typically or most commonly encountered in a community pharmacy setting. This information is intended to be a guide and is not necessarily comprehensive.

Pharmacists should note that published dosage information can vary, sometimes substantially, between sources. Information in this section has been drawn from the following reference sources, with the best effort made to present the most appropriate dosage(s) for each medicine.

- *eMIMS* (CMPMedica Australia, 2008; Apr)
- *Australian Drug Information for the Health Care Professional* (Phoenix Medical Publishing, 2008; Mar)
- *Australian Medicines Handbook* (2008)
- *Martindale: the complete drug reference* (35th edn. London: Pharmaceutical Press; 2007)
- Kemp CA, McDowell JM. *Paediatric Pharmacopoeia* (13th edn. Melbourne: Royal Children's Hospital; 2002).

Paediatric dosing

In this section omission of a paediatric dose for a medicine does not imply the medicine is not recommended for children; rather, it means the medicine is rarely used in children and/or reliable dosing data are not available and/or the medicine is generally used in specialised paediatric hospitals. The paediatric doses presented are those commonly recommended as a starting dose, but different doses may be required to suit the needs of individual patients. In general, therapy should be introduced at the lower end of a dosage range and increased as necessary.

Some medicines administered to children are given 'off label'. That is, the indication, age range or route differs from that in the approved Product Information. Such use is not illegal and, in fact, may be best practice in some cases. However, a 'contraindication' for use in children is likely to have significantly more serious implications. As with all therapy, counselling should occur and include specific reference to 'off label' use.

Care should be taken with neonates if specific doses are not available: the pharmacokinetics of medicines can vary markedly between this group and older children and adults.

The following sources may be useful if pharmacists require more detailed information on paediatric dosing:

- a Paediatric Drug Information Service
- *Paediatric Pharmacopoeia* (Pharmacy Department, The Royal Children's Hospital, Melbourne)
- *Drug Doses for Children* (The Children's Hospital at Westmead)
- *British National Formulary for Children* (RPS Publishing)
- Therapeutic Guidelines.

Unless otherwise specified, the doses given are for oral administration. When doses are based on body weight, for children greater than 12 months of age ideal body weight should be used for most drug dosing and the maximum dose should not generally exceed the usual adult dose.

The average weights and surface areas of children from birth to 14 years of age are listed in Table B.1. Approximate surface areas are given for children of the specified weight and average height for that weight. Whenever possible, and particularly in infants under 12 months, an accurate measurement of weight should be made. When using weight as a basis for dosage in oedematous or obese children,the ideal weight for height and age should be used and can be calculated using the formula:

$$\text{Ideal body weight (kg)} = \frac{[\text{height (cm)}]^2 \times 1.65}{1{,}000}$$

Table B.1 Average weights and surface areas for children aged to 14 years

Age last birthday	Average body weight (kg)	Average surface area (m^2)
Term	3.5	0.23
3 months	6.0	0.31
6 months	7.3	0.38
1	10	0.47
2	12	0.54
3	14	0.61
4	16	0.67
5	18	0.72
6	20	0.77
7	22	0.83
8	25	0.88
9	28	0.93
10	31	0.98
11	35	1.02
12	39	1.08
13	43	1.22
14	50	1.37

Additional information

Missed doses

More than 80% of patients miss doses of their medicines occasionally. When a medicine is dispensed a plan for missed doses should be provided to patients. Consumer Medicine Information leaflets may contain a section on what to do if a dose is missed. For oral contraceptives see 'Managing missed doses of oral contraceptives', in Section D. Further information about missed

doses can also be found in Australian Prescriber at www.australianprescriber.com/upload/pdf/articles/566.pdf.

Adverse drug reactions

Medicine-related adverse effects are not comprehensively or consistently addressed in this section. Pharmacists are advised to refer to the AusDI, AMH or approved Product Information for more comprehensive details.

All health professionals are encouraged to report adverse drug reactions to the TGA Adverse Drug Reactions Unit. They also have a role in helping consumers report any adverse events they have experienced.

Reports can be submitted in the following ways:

- *Phone:* Call the Adverse Medicine Events Line on 1300 134 237. Consumer reporting can also be directed to this number.
- *Online:* Submit a report electronically at www.ebs.tga.gov.au/ebs/ADRS/ADRSRepo.nsf?OpenDatabase.
- *Using the 'Blue Card':* The forms are included with hard copies of the *ADRAC Bulletin* or can be downloaded from www.tga.gov.au/adr/bluecard.htm.

A copy of the *'Blue Card'* should also be sent to the sponsor of the product in Australia.

Monographs

abacavir

nucleoside reverse transcriptase inhibitor

Cautionary advisory labels: 12

Notes

- Report fever, nausea, vomiting, diarrhoea, rash, tiredness, difficulty in breathing, sore throat or cough.
- If hypersensitivity reactions occur, stop drug and do not rechallenge.
- Drug does not cure HIV or reduce risk of transmission.
- Should be taken in combination with other antiretrovirals.

Hepatic impairment (mild): Reduce dose to maximum of 200 mg twice daily.

Hepatic impairment (moderate–severe): Contraindicated.

Pregnancy: B3. Previously commenced therapy should be continued and advice sought from an infectious diseases specialist.

Breastfeeding: Expected to be excreted into breast milk, however there is no safety data. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

300 mg twice daily or 600 mg once daily.

Paediatric dose

3 months–12 years, 8 mg/kg twice daily. Maximum 600 mg daily.

acamprosate

maintains abstinence in alcohol dependence

Modification of oral formulation

Crushing or otherwise altering tablets may alter absorption characteristics.

Cautionary advisory labels: 2, A, B

Notes

- To be used in combination with psychosocial therapy.
- Avoid alcohol during treatment.
- Treatment should be maintained during relapse.
- Usual duration of therapy is 1 year.

Renal impairment: Contraindicated if Cl_{cr} <30 mL/min.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use not recommended.

Common dosage range

Adult dose

Adults >60 kg, 666 mg three times daily.

Adults <60 kg, 666 mg morning, 333 mg midday, 333mg night.

acarbose

alpha-glucosidase inhibitor for diabetes

Cautionary advisory labels: B

Notes

- Gastrointestinal adverse effects include flatulence, abdominal pain and diarrhoea and are:
  - dose dependent, therefore start with low dose and gradually increase
  - generally not relieved by antacids
  - increased by consumption of sucrose.
- If therapy includes insulin or a sulfonylurea, advise patient to treat hypoglycaemic episodes with glucose rather than sucrose (cane sugar).
- Monitor transaminase concentrations 6-monthly.

Pregnancy: B3. Oral hypoglycaemic agents usually replaced with insulin.

Breastfeeding: Use not recommended. Low excretion expected, but no safety data on drug in infants.

Common dosage range

Adult Dose

Initial dose: 50 mg daily, gradually increased to 50 mg three times daily. A further increase may be necessary after 4 to 8 weeks. Average adult dose is 100 mg three times daily. Maximum daily dose 600 mg.

acetazolamide

systemic carbonic anhydrase inhibitor

Cautionary advisory labels: 10a, B

Notes

- Contraindicated in sulphonamide allergy.

Changes to faeces: Black discoloration.

Renal impairment: Reduce dose if moderate impairment, contraindicated if impairment is severe.

Pregnancy: B3. Consider risk of congenital malformation against dangers of uncontrolled epilepsy.

Breastfeeding: Use with caution. Low excretion expected. Consider risk of adverse effects experienced by infant against benefit of seizure control in mother.

Common dosage range

Adult dose

Chronic open-angle glaucoma, epilepsy: oral, 250 mg–1 g per 24 hours, in divided doses.

Perioperative reduction of intraocular pressure: oral/IV, initially 250–500 mg; thereafter 250 mg every 4 hours as required (maximum 1 g daily).

Congestive heart failure, drug-induced oedema: see Product Information.

Paediatric dose

Glaucoma: oral, 5–10 mg/kg (up to 250 mg) every 6 hours (under specialist supervision). Maximum daily dose 1 g.

Epilepsy: 4–30 mg/kg daily in divided doses, up to 750 mg daily.

aciclovir

guanine analogue antiviral

Cautionary advisory labels: D (oral)—some packaging contains more units than for the treatment for one episode, e.g. episodic treatment of recurrent disease

Notes

- Take at regular intervals.
- If five doses daily are prescribed, take at 4 hourly intervals while awake.
- Maintain adequate fluid intake (1.5–2 L/day) to prevent crystallisation in renal tubules.

Pregnancy: B3. Use with caution during the first trimester, but may be used during second and third trimester. Seek advice from an infectious diseases or HIV specialist.

Breastfeeding: Safe to use. Moderate amounts excreted into breast milk, but dose received by infant expected to be lower than that used in neonates.

Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

Oral, 200–800 mg up to 5 times daily depending on the condition being treated.

IV, 5–10 mg/kg over 1 hour administered every 8 hours.

Paediatric dose

3 months – 12 years

Herpes simplex (non-encephalitis), Herpes zoster with complications: 250 mg/m^2 IV every 8 hours.

Herpes simplex encephalitis, shingles (eye involvement), chickenpox encephalitis: 500 mg/m^2 IV every 8 hours.

Herpes simplex (non-encephalitis): oral, <2 years of age, 100 mg five times daily; 2 years and over, 200 mg five times daily.

Infants <3 months, immunocompromised, prevention: see Product Information.

acitretin

oral retinoid

Cautionary advisory labels: 2 (women), 5, 8, B

Notes

- Monitor LFTs and blood.
- Female
  - Effective birth control required one month before, during and 2 years after therapy.
- Male and Female
  - Do not donate blood for at least one year after discontinuing treatment.
  - May cause dry skin and mucous membranes and changes in vision.

Hepatic impairment (severe): Contraindicated.

Renal impairment (severe): Contraindicated.

Pregnancy: X. Avoid pregnancy for at least two years after ceasing therapy with acitretin. Unless contraindicated, a combined oral contraceptive with a non-androgenic progestogen is preferred, plus a barrier method.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

25–50 mg daily.

Paediatric dose

0.5–1 mg/kg daily; maximum 35 mg daily.

adalimumab

cytokine blocker for rheumatoid arthritis

Cautionary advisory labels: 6

Notes

- A skin test for tuberculosis is needed before starting this medicine.
- Report persistent fever, bruising, bleeding or pallor during treatment.
- Report persistent infection, cough, pain on urination, difficulty seeing or 'pins and needles'.
- Seek medical advice before receiving vaccinations.
- Appropriate aseptic technique, site rotation and disposal of needles and syringes.

Pregnancy: C. Use not recommended.

Breastfeeding: Use not recommended.

Common dosage range

Adult dose

40 mg SC once every 2 weeks (may increase to 40 mg once weekly if needed in patients not taking methotrexate).

Crohn's disease: see Product Information

adefovir

antiviral for chronic hepatitis B

Cautionary advisory labels: 9

Notes

- Modify dose interval in renal impairment.
- Beware of lactic acidosis or hepatotoxicity.
- Monitor LFTs following discontinuation of therapy.

Renal impairment: Dosage adjustment necessary.

Cl_{cr} 20–49 mL/min = 10 mg every 48 hours

Cl_{cr} 10–19 mL/min = 10 mg every 72 hours

Contraindicated when Cl_{cr} <10 mL/min.

Pregnancy: B3. Use not recommended. Seek advice from an infectious diseases specialist.

Breastfeeding: Use not recommended.

Common dosage range

Adult dose

10 mg daily.

adrenaline

adrenergic agonist

Notes

- Protect from light (Light sensitive).
- Instruct on administration technique.
- Note use-by date and arrange new supply in advance.

Pregnancy: A.

Breastfeeding: Use with caution. Excreted into breast milk. Monitor infant for adverse effects.

Common dosage range

Adult dose

Severe asthma or anaphylaxis: IM, 100–500 micrograms (0.1–0.5 mL of the 1:1,000 solution) initially; repeat every 5 mins if needed. Maximum single dose: 500 micrograms.

Life-threatening asthma or anaphylaxis: Slow IV infusion, 100–250 micrograms (1–2.5 mL of the 1:10,000 solution); or IM, 500 micrograms followed by IV, 25–50 micrograms (0.25–0.5 mL of the 1:10,000 solution) every five to 15 minutes.

Cardiac arrest: IV, 0.5–1 mg (5–10 mL of the 1:10,000 solution); repeat every 3–5 mins if needed.

IV infusion, 1–4 micrograms/minute.

Paediatric dose

Anaphylaxis: IM, 10 micrograms/kg (i.e. 0.01 mL/kg of 1:1,000 solution), repeated every 5 minutes if needed. Maximum single dose: 500 micrograms.

Croup: Nebulised, 0.5 mg/kg (i.e. 0.5 mL/kg adrenaline 1:1,000); maximum 5 mg (5 mL).

Cardiac arrest: IV, 10 micrograms/kg (i.e. 0.1 mL/kg of the 1:10,000 solution); repeat every 3–5 minutes if needed.

IV infusion, 0.05–1 microgram/kg/minute.

Adrenaline for self-administration

The following doses are recommended by the Australasian Society of Clinical Immunology and Allergy; for children 20–30 kg, the doses are higher than the doses recommended by the manufacturer.

Adult, child >20 kg: IM, 0.3 mg (*EpiPen*®).

Child 10–20 kg: IM, 0.15 mg (*EpiPen Jr*®).

albendazole

benzimidazole anthelmintic

Notes

- Treat all members of family simultaneously (threadworms).
- Monitor LFTs and blood counts during prolonged treatment.

Hepatic impairment: Monitor for signs of toxicity and monitor LFTs. Cease therapy if enzymes >2 x normal level.

Pregnancy: D. Use not recommended for one month prior to conception and during first trimester. If drug of choice, use with caution during second and third trimesters.

Breastfeeding: Use with caution. Maternal absorption is <5% of dose. Excretion into breast milk unknown.

Common dosage range

Adult dose

Roundworm, threadworm, hookworm: 400 mg as single dose.

Other indications: 400 mg once or twice daily (see approved Product Information).

Paediatric dose

Roundworm, threadworm, hookworm: child >6 months but <10 kg, 200 mg single dose; child >6 months and >10 kg, 400 mg single dose.

Other indications: See approved Product Information.

alendronate

bisphosphonate

Cautionary advisory labels: 20 (certain dosage forms), A, C

Notes

- Remain upright for 30 minutes after the dose and until after the first meal of the day.
- Presence of food reduces absorption significantly.
- Report signs of reflux, worsening indigestion, pain or difficulty swallowing.
- Treatment for Paget's disease is generally for 6 months.
- For osteoporosis and Paget's disease, ensure adequate intake of calcium and vitamin D (taken at different time of day).
- Consider full dental assessment and complete any dental procedures before starting treatment to minimise risk of osteonecrosis of jaw.

Renal impairment: Contraindicated if Cl_{cr} <35 mL/min.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended. Poor oral bioavailability, but no safety data on drug in infants.

Common dosage range

Adult dose

Postmenopausal osteoporosis and osteoporosis in men: 10 mg daily or 70 mg weekly.

Paget's disease: 40 mg daily for up to 6 months.

allopurinol

xanthine oxidase inhibitor

Cautionary advisory labels: 12†, B

Notes

- Maintain adequate fluid intake (1.5–2 L/day) to prevent precipitation of urate in renal tubules.
- If rash develops, seek medical advice.
- Unsuitable for management of acute attack, but continue established treatment in acute attack.
- Monitor LFTs.
- Significantly reduced dosage of azathioprine/mercaptopurine in combination with allopurinol.

Elderly: Use lower doses in the elderly due to increased adverse effects.

Hepatic impairment: Dosage adjustment necessary.

Renal impairment: Dosage adjustment necessary.

Moderate = 200 mg daily, severe = 100 mg every 2 days.

Pregnancy: B2. Use not recommended. Consider symptomatic treatment.

Breastfeeding: Use with caution. Excreted into breast milk, but dose received by infant expected to be lower than recommended paediatric doses. No adverse effects in infants have been observed.

Common dosage range

Adult dose

100–300 mg daily, although up to 900 mg daily (in divided doses) is sometimes used short term for severe conditions.

Paediatric dose

10–20 mg/kg daily in 1–2 doses, up to 600 mg daily. Use in children is rarely indicated, except in malignant conditions, especially leukaemia, and certain enzyme disorders.

† Most appropriate during initial treatment or when dosage is increased.

alprazolam
benzodiazepine

Cautionary advisory labels: 1, 9

Notes

- Regular use for more than 2–4 weeks may result in dependence and tolerance. Monitor for physical and psychological dependence and tolerance (check intervals between prescription refills).
- Caution with sudden discontinuation of long-term treatment.
- Caution with respiratory disease or sleep apnoea. Reduced respiratory drive may cause hypoxaemia.
- May cause sedation, especially when alcohol is consumed, and a 'morning-after' hangover effect.
- Caution with drugs that inhibit CYP3A4 (see Table D.1, Section D).
- Monitor blood counts and LFTs.

Changes in Urinary System: May induce or aggravate functional incontinence by sedation or impairment of mobility.

Elderly: Over-sedation, confusion, memory impairment, poor muscle coordination leading to falls and fractures.

Renal and hepatic impairment: Caution. Dosage adjustment necessary. Monitor blood counts and LFTs.

Pregnancy: C. Use should be avoided if possible, especially during first trimester. If alprazolam is required, use the lowest effective dose for the shortest duration.

Breastfeeding: Use with caution. Excreted into breast milk, with concentrations increasing with time. Adverse effects (e.g. sedation, poor feeding) may be experienced by infant. Avoid long-term use, large doses or frequent dosing.

Common dosage range

Adult dose

Anxiety: 0.5–4.0 mg daily in divided doses.

alprostadil
prostaglandin E1 for erectile dysfunction

Cautionary advisory labels: 6 (reconstituted)

Notes

- Allow to warm to room temperature before use.
- See doctor for injection technique instruction.
- Seek medical advice if erection lasts >4 hours.

Common dosage range

Adult dose

10–20 micrograms; maximum dose 60 micrograms. Use no more than once in 24 hours; may be used up to 3 times a week.

aluminium hydroxide
antacid

Notes

- For symptomatic relief of upper gastrointestinal discomfort.
- Best taken between meals and at bedtime as this is when acid levels at highest (i.e. 1–3 hours after meals).
- When used for hyperacidity, avoid precipitating factors (e.g. chocolate, fat, spices, large meals, alcohol, eating at bedtime, smoking).
- May interact with some medications. Separate doses by at least 2 hours.

Changes to faeces: Discolouration and white speckling.

Elderly: Caution. Metabolic bone disease.

Renal impairment (severe/chronic): Caution. Monitor for signs of hyperaluminaemia.

Pregnancy: A.

Breastfeeding: May be used. Avoid high doses or long-term use.

Common dosage range

Adult dose

600–1,200 mg up to four times daily.

amantadine
dopaminergic, antiviral

Cautionary advisory labels: 9, 12, 16, B

Notes

Elderly: Confusion and psychoses, orthostatic hypotension may increase risk of falls and fractures. Dose reduction may be necessary.

Hepatic impairment: Caution. Monitor clinically.

Renal impairment: Caution. Dose reduction may be necessary. Monitor plasma levels of drug.

Cl_{cr} 30–50 mL/min = 200 mg on day one, then 100 mg every 24 hours thereafter.

Cl_{cr} 15–29 mL/min = 200 mg on day one, then 100 mg every 48 hours.

Cl_{cr} <15 mL/min = 200 mg every 7 days.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use alternative where possible. Small amounts excreted. Adverse effects (e.g. urinary retention, vomiting, rash) may be experienced by infant.

Common dosage range

Adult dose

100–200 mg daily. >65 years, 100 mg once daily.

amikacin

aminoglycoside antibacterial

Notes

- Ototoxicity and nephrotoxicity may occur.
- Serum concentration monitoring is advisable, especially in patients with renal insufficiency and in neonates.

Renal impairment: Caution. Dosage adjustment necessary. Use 7.5 mg/kg as loading dose. Measure amikacin plasma levels and maintain under 35 mg/mL. Maintenance dose (12 hourly): divide normal dosage by serum creatinine (mmol/L).

Pregnancy: D. Use not recommended, except for severe or life-threatening infections where safer drugs are inappropriate.

Breastfeeding: May be used. Trace amounts excreted. Poor oral absorption by infant.

Common dosage range

Adult dose

Doses listed are a guide for <48 hours' treatment. Individualise dose based on drug concentration monitoring for longer term treatment.

IM/IV, 16–24 mg/kg once daily or in 2–3 doses. Use the higher dose for young adults and the lower one for the elderly.

Paediatric dose

Child >10 years, IM/IV 18 mg/kg once daily or 15 mg/kg daily in 2–3 doses.

Child <10 years, IM/IV 22.5 mg/kg once daily or 7.5 mg/kg three times daily.

amiloride

potassium-sparing diuretic

Cautionary advisory labels: 11, 12†, 16

Notes

- May raise serum potassium concentration.
- Caution if used in combination with ACE inhibitors, angiotensin II receptor antagonists, NSAIDs (including COX-2 inhibitors), potassium supplements, cyclosporin.

Hepatic impairment (severe): Caution. Monitor clinically.

Renal impairment: Caution. Monitor Cl_{cr} and serum electrolytes.

Pregnancy: C. Use not recommended.

Breastfeeding: Use not recommended as no data available. May suppress lactation.

Common dosage range

Adult dose

2.5–5 mg daily as a single dose. Maximum daily dose 20 mg.

Paediatric dose

0.2 mg/kg /dose once or twice daily.

aminoglutethimide

aromatase inhibitor, antineoplastic

Cautionary advisory labels: 1†, 16

Notes

- Should be commenced in hospital.
- Dose titrated up depending on tolerability.
- May reduce effectiveness of concomitant medications due to enzyme induction.

Renal impairment: Caution. Dosage adjustment necessary. Monitor clinically.

Pregnancy: D. Use not recommended.

Breastfeeding: Use not recommended.

Common dosage range

Adult dose

Cushing's syndrome: 250 mg every 6 hours; maximum 2 g daily.

aminophylline

theophylline derivative bronchodilator

Cautionary advisory labels: 5, B

Notes

- Consideration must be given to the amount of theophylline or its derivatives given in the previous 24 hours to avoid toxicity.
- Serum concentrations and response vary from one person to another; therapeutic concentrations may be achieved with considerably smaller or larger doses.
- When response is inadequate or symptoms suggest toxicity, blood concentration monitoring should be considered.
- Smokers (cigarettes or marijuana) may require larger doses.
- Many drugs influence clearance or interact.
- Each 100 mg of aminophylline is equivalent to 80 mg of theophylline.

† Most appropriate during initial treatment or when dosage is increased.

Changes to faeces: Black discolouration may occur.

Elderly: May require dosage adjustment due to reduced clearance. Clearance in >60 years is 30% lower than in healthy young adult.

Renal and hepatic impairment: Caution. Toxicity possible due to reduced clearance and low therapeutic index. In suspected toxicity monitor theophylline and reduce dose.

Pregnancy: A.

Breastfeeding: May be used. Excreted into breast milk. Monitor for adverse effects (e.g. irritability) in infant.

Common dosage range

Adult dose

IV, loading dose, 5 mg/kg.

Maintenance infusion rates:

- otherwise healthy adults, 0.5 mg/kg/hour
- patients with cor pulmonale, 0.3 mg/kg/hour
- patients with congestive heart or hepatic failure, 0.1–0.2 mg/kg/hour
- smokers, 0.8 mg/kg/hour.

Paediatric dose

IV, loading dose, 5–10 mg/kg (maximum 500 mg) over 20 minutes, followed by a continuous infusion of 1 mg/kg/hour.

amiodarone

antiarrhythmic

Cautionary advisory labels: 5, 8, 18

Notes

- Interacts with digoxin, warfarin, phenytoin and drugs metabolised by cytochrome P450 3A4. Regular monitoring required of thyroid, pulmonary, cardiac, ophthalmic and hepatic function.

Elderly: More susceptible to bradycardia and conduction defects. Start at lower end of dosing range. Monitor and adjust dose. Monitor thyroid function.

Hepatic impairment: Caution. Dose adjustment may be necessary. Monitor clinically.

Therapeutic monitoring: Therapeutic range is 1.0–2.5 mg/L (1.5–4.0 micromol/L). Time to steady state is 5 months.

Pregnancy: C. Avoid three months before and during pregnancy. If use unavoidable, newborn thyroid function should be promptly assessed.

Breastfeeding: Contraindicated. Significant amounts excreted into breast milk. Potential for interference with infant thyroid function.

Common dosage range

Adult dose

Oral, initially 200–400 mg three times daily for one week, then 200–400 mg twice daily for one week. Maintenance 100–400 mg once daily.

IV, loading, 5 mg/kg by infusion over 20 minutes to 2 hours.

Paediatric dose

Oral, 4 mg/kg three times daily for one week, then twice daily for one week, then once daily.

amisulpride

atypical antipsychotic

Cautionary advisory labels: 1, 12, 16

Notes

- Amisulpride can lower seizure threshold.
- Avoid in combination with medicines that affect heart rhythm.
- It takes 1–2 weeks for a measurable response and 2–3 months for a full trial.

Changes to urinary system: May induce or aggravate overflow/functional/stress incontinence, associated with constipation, confusion, sedation or parkinsonism.

Pregnancy: B3. Use not recommended. Refer to psychiatrist to consider withdrawal.

Breastfeeding: Use not recommended as no data available.

Common dosage range

Adult dose

Acute psychosis: 200–400 mg twice daily.

Maintenance, predominantly negative symptoms: 50–300 mg once daily.

Maintenance, mixed positive and negative symptoms: adjust dose to minimum required to control positive symptoms.

amitriptyline

tricyclic antidepressant

Cautionary advisory labels: 1, 9, 13, 16

Notes

- Orthostatic hypotension may occur when rising quickly. Provide advice about getting up slowly from sitting or lying position.

- Full benefit may not be seen for several weeks, but adverse effects may occur from start of treatment.
- Anticholinergic adverse effects are common—dry mouth, constipation, blurred vision, difficulty in passing urine.
- Medicine-free interval may be required if switching to or from other antidepressants. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- Sips of water, sugarless gum or sweets may help relieve dry mouth.
- Best taken as a single dose at night.
- Start with a low dose and titrate upwards, especially in older people.

Changes to urinary system: May discolour urine blue–green. May induce or aggravate overflow/functional incontinence due to anticholinergic urinary retention, voiding difficulty, constipation, sedation or impairment of mobility.

Elderly: Increased confusion, constipation and orthostatic hypotension leading to falls or fractures. Avoid use as a sedative due to pronounced adverse effects.

Hepatic impairment: Caution.

Therapeutic monitoring: Therapeutic range is 60–250 micrograms/L (150–900 nanomol/L).

Toxicity: Both the parent drug and the active metabolite (nortriptyline) are effective and levels should be interpreted by considering the combined levels.

Pregnancy: C. Use when clinically indicated if it is the drug of choice. There is increased risk of reversible withdrawal symptoms, not congenital malformations.

Breastfeeding: Use with caution. Small amounts excreted into breast milk. If needed, preferably taken as a single dose. Monitor for adverse effects (e.g. sedation) in infant.

Common dosage range

Adult dose

Major depression: 25–150 mg daily. Maximum daily dose 300 mg.

Other indications: see Product Information.

Paediatric dose

Enuresis: 7–10 years, 10–20 mg at bedtime; >10 years, 25–50 mg at bedtime (maximum of 3 months). Use at <7 years is not recommended.

amlodipine

dihydropyridine calcium channel blocker

Cautionary advisory labels: 9, 12†

Notes

- Dihydropyridines can cause peripheral oedema (swollen ankles).
- Use with caution in heart failure.

Hepatic impairment: Caution. Monitor clinically. Start on reduced dose of 2.5 mg daily.

Pregnancy: C. Consider alternative therapy first. If drug of choice, use with caution as maternal hypotension may produce fetal hypoxia.

Breastfeeding: Use not recommended. Expected to be excreted into breast milk, but no safety data on drug in infants.

Common dosage range

Adult dose

2.5–10 mg daily as a single dose.

Paediatric dose

Initially, <5 years, 1.25 mg once daily; >5 years, 2.5 mg once daily. Dose may be increased every 1–2 weeks.

amoxycillin

moderate spectrum beta-lactamase labile penicillin

Cautionary advisory labels: D; and for suspension also use 6, 7a

Notes

- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible during waking hours.
- Ask about any previous reaction to penicillin.
- If a skin rash occurs, seek medical advice.
- Other common adverse effects—nausea, diarrhoea, gastric upset.
- Reduce dose in severe renal or hepatic impairment.

Renal impairment (severe): Caution. Dosage adjustment necessary.

Cl_{cr} 10–30 mL/min = 250–500 mg twice daily.

Cl_{cr} <10 mL/min = 250–500 mg once daily.

Pregnancy: A.

Breastfeeding: May be used. Trace amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

† Most appropriate during initial treatment or when dosage is increased.

Common dosage range

Adult dose

Oral, 250–500 mg eight-hourly or 1 g twice daily.

IM/IV, 250 mg to 1 g every six to eight hours.

Uncomplicated UTI: 3 g as a single dose.

Other indications: see Product Information.

Paediatric dose

Oral, 7.5–25 mg/kg every eight hours.

IM/IV, 10–25 mg/kg every eight hours. Maximum 50 mg/kg every four hours.

Acute otitis media: 15 mg/kg up to 500 mg orally, eight hourly for five days. If compliance is a problem, 30 mg/kg (maximum 1 g) orally, 12-hourly for five days.

amoxycillin with clavulanic acid

broad spectrum penicillin

Cautionary advisory labels: 13, D, F (solid dose forms), 6, 7a, D, F (suspension)

Notes

- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible during waking hours.
- Ask about any previous reaction to penicillin.
- If a skin rash occurs, seek medical advice.
- Other common adverse effects—nausea, diarrhoea, gastric upset.

Hepatic impairment: Caution. Limited data available. Dose adjustment may be necessary

Renal impairment: Caution. Dosage adjustment necessary.

Cl_{cr} 10–30 mL/min = 500/125 mg every 12 hours.

Cl_{cr} <10 mL/min = 500/125 mg every 24 hours.

Pregnancy: B1. May be used.

Breastfeeding: Use with caution. Unknown amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Doses are based on amoxycillin component.

Adult dose

Oral, 250–500 mg eight-hourly or 500–875 mg every 12 hours.

Paediatric dose

7.5–15 mg/kg every eight hours; (up to 22.5 mg/kg every eight hours in severe infections).

Duo formulation, 12.5–22.5 mg/kg every 12 hours.

amphotericin B

polyene antifungal

Cautionary advisory labels: D

Notes

- In oral thrush, lozenges should be sucked after meals and retained in the oral cavity as long as possible.
- Minimal absorption occurs following oral administration.
- IV—monitor renal function, haemopoietic function and electrolytes.

Changes to faeces: Black discolouration.

Renal impairment: Caution.

Pregnancy: Oral, B2; IV, B2 or B3 depending on formulation. Lozenges are safe to use. Consult infectious diseases specialist for IV use.

Breastfeeding: Lozenges are safe to use. Use intravenously with caution, although poor oral absorption by infant.

Common dosage range

Adult and paediatric dose

Oral candidiasis; 10 mg lozenge four times daily.

IV, see Product Information.

ampicillin

moderate-spectrum beta-lactamase labile penicillin

Cautionary advisory labels: 3b, D

Notes

- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible during waking hours.
- Ask about any previous reaction to penicillin.
- If a skin rash occurs, seek medical advice.
- Other common adverse effects—nausea, diarrhoea, gastric upset.
- Reduce dose in severe renal or hepatic impairment.

Hepatic impairment: Caution.

Renal impairment: Caution. Monitor clinically. Dosage adjustment necessary.

Cl_{cr} 10–50 mL/min = usual dose, every 6–12 hours.

Cl_{cr} <10 mL/min = usual dose, every 12–16 hours.

Pregnancy: A.

Breastfeeding: May be used. Trace amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

IM/IV, 500 mg–1 g every 4–6 hours.

Meningitis or septicaemia: 200 mg/kg/day in divided doses every 4–6 hours. Maximum 14 g daily.

Paediatric dose

IM/IV, 10–25 mg/kg every 6 hours. Maximum 50 mg/kg every 4 hours.

anagrelide

platelet production inhibitor

Cautionary advisory labels: 1, 16

Notes

- Monitor LFTs.

Hepatic impairment: Caution. Monitor plasma levels of drug. Dosage adjustment necessary.

Renal impairment: Caution.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended. Excretion into breast milk is expected, but no data available.

Common dosage range

Adult dose

Initial dose 0.5 mg four times daily or 1 mg twice daily. Maximum 2.5 mg per dose or 10 mg daily.

aprepitant

antiemetic

Cautionary advisory labels: 5

Notes

- May reduce efficacy of oral contraceptives; extra precautions need to be taken for 28 days after the last dose.
- Monitor patients on warfarin and phenytoin for two weeks after taking aprepitant because efficacy of these may be reduced.
- Halve the dose of dexamethasone when used together with aprepitant.
- Many drug interactions—care is needed (see Table D.1, Section D).
- Caution in patients taking cyclosporin, sirolimus or tacrolimus.
- Given with corticosteroid and $5HT_3$ antagonist.

Pregnancy: B1. Use not recommended.

Breastfeeding: Use not recommended as no data available.

Common dosage range

Adult dose

125 mg on day one, 80 mg on second and third day.

aripiprazole

atypical antipsychotic

Cautionary advisory labels: 1, 16†

Notes

- May cause interactions (see Table D.1, Section D).
- Seek medical advice if experiencing overheating and dehydration.

Pregnancy: B3. Use not recommended. Refer to psychiatrist to consider withdrawal.

Breastfeeding: Use not recommended. Excretion into breast milk is expected, but no data available.

Common dosage range

Adult dose

10–30 mg daily. Usual maintenance dose 15 mg daily.

artemether with lumefantrine

antimalarial

Cautionary advisory labels: 12, A, B

Notes

Hepatic impairment: Caution. Monitor ECG and serum potassium.

Renal impairment: Caution. Monitor ECG and serum potassium.

Pregnancy: D. Use not recommended.

Breastfeeding: Use not recommended. Due to long half-life of lumefantirine, breastfeeding should be avoided for one month after last dose.

Common dosage range

Adult and paediatric doses

Each tablet contains 20 mg artemether and 120 mg lumefantrine. It is a six-dose course. Doses are taken at 8, 24, 36, 48 and 60 hours after the first dose.

>12 years and >35 kg: four tablets.

5–15 kg: one tablet.

15–25 kg: two tablets.

25–35 kg: three tablets.

Note: the approved Product Information states that the safety and efficacy of this product in children aged <12 years have not been adequately assessed.

† Most appropriate during initial treatment or when dosage is increased.

aspirin

analgesic, anti-inflammatory, antiplatelet, antipyretic

Modification of oral formulation

Before crushing or otherwise altering enteric-coated tablets or capsules, consider the increased risk of local gastrointestinal irritant effect.

Cautionary advisory labels: 13, A*, B

Notes

- Avoid exposing soluble aspirin tablets to air, especially when loaded into dose administration aids. Disperse all soluble preparations in water before taking.
- May be contraindicated in peptic ulcer.
- Caution if taking warfarin or other anticoagulants.
- May exacerbate heart failure or induce bronchospasm in sensitive patients. Advise accordingly.
- Use paracetamol instead of aspirin for children less than 12 years of age (see warning under dosage concerning Reye's syndrome).
- For enteric-coated preparations avoid concurrent use of antacids.
- Cease 7 days before planned surgery.
- Analgesic use:
  - Also consider topical and non-drug options—e.g. hot packs, relaxation, physiotherapy.
  - Inquire about a pain management plan.
  - Inquire if the pain relief required is for acute or chronic pain.
- Antiplatelet use:
  - If intolerant of or unable to use aspirin, consider clopidogrel as alternative.

Changes to faeces: Pink red or black colouration may indicate medicine-induced gastrointestinal bleeding.

Elderly: Gastric ulceration, sodium and water retention, exacerbation of hypertension and heart failure, renal dysfunction, tinnitus, nausea, anorexia, dizziness.

Hepatic impairment: Caution. Monitor clinically. Hypoalbuminaemia will result in salicylate toxicity (reduction in bound salicylate).

Renal impairment (moderate): Dosage adjustment necessary. Increase dose interval to 1.5–3 times normal.

Renal impairment (severe): Contraindicated when Cl_{cr} <10 mL/min.

Pregnancy: C. Low dose may be used with caution during first and second trimester. Alternatives should be considered for analgesia. Use not recommended during third trimester.

Breastfeeding: Small amounts excreted in breast milk. Consider risk of Reye's syndrome. Occasional or low doses may be used. Avoid high or prolonged dosing especially during neonatal period. Avoid breastfeeding one to two hours after dose to minimise amount infant receives.

Common dosage range

Adult dose

Analgesic, anti-inflammatory: 300–900 mg/dose 4–6 hourly (maximum 4 g daily).

Acute rheumatism: 4–8 g daily in divided doses.

Antiplatelet activity: 75–150 mg daily (150–300 mg daily may be required in acute conditions).

Paediatric dose

Aspirin has been associated with Reye's syndrome. Avoid use for analgesia in children <12 years and in those aged 12–16 years with, or recovering from, chicken pox, influenza or fever. May be used for rheumatic fever, juvenile rheumatoid arthritis and Kawasaki's disease.

Rheumatic fever and juvenile rheumatoid arthritis: Initial 15–20 mg/kg/dose six-hourly. Maintenance 20 mg/kg/dose 4–6 hourly.

Kawasaki's disease: 10 mg/kg every eight hours until fever settles, then 3–5 mg/kg once daily.

Antiplatelet activity: 3–5 mg/kg daily.

atazanavir

antiretroviral protease inhibitor

Cautionary advisory labels: 5, B

Notes

- Rash occurs in approximately 20% of patients in the first three weeks of treatment. In most patients this resolves within two weeks while continuing treatment. If it does not, seek medical advice.
- Monitor patients on CYP3A4 substrates with narrow therapeutic index due interaction.

Hepatic impairment (moderate): Caution. Dosage adjustment necessary. Reduce dose to 300 mg once daily.

Hepatic impairment (severe): Contraindicated.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Pregnancy: B2. Use not recommended. Seek advice from an infectious diseases specialist.

Breastfeeding: Use not recommended as no data available. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

400 mg once daily or 300 mg with ritonavir.

atenolol

beta-blocker

Cautionary advisory labels: 9, 12†

Trigger Points

- If patient has history of asthma or other lung disease, seek medical advice before dispensing.
- Caution if patient suffers from diabetes (can mask hypoglycaemic attack), hyperlipidaemia, peripheral vascular disease, hyperthyroidism, uncontrolled heart failure, asthma, chronic obstructive pulmonary disease.

Renal impairment:

Cl_{cr} 15–35 mL/min = 50 mg daily or 100 mg on alternate days.

Cl_{cr} <15 mL/min = 50 mg on alternate days or 100 mg every fourth day.

Pregnancy: C. Use not recommended in first trimester. If drug of choice, use with caution in second and third trimesters.

Breastfeeding: Consider alternatives as it is excreted into breast milk to a greater extent than other beta-blockers. If used, monitor for adverse effects (e.g. bradycardia, hypotension) in infant.

Common dosage range

Adult dose

Oral, 50–100 mg daily (maximum 200 mg daily).

Paediatric dose

Oral, 1–2 mg/kg/dose once daily.

atomoxetine

SNRI for ADHD

Cautionary advisory labels: 5, 12†

Notes

- Avoid use within two weeks of discontinuing a monoamine oxidase inhibitor.
- Dose adjustment may be required in patients also taking CYP2D6 inhibitor medicines (see Table D.1, Section D).
- Do not open capsules. If powder comes in contact with eye, flush with water and contact doctor.

Hepatic impairment (moderate): Give half the usual recommended dose.

Hepatic impairment (severe): Give one quarter of the usual recommended dose.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended as limited data available.

Common dosage range

Adult and paediatric doses

Give as a single dose in the morning or as two doses (in the morning and late afternoon).

<70 kg: initially 0.5 mg/kg/day for three days, increasing to 1.2 mg/kg daily.

>70kg: initially 40 mg daily for three days, increasing to total daily dose of approximately 80 mg.

Maximum dose: 1.4 mg/kg or 100 mg, whichever is less.

atorvastatin

HMG-CoA reductase inhibitor

Cautionary advisory labels: 18

Notes

- If muscle pain, tenderness or weakness occurs, seek medical advice.
- May be taken at any time during the day.
- Important to follow a low-fat diet and other measures such as exercise and weight control.
- Increased risk of adverse effects in combination with gemfibrozil.

Hepatic impairment: Caution. Monitor clinically.

Pregnancy: D. Lipid-lowering therapy not recommended during pregnancy.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

10–80 mg once daily.

† Most appropriate during initial treatment or when dosage is increased.

atovaquone with proguanil

antimalarial

Cautionary advisory labels: B, D

Notes

Renal impairment (severe): Caution. Consider alternative therapy.

Pregnancy: B2. Use not recommended, although previously commenced therapy may be continued. Seek advice from an infectious diseases specialist.

Breastfeeding: Use not recommended. Excretion into breast milk expected, but no safety data on drug in infants.

Common dosage range

Prophylaxis: tablets should be taken once daily starting 1–2 days before entering an endemic area and continuing for 7 days after leaving the area.

Treatment: tablets should be taken once daily for three days.

Adult dose

Prophylaxis: one tablet (250/100 mg atovaquone/proguanil) daily.

Treatment: four tablets (250/100 mg atovaquone/proguanil) daily.

Paediatric dose

Prophylaxis:
11–20 kg: one tablet (62.5/25 mg atovaquone/proguanil) daily.

21–30 kg: two tablets (62.5/25 mg atovaquone/proguanil) daily.

31–40 kg: three tablets (62.5/25 mg atovaquone/proguanil) daily.

>40 kg: one tablet (250/100 mg atovaquone/proguanil) daily.

Treatment:

11–20 kg: one tablet (250/100 mg atovaquone/proguanil) daily.

21–30 kg: two tablets (250/100 mg atovaquone/proguanil) daily.

31–40 kg: three tablets (250/100 mg atovaquone/proguanil) daily.

>40 kg: four tablets (250/100 mg atovaquone/proguanil) daily.

auranofin

gold salt for rheumatoid arthritis

Cautionary advisory labels: B

Notes

- Mouth ulcers or stomatitis may be sign of systemic toxicity.
- Avoid in hypersensitivity to gold compounds or other heavy metals.
- Effect may not be evident for 3–4 months.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use contraindicated. Potential to cause adverse effects (e.g. rash, nephritis, hepatitis, haematological abnormalities) in infants.

Common dosage range

Adult dose

3–9 mg daily (increasing gradually) in one to three divided doses.

aurothiomalate

gold salt for rheumatoid arthritis

Notes

- Mouth ulcers or stomatitis may be sign of systemic toxicity.
- Monitor for 30 minutes after administration due to risk of anaphylaxis.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use contraindicated. Potential to cause adverse effects (e.g. rash, nephritis, hepatitis, haematological abnormalities) in infants.

Common dosage range

Adult dose

Maintenance: IM, 25–50 mg every 4–6 weeks.

Paediatric dose

Juvenile rheumatoid arthritis: 1 mg/kg (maximum 50 mg) every 2–4 weeks.

azathioprine

cytotoxic immunosuppressant

Cautionary advisory labels: 8, 21, A*, B

Notes

- Periodic blood monitoring is necessary.
- Advise patient to report any bleeding or excess bruising and to seek medical advice.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

- Caution when taken with allopurinol (significant dose reduction required).
- If gradual withdrawal of dose is required it should be done under supervision.
- Protect from light.

Renal impairment: Dose is modified according to creatinine clearance.

Cl_{cr} 10–50 mL/min, use 75% of usual dose.

Cl_{cr} <10 mL/min, use 50% of usual dose.

Pregnancy: D. Use with caution if no alternative, with maternal monitoring to reduce risk of immunosuppression in newborn.

Breastfeeding: Use not recommended. Small amounts excreted into breast milk. Potential for adverse effects in infants.

Common dosage range

Adult and paediatric doses

Organ transplantation: IV/oral, initially up to 5 mg/kg daily.

Maintenance: 1–4 mg/kg daily.

Auto-immune disorders: Oral, 1 mg/kg daily, increasing over several weeks to a maximum of 2.5 mg/kg daily.

Maintenance, adults: 50–150 mg daily.

azelastine

nasal antihistamine

Notes

- Azelastine is suitable for chronic use.
- Prime pump before dose delivery.
- Keep head up during dose delivery.
- Discard 6 months after opening.
- See 'Nasal instillations' in 'General formulary', Section A, for instructions on use.

Renal impairment: Caution. Drug is absorbed through nasal mucosa.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended as limited data available.

Common dosage range

Adult dose

1 spray (0.14 mg) into each nostril twice daily.

Paediatric dose

Children >5 years, 1 spray (0.14 mg) into each nostril twice daily.

azithromycin

macrolide antibacterial

Cautionary advisory labels: D (multiple dosing)

Notes

- Confirm appropriate antibiotic and dose regimen.
- Inquire about any serious allergic reaction to macrolide antibiotics.
- May cause nausea, diarrhoea or gastric upset.
- Avoid in combination with aluminium- and magnesium-containing antacids.

Hepatic impairment (severe): Caution.

Renal impairment (severe): Caution.

Pregnancy: B1. Use not recommended in first trimester. When other regimens not tolerated, appears safe to use in second and third trimesters.

Breastfeeding: Use with caution as limited data available. Single 1 g doses likely to be safe. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

Sexually transmitted chlamydia infections: 1 g single dose.

Other indications: 500 mg daily for three days or 500 mg on day one and 250 mg daily for four days.

Paediatric dose

Streptococcal pharyngitis and tonsillitis: 10–20 mg/kg once daily for three days (maximum 500 mg).

Chlamydial conjunctivitis and trachoma: 20 mg/kg as a single dose or once weekly for up to three weeks.

baclofen

muscle relaxant

Cautionary advisory labels: 1, 9, B

Notes

- Treatment generally commenced in hospital at low dose and gradually increased.

Renal impairment: Caution. Dosage adjustment necessary. Reduce dose to 5 mg daily.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use with caution. Small amounts (~0.1% of maternal dose) excreted in breast milk. Monitor for adverse effects in infant.

Common dosage range

Adult dose

15 mg daily in divided doses, increasing to 30–75 mg daily (maximum 100 mg daily).

Paediatric dose

0.5 mg/kg daily in 3–4 doses, increasing gradually to 2 mg/kg daily.

beclomethasone

inhaled or nasal corticosteroid

Cautionary advisory labels: 14

Notes

Oral inhalation

- Inquire about an asthma management plan.
- A preventive medication intended for continual and regular use, not for use during acute asthma attacks.
- Use after beta$_2$ agonist if being used concurrently.
- Check inhaler technique and compliance.
- Rinse mouth with water after use to decrease systemic absorption and minimise risk of oral thrush.
- If asthma is well controlled, try a dose reduction of 25% every 3 months.
- Cover eyes during nebulisation because of possible leakage from mask.
- Systemic effects may include bone density loss, glaucoma, cataract, skin thinning, impaired growth, adrenal suppression.

Pregnancy: B3. Inhaled and nasal corticosteroids safe to use. Women planning a pregnancy should switch to budesonide.

Breastfeeding: May be used.

Dosage range

Adult dose

Oral inhalation: 50–200 micrograms twice daily; severe asthma: up to 400 micrograms twice daily. Consider specialist referral for patients who require >800 micrograms daily.

Nasal spray: Two sprays into each nostril twice daily; reduce to one spray into each nostril twice daily when symptoms controlled.

Paediatric dose

Monitor development and growth carefully in children on long-term therapy.

Oral inhalation: >5 years, 50 micrograms twice daily; up to 400 micrograms daily in severe persistent asthma.

Nasal spray: 3–12 years, one spray into each nostril twice daily; reduce to one spray into each nostril daily when symptoms controlled.

benzathine penicillin

beta-lactamase labile penicillin

Notes

- May cause diarrhoea.
- If a skin rash occurs, seek medical advice.
- Ask about any previous reaction to penicillin.

Renal impairment: Caution. Dose adjustment may be necessary.

Pregnancy: A.

Breastfeeding: May be used. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

1.8g = 2.4 milllion units.

Adult dose

IM, 0.9–1.8 g deep IM, single dose, or may be repeated at weekly intervals (e.g. for syphilis, three successive weeks).

Paediatric dose

Prophylaxis, rheumatic fever: IM, 900 mg every 3–4 weeks.

Other indications: See approved Product Information.

benzhexol

anticholinergic, anti-Parkinsonian

Cautionary advisory labels: 1, 9 (long-term regular therapy)

Notes

Changes to urinary system: May induce or aggravate overflow incontinence due to reduced detrusor activity, voiding difficulty, urinary retention or constipation.

Elderly: Confusion, psychoses, constipation, urinary retention, blurred vision, orthostatic hypotension leading to falls and fractures. Counsel about rising slowly and cautiously.

Renal and hepatic impairment: Caution. Monitor clinically.

Pregnancy: B1. Use not recommended.

Breastfeeding: Use with caution, especially in neonatal period. Limited data available. Risk of anticholinergic effects. May suppress lactation.

Common dosage range

Adult dose

1 mg daily initially, increasing gradually to 5–15 mg daily in 3–4 divided doses.

Paediatric dose

Short-term salivary control: >3 years, 1 mg twice daily, increasing at two-weekly intervals to 2 mg 2–3 times daily.

benztropine

anticholinergic, anti-Parkinsonian

Cautionary advisory labels: 1, 9 (long-term regular therapy)

Notes

Changes to urinary system: May induce or aggravate overflow incontinence due to reduced detrusor activity, voiding difficulty, urinary retention or constipation.

Elderly: Confusion, psychoses, constipation, urinary retention, blurred vision, orthostatic hypotension leading to falls and fractures. Counsel about rising slowly and cautiously.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use with caution, especially in neonatal period. Limited data available. Risk of anticholinergic effects. May suppress lactation.

Common dosage range

Adult dose

Parkinson's disease: Initial dose, 0.5–1 mg daily; increase gradually up to 6 mg daily in divided doses.

Drug-induced extrapyramidal disorders: 1–4 mg once or twice daily.

Paediatric dose

Children >3 years

Drug-induced extrapyramidal disorders:
20–50 micrograms/kg once or twice daily; maximum 6 mg daily.

Acute dystonic reaction: IM/IV, 0.02 mg/kg/dose. May be repeated after 15 minutes.

benzylpenicillin (penicillin G)

beta-lactamase labile narrow-spectrum penicillin

Notes

- Confirm appropriate antibiotic and dose regimen.
- May cause diarrhoea.
- If a skin rash occurs, seek medical advice.
- Ask about any previous reaction to penicillin.

Renal impairment (severe): Caution. Dose adjustment may be necessary. Large doses (20 g) cause convulsions.

Pregnancy: A.

Breastfeeding: May be used. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

IV, 0.6–1.2 g every 4–6 hours depending on type and severity of infection. Maximum 18 g daily (e.g. endocarditis, meningitis); up to 24 g daily on specialist advice.

Paediatric dose

IM/IV, 30–60 mg/kg every 4–6 hours.

Dose equivalence

600 mg = 1 million units.

betamethasone

corticosteroid

Notes

Changes to Faeces: Pink, red, black faeces may indicate medicine-induced gastrointestinal bleeding.

Pregnancy: Topical: A; IM: C. Safe for topical use. Maternal blood glucose should be monitored for IM use.

Breastfeeding: Safe to use topically provided breast area is free of corticosteroid before breastfeeding. Use with caution systemically. Monitor infant if repeated doses are required.

Common dosage range

Adult dose

IM, 5.7–11.4 mg.

Paediatric dose

IM, <1 year: 1 mg; 1–5 years: 2 mg; 6–12 years: 4 mg. Monitor development and growth carefully in children on long-term therapy.

bimatoprost

ocular prostaglandin analogue for glaucoma

Cautionary advisory labels: 7b

Notes

- Administer eye drops in the evening for best effect.
- Separate from other drops by 5 minutes.
- Apply pressure to tear duct after dosing to minimise systemic absorption.
- Do not allow dropper to touch eye.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended as limited data available.

Common dosage range

Adult dose

1 drop daily (in the evening).

biperiden

anticholinergic, anti-Parkinsonian

Cautionary advisory labels: 1,9 (long-term regular therapy)

Notes

Changes to urinary system: May induce or aggravate overflow incontinence due to reduced detrusor activity, voiding difficulty, urinary retention or constipation.

Elderly: Orthostatic hypotension leading to falls and fractures, confusion, psychoses, constipation, blurred vision.

Pregnancy: B2. Use not recommended.

Breastfeeding: Not recommended as limited data available. May suppress lactation.

Common dosage range

Adult dose

Parkinson's disease: 1 mg twice daily, increasing to 1–4 mg 3–4 times daily.

Drug-induced extrapyramidal disorders: 1–2 mg 1–4 times daily.

Paediatric dose

Initial dose, 0.5–1 mg 1–3 times daily; increase gradually until optimal effect is reached; maximum 12 mg daily.

bisacodyl

stimulant laxative

Modification of oral formulation

Before crushing or otherwise altering enteric coated tablets, consider the increased risk of local gastrointestinal irritant effect.

Notes

- Discuss increased fibre, fluid intake and increased level of physical activity.
- Chronic management: may require combination treatment.
- Faecal impaction may present as faecal soiling or diarrhoea.
- Opioid-induced: use a stool softener or stimulant and hyperosmotic (see 'Prevention and treatment of opioid-induced constipation', Section D).

Pregnancy: A.

Breastfeeding: May be used. Avoid large doses due to risk of diarrhoea in infant.

Common dosage range

Adult dose

Oral, 5–15 mg at night.

Rectal, 10 mg once daily when required.

Paediatric dose

>3 years, oral 5–10 mg at night; rectal 5–10 mg once daily as required.

6 months to 3 years, rectal 5 mg once daily as required.

Bowel preparation: Refer to local protocol.

bisoprolol

beta-blocker for heart failure

Cautionary advisory labels: 9, 12, A (not chewed)

Notes

- Increase dose slowly.
- Take dose in the morning with food.
- Use in combination with ACE inhibitor and diuretic.
- If patient has history of asthma or other lung disease, seek medical advice before dispensing.
- Caution if patient suffers from diabetes (can mask hypoglycaemic attack), hyperlipidaemia, peripheral vascular disease, hyperthyroidism, uncontrolled heart failure, asthma, chronic obstructive pulmonary disease.

Renal and hepatic impairment: Caution. Monitor clinically. Start at low dose, careful titration of dose.

Pregnancy: C. Use not recommended in first trimester. If drug of choice, use with caution in second and third trimesters.

Breastfeeding: Consider alternatives first. Excretion in breast milk expected. If used, monitor for adverse effects (e.g. bradycardia, hypotension) in infant.

Common dosage range

Adult dose

Initially 1.25 mg daily, increasing dose slowly at four-week intervals. Maximum 10 mg daily.

bosentan

pulmonary vasodilator

Cautionary advisory labels: 1, 5, 16

Notes

Hepatic impairment (moderate–severe): If serum transaminase elevations are accompanied by increases in bilirubin greater than twice normal upper limit, cease treatment.

Pregnancy: X.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

Initially, 62.5 mg twice daily for four weeks. Maintenance dose 125 mg twice daily.

Paediatric dose

Children >3 years:

10–20 kg: 31.25 mg once daily for four weeks. Maintenance dose 31.25 mg twice daily.

20–40 kg: 31.25 mg twice daily for four weeks. Maintenance dose 62.5 mg twice daily.

brinzolamide

ocular carbonic anhydrase inhibitor for glaucoma

Cautionary advisory labels: 7b

Notes

- Shake well before use.
- Wait 5 minutes before administering other drops.
- Drops may cause discomfort on instillation.
- Apply pressure to tear duct after instillation to avoid systemic absorption.

Hepatic impairment (severe): Caution.

Renal impairment (severe): Contraindicated.

Pregnancy: B3. If drug of choice, use with caution.

Breastfeeding: Use with caution. Excretion in breast milk expected, but no safety data on drug in infants.

Common dosage range

Adult dose

1 drop twice daily.

bromazepam

benzodiazepine

Cautionary advisory labels: 1, 3b, 9

Notes

- Monitor patient for physical and psychological dependence and tolerance (check intervals between prescription refills).
- Regular use for more than 2–4 weeks may result in dependence and tolerance.
- Beware of sudden discontinuation of long-term treatment.
- Patient may experience a 'morning-after hangover effect'.
- Caution with respiratory disease or sleep apnoea reduced respiratory drive may cause hypoxaemia.

Changes to urinary system: May induce or aggravate functional incontinence due to sedation or impairment of mobility.

Elderly: Over-sedation, confusion, memory impairment, poor muscle coordination leading to falls and fractures.

Hepatic and renal impairment: Caution. Dosage adjustment may be necessary.

Pregnancy: C. Use should be avoided if possible, especially during first trimester. If bromazepam is required, use the lowest effedtive dose for the shortest duration.

Breastfeeding: Consider alternatives first. Should be avoided due to long half-life.

Common dosage range

Adult dose

6–60 mg daily in 2–3 divided doses.

bromocriptine

dopamine agonist

Cautionary advisory labels: 5, 12, 16, B

Notes

- Involved in many drug interactions via P450 cytochrome system (see Table D.1, Section D).

Elderly: Confusion, psychoses, orthostatic hypotension leading to falls and fractures. Counsel to rise slowly and cautiously.

Hepatic impairment: Caution. Dosage adjustment necessary.

Pregnancy: A.

Breastfeeding: Use not recommended. Suppresses lactation. Use requires strict monitoring for adverse effects (cardiovascular and gastrointestinal) in infant.

Common dosage range

Adult dose

Hyperprolactinaemia, inhibition of lactation: 2.5–7.5 mg daily in 2–3 doses.

Acromegaly: 1.25 mg daily, increased gradually to 10–30 mg daily.

Parkinson's disease: up to 40 mg daily in divided doses.

budesonide

inhaled corticosteroid, oral for Crohn's disease, nasal spray

Cautionary advisory labels: 9, A, F (oral capsules); 14 (oral inhalers/nebuliser solution)

Notes

Oral inhalation

- Discuss an asthma management plan.
- A preventive medication intended for continued and regular use. Not for use during acute attacks.
- Counsel a regular dosage schedule even if no symptoms are present.
- Check technique and compliance.
- Rinse mouth with water after use to decrease systemic absorption and minimise risk of oral thrush.
- Cover eyes during nebulisation because of possible leakage from a mask.
- If asthma is well controlled try a dose reduction of 25% every 3 months.
- Systemic effects may include bone density loss, glaucoma, cataract, skin thinning, impaired growth, adrenal suppression.
- Use after beta$_2$ agonist if being used concurrently.

Nasal spray

- Delayed response: 2–3 days.
- Clear nasal secretions prior to use.

Pregnancy: A—inhaled, nasal. B3—oral. Only inhaled and nasal corticosteroids safe to use. Alternatives to oral doses should be considered due to risk of infant hypo-adrenalism.

Breastfeeding: Inhaled and intranasal doses may be used. Oral use not recommended: limited data available.

Common dosage range

Adult dose

Turbuhaler, 400–800 micrograms daily in 2–4 doses. Severe cases may require up to 2,400 micrograms daily.

Respules, 0.5–1 mg twice daily.

Nasal Spray, 32–128 micrograms each nostril daily.

Crohn's disease: oral, 9 mg once daily in the morning.

Paediatric dose

Titrate to lowest effective dose. Monitor development and growth carefully in children on long-term therapy.

Turbuhaler, initially 200–400 micrograms daily in two divided doses. Up to 800 micrograms daily may be needed.

Respules, 0.25–1.0 mg twice a day.

Croup: 2 mg via nebuliser, may be repeated 12-hourly.

Nasal spray, not recommended in children under 6 years.

bumetanide

loop diuretic

Cautionary advisory labels: 16

Notes

- Time dose to suit lifestyle—usually in the morning to avoid diuresis interfering with sleep.
- Caution with use in gout, prostatic obstruction.
- Care with NSAIDs, lithium, thiazide diuretics, digoxin.
- Monitor electrolytes particularly for hypokalaemia and hyponatraemia.
- Caution if prior allergy to sulfonamides.

Changes to urinary system: May induce or aggravate urge incontinence due to polyuria, constipation or frequency.

Elderly: Impaired glucose tolerance, hyperuricaemia, orthostatic hypotension leading to falls and fractures. Counsel about rising slowly and cautiously.

Hepatic impairment (severe): Caution.

Renal impairment (mild): Caution. Dose adjustment may be necessary.

Renal impairment (severe): Contraindicated, when patient is suffering from anuria.

Pregnancy: C. Use not recommended.

Breastfeeding: Use not recommended: no data available. May suppress lactation.

Common dosage range

Adult dose

0.5–4 mg once or twice daily. Maximum 10 mg daily.

buprenorphine

opioid analgesic

Cautionary advisory labels: 1, 21 (patches)

Notes

- Constipation may be a problem with chronic use. Start treatment with stimulant or osmotic laxative (see 'Prevention and treatment of opioid-induced constipation', Section D).
- Ask about nausea or vomiting.
- May be used for opioid dependence (see 'Opioid substitution therapy', Section A).

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to inhibition of the voiding reflex, constipation, confusion, reduced detrusor activity or urinary retention.

Hepatic impairment (severe): Caution. Monitor clinically.

Pregnancy: C. Previously commenced therapy can be maintained as not associated with birth defects, however methadone substitution is treatment of choice for opioid dependence.

Breastfeeding: Use not recommended as limited data available. Known to be excreted in breast milk.

Common dosage range

Adult dose

Pain:

IM/IV, 0.3–0.6 mg every 6–8 hours.

Sublingual, 0.2–0.4 mg every 6–8 hours.

Patch, initially 5 micrograms/hr; titrate dose to effect by adding another patch or changing to a higher strength patch. Do not increase dose at intervals of <3 days; do not apply >2 patches concurrently; maximum dose 2 x 20 micrograms/hour patches. Each patch must be changed every 7 days.

bupropion

for nicotine dependence

Cautionary advisory labels: 5, 12†, 16†, A

Notes

- Involved in many drug interactions via P450 cytochrome system—antagonist (see Table D.1, Section D).
- Take for 7 days before cessation of smoking.
- Encourage smoking cessation program, behavioural interventions and counselling.
- Do not add or stop alcohol.
- May cause increased sweating.
- Contraindicated in epilepsy.

Hepatic impairment (severe): Caution. Dosage adjustment necessary. Do not exceed 150 mg on alternate days. Monitor clinically.

Renal impairment: Caution. Dosage adjustment necessary. Monitor clinically.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use not recommended. Excreted in breast milk and appears to accumulate. No safety data on drug in infants.

Common dosage range

Adult dose

150 mg daily for three days, increasing to 150 mg twice daily (at least 8 hours between successive doses). Treatment for at least 7 weeks.

buspirone

non-benzodiazepine anxiolytic

Cautionary advisory labels: 1, 18

Notes

- For possible medicine interactions (see Table D.1, Section D).
- Grapefruit juice may increase the risk of drug toxicity.

Hepatic impairment (mild–moderate): Caution. Dosage adjustment necessary.

Hepatic impairment (severe): Contraindicated.

Renal impairment: Caution. Dosage adjustment necessary; monitor clinically.

Pregnancy: B1. Use not recommended.

Breastfeeding: Use not recommended: limited data available. Excretion in breast milk expected.

Common dosage range

Adult dose

Initially 5 mg three times daily; increase by 5 mg every 2–3 days until optimal response achieved. Usual range 20–30 mg daily in 2–3 divided doses. Maximum daily dose 60 mg.

busulfan

cytotoxic alkylating agent

Modification of oral formulation

Avoid crushing or altering tablet due to occupational health and safety risks.

Cautionary advisory labels: 21

Pregnancy: D. Use not recommended.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

Chronic myeloid leukaemia

Induction of remission: oral, 60 micrograms/kg (maximum 4 mg) daily.

Maintenance: 0.5–2 mg daily.

Polycythaemia vera, essential thrombocythaemia

Induction of remission: 4–6 mg daily.

Myelofibrosis

Initially 2–4 mg daily.

† Most appropriate during initial treatment or when dosage is increased.

cabergoline

ergoline derivative with dopamine D_2 receptor agonism

Cautionary advisory labels: 12†, B

Notes

- Somnolence and sudden sleep onset episodes have been reported.
- Avoid concomitant administration with other ergot alkaloids and with agents with dopamine antagonist activity, e.g. phenothiazines, metoclopramide.
- Cardiovascular examination should be conducted prior to initiation of therapy.
- Monitor patients for shortness of breath, cough, dyspnoea.

Pregnancy: B1.

Breastfeeding: Use not recommended as no data available.

Common dosage range

Adult dose

0.5–1 mg daily, increasing over several weeks to 2–3 mg daily.

caffeine

central nervous system stimulant

Notes

- For possible medicine interactions see Table D.1, Section D.
- Use no less than 6 hours before intending to sleep.

Changes to urinary system: May induce or aggravate urge incontinence due to enhanced detrusor activity (instability) and frequency urgency.

Hepatic impairment (severe): Caution. Monitor clinically.

Pregnancy: A. May be used as not associated with birth defects, however >300 mg daily associated with spontaneous abortions.

Breastfeeding: Small amounts excreted in breast milk. Occasional, small doses may be used. Avoid large or frequent doses. Monitor for adverse effects (e.g. insomnia, irritability) in infant.

Common dosage range

Adult dose

Central nervous system stimulant: 100 mg up to three-hourly; maximum 600 mg daily.

Headache (in combination with ergotamine):

Tablets, (100 mg caffeine) two as a single dose, then up to six per day or 10 per week.

Suppository, (100 mg caffeine) one as a single dose, up to 3 daily or 5 per week.

Paediatric dose

Neonatal apnoea: IV/oral loading dose, 20 mg/kg caffeine citrate (equivalent to 10 mg/kg caffeine base).

Maintenance, 5 mg/kg caffeine citrate once daily.

Note: the IV formulation contains caffeine citrate and the oral formulation uses caffeine base.

calcitriol

active form of vitamin D, 1,25-dihydroxycholecalciferol

Cautionary advisory labels: 5

Notes

- Report any symptoms of hypercalcaemia—such as weakness, nausea, vomiting, thirst, constipation, headache, apathy or polyuria.
- High risk of hypercalcaemia if used with calcium supplements. Monitor calcium concentration.

Renal impairment: Caution. Dosage adjustment necessary. Monitor clinically.

Pregnancy: B3. Use not recommended in first trimester. If drug of choice, use with caution in second and third trimesters.

Breastfeeding: Use with caution. Excretion in breast milk expected. Monitor closely for hypercalcaemia in infant.

Common dosage range

Adult dose

Osteoporosis: initial dose 0.25 microgram twice daily.

Hypoparathyroidism: 0.5–1 microgram daily.

Other indications: See approved Product Information.

Paediatric dose

Initial dose (infants), 0.02 microgram/kg up to 0.25 microgram once daily.

Child 1–5 years, 0.25–0.75 microgram daily.

Monitor calcium levels.

† Most appropriate during initial treatment or when dosage is increased.

calcium carbonate

antacid, calcium supplement

Notes

- Calcium supplement best taken at bedtime to maximise absorption into bones.
- Tablets are large. If swallowing is a problem, recommend chewable or effervescent dosage form.
- Encourage sufficient dietary intake of calcium.
- Calcium may interfere with the absorption of some medications. Advise if necessary to separate dose administration.
- Symptoms of hypercalcaemia unlikely, but if symptoms (such as nausea, vomiting, constipation, headache, polyuria, thirst or apathy) occur, seek medical advice.
- May cause constipation.

Renal impairment: Caution.

Pregnancy: A.

Breastfeeding: May be used at recommended daily doses. Significant amounts secreted. Monitor for hypercalcaemia in infant when high doses used.

Common dosage range

Adult dose

Oral, 600–1,200 mg daily. 1,500 mg calcium carbonate is equivalent to 600 mg elemental calcium.

Paediatric dose

Hypocalcaemia (doses expressed as elemental calcium): neonates, 50 mg per dose 4–6 times/day; 1 month to 4 years, 100 mg per dose 2–5 times/day; 4–12 years, 500–1,000 mg daily.

calcium folinate

chemoprotectant, fluorouracil modulator

Cautionary advisory labels: 3b

Pregnancy: A.

Breastfeeding: Use with caution. Excreted in breast milk. Acute use considered safe.

Common dosage range

Adult dose

Anaemia: Oral, 5–15 mg daily.

Other indications: See approved Product Information.

calcium salts

electrolyte

Notes

- High doses (3.5 g three times daily) are used in dialysis treatment as a phosphate binder.
- Monitor calcium concentration in renal impairment or when used with calcitriol.
- Severe hypercalcaemia may manifest as dementia.

Renal impairment: Caution. Monitor for signs of hypercalcaemia.

Pregnancy: Safe to use.

Breastfeeding: May be used at recommended daily doses. Significant amounts secreted. Monitor for hypercalcaemia in infant when high doses used.

Common dosage range

Adult dose

Hypocalcaemia: 3.5–7 mmol elemental calcium every 1–3 days according to response.

Other indications: See approved Product Information.

Paediatric dose

Hypocalcaemia: 0.5–3.5 mmol/kg elemental calcium every 1–3 days until response. Monitor calcium levels.

IV injections must be given slowly or as an IV infusion.

1 mmol Ca^{++} = 40 mg elemental calcium.

candesartan

angiotensin II receptor antagonist

Cautionary advisory labels: 11, 12†, 16†

Notes

- Monitor renal function and potassium concentration.
- Caution if the patient is taking NSAIDs (including COX-2 inhibitors) or lithium.
- Provide advice on avoiding foods and drugs with high potassium content.
- Blood pressure should be closely monitored during initiation of therapy.
- Can cause cough (which may also be a symptom of heart failure). Establish whether cough is productive or unproductive.
- If persistent dry cough or swelling of face, lips or tongue is experienced, seek medical advice.
- A combination product of candesartan with a diuretic is available. Check that patient knows which product is being taken.

† Most appropriate during initial treatment or when dosage is increased.

Hepatic impairment (severe): Caution.

Renal impairment (severe): Caution. Monitor Clinically. Dose adjustment may be necessary.

Cl_{cr} <30 mL/minute, use a starting dose of 4 mg once daily.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as possible if pregnancy is suspected.

Breastfeeding: Use not recommended. Excretion in breast milk expected.

Common dosage range

Adult Dose

Hypertension: initially 8–16 mg daily, maximum 32 mg daily.

Heart failure: initially 4 mg daily; double the dose at two-weekly intervals to the highest tolerated dose (maximum 32 mg daily).

captopril

angiotensin-converting enzyme inhibitor

Cautionary advisory labels: 3b (when dose is less than 50 mg), 7a (solution), 11, 12, 16†

Notes

- Captopril solution should be mixed with a suitable drink (such as water, fruit juice, tea or coffee) and drunk immediately after mixing.
- Monitor renal function and potassium concentration.
- Caution if the patient is taking NSAIDs (including COX-2 inhibitors) or lithium.
- Provide advice on avoiding foods and drugs with high potassium content.
- Blood pressure should be closely monitored during initiation of therapy.
- Can cause cough (which may also be a symptom of heart failure). Establish whether cough is productive or unproductive.
- If persistent dry cough or swelling of face, lips or tongue is experienced, seek medical advice.
- May cause metallic taste or lack of taste.

Changes to urinary system: May induce or aggravate stress incontinence due to cough-induced sphincter weakness.

Elderly: Orthostatic hypotension may occur when rising quickly. Advise rising slowly from seated or lying positions.

Hepatic impairment (severe): Caution.

Renal impairment (severe): Caution. Monitor clinically. Start at low dose, with careful titration of dose.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as possible if pregnancy is suspected.

Breastfeeding: May be used. Very small amounts excreted in breast milk. Monitor for adverse effects (e.g. hypotension, bradycardia) in infants.

Common dosage range

Adult dose

Hypertension: initially 6.25–12.5 mg twice daily, increasing at intervals of 2–4 weeks to 25–50 mg twice daily.

Heart failure: initially 6.25 mg three times daily, increasing at 2-week intervals to 25–75 mg twice daily. Maximum 150 mg daily.

Other indications: See approved Product Information.

Paediatric dose

Initially, 0.1–0.25 mg/kg/dose every eight hours, increasing to a maximum of 2 mg/kg/dose.

carbamazepine

antiepileptic

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets will alter absorption characteristics.

Cautionary advisory labels: 5, 9, 12†, 13, 18, A*, B

Notes

- To avoid throat irritation, do not lie down for 15–30 minutes after taking.
- Carbamazepine is a drug of low therapeutic index and is involved in significant drug interactions (see Table D.1, Section D).
- May reduce tolerance of alcohol.
- Controlled-release tablets may be halved but not crushed.
- Cross-sensitivity to oxcarbazepine is high: avoid use in patients allergic to oxcarbazepine.
- Monitor LFTs; cease therapy if hepatic function deteriorates.

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Elderly: Hyponatraemia (SIADH) may occur.

Hepatic impairment (severe): Caution. Monitor clinically.

Renal impairment (severe): Caution. Monitor clinically.

Therapeutic monitoring: Therapeutic range: 6–12 mg/L (20–40 micromol/L). Time to steady state: 7–10 days.

Toxicity: Sedation, ataxia. Induces its own metabolism.

Pregnancy: D. Consider risk of congenital malformation against dangers of uncontrolled epilepsy. Consider folic acid (5 mg) and vitamin K supplementation.

Breastfeeding: May be used. Small amounts are excreted in breast milk. Monitor for adverse effects (e.g. drowsiness, poor sucking, allergic skin reaction, jaundice) in infant. Consider periodic infant serum level monitoring.

Common dosage range

Adult dose

Epilepsy: initially 100 mg twice daily; increase gradually until optimum response achieved, generally at 400 mg two or three times daily. Up to 2 g daily may be required.

Other indications: See approved Product Information.

Paediatric dose

Epilepsy: initially 5–8 mg/kg daily; increase gradually to 10–20 mg/kg daily in 2–3 doses. Maximum 30 mg/kg daily.

carvedilol

beta-blocker with alpha-blocker effect

Cautionary advisory labels: 9, 12†, 13, 16

Notes

- Protect tablets from light and humidity: may discolour.
- Caution if patient suffers from diabetes (can mask hypoglycaemic attack), hyperlipidaemia, peripheral vascular disease, hyperthyroidism, unstable heart failure, asthma, chronic obstructive pulmonary disease.
- In heart failure, should be used only in combination with ACE inhibitors and/or diuretics.

Hepatic impairment (severe): Contraindicated.

Renal impairment (severe): Caution. Monitor clinically. Dose adjustment may be necessary.

Pregnancy: C. Use not recommended in first trimester. If drug of choice, use with caution in second and third trimesters.

Breastfeeding: Consider alternatives first (e.g. labetolol, metoprolol). Use with caution. Excretion in breast milk expected.

Common dosage range

Adult dose

Hypertension: 12.5 mg/day for two days, then 25 mg daily; may increase at intervals ≥2 weeks to maximum 50 mg daily.

Heart failure: initially 3.125 mg twice daily for 2 weeks; increase at intervals of at least 2 weeks to 25–50 mg twice daily.

cefaclor

moderate-spectrum cephalosporin

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets will alter absorption characteristics.

Cautionary advisory labels: A*, D

Suspension – 6, 7a, D

Notes

- Confirm appropriate antibiotic and dose regimen.
- Inquire about severe or immediate allergic reaction to a penicillin (including urticaria, anaphylaxis and interstitial nephritis).
- Space doses as evenly as possible during waking hours.
- If a skin rash occurs, seek medical advice.
- Common adverse effects—nausea, diarrhoea, gastric upset.

Hepatic impairment (severe): Caution. Limited data available.

Renal impairment (severe): Caution. Monitor clinically.

Pregnancy: B1. Should be used only if it is the drug of first choice.

Breastfeeding: May be used. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Common dosage range

Adult Dose

250–500 mg every eight hours or 375–750 mg every 12 hours (controlled-release tablet). Maximum 2 g daily.

Paediatric dose

10–15 mg/kg every eight hours or 20 mg/kg (maximum 1 g/dose) every 12 hours.

cefepime

broad-spectrum antipseudomonal cephalosporin

Notes

Renal impairment: Caution. Dose adjustment necessary. Refer to approved Product Information.

Pregnancy: B1. Should be used only if it is the drug of first choice.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

IM/IV, 1 g every 12 hours.

Severe infections: IV, 2 g every 8–12 hours. Maximum 6 g daily.

Paediatric dose

>2 months, IM/IV, 50 mg/kg every 12 hours; more severe infections, every eight hours.

cefotaxime

broad-spectrum cephalosporin

Notes

Hepatic impairment (severe): Caution. Monitor clinically.

Renal impairment: Caution. Transient rises in creatinine and urea have been reported. Dose adjustment necessary.

Pregnancy: B1. Should be used only if it is the drug of first choice.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

Moderately severe infections: IM/IV, 1 g every 8–12 hours.

Severe infections: IV, 2 g every 8–12 hours.

Maximum daily dose 12 g.

Specific indications: see approved Product Information.

Paediatric dose

IM/IV, 100–150 mg/kg daily in 2–4 divided doses. *Meningitis:* 50 mg/kg every 6 hours.

cefoxitin

moderate-spectrum anti-anaerobic cephalosporin

Notes

Renal impairment: Caution. Dose adjustment necessary.

Cl_{cr} 10–29 mL/min 1–2 g every 12–24 hours.

Cl_{cr} <10 mL/min 0.5–1 g every 12–24 hours.

IM injection painful: not generally recommended.

Pregnancy: B1. Should be used only if it is the drug of first choice.

Breastfeeding: May be used. Trace amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

IV/IM, 1–2 g eight-hourly. Maximum 12 g daily.

Severe infections: IV, 2–3 g every 6–8 hours or 2 g every four hours.

Paediatric dose

Mild to moderate infections: IV, 20–40 mg/kg every eight hours.

Severe infections: IV, 40 mg/kg every six hours.

ceftazidime

broad-spectrum antipseudomonal cephalosporin

Notes

Hepatic impairment (severe): Caution. Monitor clinically, and LFTs.

Renal impairment: Caution. Dose adjustment necessary.

Cl_{cr} 16–30 mL/min 1 g every 24 hours.

Cl_{cr} 6–15 mL/min 500 mg every 24 hours.

Cl_{cr} <5 mL/min 500 mg every 48 hours.

Note: contains sodium carbonate 118 mg/g.

IM injection painful; not generally recommended.

Pregnancy: B1. Should be used only if it is the drug of first choice.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

IM/IV, 1–2 g every 8–12 hours. Maximum dose 6 g daily.

Paediatric dose

>1 year: IM/IV, 25–100 mg/kg/day in 2–3 divided doses; maximum 6 g daily.

<1 year: 25–100 mg/kg/day in two divided doses.

ceftriaxone

broad-spectrum cephalosporin

Notes

Hepatic impairment (severe): Caution. Monitor clinically and plasma drug levels.

Renal impairment: Caution. Monitor clinically. Plasma levels should not exceed 280 micrograms/mL. Dose reduction may be necessary. See approved Product Information.

Pregnancy: B1. Should be used only if it is the drug of first choice.

Breastfeeding: May be used. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

IM/IV, 1–2 g once daily (or in 2 divided doses). Maximum 4 g daily.

Prophylaxis for Neisseria meningitidis contacts: IM, 250 mg as a single dose.

Specific indications: see approved Product Information.

Paediatric dose

IM/IV, 50 mg/kg once daily; maximum 2 g daily.

Meningitis: IM/IV, 100 mg/kg daily or in 2 divided doses. Maximum 4 g daily.

Prophylaxis for Haemophilus influenzae type B meningitis contacts: IM, 50 mg/kg daily (up to 1 g) for two days.

Prophylaxis for Neisseria meningitidis contacts: IM, 125 mg as a single dose.

cefuroxime

moderate-spectrum antihaemophilus cephalosporin

Cautionary advisory labels: B, D (oral)

Notes

- Confirm appropriate antibiotic and dose regimen.
- inquire about a severe or immediate allergic reaction to penicillin (including urticaria, anaphylaxis or interstitial nephritis).
- Space doses as evenly as possible during waking hours.
- If a skin rash occurs, seek medical advice.
- Adverse effects—nausea, diarrhoea, gastric upset.

Renal impairment: Caution. Dose adjustment necessary.

Cl_{cr} 10–20mL/min 750 mg every 12 hours.

Cl_{cr} <10 mL/min 750mg every 24 hours.

Pregnancy: B1. Should be used only if it is the drug of first choice.

Breastfeeding: May be used. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

250–500 mg twice daily.

Gonococcal infection: 1 g single dose.

celecoxib

selective NSAID (COX-2 inhibitor)

Cautionary advisory labels: 10a, 12†

Notes

- Use with caution in patients with a history of ischaemic heart disease, peripheral vascular disease and/or cerebrovascular disease.
- Maximum response should be seen in 1–3 weeks.
- Alert patient to signs of gastrointestinal bleeding, (black stools or dark coffee-coloured vomit).
- Caution if taking warfarin or other anticoagulants.
- To lessen gastrointestinal complications, use lowest effective dose and take paracetamol as an alternative analgesic.
- Check use of over-the-counter NSAIDs.
- Caution in the presence of diabetes, asthma or a peptic ulcer, hypertension or heart failure.
- Clarify the indication for treatment.
- Avoid in patients with sulfonamide allergy.
- Consider stopping 2–3 days before planned surgery; seek medical advice.

Changes to faeces: Pink, red, black discolouration may indicate medicine-induced gastrointestinal bleeding.

Elderly: Gastric ulceration, renal dysfunction, dizziness, confusion, sodium and water retention, exacerbation of hypertension, heart failure.

Hepatic impairment (moderate): Dosage adjustment necessary. Give 50% of usual dose.

Hepatic impairment (severe): Contraindicated.

† Most appropriate during initial treatment or when dosage is increased.

Renal impairment (moderate): Caution.

Renal impairment (severe): Contraindicated.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: limited data available. Excretion in breast milk expected.

Common dosage range

Adult dose

Osteoarthritis: 200 mg daily in 1–2 divided doses.

Rheumatoid arthritis: 100 mg twice daily. May be increased to 200 mg twice daily (short term).

cephalexin

moderate-spectrum cephalosporin

Cautionary advisory labels: D and for suspension also 6, 7a

Notes

- Confirm appropriate antibiotic and dose regimen.
- Inquire about severe or immediate, allergic reaction to penicillin (including urticaria, anaphylaxis or interstitial nephritis).
- Space doses as evenly as possible during waking hours.
- If a skin rash occurs, seek medical advice.
- Common adverse effects—nausea, diarrhoea, gastric upset.

Renal impairment: Monitor clinically. Dose adjustment may be necessary. Give usual loading dose. Maintenance dose reduction.

Cl_{cr} 11–40 mL/min 500 mg every 8–12 hours.

Cl_{cr} 5–10 mL/min 250 mg every 12 hours.

Cl_{cr} <5 mL/min 250 mg every 12–24 hours.

Pregnancy: A.

Breastfeeding: May be used. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

250 mg–1,000 mg every 6, 8 or 12 hours. Maximum daily dose 4 g.

Prophylaxis for urinary tract infection: 250 mg at night.

Paediatric dose

Moderate infections: 25–50 mg/kg daily in four divided doses.

Severe infections: 50–100 mg/kg daily in four divided doses.

Maximum daily dose 4 g.

Prophylaxis for urinary tract infection: 12.5 mg/kg (maximum 250 mg) at night.

cephalothin

moderate-spectrum cephalosporin

Notes

Renal Impairment: Caution. Monitor clinically. Give usual loading dose. Maintenance dose reduction:

Cl_{cr} 25–50 mL/min 1.5 g every 6 hours.

Cl_{cr} 10–25 mL/min 1.0 g every 6 hours.

Cl_{cr} 2–10 mL/min 500 mg every 6 hours.

Note: formulated with sodium bicarbonate; total sodium content approximately 63 mg (sodium ion 2.8 mEq) per gram.

IM injection painful: not generally recommended.

Pregnancy: A.

Breastfeeding: May be used. Trace amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

IV, 0.5–1 g every 4–6 hours.

Severe infections: 2 g four-hourly. Maximum 12 g daily.

Paediatric dose

<2 kg bodyweight, 20 mg/kg twelve hourly;
≥2 kg body weight, 80–160 mg/kg/day in divided doses.

cephazolin

moderate-spectrum cephalosporin

Notes

Renal impairment: Caution. Monitor clinically. Dosage adjustment necessary. Give 500 mg loading dose. Maintenance dose reduction—see approved Product Information.

IM injection painful: not generally recommended.

Pregnancy: B1. May be used.

Breastfeeding: May be used. Trace amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

IV, 250–500 mg every eight hours; or 0.5–1 g every 12 hours, or every 6–8 hours; usual maximum is 6 g daily, although up to 12 g daily has been used.

Paediatric dose

IV, mild to moderate infections: 25–50 mg/kg daily in 3–4 divided doses; severe infections: 100 mg/kg daily in 3–4 divided doses.

cetirizine

less-sedating antihistamine

Cautionary advisory labels: 1, 13

Notes

- Take once a day at the same time each day.

Renal impairment: Caution. Dosage adjustment necessary. Use half the usual recommended dose.

Cl_{cr} 11–31 mL/min 5 mg daily.

Pregnancy: B2. Use not recommended. Consider use of sedating antihistamines first. If less-sedating antihistamine required, loratadine is preferred.

Breastfeeding: Use not recommended: limited data available. Excreted in breast milk. Loratadine or short-acting sedating antihistamines preferred.

Common dosage range

Adult dose

Initially, 10 mg once daily; maximum 20 mg once daily.

Paediatric dose

1–2 years: 0.25 mg/kg twice daily.

2–6 years: 2.5–5 mg twice daily.

6–12 years: 5 mg twice daily.

charcoal, activated

gastrointestinal decontaminant

Notes

Changes to faeces: Black colouration.

Pregnancy: Safe to use as not absorbed from gastrointestinal tract. Consider risk of toxic substance to mother/fetus if detoxification is not carried out.

Breastfeeding: May be used. Not absorbed from gastrointestinal tract so no excretion in breast milk.

Common dosage range

Adult and paediatric dose

1 gram/kg body weight as a single dose, up to a maximum of 50 grams.

Consult a Poisons Information Centre (phone 13 11 26) for more detailed information.

chloral hydrate

hypnotic

Cautionary advisory labels: 1a, 2, 12

Notes

- To reduce gastrointestinal effects, dilute dose with water or juice.
- Treatment should not be for longer than 2 weeks as tolerance and dependence may occur.
- Tachycardia, palpitations, facial flushing and dysphoria may occur after ingesting alcohol while taking chloral hydrate.

Renal and hepatic impairment (severe): Caution. Dose may need to be reduced.

Pregnancy: A. Should be used only when clinically indicated as it crosses the placenta, e.g. sedation during diagnostic procedures.

Breastfeeding: Use not recommended as excreted in breast milk. May cause sedation in infant.

Common dosage range

Adult dose

Hypnotic or premedication: 0.5–1 g 15–30 minutes before bedtime or 30 minutes before surgery.

Maximum 2 g daily.

Paediatric dose

Hypnotic or premedication: 25–50 mg/kg 15–30 minutes before bedtime or 30 minutes before surgery.

Maximum dose 1 g.

chlorambucil

cytotoxic alkylating agent

Modification of oral formulation

Avoid crushing or altering tablet due to occupational health and safety risks.

Cautionary advisory labels: 6, 12†, 21

Notes

- Take at the same time each day.
- Avoid crowds and people with infections.
- Report signs of infection or unusual bleeding.
- Nausea and vomiting may occur.

Hepatic impairment (severe): Dose reduction necessary.

Renal impairment: Caution. Monitor clinically for signs of additional myelosuppression.

Pregnancy: D.

† Most appropriate during initial treatment or when dosage is increased.

Breastfeeding: Use not recommended. Potential for serious adverse effects in infant.

Common dosage range

Adult and Paediatric dose

0.1–0.2 mg/kg daily (consult specialist protocols).

chloramphenicol

broad-spectrum antibacterial

Cautionary advisory labels: 7b

Notes

- Confirm appropriate antibiotic and dose regimen.
- Use only for severe infections and where no other safer antibiotic is suitable.
- Space doses as evenly as possible during waking hours.
- If a skin rash occurs, seek medical advice.
- Common adverse effects—nausea, diarrhoea, gastric upset, reversible bone marrow suppression.
- Plasma chloramphenicol concentrations should be monitored to avoid toxicity.

Changes to Faeces: Blue, black discolouration.

Renal and hepatic impairment (severe): Caution. Dose adjustment may be necessary. Monitor plasma levels of drug.

Therapeutic monitoring: Therapeutic range: trough <10 mg/L (<31 micromol/L); peak <25 mg/L (<78 micromol/L).

Pregnancy: A. Topical therapy is safe to use. IV and oral therapy should be used only if it is the drug of first choice.

Breastfeeding: Topical therapy may be used. Systemic therapy is not recommended. Small amounts excreted in breast milk. Potential for serious toxicity in infant.

Common dosage range

Adult dose

12.5–25 mg/kg every six hours. Maximum 4 g daily.

Paediatric dose

12.5 mg/kg every 6–8 hours.

chloroquine

antimalarial

Cautionary advisory labels: 13, B

Notes

- For malaria prophylaxis, take regularly, at the same time and on the same day each week. Start one week before entering and continue for four weeks after leaving an endemic area.
- Provide counselling regarding protective clothing and the use of repellents for malaria prophylaxis.
- Visual disturbances should be reported immediately. Regular eye checks recommended for long-term use.
- See doctor if a fever develops.
- 155 mg chloroquine base is equivalent to 250 mg chloroquine phosphate.

Changes to urinary system: Rust yellow, brown discolouration of urine.

Renal and hepatic impairment (severe): Caution. Dose may need to be reduced. Monitor clinically.

Pregnancy: D. May be used for prophylaxis if it is the drug of first choice and travel to areas of risk cannot be postponed. For treatment, seek advice from an infectious diseases specialist.

Breastfeeding: May be used. Small amounts excreted in breast milk, although unlikely to cause harm nor confer any benefit.

Common dosage range

Adult dose

Malaria prophylaxis: two tablets (310 mg base) once weekly.

Malaria treatment: four tablets (620 mg base) as a single dose, then two tablets (310 mg) 8 hours later and 310 mg on days 2 and 3; then 310 mg once a week for four weeks.

Rheumatoid arthritis: one tablet (155 mg) once or twice daily.

Paediatric dose

Malaria prophylaxis: 1–4 years, half a tablet (77.5 mg) once weekly; 4–8 years, one tablet (155 mg) once weekly; >8 years, two tablets (310 mg) once weekly.

Malaria treatment: 10 mg/kg (maximum 620 mg) as a single dose, then 5 mg/kg (maximum 310 mg) six hours later, then 5 mg/kg (maximum 310 mg) on days 2 and 3.

chlorpheniramine

sedating antihistamine

Cautionary advisory labels: 1, 13

Notes

Elderly: Increased risk of confusion, dizziness, hypotension and sedation.

Pregnancy: A.

Breastfeeding: May be used.

Common dosage range

Adult dose

4 mg every 4–8 hours; maximum 24 mg daily.

Paediatric dose

2–5 years, 1 mg every 4–8 hours (maximum 6 mg daily); 6–12 years, 2 mg every 4–8 hours (maximum 12 mg daily); ≥12 years, adult dose.

chlorpromazine

conventional antipsychotic

Modification of oral formulation

Before crushing or altering tablet, consider occupational health and safety risks. Chlorpromazine may cause contact dermatitis.

Cautionary advisory labels: 1, 8, 9 (long-term regular therapy), 16

Notes

- Extrapyramidal and anticholinergic adverse effects are common—e.g. dry mouth, constipation, blurred vision, difficulty in passing urine. Advise accordingly.
- Avoid concurrent use of more than one antipsychotic.
- Withdraw antipsychotics slowly if stopping the medication.
- Orthostatic hypotension may occur, especially after parenteral administration.

Changes to urinary system: Pink, red, red–brown urine discolouration. May induce or aggravate overflow/functional incontinence due to anticholinergic urinary retention, voiding difficulty or impaired mobility.

Elderly: Confusion, sedation, orthostatic hypotension leading to falls and fractures. Counsel about rising slowly after sitting or lying down.

Hepatic impairment: Caution. Dosage adjustment necessary.

Renal impairment: Caution.

Pregnancy: C. Use only if drug of choice. Use minimal effective dose.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. sedation) in infant.

Common dosage range

Adult dose

Chronic psychoses: 25–100 mg 3–4 times daily; maximum 1,000 mg daily.

Acute psychoses, severe behaviour disturbance: 50–100 mg up to every two hours as needed, up to 500 mg daily.

Agitation, anxiety, disturbed behaviour: 25–50 mg up to three times daily.

Paediatric dose

Oral, 0.5–1 mg/kg every 4–6 hours.

IV/IM, 0.25–1mg/kg every 6–8 hours.

Maximum (all routes): <5 years, 40 mg daily; ≥5 years, 75 mg daily.

chlorthalidone

diuretic

Cautionary advisory labels: 16, B

Notes

- Monitor electrolytes particularly for hypokalaemia, hyponatraemia and hypomagnesaemia.
- Caution if patient suffers from diabetes, gout or dyslipidaemia (metabolic disturbances mainly associated with high dose).
- Caution with sulphonamide allergy.

Changes to urinary system: May induce or aggravate urge incontinence, associated with polyuria, constipation, urinary frequency.

Elderly: Orthostatic hypotension leading to fractures and falls. Counsel about rising slowly after sitting or lying down.

Hepatic impairment (severe): Caution. Monitor clinically.

Renal impairment: Caution. Use loop diuretic if Cl_{cr} <30 mL/min.

Contraindicated if Cl_{cr} <10 mL/min.

Pregnancy: C. Use not recommended.

Breastfeeding: Use not recommended. Excreted in breast milk and may accumulate. May suppress lactation.

Common dosage range

Adult dose

Hypertension: 12.5–50 mg daily.

Stable chronic heart failure: 25–50 mg daily or 100 mg every alternate day.

Paediatric dose

Up to 2 mg/kg on alternate days.

cimetidine

H_2 antagonist

Cautionary advisory labels: 5

Notes

- Query long-term use without investigation.
- If nausea, severe vomiting, epigastric pain, black or blood-stained stools are experienced during or after treatment, seek medical advice.

- Caution: cimetidine is involved in many drug interactions via P450 cytochrome system—consider alternative H_2 antagonist (see Table D.1, Section D).
- Confusion is more common in patients with renal impairment.
- Avoid rapid injection; may cause hypotension and cardiac arrhythmias.

Elderly: Confusion.

Renal impairment: Caution. Dosage reduction necessary.

Cl_{cr} 30–50 mL/min 200 mg four times daily.

Cl_{cr} 15–30 mL/min 200 mg three times daily.

Cl_{cr} <15 mL/min 200 mg twice daily.

Pregnancy: B1. May be used when conservative treatment with antacids has failed. If an H_2 antagonist is required, ranitidine and famotidine are preferred.

Breastfeeding: May be used short term. Excreted into breast milk and may accumulate. If an H_2 antagonist is required, famotidine is preferred.

Common dosage range

Adult dose

400–800 mg daily in single or divided doses.

Specific indications: see approved Product Information.

Paediatric dose

20–40 mg/kg daily in 3–4 divided doses.

ciprofloxacin

quinolone antibacterial

Cautionary advisory labels: 3b, 4, 8, 12, D

Notes

- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible during waking hours.
- Maintain adequate fluid intake (1.5–2 L/day).
- Common adverse effects—nausea, diarrhoea, gastric upset.
- Caffeine effects may be enhanced.
- Controversy remains over the possibility of quinolones causing arthropathy in children. Caution with use in prepubertal children.
- Report Achilles tendon tenderness immediately to doctor.

Renal impairment: Caution. Dosage adjustment necessary.

Cl_{cr} 30–50 mL/min 250–500 mg 12 hourly.

Cl_{cr} 5–29 mL/min 250–500 mg every 18 hours.

Hepatic impairment: Caution. Monitor clinically.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended. Varying amounts excreted in breast milk.

Common dosage range

Adult dose

Uncomplicated urinary tract infection: 250 mg 12-hourly.

Complicated urinary tract infection: 500 mg 12-hourly.

Respiratory, skin, gastrointestinal and more complicated infections: 500–750 mg 12-hourly (see approved Product Information for specific indications).

IV, 200–400 mg 12-hourly infused over 30–60 minutes.

Paediatric dose

5–10 mg/kg 12-hourly.

Cystic fibrosis: 15 mg/kg (max 750 mg) 12-hourly.

citalopram

selective serotonin reuptake inhibitor

Cautionary advisory labels: 5, 9, 12

Notes

- Medicine-free interval may be required when switching to/from other antidepressants. See NPS switching chart at: www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- May increase the anticoagulant response to warfarin. Monitor INR.
- Indications other than depression include obsessive compulsive disorder, anxiety, panic and eating disorders.
- SSRIs inhibit the cytochrome P450 enzymes—citalopram, escitalopram and sertraline the least. See Table D.1, Section D.
- Usually given as a morning dose due to activating effects, although occasionally may cause somnolence and can be taken at night.
- Full benefit may not be seen for several weeks but adverse effects may occur from start of treatment.
- The efficacy and safety of citalopram for the treatment of major depressive disorder has not been established in individuals aged less than 18 years.

Changes to urinary system: May induce or aggravate urge/functional incontinence due to enhanced detrusor activity (instability), sedation or impaired mobility.

Elderly: Hyponatraemia (SIADH) may occur.

Hepatic impairment: Caution. Start at low dose and carefully titrate dose. Start with 20 mg daily. In non-responders titrate carefully to maximum 40 mg daily.

Renal impairment (severe): Caution.

Pregnancy: C. Use when clinically indicated if it is the drug of choice. There is increased risk of reversible withdrawal symptoms, not congenital malformations.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. sedation, restlessness, irritability, poor feeding) in infant.

Dosage range

Adult dose

20–60 mg daily.

clarithromycin

macrolide antibacterial

Cautionary advisory labels: 5, D

Notes

- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible during waking hours.
- Common adverse effects—nausea, diarrhoea, gastric upset.
- Maintain adequate fluid intake (1.5–2 L/day).
- Suspension should not be refrigerated and expires after 14 days.

Hepatic impairment (severe): Caution. Dosage adjustment necessary.

Renal impairment (severe): Caution. Dosage adjustment necessary.

Cl_{cr} <30 mL/min use 50% of usual dose.

Pregnancy: B3. Use only when no alternative macrolide can be used.

Breastfeeding: Use with caution. Excreted, and may concentrate, in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

250–500 mg twice daily.

Paediatric dose

7.5 mg/kg (maximum 500 mg) twice daily.
Mycobacterium infections: 7.5–15 mg/kg twice daily.

clindamycin

lincosamide antibacterial

Cautionary advisory labels: D

Notes

- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible during waking hours.
- Report episodes of prolonged diarrhoea to doctor.
- Common adverse effects—nausea, gastric upset, rash.
- Maintain adequate fluid intake (1.5–2 L/day).
- IV doses should be given by infusion over 20–60 minutes.

Changes to faeces: Black discolouration.

Hepatic impairment (severe): Caution. Dose reduction necessary. Monitor plasma drug levels.

Renal impairment (severe): Caution. Dose reduction necessary. Monitor plasma drug levels.

Pregnancy: A. For vaginal administration, only category A when fetal membranes still intact.

Breastfeeding: May be used vaginally. Use with caution when administered systemically. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Dosage range

Adult dose

Oral, 150–450 mg every 6 hours.

IV, 600–2,700 mg daily given in 2–4 doses, usually 450–900 mg every 8 hours. Maximum IV 4.8 g daily.

Paediatric dose

Oral, 5–7.5 mg/kg every 6–8 hours.

IM/IV, 10 mg/kg every 6–8 hours.

clobazam

benzodiazepine

Cautionary advisory labels: 1, 9

Notes

- Regular use for more than 2–4 weeks may result in dependence and tolerance.
- Monitor patient for physical and psychological dependence and tolerance (check intervals between prescription refills).
- Beware sudden discontinuation of long-term treatment.
- May cause a 'morning-after' hangover effect.
- Inquire about respiratory disease or sleep apnoea. Reduced respiratory drive may cause hypoxaemia.

Changes to urinary system: May induce or aggravate functional incontinence due to sedation or impairment of mobility.

Elderly: A low dose of a short- to medium-acting drug is preferred for sedation in an elderly patient.

Over-sedation, confusion, memory impairment, poor muscle coordination may cause falls and fractures.

Hepatic impairment (severe): Caution due to increased responsiveness and higher susceptibility to adverse effects. Start at low dose, carefully titrate upwards.

Renal impairment (severe): Caution due to increased responsiveness and higher susceptibility to adverse effects. Start at low dose, carefully titrate upwards.

Pregnancy: C. Use should be avoided if possible, especially during first trimester. If clobazam is required, use the lowest effective dose for the shortest duration.

Breastfeeding: Consider alternatives first. Excretion in breast milk expected. Should be avoided due to long half-life.

Common dosage range

Adult dose

10–30 mg daily in divided doses. Maximum dose 60–80 mg daily.

Paediatric dose

Epilepsy: 0.1–1 mg/kg daily in 1–2 doses, depending on type and severity of epilepsy.

clodronate

bisphosphonate

Cautionary advisory labels: 3b (1 hour before or 2 hours after), 4, A

Notes

- Presence of food reduces absorption significantly.
- Maintain adequate fluid intake (1.5–2 L/day).

Renal impairment (severe): Caution.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

1.6–3.2 g daily in divided doses.

clofazimine

antileprotic

Cautionary advisory labels: 8, 12, B

Notes

- Causes discolouration to skin, bodily fluid, hair, corneum, breast milk, which is reversible on cessation of therapy but may take a number of months.

Chages to faeces: Red, brown–black discolouration.

Renal and hepatic impairment (severe): Caution.

Pregnancy: C. Seek advice from an infectious diseases specialist.

Breastfeeding: Use not recommended. Excreted in breast milk. May produce skin discolouration in infants.

Common dosage range

Adult dose

Multibacillary leprosy: 300 mg once a month under supervision, plus 50 mg once daily self-administered in multidrug regimen.

Paediatric dose

<10 years: 1 mg/kg once daily and 100 mg once a month.

>10 years: 1 mg/kg once daily and 150 mg once a month.

clomiphene

oestrogen receptor antagonist for ovulatory failure

Cautionary advisory labels: 12

Hepatic impairment (severe): Contraindicated

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: no data available. May suppress lactation.

Common dosage range

Adult dose

50–100 mg daily for five days, starting on or about the fifth day of the menstrual cycle if spontaneous or progestogen-induced uterine bleeding has occurred or at any time if recent uterine bleeding has not occurred.

clomipramine

tricyclic antidepressant

Cautionary advisory labels: 1, 9, 13, 16

Notes

- Orthostatic hypotension may occur when rising quickly while being treated. Advise about getting up slowly after sitting or lying down.
- Full benefit may not be seen for several weeks, although adverse effects may occur from start of treatment.
- Anticholinergic adverse effects are common—dry mouth, constipation, blurred vision, difficulty in passing urine.
- Medicine-free interval may be required if switching to/from other antidepressants. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- Sips of water, sugarless gum or sweets may help relieve dry mouth.

- Best taken as a single dose at night.
- Start with a low dose and titrate upwards, especially in older people.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to anticholinergic effects—reduced detrusor activity, urinary retention, voiding difficulty, constipation, sedation or impairment of mobility.

Elderly: Confusion, constipation, orthostatic hypotension leading to falls and fractures.

Renal and hepatic impairment (severe): Caution. Dose adjustment may be necessary.

Pregnancy: C. Use when clinically indicated if it is the drug of choice. There is increased risk of reversible withdrawal symptoms, not congenital malformations.

Breastfeeding: Use with caution. Small amounts excreted into breast milk. If needed, preferably taken as a single dose. Monitor for adverse effects (e.g. sedation) in infant.

Common dosage range

Adult dose

50–150 mg daily in divided doses. Maximum 300 mg daily.

clonazepam

antiepileptic benzodiazepine

Cautionary advisory labels: 1, 9

Notes

- Inquire about respiratory disease or sleep apnoea. Reduced respiratory drive may cause hypoxaemia.
- Abrupt withdrawal may result in pronounced restlessness, irritability, insomnia and hand tremors. Decrease gradually when switching to another anticonvulsant.
- Monitor FBC, LFTs.

Changes to urinary system: May induce or aggravate functional incontinence due to sedation or impairment of mobility.

Elderly: Over-sedation, confusion, memory impairment, poor muscle coordination leading to falls and fractures.

Renal and hepatic impairment (severe): Caution. Dose adjustment may be necessary.

Therapeutic monitoring: Therapeutic range is 15–50 micrograms/L (0.05–0.16 micromol/L).

Pregnancy: C. Use should be avoided if possible, especially during first trimester. If clonazepam is required, use the lowest effective dose for the shortest duration.

Breastfeeding: Use with caution. Excreted into breast milk, with concentrations increasing with time. Adverse effects (e.g. sedation, poor feeding) may be experienced by infant. Avoid long-term use, large doses or frequent dosing.

Common dosage range

Adult dose

Oral, 0.5–1 mg daily, increasing to 2–8 mg daily in divided doses. Maximum 20 mg daily.

Status epilepticus: 1 mg by slow IV injection; repeat if necessary.

Paediatric dose

Oral, initially 0.01–0.03 mg/kg daily in 2–3 divided doses, increasing by 0.25–0.5 mg every third day until control is achieved (maximum 0.2 mg/kg daily).

Status epilepticus: 50 micrograms/kg (maximum 1 mg) by slow IV injection; repeat if necessary.

clonidine

alpha-adrenergic blocker

Cautionary advisory labels: 1, 9, 16

Notes

- Beware abrupt cessation of drug: may cause rapid rebound hypertension.
- May cause drowsiness, dry mouth, constipation, headache or fatigue.

Elderly: More sensitive to hypotensive effect.

Hepatic impairment: Clonidine is metabolised in the liver (and excreted by the kidneys). Response to drug should be monitored since half-life may be prolonged.

Renal impairment (severe): Caution. Dose adjustment may be necessary.

Cl_{cr} <30 mL/min initially use low end of dose range and titrate according to response.

Pregnancy: B3. Use not recommended in first trimester. Use with caution when adequate blood pressure control is not achieved with methyldopa or labetalol.

Breastfeeding: Use not recommended. Excreted in breast milk and limited safety data on drug in infants. May suppress lactation.

Common dosage range

Adult dose

Hypertension: oral, 50–100 micrograms 2–3 times a day; maximum daily dose 900 micrograms.

IM/IV, 150–300 micrograms repeated every 3–6 hours if necessary (maximum 750 micrograms in 24 hours).

Menopausal flushing, migraine prophylaxis: 50–150 micrograms daily in two divided doses.

Paediatric dose

Hypertension: IV, 5 micrograms/kg/eight-hourly.

Oral, 1–4 micrograms/kg eight-hourly.

Migraine prophylaxis: oral, 0.5 microgram/kg 12-hourly.

Attention deficit hyperactivity disorder: oral, 1 microgram/kg at night, increasing every 3–7 days to a maximum of 10 micrograms/kg daily in 2–3 doses.

clopidogrel

thienopyridine antiplatelet agent

Cautionary advisory labels: 9, 10a

Notes

- Used in secondary prevention of cardiovascular and cerebrovascular events. Advise on importance of continuing therapy.
- Cease seven days prior to planned surgery.
- Adverse effects uncommon, but gastric bleeding may occur.

Changes to faeces: Pink, red, black discolouration may indicate medicine-induced gastrointestinal bleeding.

Renal and hepatic impairment (severe): Caution. Monitor for signs of bleeding.

Pregnancy: B1. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

75 mg daily.

clozapine

atypical antipsychotic

Cautionary advisory labels: 1, 9, 12, 16

Notes

- Complete blood examination and hepatic function tests should be conducted regularly.
- It takes 1–2 weeks for a measurable response and 2–3 months for a full trial.
- Commonly causes weight gain and hypersalivation.

Changes to urinary system: May induce or aggravate overflow/functional /stress incontinence due to constipation, confusion, sedation or parkinsonism.

Renal and hepatic impairment (severe): Contraindicated.

Pregnancy: C. Use only if drug of choice. Use minimal effective dose.

Breastfeeding: Use not recommended. Excretion and concentration in breast milk expected. Potential for serious adverse effects in infant.

Common dosage range

Adult dose

12.5 mg once or twice on first day, 25 mg once or twice on the second day, then increase as tolerated. Usual range, 200–600 mg daily; maximum dose 900 mg daily.

codeine

opioid analgesic, antidiarrhoeal

Cautionary advisory labels: 1 (greater than 20 mg dose)

Notes

- Constipation may be a problem with chronic use. Start treatment with stimulant or osmotic laxative (see 'Prevention and treatment of opioid-induced constipation', Section D).
- Inquire if nausea or vomiting occurs.
- Codeine more likely to produce central nervous system effects, especially in the elderly; loperamide preferred (antidiarrhoeal).
- Combination with paracetamol: maximum dose of the combined product is determined by the paracetamol component—i.e. 4 g/24 hours for adults.
- Used as antidiarrhoeal for acute symptomatic treatment only. Avoid in children under 6 years.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to inhibition of the voiding reflex, constipation, confusion, reduced detrusor activity or urinary retention.

Renal and hepatic impairment (severe): Caution. Dosage adjustment necessary.

Pregnancy: A.

Breastfeeding: May be used in recommended doses (<240 mg daily). Trace amounts excreted in breast milk.

Common dosage range

Adult dose

Pain: 30–60 mg every 4 hours; maximum 240 mg in 24 hours.

Cough suppression: 15–30 mg 3–4 times daily.

Diarrhoea: 30–60 mg 3–4 times daily.

Paediatric dose

Cough suppression: 0.25–0.5 mg/kg/dose given every 6–8 hours.

Pain: oral/IM/IV, 0.5–1.0 mg/kg/dose given every 4 hours when required.

colchicine

for gout and hyperuricaemia

Cautionary advisory labels: 5

Notes

- If tarry stools, sore throat, fever or mouth ulcers occur, seek medical advice.

Changes in faeces: Grey discolouration.

Renal impairment: Caution. Dosage adjustment necessary.

Cl_{cr} 10–50 mL/min give 50% of usual dose.

Contraindicated if Cl_{cr}<10mL/min, and in patients with both renal and hepatic impairment, or those with severe renal or hepatic impairment.

Pregnancy: D. Use not recommended. Consider corticosteroid as alternative first.

Breastfeeding: Use with caution. Variable amounts excreted in breast milk. If required, a bedtime dose and avoidance of overnight feeds is suggested.

Common dosage range

Adult dose

Acute gout: 1 mg initially; then 500 micrograms every six hours until pain relief or toxicity (nausea, vomiting, diarrhoea) occurs. Maximum total dose is 2.5 mg in first 24 hours and 6 mg over a 4 day course. Course should not be repeated within 3 days.

cortisone acetate

glucocorticoid

Cautionary advisory labels: 9, B

Notes

Changes to faeces: Pink, red, black discolouration may indicate medicine-induced gastrointestinal bleeding.

Hepatic impairment (severe): Caution. Dosage reduction necessary.

Pregnancy: A.

Breastfeeding: May be used. Small amounts excreted in breast milk. Avoid feeding 3–4 hours after dose.

Common dosage range

Adult dose

Adrenocortical insufficiency: 10–37.5 mg daily in two doses with two-thirds of dose given in the morning.

Other indications: 25–300 mg/day as a single dose or in divided doses.

Paediatric dose

Adrenocortical insufficiency: 15–25 mg/m^2 daily in three divided doses.

Anti-inflammatory, immunosuppressant: 2.5–10 mg/kg daily in 3–4 doses.

Monitor development and growth carefully in children on long-term therapy.

cromoglycate

mast cell stabiliser for asthma

Cautionary advisory labels: 22 (capsules for inhalation)

Notes

- Requires regular use.
- Not for acute asthma relief.
- Paradoxical bronchospasm may occur. If it does, seek medical advice.
- First-line treatment in children.
- Need 4-week therapeutic trial.
- With regular dosage may be able to reduce corticosteroid.

Pregnancy: A.

Breastfeeding: May be used. Minimal maternal systemic absorption, so minimal excretion expected.

Common dosage range

Adult dose

MDI/DPI: 5–20 mg three or four times daily.

Nasal spray: 2%, 1 spray into each nostril 4–6 times daily; 4%, one spray into each nostril 2–4 times daily.

Paediatric dose

MDI: 10 mg three times daily, reducing to twice daily if possible.

Nebuliser: 20 mg 2–4 times daily.

Nasal spray: As for adult dose.

cyclophosphamide

cytotoxic alkylating agent

Modification of oral formulation

Avoid crushing or altering tablet due to occupational health and safety risks.

Cautionary advisory labels: 8, 21, G

Notes

- Take at the same time each day.
- Avoid crowds and people with infections.
- Report signs of infection or unusual bleeding.
- Drink plenty of water and empty bladder frequently.
- Report any bladder irritation to prescriber.
- Nausea and vomiting may occur.

Hepatic impairment (severe): Caution.

Renal impairment (severe): Caution dosage reduction necessary.

Pregnancy: D. Use not recommended.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

Antineoplastic: oral, 1–5 mg/kg daily.

IV, 10–15 mg/kg every 7–10 days, or 3–5mg/kg twice weekly.

Immunosuppressant: oral, 1–3mg/kg daily.

Paediatric dose

Antineoplastic: oral, 2–5 mg/kg or 50–150 mg/m^2 twice a week.

Immunosuppressant: oral, 1–3mg/kg daily.

cyclosporin

calcineurin inhibitor, immunosuppressant

Cautionary advisory labels: 5, 8, 18 and also 7a for oral solution

Notes

- To determine the correct maintenance dose, blood concentration monitoring 2 hours post-dose is recommended.
- Oral solution should be diluted in orange juice or chocolate milk or milk before administration. The same diluent should always be used.
- IV administration should be used only if the patient is unable to take the drug by mouth. The injection solution contains polyethoxylated castor oil. There is a risk of anaphylactic reactions associated with IV administration of polyethoxylated castor oil.

Renal impairment (severe): Caution. Dosage reduction necessary. Start at 2.5 mg/kg/day and adjust. Monitor serum drug levels and serum creatinine.

Refer 'Optimal medicine concentration ranges', Section D.

Pregnancy: C. For use seek specialist advice.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

Organ transplantation: oral, 8–15 mg/kg daily in two doses before surgery and for 1–2 weeks postoperatively, then reduce to maintenance dose of 2–6 mg/kg daily in divided doses.

IV infusion, 2–6 mg/kg daily until patient can tolerate oral solution.

Rheumatoid arthritis, psoriasis, nephrotic syndrome or atopic dermatitis: 2.5–5 mg/kg daily in divided doses.

Paediatric dose

Organ transplantation: Same as adult dose. Children may require higher or more frequent dosing because of accelerated clearance.

Juvenile chronic arthritis: 3–5 mg/kg daily in two doses.

Nephrotic syndrome: 1–6 mg/kg daily in two doses.

cyproheptadine

sedating antihistamine

Cautionary advisory labels: 1, 13

Notes

Hepatic impairment (severe): Caution.

Pregnancy: A.

Breastfeeding: Use not recommended. Excretion in breast milk is expected. May suppress lactation.

Common dosage range

Adult dose

4–20 mg daily in divided doses. Maximum daily dose 32 mg.

Paediatric dose

2–6 years: 2 mg 2–3 times daily; maximum 12 mg daily.

7–14 years: 4 mg three times daily; maximum 16 mg daily.

cyproterone

anti-androgen

Cautionary advisory labels: 12, B

Notes

Use as Oral contraceptive:

- Beware of reduced efficacy resulting from concurrent use with antiepileptic and antibacterial medicines.
- Vomiting or diarrhoea may compromise contraceptive effectiveness.
- Advise on the procedures if a dose has been missed for more than 12 hours.

Hepatic impairment (severe): Contraindicated

Pregnancy: B3 (oral contraceptive doses). Previously commenced therapy should be discontinued as soon as pregnancy is suspected.

D (higher doses): No indication for use during pregnancy; use not recommended.

Breastfeeding: Use not recommended. Small amounts excreted in breast milk. No safety data on drug in infants.

Common dosage range

Adult dose

Females

Acne, contraception: (in combination with ethinyloestradiol) 2 mg daily for 21 days.

Androgenisation: initially, 50–100 mg daily; may be as low as 10 mg daily for maintenance.

Males

50–100 mg 1–3 times daily.

dantrolene

muscle relaxant

Cautionary advisory labels: 1, 8

Notes

- Monitor LFTs before and during therapy.

Changes to urinary system: May discolour urine orange or red.

Hepatic impairment (severe): Contraindicated in hepatitis/cirrhosis.

Renal impairment (severe): Caution. Dosage adjustment necessary.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

Oral, 25–200 mg daily in divided doses; maximum dose, 400 mg daily (risk of hepatotoxicity is increased at doses >200 mg daily).

Paediatric dose

Oral, initially 0.5 mg/kg twice daily; may be increased to a maximum of 2 mg/kg three times daily.

dapsone

antileprotic

Cautionary advisory labels: B

Notes

Renal and hepatic impairment: Caution.

Pregnancy: B2. Use not recommended in first trimester. If drug of choice, use with caution in second and third trimesters. Seek advice from an infectious diseases specialist.

Breastfeeding: Use not recommended. Excretion and accumulation in breast milk expected. Potential for serious adverse effects in infant.

Common dosage range

Adult dose

50–100 mg daily.

Dermatitis herpetiformis: dose may be increased up to 300 mg daily but should be reduced to the lowest effective maintenance dose as soon as possible.

Paediatric dose

1–2 mg/kg (maximum 100 mg) once daily.

darbepoetin

haemopoietic agent

Cautionary advisory labels: 6

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult and Paediatric dose

Anaemia of chronic renal failure, Initially, SC, IV, 0.45 microgram/kg once a week, adjust dose according to response.

dasatinib

inhibitor of multiple oncogenic kinases

Cautionary advisory labels: 4 (antacids), 5, 12, A

Notes

- Women of child-bearing age must use appropriate contraception.
- Separate dasatinib doses from antacid administration by at least 2 hours.
- Drugs that decrease gastric pH—e.g. proton pump inhibitors, H_2 antagonists—should be avoided as the dissolution of dasatinib is pH dependent.

Pregnancy: D.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

70 mg twice daily. Dose reduction/cessation may be necessary if neutropenia or thrombocytopenia occurs during therapy.

deferiprone

iron chelator

Cautionary advisory labels: 13

Notes

- Nausea, vomiting, abdominal pain and increased appetite are common adverse effects.
- Monitor neutrophil count for agranulocytosis.
- Monitor serum ferritin to assess effectiveness of treatment.
- May need zinc supplementation during treatment.

Changes to urinary system: May discolour urine red–brown .

Renal and hepatic impairment: Caution. No data. Monitor clinically.

Pregnancy: D. Use not recommended.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

25 mg/kg three times daily, calculated to nearest half tablet.

delavirdine

antiviral non-nucleoside reverse transcriptase inhibitor

Cautionary advisory labels: 5

Notes

- Does not cure HIV or eliminate risk of transmission.
- May interact with many medicines (see Table D.1, Section D).
- Should be taken in combination with other antiretrovirals.

Renal and hepatic impairment: Caution. No data. Monitor clinically.

Pregnancy: B3. Previously commenced therapy should be continued and advice sought from an infectious diseases specialist.

Breastfeeding: Use not recommended. Expected to be excreted into breast milk. No safety data on drug in infants. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

400 mg three times daily.

desferrioxamine

iron-chelating agent

Notes

Changes to urinary system: May discolour urine red.

Renal impairment (severe): Contraindicated. Elimination may be prolonged, as much as eight-fold.

Pregnancy: B3. Chronic use not recommended. Use in acute poisoning may be appropriate.

Breastfeeding: Use not recommended.

Common dosage range

Adult dose

Acute iron overdose: IV infusion, 15 mg/kg/hour.

Chronic iron overload: 20–60 mg/kg/day.

desloratadine

less-sedating antihistamine

Notes

- May cause dry mouth, headache or fatigue.

Renal and hepatic impairment (severe): Caution. Increase dosing interval to every 48 hours.

Pregnancy: B1. Use not recommended. Consider use of sedating antihistamines first. If less-sedating antihistamine required, loratadine is preferred.

Breastfeeding: May be used. Small amounts expected to be excreted in breast milk.

Common dosage range

Adult dose

5 mg daily.

desmopressin

antidiuretic hormone analogue

Cautionary advisory labels: 5, 13

Notes

- When used for primary enuresis, avoid fluid intake after dinner time.
- For enuresis, treatment periods should not exceed 3 months without at least a one-week break from treatment.
- Cease treatment if there are signs of water retention and/or hyponatraemia.
- Intranasal administration causes higher incidence of hyponatraemia.

Elderly: Increased risk of hyponatraemia. Avoid overhydration.

Renal impairment (moderate–severe): Contraindicated when Cl_{cr} <50 mL/min.

Pregnancy: B2. Use not recommended in first trimester. Seek specialist advice for use in second and third trimesters.

Breastfeeding: Use with caution. Trace amounts excreted in breast milk. Adverse effects in infants unlikely.

Common dosage range

Adult dose

Cranial diabetes insipidus

Intranasal, 10–40 micrograms daily in one or two doses, divide between nostrils.

Oral, initially 0.1 mg three times daily; maintenance 0.1–0.2 mg 3 times daily. Maximum 1.2 mg daily.

IM/IV, 1–4 micrograms daily.

Primary nocturnal enuresis

Oral, 0.2–0.4 mg at bedtime.

Paediatric dose

Cranial diabetes insipidus

Intranasal, 2.5–20 micrograms daily in 1–2 doses.

Oral, 0.1–0.2 mg three times daily; maximum 1.2 mg daily.

Nocturnal enuresis (>6 years)

Intranasal, initially 20 micrograms at bedtime; maintenance 10–40 micrograms at bedtime. Give half of dose in each nostril.

Oral, 0.2–0.4 mg at bedtime.

dexamethasone

corticosteroid

Cautionary advisory labels: 9 (Oral, except short courses), B

Notes

- May interact with many medicines (see Table D.1, Section D).

Changes to faeces: Pink, red, or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Hepatic impairment (severe): Caution. Dose reduction may be necessary.

Pregnancy: A.

Breastfeeding: Use with caution. Excretion in breast milk expected, although adverse effects in infant considered unlikely. If a corticosteroid is required, prednisolone is preferred.

Common dosage range

Adult dose

Oral, 0.5–10 mg daily in divided doses.

Paediatric dose

Croup: oral/IV/IM, 0.15–0.6 mg/kg as a single dose.

Meningitis: IV, 0.6 mg/kg daily in 4 doses for 4 days or 0.8 mg/kg daily in 2 doses for 2 days (therapy should ideally begin before first dose of antibiotics).

Antiemetic: 0.1–0.2 mg/kg/dose (up to 8 mg) six-hourly.

Monitor development and growth carefully in children on long-term therapy.

dexamphetamine

psychostimulant

Notes

- To minimise insomnia, avoid taking doses later than 2.00 pm.
- Weight and height may be monitored, although effect on these parameters is probably insignificant.

Renal impairment (severe): Caution.

Pregnancy: B3. Previously commenced therapy should be tapered off as soon as pregnancy is suspected. If drug of choice in narcolepsy, minimum effective dose may be used.

Breastfeeding: Use not recommended. Excretion and concentration in breast milk. Potential for adverse effects (e.g. insomnia, irritability, poor feeding) in infant.

Common dosage range

Adult dose

5–60 mg daily in divided doses.

Paediatric dose

Initially, 0.15–0.5 mg/kg daily in two doses, usually morning and early afternoon. Increase at weekly intervals up to a maximum of 0.5 mg/kg daily or, for adolescents, 40 mg daily.

dexchlorpheniramine

sedating antihistamine

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets will alter absorption characteristics.

Cautionary advisory labels: 1, 13, A*

Notes

Elderly: Likely to cause dizziness, sedation and postural hypotension leading to falls.

Pregnancy: A.

Breastfeeding: May be used. Small amounts expected to be excreted in breast milk. Monitor for adverse effects (e.g. sedation) in infant. Avoid sustained-release preparations.

Common dosage range

Adult dose

2 mg four times daily, or 6 mg controlled-release 12-hourly.

Paediatric dose

>2 years, 0.04 mg/kg/dose every eight hours.

dextromethorphan

opioid cough suppressant

Notes

- Serotonin excess may occur; potential for adverse effects including serotonin syndrome exists, particularly when combined with other serotonergic medicines.
- Caution may effect ability to drive or operate machinery.
- Not for productive cough. If cough persists for >7 days consult doctor.

Hepatic impairment (severe): Caution.

Pregnancy: A

Breastfeeding: May be used. Small amounts excreted in breast milk.

Common dosage range

Adult dose

10–20 mg every four hours or 30 mg every 6–8 hours. Maximum 120 mg daily.

Paediatric dose

2–6 years: 2.5–5mg every four hours or 7.5 mg every 6–8 hours. Maximum 30 mg daily.

>6 years: 5–10mg every four hours or 15 mg every 6–8 hours. Maximum 60 mg daily.

dextropropoxyphene

opioid analgesic

Cautionary advisory labels: 1

Notes

- Long-term use may result in tolerance and/or dependence.
- Constipation may be a problem with chronic use. Start treatment with stimulant or osmotic laxative (see 'Prevention and treatment of opioid-induced constipation', Section D).
- Inquire about nausea or vomiting.
- Other adverse effects include hallucinations and cardiotoxicity (active metabolite).
- Offers no advantage over paracetamol for acute pain.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to inhibition of the voiding reflex, constipation, confusion, reduced detrusor activity, retention, polydipsia, nocturia or frequency.

Elderly: Best avoided in the elderly due to risk of adverse effects associated with accumulation.

Renal and hepatic impairment (severe): Caution. Monitor clinically.

Pregnancy: C. Particularly avoid high doses or prolonged use near term.

Breastfeeding: May be used short term. Very small amounts excreted in breast milk. Monitor for adverse effects (e.g. sedation) in infant.

Common dosage range

Adult dose

100 mg every four hours. Maximum 600 mg daily.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

diazepam

benzodiazepine

Cautionary advisory labels: 1 or 1a, 9

Notes

- Regular use for more than 2–4 weeks may result in dependence and tolerance.
- Beware sudden discontinuation of long-term treatment.
- Beware of sedation, especially when alcohol is consumed.
- Monitor patient for physical and psychological dependence and tolerance (check intervals between prescription refills).
- May cause a 'morning-after' hangover effect. Consider using a shorter acting benzodiazepine—e.g. temazepam or oxazepam.
- Caution with respiratory disease or sleep apnoea. Reduced respiratory drive may cause hypoxaemia.
- Monitor LFTs and FBC.

Changes to urinary system: May induce or aggravate functional incontinence due to sedation, or impairment of mobility.

Elderly: May cause over-sedation, confusion, memory impairment, poor muscle coordination resulting in falls and fractures.

Hepatic impairment (severe): Contraindicated.

Renal and hepatic impairment (mild–moderate): Caution. Dose reduction necessary.

Pregnancy: C. Use should be avoided if possible, especially during first trimester. If diazepam is required, use the lowest effective dose for the shortest duration.

Breastfeeding: Use with caution. Excreted in breast milk, with concentrations increasing with time. Adverse effects (e.g. sedation, poor feeding) may be experienced by infant. Avoid long-term use, large doses or frequent dosing. If a benzodiazepine is required, a shorter acting one is preferred.

Common dosage range

Adult dose

Oral, 5–40 mg daily in divided doses.

Seizures: IV, 0.15–0.3 mg/kg (10–20 mg) repeated to a maximum of 50 mg over 60 minutes.

Paediatric dose

Muscle spasm, anxiety: oral, 0.05–0.3 mg/kg 2–3 times daily.

Status epilepticus: IV, 0.1–0.3 mg/kg/dose, repeated every 15–30 minutes as required.

Rectal, 0.3–0.5 mg/kg/dose.

diclofenac

NSAID

Modification of oral formulation

Before crushing or otherwise altering tablets, consider the increased risk of local gastrointestinal irritant effect.

Cautionary advisory labels: 10a, 12†, A*, B

Notes

- Maximum response should be seen in 1–3 weeks.
- Alert patient to signs of gastrointestinal bleeding (black stools or dark coffee-coloured vomit).
- Caution if taking warfarin or other anticoagulants.
- To lessen gastrointestinal complications use lowest effective dose or take paracetamol as an alternative analgesic.
- Check use of over-the-counter NSAIDs.
- Caution with hypertension or heart failure, diabetes, asthma or peptic ulcer.
- Consider stopping 2–3 days before planned surgery; seek medical advice.

Changes to faeces: Pink, red, or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Elderly: Gastric ulceration, renal dysfunction, dizziness, sodium and water retention, exacerbation of hypertension or heart failure.

Renal and hepatic impairment (severe): Contraindicated.

Pregnancy: C. Alternatives to NSAIDs should be considered for analgesia. Use not recommended during third trimester.

Breastfeeding: May be used. Trace amounts excreted in breast milk. Diclofenac and ibuprofen are the NSAIDs of choice in breastfeeding mothers.

Common dosage range

Adult dose

75–150 mg daily in 2–3 divided doses.

Paediatric dose

Oral, rectal, 1–3 mg/kg daily in 2–3 doses.

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

dicloxacillin

beta–lactamase resistant penicillin

Cautionary advisory labels: 3a, D

Notes

- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible during waking hours.
- Ask about any previous reaction to penicillin.
- If a skin rash occurs, seek medical advice.
- Other common adverse effects—nausea, diarrhoea, gastric upset.
- If signs of jaundice occur, seek medical advice (higher risk if age >55 years and length of course >2 weeks).

Renal and hepatic impairment (severe): Caution. Dosage reduction necessary.

Pregnancy: B2. May be used.

Breastfeeding: May be used. Excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

Oral, 250–500 mg six-hourly.

IV, 250 mg–1 g six-hourly.

Paediatric dose

Oral/IM/IV, 50–100 mg/kg daily in four divided doses. IV dose may be doubled in severe infection.

didanosine

antiviral, nucleoside reverse transcriptase inhibitor

Cautionary advisory labels: 3b, A*.
Suspension – 6, 7a

Notes

Renal and hepatic impairment (severe): Caution. Dose adjustment necessary. See approved Product Information.

Pregnancy: B2. Previously commenced therapy should be continued and advice sought from an infectious diseases specialist.

Breastfeeding: Expected to be excreted into breast milk, but no safety data on drug in infants. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

<60 kg: 250 mg once daily.

≥60 kg: 400 mg once daily.

digoxin

cardiac glycoside

Cautionary advisory labels: 5

Notes

- Narrow therapeutic index and involved in significant drug interactions.
- Concomitant administration of antacids may reduce absorption of digoxin. Digoxin concentration may be increased by co-administration of verapamil, nifedipine, spironolactone, quinidine or amiodarone.
- Potassium, calcium and magnesium concentrations should be monitored, particularly when diuretics are also given.
- Anorexia, nausea, vomiting or blurred vision may indicate toxicity.
- Extreme caution is required in very low birth weight infants and in patients with impaired renal function; reduced dosage and plasma concentration monitoring should be used.

Elderly: Age-related renal impairment and possible increased sensitivity of the myocardium may require a reduced dose.

Renal impairment: Caution. Dose adjustment necessary. Monitor clinically.

Clinicans may use reduced loading dose:

Cl_{cr} <60 mL/min oral/IV, 125–250 micrograms 4–6 hourly. Maximum 750 micrograms in 24 hours.

Maintenance dose:

Cl_{cr} 30–60 ml/min oral/IV, 62.5–250 micrograms daily.

Cl_{cr} 10–30 ml/min oral/IV, 62.5–125 micrograms daily.

Cl_{cr} <10 ml/min oral/IV, 62.5 micrograms daily or alternate days.

Therapeutic monitoring: Therapeutic range:

Atrial fibrillation and heart failure 0.5–1.0 micrograms/L (0.6–1.3 nanomol/L).

Time to steady state: 6–20 days depending on renal function.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Signs of Toxicity

Therapeutic range is a guide only and toxicity may occur within the manufacturer's recommended range for atrial fibrillation. Anorexia, nausea, vomiting or blurred vision may indicate toxicity.

Pregnancy: A.

Breastfeeding: May be used. Small amounts excreted in breast milk.

Common dosage range

Adult dose

Loading: 250–500 micrograms every 4–6 hours to a maximum of 1.5 mg.

Maintenance: 62.5–250 micrograms daily.

Paediatric dose

Loading: give half of the loading dose initially, then a quarter of the dose at 6–12 hours, and the last quarter at 12–18 hours.

Up to 2 years: oral/IV, 30–40 micrograms/kg.

>2 years: 30 micrograms/kg.

Maintenance: oral, 5–10 micrograms/kg daily in 1 or 2 doses. Maximum 250 micrograms daily.

dihydrocodeine

opioid analgesic

Cautionary advisory labels: 1 (doses greater than 20 mg)

Notes

- May cause nausea, vomiting or constipation (see 'Prevention and treatment of opioid-induced constipation', Section D).

Renal impairment (severe): Caution. Dose adjustment necessary.

Pregnancy: A.

Breastfeeding: Use with caution: limited data available. Excretion in breast milk is expected. Monitor for adverse effects (e.g. sedation) in infant.

Common dosage range

Adult dose

10–20 mg 4–6 hourly.

Paediatric dose

2–5 years: 2.5–5 mg up to 6 times daily.

>5 years: 5–10 mg up to 6 times daily.

dihydroergotamine

ergot alkaloid

Cautionary advisory labels: 5,18

Notes

- Parenteral use is more common due to extremely low oral bioavailability.
- Avoid use if a triptan has been used in the previous 24 hours, due to increased risk of vasospasm.
- Avoid use if there is a history of venous thrombosis due to vasoconstricting properties.

Changes to faeces: Pink, red or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Renal and hepatic impairment (moderate): Caution. Dose adjustment necessary.

Renal and hepatic impairment (severe): Contraindicated.

Pregnancy: C. Use not recommended. Has the potential to decrease fetal blood supply and trigger premature uterine contractions.

Breastfeeding: Contraindicated.

Common dosage range

Adult dose

Orthostatic hypotension: oral, initially 1.25–2.5 mg three times daily. Maximum dose 40–60 mg daily.

Migraine and cluster headache: SC/IM, 0.5–1 mg repeated at hourly intervals up to 3 mg daily. Maximum dose 6 mg weekly.

diltiazem

calcium channel blocker

Modification of oral formulation

Crushing or otherwise altering controlled-release capsules will alter absorption characteristics.

Cautionary advisory labels: 9, 12†, A*

Notes

- Involved in numerous interactions (see Table D.1, Section D).

Renal and hepatic impairment: Caution. Monitor clinically.

Pregnancy: C. Consider alternative therapy first. If drug of choice, use with caution: maternal hypotension may produce fetal hypoxia.

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Breastfeeding: Use with caution: limited data available. Freely diffuses into breast milk, but no safety data on drug in infants. If a calcium channel blocker is required, nifedipine is preferred.

Common dosage range

Adult dose

Angina: initially 30 mg four times daily, increasing to 180–240 mg daily in 3–4 doses. Maximum 360 mg daily. Controlled-release preparation, initially 180 mg once daily; increase as required to 360 mg once daily.

Hypertension: controlled-release, initially 180–240 mg once daily; maintenance 240–360 mg once daily.

dimenhydrinate

sedating antihistamine

Cautionary advisory labels: 1, 13

Pregnancy: A

Breastfeeding: Use with caution. Small amounts excreted into breast milk. Monitor for adverse effects (e.g. sedation, irritability) in infant.

Common dosage range

For motion sickness, take first dose 30 minutes before travel.

Adult dose

50–100 mg every 4–6 hours. Maximum 400 mg daily.

Paediatric dose

≥2 years: 1.25 mg/kg every 6–8 hours. Maximum 75 mg per dose.

diphenhydramine

sedating antihistamine

Cautionary advisory labels: 1, 13

Notes

Hepatic impairment (severe): Caution. Dose reduction may be necessary.

Pregnancy: A

Breastfeeding: May be used. Excreted in breast milk. Monitor for adverse effects (e.g. sedation, irritability) in infant.

Common dosage range

Adult dose

Sedative–hypnotic: 50 mg at night.

Paediatric dose

Antiemetic: ≥2 years, 1–1.5 mg/kg six-hourly. Maximum 300 mg daily.

diphenoxylate

opioid antidiarrhoeal

Cautionary advisory labels: 1, 13

Notes

Diphenoxylate hydrochloride with atropine sulphate:

- For short-term treatment of diarrhoea.
- Maintenance of adequate hydration important using oral rehydration preparation.
- Reduce the dose as soon as symptoms improve.
- If condition does not respond, seek further medical advice.
- Avoid in children under 12 years old.
- Likely to produce central nervous system effects, especially in the elderly. Consider loperamide instead.

Hepatic impairment (severe): Contraindicated. Risk of hepatic coma.

Pregnancy: C. May be used in combination with atropine for short-term use. Avoid high doses at or near term due to risk of respiratory depression in newborn.

Breastfeeding: Occasional doses may be used. Excretion in breast milk is expected.

Common dosage range

Adult dose

5 mg 3–4 times daily. Maximum 20 mg daily.

dipyridamole

antiplatelet agent

Cautionary advisory labels: 16, A*

Notes

- Cease 7 days before planned surgery.
- Potential vasodilator, high dose used with caution when severe coronary artery disease exists.

Renal and hepatic impairment: Caution.

Renal impairment (severe): Contraindicated.

Pregnancy: B1. Not recommended in first trimester. Used in second and third trimesters only in high-risk pregnancies.

Breastfeeding: May be used. Very small amounts excreted in breast milk.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Common dosage range

Adult dose

Antithrombotic: 300–600 mg daily in 3–4 doses.

Secondary prevention of stroke and transient ischaemic attack: controlled-release, 200 mg twice daily.

disopyramide

antiarrhythmic agent

Cautionary advisory labels: 9, A

Notes

- Drug choice dictated by arrhythmia type and co-existing medical conditions.
- Caution with medicines that prolong the QT interval.

Hepatic impairment: Caution. Dose reduction necessary. Reduce dose by 25%. Monitor clinically.

Renal impairment: Caution. Dose reduction necessary. See approved Product Information.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. anticholinergic effects) in infant.

Common dosage range

Adult dose

Initially 400–600 mg daily in 3–4 doses; reduce to maintenance dose of 300–400 mg daily. Maximum 800 mg daily.

disulfiram

long-term treatment for alcoholism

Cautionary advisory labels: 2, 5

Notes

- Take as a single daily dose, preferably on waking and with food.
- Disulfiram effect may last for 7–14 days after ceasing therapy.
- Initiate at least 24 hours after last alcohol intake.
- Patients must be advised to strictly avoid alcohol, noting that there may be alcohol in foods and other drug products.

Renal and hepatic impairment (severe): Caution.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use not recommended as limited data available. Excretion in breast milk expected.

Common dosage range

Adult dose

Initially 100 mg daily. Maintenance 200 mg daily. Maximum 300 mg daily.

docusate

stool softener

Notes

- Assess for possible causes of constipation.
- Consider increased fibre, fluid intake and exercise.
- Chronic management of constipation may require combination treatment.
- Opioid-induced: use a stool softener/stimulant and hyperosmotic. See 'Prevention and treatment of opioid-induced constipation', Section D.
- Faecal impaction may present as faecal soiling or diarrhoea.

Pregnancy: A

Breastfeeding: May be used.

Common dosage range

Adult dose

Oral, 100–480 mg daily.

Paediatric dose

3–6 years: oral, 50 mg daily.

6–12 years: oral, 50–120 mg daily.

dolasetron

$5HT_3$ antagonist, antiemetic

Notes

- Confirm other medicines have not been lost due to vomiting.
- May interact with many medicines (see Table D.1, Section D).

Pregnancy: B1. Consider alternatives first. If a $5HT_3$ antagonist is required, ondansetron is preferred.

Breastfeeding: Use not recommended: limited data available. If a $5HT_3$ antagonist is required, ondansetron is preferred.

Common dosage range

Adult dose

Cancer chemotherapy: oral, 200 mg daily.

IV, 100 mg 30 minutes before chemotherapy.

Post-operative nausea and vomiting

Prevention: oral 50 mg before induction of anaesthesic or IV, 12.5 mg at end of anaesthesia.

Treatment: IV, 12.5 mg once daily.

domperidone

dopamine antagonist, antiemetic

Cautionary advisory labels: C

Notes

- Confirm other medicines have not been lost due to vomiting.
- Caution: may cause or worsen depression.
- May interact with many medicines (see Table D.1, Section D).

Elderly: Reduce dose to avoid extrapyramidal effects.

Renal and hepatic impairment (severe): Caution. Dose reduction necessary for repeated doses.

Pregnancy: B2. Consider alternatives first.

Breastfeeding: May be used short term. Excretion in breast milk in small amounts expected.

Common dosage range

Adult dose

Oral, 10–20 mg every 6–8 hours.

Maximum 80 mg daily.

Lactation stimulation, 10 mg three times daily; taper dose over 7–10 days before stopping.

Paediatric dose

Oral, 0.2–0.4 mg/kg 4–8 hourly.

Maximum 40 mg daily.

donepezil

cholinesterase inhibitor

Cautionary advisory labels: 12, 16

Notes

- Take at same time each day, generally at bedtime but can be given in the morning if vivid dreams occur at night.
- Use with caution in patients with asthma or history of COAD, epilepsy, arrhythmia, peptic ulcer disease or Parkinson's disease.
- Report gastrointestinal bleeding, fainting or urinary incontinence.
- If treatment is interrupted for several days, re-titrate dose to minimise adverse effects, e.g. nausea and vomiting.
- Avoid anticholinergics due to antagonistic effects.

Changes to urinary system: May induce or aggravate urge incontinence due to enhanced cholinergic effect, detrusor instability, frequency, or urgency.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

5–10 mg once daily immediately before retiring. Maximum dose 10 mg daily.

dothiepin

tricyclic antidepressant

Cautionary advisory labels: 1, 9, 13, 16

Notes

- Orthostatic hypotension may occur when rising quickly. Advise getting up slowly after sitting or lying down.
- Full benefit may not be seen for several weeks, although adverse effects may occur from start of treatment.
- Anticholinergic adverse effects are common—dry mouth, constipation, blurred vision, difficulty in passing urine.
- Medicine-free interval may be required if switching to/from other antidepressants. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- Sips of water, sugarless gum/sweets may help relieve dry mouth.
- Best taken as a single dose at night.
- Start with a low dose and titrate upwards, especially in older people.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to anticholinergic effects—reduced detrusor activity, urinary retention, voiding difficulty, constipation, sedation, impairment of mobility.

Elderly: Confusion, constipation, orthostatic hypotension leading to falls or fractures. Avoid use for sedation in elderly due to adverse effects.

Hepatic impairment (severe): Contraindicated.

Renal and hepatic impairment (mild–moderate): Caution. Dose adjustment necessary .

Pregnancy: C. Use when clinically indicated if it is the drug of choice. There is increased risk of reversible withdrawal symptoms, not congenital malformations.

Breastfeeding: Use with caution. Small amounts excreted into breast milk. If needed, preferably taken as a single dose. Monitor for adverse effects (e.g. sedation) in infant.

Common dosage range

Adult dose

Initially 25 mg three times a day, increasing gradually if necessary; maintenance 75–150 mg daily.

Maximum 200 mg daily.

doxepin

tricyclic antidepressant

Cautionary advisory labels: 1, 9, 13, 16

Notes

- Orthostatic hypotension may occur when rising quickly. Advise getting up slowly after sitting or lying down.
- Full benefit may not be seen for several weeks, although adverse effects may occur from start of treatment.
- Anticholinergic adverse effects are common—dry mouth, constipation, blurred vision, difficulty in passing urine.
- Medicine-free interval may be required if switching to/from other antidepressants.
  See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- Sips of water, sugarless gum/sweets may help relieve dry mouth.
- Best taken as a single dose at night.
- Start with a low dose and titrate upwards, especially in older people.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to anticholinergic effects—reduced detrusor activity, urinary retention, voiding difficulty, constipation, sedation, or impairment of mobility.

Elderly: Confusion, constipation, orthostatic hypotension leading to falls or fractures.

Renal and hepatic impairment: Caution. Dose adjustment may be necessary.

Pregnancy: C. Use when clinically indicated if it is the drug of choice. There is increased risk of reversible withdrawal symptoms, not congenital malformations.

Breastfeeding: Consider alternatives first. Excreted in breast milk and may accumulate due to long half-life.

Common dosage range

Adult dose

30–300 mg daily in three divided doses. Maximum 150 mg/dose and 300 mg daily.

doxycycline

tetracycline antibacterial

Modification of oral formulation

Before crushing or otherwise altering tablets or capsules, consider the increased risk of local irritant effect.

Cautionary advisory labels: 4 (delete dairy products), 8, B, D

Notes

- Confirm appropriate antibiotic and dose regimen.
- Take drug with food and a large glass of water.
- Do not lie down for at least 1 hour after taking medication.
- May decrease effectiveness of oral contraceptive pill.
- Common adverse effects—nausea, diarrhoea, gastric upset, candidal infections.
- Doxycycline should not be used in children under 8 years of age because of the risk of permanent discolouration of teeth.

Hepatic impairment: Caution.

Pregnancy: D. Use contraindicated in second and third trimesters due to effects on fetal teeth and bone growth.

Breastfeeding: Use with caution; short courses only. Theoretical risk of adverse effects on infant teeth and bone growth. Short courses of doxycycline for the mother, of up to 10 days, appear to be safe for the infant.

Common dosage range

Adult dose

200 mg as a first dose, thereafter 100 mg daily; severe infections, 100 mg 12-hourly.

Acne: 50 mg daily.

Malaria prophylaxis: 100 mg daily, beginning two days before and continued for four weeks after exposure.

Paediatric dose

>8 years, 4 mg/kg (up to 200 mg) in two doses on day 1, then 2 mg/kg daily (maximum 100 mg) in 1–2 doses. Severe infection, 4 mg/kg daily (maximum 200 mg) in 1–2 doses.

Acne: 50 mg daily.

Malaria prophylaxis: 2 mg/kg up to 100 mg daily, beginning two days before and continued for four weeks after exposure.

duloxetine

selective serotonin/noradrenaline reuptake inhibitor, antidepressant

Cautionary advisory labels: 5, 9, 12, A

Notes

- High incidence of hepatic disease in patients consuming large quantities of alcohol.
- May increase the anticoagulant response to warfarin. Monitor INR.
- Co-administration with drugs with serotonergic activity may result in serotonin syndrome.

Renal impairment: A dose of 30 mg daily is recommended.

Pregnancy: B3.

Breastfeeding: Not recommended.

Common dosage range

Adult dose

30 mg daily for one week, increasing to 60 mg daily.

dydrogesterone

progestogen

Notes

Hormone replacement therapy

- Does not provide contraceptive cover during perimenopause.
- Irregular or atypical bleeding may indicate endometrial irregularity—seek medical advice.

Hepatic impairment: Caution.

Pregnancy: D. Use not recommended. Previously commenced therapy should be discontinued as soon as pregnancy is suspected.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

5–30 mg daily, in single or divided doses.

Specific indications: see approved Product Information.

eformoterol

long-acting beta$_2$ agonist bronchodilator

Cautionary advisory labels: 22 (capsules for inhalation)

Notes

- May be used for symptom relief in patients already receiving inhaled corticosteroids and regular eformoterol or in combination with budesonide.
- Long acting—use twice a day.
- If paradoxical bronchospasm occurs, seek medical advice.
- May cause tachycardia or tremor.
- Review delivery device technique.
- Counsel on cleaning and disposal of device.

Pregnancy: B3. May be used.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

6–24 micrograms twice daily. Maximum regular dose 48 micrograms daily. Additional doses can be taken as needed to relieve symptoms, up to a maximum total of 72 micrograms daily.

Paediatric dose

>5 years, 6–12 micrograms twice a day.

emtricitabine

nucleoside analogue for HIV treatment

Cautionary advisory labels: 12, A

Notes

- May cause discolouration of skin on palms and/or soles of feet.
- Nausea, vomiting, stomach pain, fatigue or weakness may indicate lactic acid build-up.

Renal impairment: Caution. Dose adjustment necessary.

Cl_{cr} 30–49 mL/min 200 mg every 48 hours.

Cl_{cr} 15–29 mL/min 200 mg every 72 hours.

Cl_{cr} <15 mL/min 200 mg every 96 hours.

Pregnancy: B1. Previously commenced therapy should be continued and advice sought from an infectious diseases specialist.

Breastfeeding: Use not recommended: no data available. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

200 mg once daily.

Paediatric dose

>33kg, 200 mg once daily.

enalapril

angiotensin-converting enzyme inhibitor

Cautionary advisory labels: 11, 12†, 16†

Notes

- Monitor renal function and potassium concentration.
- Provide advice on avoiding foods and drugs with high potassium content.
- Caution if the patient is taking NSAIDs (including COX-2 inhibitors) or lithium.
- Blood pressure should be closely monitored during initiation of therapy.
- Can cause cough (cough can also be a symptom of heart failure). Establish if the cough is productive or unproductive.
- If persistent dry cough or swelling of face, lips or tongue is experienced, seek medical advice.
- May cause metallic taste or lack of taste.
- A combination of enalapril with a diuretic product is also available. Check that patient knows which product is being taken.

Changes to urinary system: May induce or aggravate stress incontinence due to cough-induced sphincter weakness.

Elderly: May cause renal impairment, hyperkalaemia, orthostatic hypotension leading to falls and fractures.

Renal impairment: Caution. Dose adjustment necessary.

Cl_{cr} <30 mL/min initial dose 2.5 mg, titrate carefully.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as possible if pregnancy is suspected.

Breastfeeding: Use with caution. Very small amounts excreted in breast milk. No adverse effects reported in infants.

Common dosage range

Adult dose

2.5–40 mg daily in 1–2 doses.

Paediatric dose

0.1 mg/kg daily in 1–2 doses, increased gradually to maximum of 1 mg/kg daily.

enfuvirtide

antiretroviral for HIV treatment

Cautionary advisory labels: 12

Notes

- Seek medical advice if any of the following occur:
  - allergic reaction
  - cough with fever, rapid breathing and shortness of breath (pneumonia)
  - dizziness, nausea, tiredness or weakness.
- Injection site reactions are common.
- Does not cure HIV or eliminate risk of transmission.
- Should be taken in combination with other antiretrovirals.

Renal and hepatic impairment: Caution. Limited data available.

Pregnancy: B2. Previously commenced therapy should be continued and advice sought from an infectious diseases specialist.

Breastfeeding: Use not recommended: no data available. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

90 mg twice daily in combination therapy.

Paediatric dose

>6 years: SC, 2 mg/kg (maximum 90 mg) twice daily.

entacapone

catechol-O-methyltransferase inhibitor

Cautionary advisory labels: 4 (delete milk, antacids, calcium), 5, 9, 12, 16

Notes

Changes to urinary system: May cause brownish orange discolouration of urine.

Hepatic impairment: Caution.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

200 mg with each levodopa/dopa decarboxylase inhibitor dose. Maximum 2,000 mg daily.

† Most appropriate during initial treatment or when dosage is increased.

eplerenone
aldosterone antagonist

Cautionary advisory labels: 5, 11, 12, 18

Notes

- Provide advice on food and drugs with high potassium content.
- May cause hyperkalaemia; caution if used in combination with ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, potassium supplements, cyclosporin.

Renal and hepatic impairment (moderate–severe): Contraindicated when Cl_{cr} <50 mL/min, due to risk of hyperkalaemia.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Initially 25 mg once daily; maintenance 50 mg once daily.

epoetin alpha
haemopoietic agent

Cautionary advisory labels: 6

Notes

- Risk of increased mortality, serious cardiovascular and thrombo-embolic events.
- Measure haemoglobin levels regularly in cancer patients receiving chemotherapy.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult Dose

Anaemia of chronic renal failure: IV/SC, 50 units/kg three times a week; increase or decrease by 25 units/kg/dose each month until desired haemoglobin level is obtained. Maximum recommended dose 200 IU/kg three times per week.

Other indications: See approved Product Information.

eprosartan
angiotensin II receptor antagonist

Cautionary advisory labels: 11, 12†, 16†

Notes

- Monitor renal function and potassium concentration.
- Caution if the patient is taking NSAIDs (including COX-2 inhibitors) or lithium.
- Provide advice on avoiding foods and drugs with high potassium content.
- Blood pressure should be closely monitored during initiation of therapy.
- Can cause cough (cough can also be a symptom of heart failure). Establish nature of cough, productive or unproductive.
- If persistent dry cough or swelling of face, lips or tongue is experienced, seek medical advice.
- A combination product of eprosartan with a diuretic is also available. Check that patient knows which product is being taken.

Elderly: Renal impairment, hyperkalaemia.

Renal and hepatic impairment: Caution. Dose adjustment necessary. Starting dose of 400 mg daily, titrated carefully to response.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as possible if pregnancy is suspected.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Initially 600 mg once daily; may be increased to 800 mg once daily.

ergocalciferol
vitamin D_2, calciferol

Notes

Renal impairment (severe): Caution. Use activated form of vitamin D due to the inability to convert to active form.

Pregnancy: Safe at therapeutic doses.

Breastfeeding: Use with caution. Excretion in breast milk expected. Monitor for hypercalcaemia in infant.

† Most appropriate during initial treatment or when dosage is increased.

Common dosage range

Adult dose

<50 years: 5 micrograms (200 IU) daily.

51–70 years: 10 micrograms (400 IU) daily.

>70 years: 15 micrograms (600 IU) daily.

Available only in over-the-counter vitamin and mineral preparations.

ergotamine

ergot alkaloid

Notes

- Use (orally or rectally) as soon as possible after onset of migraine or cluster headache. May be repeated after 30 minutes.
- Advise patient to stop treatment if numbness and tingling of extremities (peripheral vasoconstriction) chest pain or shortness of breath occurs.
- Avoid use if a triptan has been used in the previous 24 hours.

Changes to faeces: Pink, red, black discoloration may indicate medicine-induced gastrointestinal bleeding.

Renal and hepatic impairment (moderate–severe): Contraindicated.

Pregnancy: C. Use not recommended.

Breastfeeding: Use contraindicated. Potential for severe adverse effects in infant.

Common dosage range

Adult dose

Oral, 1–2 mg as soon as possible after onset; repeat if necessary after 30–60 minutes.

Rectal, 2 mg as soon as possible after onset; repeat if necessary after 30–60 minutes.

Maximum dose 6 mg daily, 10 mg weekly. Minimum interval of 4 days between courses.

erythromycin

macrolide antibacterial

Modification of oral formulation

Before crushing or otherwise altering tablets or capsules consider medicine stability issues and risk of altered absorption characteristics.

Cautionary advisory labels: 5, A, C, D

Notes

- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible.
- May cause diarrhoea, nausea, diarrhoea, gastric upset or candidal infection.
- May decrease the effectiveness of oral contraceptives.
- Monitor for signs of hepatic toxicity.
- Useful as a prokinetic agent.
- Erythromycin may inhibit the metabolism of several drugs, including non-sedating antihistamines, carbamazepine and theophylline (see Table D.1, Section D).

Hepatic impairment (severe): Contraindicated.

Renal impairment (severe): Caution. Dose reduction may be necessary. If Cl_{cr} <10 mL/min give 75–100% of normal dose.

Pregnancy: A

Breastfeeding: May be used. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

Oral, 175–500 mg 6–8 hourly; maximum dose 4 g daily.

IV (erythromycin lactobionate), 3.75–5 mg/kg 6-hourly.

Specific indications: see approved Product Information.

Paediatric dose

Oral/IV, 7.5 mg/kg 6-hourly. Maximum 12.5 mg/kg 6-hourly or 15 mg/kg 8-hourly.

Specific indications: see approved Product Information.

IM injection is not recommended: it is extremely painful. Rapid IV injections should be avoided since they can result in pain, thrombophlebitis and ototoxicity.

erythromycin ethyl succinate

macrolide antibacterial

Cautionary advisory labels: 5, D; and for suspension also use 6, 7a

Notes

- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible.
- May cause diarrhoea, nausea, diarrhoea, gastric upset or candidal infection.
- May decrease the effectiveness of oral contraceptives.
- Monitor for signs of hepatic toxicity.
- Useful as a prokinetic agent.
- Erythromycin may inhibit the metabolism of several drugs, including non-sedating antihistamines, carbamazepine and theophylline (see Table D.1, Section D).

Hepatic impairment (severe): Contraindicated.

Renal impairment (severe): Caution. Dose reduction may be necessary. If Cl_{cr} <10 mL/min give 75–100% of normal dose.

Pregnancy: A

Breastfeeding: May be used. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

1.6–4 g daily in 2–4 divided doses.

Paediatric dose

30–50 mg/kg daily in 2–4 divided doses. Maximum 4 g daily.

escitalopram

selective serotonin reuptake inhibitor

Cautionary advisory labels: 5, 9, 12

Notes

- Medicine-free interval may be required when switching to/from any other antidepressants. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- May increase the anticoagulant response to warfarin. Monitor INR.
- Indications other than depression include OCD, anxiety, panic and eating disorders.
- SSRIs inhibit the cytochrome P450 system (citalopram, escitalopram and sertraline cause the least inhibition).
- Usually given as a morning dose due to activating effects (occasionally may cause somnolence and be taken at night).
- Full benefit may not be seen for several weeks but adverse effects may occur from start of treatment.
- The efficacy and safety of escitalopram for the treatment of major depressive disorder has not been established in individuals aged less than 18 years of age.

Changes to Urinary System: May induce or aggravate urge/functional incontinence due to enhanced detrusor activity (instability), sedation or impairment of mobility.

Elderly: Hyponatraemia (SIADH) may occur.

Hepatic impairment: Caution. Dose reduction necessary. Initiate with 5 mg and titrate carefully to 10 mg if necessary.

Renal impairment (mild–moderate): Caution. Monitor clinically.

Renal impairment (severe): Caution. Limited data available. Dose reduction may be necessary.

Pregnancy: C. Use when clinically indicated if it is the drug of choice. There is increased risk of reversible withdrawal symptoms, not congenital malformations.

Breastfeeding: Use not recommended: limited data available. Excreted in breast milk. Consider other SSRIs first.

Common dosage range

Adult dose

10–20 mg daily.

esomeprazole

proton pump inhibitor, S-isomer of omeprazole

Modification of oral formulation

Before crushing or otherwise altering enteric-coated tablets, consider medicine stability issues.

Cautionary advisory labels: A* (can be dispersed in non-carbonated water)

Notes

- Raised gastric pH can reduce bioavailability of ketoconazole, itraconazole (capsule form), iron salts and digoxin.
- Generally well tolerated.
- See doctor immediately if nausea, severe vomiting, epigastric pain or diarrhoea with blood-stained stools during or after treatment is experienced.
- Esomeprazole is an inhibitor of cytochrome P450 system (see Table D.1, Section D).

Hepatic impairment (severe): Caution dose reduction necessary, maximum oral/IV dose 20 mg daily.

Pregnancy: B3. May be used when treatment with antacids and H_2 antagonists has failed. If a proton pump inhibitor is required, omeprazole is preferred.

Breastfeeding: Use with caution. Excreted in breast milk. Likely to be destroyed in infant's stomach, but no safety data on drug in infants. H_2 antagonists preferred.

Common dosage range

Adult dose

20–80 mg daily.

Paediatric dose

>12 years: 20–40 mg daily.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

etanercept

immuno-modifier, anti-tumour necrosis factor

Cautionary advisory labels: 6, 16

Notes

- Contact doctor urgently if there is persistent fever, sore throat, bruising, bleeding or rash.
- Some vaccines should not be given while taking etanercept.

Renal and hepatic impairment: Caution. No data.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

SC, 50 mg once weekly or 25 mg twice weekly.

Paediatric dose

Juvenile chronic arthritis: 4–17 years, SC, 0.4 mg/kg (maximum 25 mg) twice weekly.

ethacrynic acid

loop diuretic

Cautionary advisory labels: 16, B

Notes

- Caution with use in gout, prostatic obstruction.
- Care with NSAIDs, lithium, thiazide diuretics, digoxin (electrolyte-based).
- Time dose to suit lifestyle—usually in the morning to avoid diuresis interfering with sleep.
- Monitor electrolytes particularly for hypokalaemia and hyponatraemia.

Changes to faeces: Black discolouration.

Changes to urinary system: May induce or aggravate urge incontinence due to polyuria, constipation or frequency.

Elderly: May cause hypokalaemia, impaired glucose tolerance, hyperuricaemia or orthostatic hypotension resulting in falls and fractures.

Hepatic impairment (severe): Caution. Monitor clinically.

Renal impairment: Caution. Dose adjustment may be necessary. If normal dose ineffective, titrate to higher dose according to response. Maximum 400 mg daily.

Pregnancy: C. Use not recommended.

Breastfeeding: Use not recommended. Excreted in breast milk, but no safety data on drug in infants.

Common dosage range

Adult dose

50–150 mg daily (>50 mg as two doses).

Maximum 400 mg daily.

Paediatric dose

>2 years: 25 mg daily. May be increased in 25 mg increments as needed.

ethambutol

antimycobacterial

Notes

- Regular testing of visual acuity and colour discrimination should be carried out.
- Encourage compliance and completion of prescribed combination regimen.
- If gastric intolerance occurs, take after food.

Renal impairment: Caution. Dose adjustment necessary; monitor plasma levels of drug and for visual toxicity.

Cl_{cr} 30–60 mL/min 15–20 mg/kg every 24 hours.

Cl_{cr} 10–30 mL/min 10–15 mg/kg every 24 hours.

Cl_{cr} <10 mL/min 15–20 mg/kg every 48 hours.

Pregnancy: A

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor infant for jaundice.

Common dosage range

Adult dose

15–25 mg/kg daily or 30 mg/kg three times a week or 50 mg/kg twice weekly. Maximum daily dose 2.5 g.

Paediatric dose

>6 years: same as adult dose.

etidronate

bisphosphonate

Cautionary advisory labels: 4, A, C (2 hours)

Notes

- May cause heartburn, nausea, vomiting, abdominal pain—remain upright for 30 minutes after dose.
- Presence of food reduces absorption significantly.
- Treatment for Paget's disease is generally for 6 months.
- For osteoporosis, ensure adequate intake of calcium and vitamin D (taken at different time of day).

Renal impairment (mild–moderate): Caution. Dose adjustment necessary; monitor plasma and urinary calcium concentrations.

Renal impairment (severe): Contraindicated.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended. Excretion in breast milk expected. Potential for serious adverse effects in infant.

Common dosage range

Adult dose

Paget's disease: 5–10 mg/kg daily for up to 6 months.

Osteoporosis: 400 mg daily for 14 days followed by 76-days of 500 mg calcium supplementation daily.

Other indications: See approved Product Information.

etoposide

podophyllotoxin cytotoxic, antineoplastic

Modification of oral formulation

Avoid crushing or altering capsule due to occupational health and safety risks.

Cautionary advisory labels: 18, 21, C

Notes

Hepatic impairment (mild–moderate): Caution. Monitor clinically; risk of more profound myelotoxicity.

Hepatic impairment (severe): Contraindicated.

Renal impairment: Caution. Dose adjustment may be necessary; monitor clinically.

Cl_{cr} 15–50 mL/min use 75% of normal dose.

Cl_{cr} <15 mL/min use 50% of normal dose.

Pregnancy: D. Use contraindicated.

Breastfeeding: Use contraindicated. Potential for severe adverse effects in infant.

Common dosage range

Adult dose

Oral, 100–200 mg/m^2 daily for five days, repeated every 3–4 weeks. Total dose should not exceed 650 mg/m^2 per course.

IV infusion, 50–100 mg/m^2 daily for five days or 100 mg/m^2 on days 1, 3 and 5, repeated every 3–4 weeks. Total dose should not exceed 400 mg/m^2 per course.

everolimus

immunosuppressant

Cautionary advisory labels: 5, 8, 18, A*

Notes

- Bioavailability is increased when co-administered with cyclosporin. Dose adjustment may be needed.
- Dispersible tablets are available for patients unable to swallow whole tablets.
- Take consistently either with or without food.
- Clinically significant medicine interactions may occur (see Table D.1, Section D).

Hepatic impairment: Caution. No data; monitor whole blood trough levels of everolimus; dose adjustment may be necessary (to 50% of normal dose).

Renal impairment: Caution. Monitor clinically.

Therapeutic monitoring: Therapeutic range:

Trough, 3–8 micrograms/L.

Time to steady state 4–5 days.

Pregnancy: C. Use not recommended.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

Initial dose 0.75 mg twice daily.

exenatide

incretin mimetic, antihyperglycaemic agent

Cautionary advisory labels: 6, 7b

Notes

- Can be administered up to 60 minutes before morning and evening meals. It should not be administered after a meal. When added to metformin therapy the dose of metformin can be continued. However, when added to sulfonylurea therapy a reduction in the dose of sulfonylurea may be necessary to reduce the risk of hypoglycaemia.
- Exenatide slows gastric emptying and is therefore used with caution in patients receiving oral medication that require rapid gastrointestinal absorption or medication associated with local gastrointestinal irritation such as bisphosphonates and tetracyclines.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

- Exenatide should be initiated at 5 micrograms per dose administered twice daily for at least one month to improve tolerability (e.g. nausea). The dose may then be increased to 10 micrograms twice daily. Doses higher than 10 micrograms twice daily are not recommended.
- Enteric-coated formulations or products where peak plasma concentrations are clinically relevant should be administered at least 1 hour before or 4 hours after exenatide injections.
- Avoid in patients with a history of pancreatic disease (e.g. pancreatitis).

Pregnancy: C.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

Initiate at 5 micrograms per dose twice daily for at least one month to improve tolerability (e.g. nausea). The dose may then be increased to 10 micrograms twice daily. Doses higher than 10 micrograms twice daily are not recommended.

ezetimibe

inhibits cholesterol absorption

Cautionary advisory labels: 5

Notes

- May be administered at the same time as a concurrent HMG-CoA reductase inhibitor (statin).
- Important to follow a low-fat diet and other measures such as exercise and weight control.
- When taken in combination with a statin monitor LFTs.
- Give at least 2 hours before or 4 hours after a bile acid sequestrant.

Hepatic impairment (moderate–severe): Contraindicated.

Pregnancy: B3. Lipid-lowering therapy not recommended during pregnancy.

Breastfeeding: Use not recommended: limited data available. Excretion in breast milk expected.

Common dosage range

Adult dose

10 mg once daily.

famciclovir

guanine analogue, antiviral

Cautionary advisory labels: D—some packaging contains more units than for the treatment for one episode, e.g. episodic treatment of recurrent disease

Notes

- Herpes zoster: initiate treatment as soon as possible after diagnosis is made.
- Herpes labialis: start treatment at the earliest sign or symptom, such as tingling, itching or burning.
- Genital herpes: avoid sexual intercourse when symptoms are present.
- Use condoms between episodes to reduce risk of transmission: asymptomatic viral shedding can occur.

Hepatic impairment: Caution. Monitor clinically.

Renal impairment: Caution. Dose adjustment necessary. Severe impairment increases risk of neurotoxicity. For recurrent herpes labialis.

Cl_{cr} 40–59 mL/min 750 mg as a single daily dose.

Cl_{cr} 20–39 mL/min 500 mg as a single daily dose.

Cl_{cr} 10–20 mL/min 250 mg as a single daily dose.

Pregnancy: B1. More experience with aciclovir in pregnancy. Seek advice from an infectious diseases specialist.

Breastfeeding: Use not recommended: limited data available. Aciclovir preferred.

Common dosage range

Adult dose

Immuno-competent: 125–250 mg 2–3 times daily. Doses are generally higher if immuno-compromised.

Paediatric dose

Shingles: 5 mg/kg three times daily.

famotidine

H_2 antagonist

Notes

- If symptoms do not improve after two weeks of treatment, seek medical advice.
- If nausea, severe vomiting, epigastric pain, black or blood-stained stools are experienced during or after treatment, seek medical advice.
- Question long-term use without investigation.

Renal impairment (moderate–severe): Caution. Dose adjustment necessary.

Cl_{cr} <50 mL/min use 50% of normal dose, or give every 36 to 48 hours.

Monitor for signs of central nervous system toxicity.

Pregnancy: B1. May be used when conservative treatment with antacids has failed. If an H_2 antagonist is required, ranitidine and famotidine are preferred.

Breastfeeding: May be used. Excreted into breast milk and may accumulate. If an H_2 antagonist is required, famotidine is preferred.

Common dosage range

Adult dose

20–40 mg daily in 1–2 doses.

Paediatric dose

Oral, 1–2 mg/kg daily in two divided doses.

felodipine

dihydropyridine calcium channel blocker

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets will alter absorption characteristics.

Cautionary advisory labels: 9, 12†, 18, A

Notes

- Dihydropyridines can cause peripheral oedema (swollen ankles).
- Potentially significant drug interactions may occur (see Table D.1, Section D).

Elderly: Peripheral oedema.

Hepatic impairment: Caution. Dose adjustment may be necessary. Initiate with 2.5 mg daily.

Pregnancy: C. Consider alternative therapy first. If drug of choice, use with caution as maternal hypotension may produce fetal hypoxia.

Breastfeeding: Use with caution: limited data available. If a calcium channel blocker is required, nifedipine is preferred.

Common dosage range

Adult dose

5 mg once daily (2.5 mg once daily in elderly); maintenance 5–10 mg once daily.

Maximum dose 20 mg daily.

Paediatric dose

0.2–0.5 mg/kg once daily.

fenofibrate

fibric acid derivative

Cautionary advisory labels: 8, A

Notes

- If muscle pain, tenderness or weakness is experienced, seek medical advice.
- Risk of adverse effects is increased when combined with a 'statin'.
- Continue to follow low-fat diet and lifestyle modification such as exercise and weight control.
- Monitor LFTs, stop therapy if transaminases elevated >3 times upper limit of normal.

Hepatic impairment (severe): Contraindicated.

Renal impairment: Caution. Dose adjustment necessary.

Cl_{cr} 20–60 mL/min 134 mg daily.

Cl_{cr} 10–20mL/min 67 mg daily.

Pregnancy: B3. Lipid-lowering therapy not recommended during pregnancy.

Breastfeeding: Use not recommended as limited data available.

Common dosage range

Adult dose

145 mg daily.

fentanyl

opioid

Cautionary advisory labels: 1, 21 (patches and lozenges)

Notes

- Generally recommended for use only in patients who are stabilised on opioid therapy due to risk of respiratory depression.
- Patches: may take up to 72 hours to achieve maximal effect after initial dose. The use of other analgesics should be continued and gradually phased out.
- Lozenges: initial effect within 5–10 minutes; maximal effect within 20–40 minutes.
- Constipation may be a problem with chronic use. Start treatment with stimulant or osmotic laxative. May cause nausea or vomiting.
- Ensure transdermal patches are disposed of responsibly.

† Most appropriate during initial treatment or when dosage is increased.

Renal and hepatic impairment: Caution. Monitor for signs of toxicity—drowsiness, respiratory depression.

Pregnancy: C. Use only if drug of choice. High doses or prolonged use at or near term may cause respiratory depression and withdrawal in newborn.

Breastfeeding: May be used for single dose or short-term use. Excreted in breast milk but has low oral bioavailability. Monitor for adverse effects (e.g. sedation) in infant.

Common dosage range

Adult dose

Patch, 25–300 micrograms/hour. See approved Product Information.

Lozenge, initially 200 micrograms. May be repeated once after 30 minutes if required. See approved Product Information.

Dose equivalence: 25 micrograms per hour patch is approximately equivalent to 90 mg/24 hours oral morphine or 30–40 mg/24 hours parenteral morphine.

Paediatric dose

Analgesia: IV, 0.5–4 micrograms/kg 2–3 hourly.

Anaesthesia: IV, 0.5–3 micrograms/kg. See approved Product Information.

ferrous salts

haematinic, iron supplement

Modification of oral formulation

Before crushing or otherwise altering tablets or capsules, consider the increased risk of local irritant effect.

Cautionary Advisory Labels:

Ferrous fumarate: 13, B*

Ferrous gluconate: 4 (delete dairy products), 13, C

Ferrous sulfate: 4 (delete dairy products), 13, A*, C

Notes

- Ferrous sulfate: if gastric intolerance occurs, take after meals.

Changes to urinary system: Black discolouration.

Changes to faeces: Black discolouration.

Renal and hepatic impairment: Caution. No data.

Pregnancy: A. (Except iron sucrose: B3). All may be used.

Breastfeeding: May be used. Small amounts excreted in breast milk. Avoid excessive doses.

Common dosage range

Adult dose

100–200 mg elemental iron daily.

Paediatric dose

2–3 mg/kg elemental iron daily. Maximum 7 mg/kg daily.

Note: 5mL ferrous sulfate oral solution (*Ferro-liquid*®) contains 30 mg of elemental iron.

fexofenadine

less-sedating antihistamine

Notes

Renal impairment (severe): Caution. Dose adjustment necessary. Dose 60 mg daily.

Pregnancy: B2. Use not recommended. Consider use of sedating antihistamines first. If less-sedating antihistamine required, loratadine is preferred.

Breastfeeding: Use not recommended. Excretion in breast milk expected, but no safety data on drug in infants. Loratadine or short acting sedating antihistamines preferred.

Common dosage range

Adult dose

120–180 mg daily in single (controlled-release) or divided doses.

Paediatric dose

6–11 yrs: 30 mg twice daily.

flecainide

antiarrhythmic

Cautionary advisory labels: 9, 12, 13

Notes

- Drug choice dictated by arrhythmia type and co-existing medical conditions.
- May increase QRS duration and prolong QT intervals. May have additive effect with medicines that also prolong the QT interval.

Elderly: Increased half-life may require dose reduction.

Renal and hepatic impairment (severe): Contraindicated, unless plasma level monitoring can be performed. Dose adjustment necessary.

Cl_{cr} <20 mL/min 100 mg daily, monitor levels.

Pregnancy: B3. Seek specialist advice. May be used to treat maternal and fetal arrhythmias.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Breastfeeding: May be used. Minimal excretion in breast milk. Monitor for adverse effects in infants.

Common dosage range

Adult dose

Oral, 50–100 mg every 12 hours; may be increased by 50 mg every four days up to a maximum 400 mg daily.

IV, 2 mg/kg administered over at least 10 minutes; maximum 150 mg/dose.

Paediatric dose

IV, 0.5 mg/kg/dose; maximum 2 mg/kg.

Oral, initially 2 mg/kg twice daily, increasing at intervals ≥4 days, to a maximum of 6 mg/kg daily.

flucloxacillin

penicillin antibacterial

Cautionary advisory labels: C or 3b, D; and for suspension also use 6 and 7a

Notes

- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible during waking hours.
- Ask about any previous reaction to penicillin.
- If a skin rash occurs, seek medical advice.
- Other common adverse effects—nausea, diarrhoea, gastric upset.
- If signs of jaundice occur, seek urgent medical advice (higher risk if age >55 years and length of course >2 weeks).

Elderly: Increased risk of hepatotoxicity.

Renal and hepatic impairment (severe): Caution. Dose adjustment necessary.

Pregnancy: B1. May be used.

Breastfeeding: May be used. Trace amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

Oral, 250–500 mg every 6 hours. Maximum 4 g daily.

IV, 1–2 g every 6 hours. Maximum 12 g daily.

Paediatric dose

Oral, 12.5–25 mg/kg 6-hourly.

IV, 25–50 mg/kg every 4–6 hours.

fluconazole

triazole antifungal agent

Cautionary advisory labels: 5, D

Notes

- Advise patient to seek medical advice if they suffer from nausea, decreased appetite, pale faeces, or yellowing of the skin or whites of eyes.
- Monitor LFTs where suspected hepatic insufficiency.

Renal Impairment: Caution. Dose adjustment necessary.

Cl_{cr} 21–50 mL/min normal dose for two days then 50% usual dose every 24 hours.

Cl_{cr} 10–20 mL/min normal dose for two days then 25–50% usual dose every 24 hours.

Pregnancy: D. High doses or prolonged therapy contraindicated. Single oral 150 mg dose unlikely to pose any teratogenic risk.

Breastfeeding: May be used short term. Small amounts excreted in breast milk. Regular doses or long-term use not recommended as limited data available.

Common dosage range

Adult dose

Generally 50–400 mg daily.

Vulvovaginal candidiasis: 150 mg single dose.

Onchomycosis: 150–300 mg weekly for 3–12 months.

Other indications: See approved Product Information.

Paediatric dose

Superficial and oral candidiasis: Oral, 6 mg/kg (maximum 200 mg) on day one, then 3 mg/kg once daily.

Systemic infections: IV/oral, 12 mg/kg (maximum 400 mg) on day one, then 6 mg/kg once daily.

fludrocortisone

mineralocorticoid

Cautionary advisory labels: 9, B

Notes

- Monitor electrolytes and blood pressure.
- Monitor clinically for signs of heart failure.

Renal and hepatic impairment: Caution.

Pregnancy: A. Monitor maternal blood glucose due to risk of hyperglycaemia.

Breastfeeding: Use with caution: limited data available. Only small amounts excreted with maternal replacement doses.

Common dosage range

Adult and paediatric dose

50–100 micrograms once or twice daily.

Monitor development and growth carefully in children on long-term therapy.

flunitrazepam

benzodiazepine

Cautionary advisory labels: 1 or 1a, 9

Notes

- Regular use for more than 2–4 weeks may result in dependence and tolerance.
- Monitor patient for physical and psychological dependence and tolerance (check intervals between prescription refills).
- May cause a 'morning-after' hangover effect.
- Caution with respiratory disease or sleep apnoea as reduced respiratory drive may cause hypoxaemia.
- Risk of blood dyscrasias. Monitor FBC and LFTs.

Changes to urinary system: May induce or aggravate functional incontinence due to sedation or impairment of mobility.

Elderly: May cause over-sedation, confusion, memory impairment, or poor muscle coordination resulting in falls and fractures.

Renal and hepatic impairment (moderate): Caution. Dose reduction may be necessary. Titrate dose carefully. Monitor patient for signs of toxicity.

Hepatic impairment (severe): Contraindicated.

Pregnancy: C. Use should be avoided if possible, especially during first trimester. If flunitrazepam is required, use the lowest effective dose for the shortest duration.

Breastfeeding: Use with caution. Excreted into breast milk, with concentrations increasing with time. Adverse effects (e.g. sedation, poor feeding) may be experienced by infant. Avoid long-term use, large doses or frequent dosing. If a benzodiazepine is required, a shorter acting one is preferred.

Common dosage range

Adult dose

0.5–2 mg at night.

fluoxetine

selective serotonin reuptake inhibitor, antidepressant

Cautionary advisory labels: 5, 9, 12

Notes

- Medicine-free interval may be required when switching to/from other antidepressants. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- May increase the anticoagulant response to warfarin. Monitor INR.
- Indications other than depression include obsessive compulsive disorder, anxiety, panic and eating disorders.
- SSRIs inhibit the cytochrome P450 enzymes (citalopram, escitalopram and sertraline the least—see Table D.1, Section D).
- Usually given as a morning dose due to activating effects—occasionally may cause somnolence and be taken at night.
- Dispersible tablet can be used when difficulty swallowing.
- Full benefit may not be seen for several weeks but adverse effects may occur from start of treatment.
- The efficacy and safety of fluoxetine for the treatment of major depressive disorder has not been established in individuals aged less than 18 years.

Changes to urinary system: May induce or aggravate urge/functional incontinence due to enhanced detrusor activity (instability), sedation or impairment of mobility.

Elderly: Hyponatraemia (SIADH) may occur.

Renal and hepatic impairment: Caution. Dose reduction may be necessary.

Pregnancy: C. Use when clinically indicated if it is the drug of choice. There is increased risk of reversible withdrawal symptoms, not congenital malformations.

Breastfeeding: Use not recommended. 10% of dose excreted in breast milk and may accumulate due to long half-life. Consider other SSRIs first.

Common dosage range

Adult dose

20–80 mg daily. Doses over 20 mg to be given twice daily, morning and noon.

Paediatric dose

>5 years: 0.5–1 mg/kg daily as a single morning dose.

fluphenazine

conventional antipsychotic agent

Cautionary advisory labels: 1, 8, 9 (long-term regular therapy), 16

Notes

- May cause anticholinergic, hypotensive and extrapyramidal effects (dystonia, akathisia, parkinsonism, tardive dyskinesia).
- Compliance may be a problem.
- Avoid concurrent use of more than one antipsychotic.
- Withdraw antipsychotics slowly if stopping the medication.

Changes to urinary system: May discolur urine pink, red or red–brown.

Elderly: Confusion, sedation, extrapyramidal effects (e.g. parkinsonism), constipation, urinary retention, blurred vision, orthostatic hypotension leading to falls and fractures.

Hepatic impairment (severe): Caution. Dose reduction necessary. Give half dose.

Renal impairment (severe): Contraindicated.

Pregnancy: C. Use only if drug of choice. Use minimal effective dose.

Breastfeeding: Use with caution. Excretion of small amounts expected. Monitor for adverse effects (e.g. sedation) in infant.

Common dosage range

Adult dose

IM, 12.5–50 mg every 2–6 weeks. Maximum 100 mg every two weeks.

flutamide

non-steroidal anti-androgen

Cautionary advisory labels: 8

Notes

- Monitor for signs of hepatic toxicity (jaundice).
- Monitor LFTs.

Changes to urinary system: May discolour urine amber or yellow–green.

Hepatic impairment (moderate): Caution. Monitor clinically.

Hepatic impairment (severe): Contraindicated.

Pregnancy: Use not recommended. Indicated for male use only.

Breastfeeding: Use not recommended. Indicated for male use only.

Common dosage range

Adult dose

250 mg three times daily.

fluticasone

inhaled corticosteroid

Cautionary advisory labels: 14 (oral inhalation)

Notes

- Inquire about asthma management plan.
- A preventive medication intended for continued and regular use even if no symptoms present. Not for use during acute attacks.
- Review technique and compliance.
- Rinse mouth with water after use to decrease systemic absorption and minimise risk of oral thrush.
- Cover eyes during nebulisation because of possible leakage from a mask.
- If asthma is well controlled, try a dose reduction of 25% every three months. Titrate dose to lowest possible dose for effective control.
- Systemic effects may include bone density loss, glaucoma, cataract, skin thinning, impaired growth, adrenal suppression.
- Use after beta$_2$ agonist if being used concurrently.
- May take >1 week to achieve full benefit.

Renal and hepatic impairment: Safe to use, no dosage adjustment necessary.

Pregnancy: B3. May be used. Women planning a pregnancy should switch to budesonide.

Breastfeeding: May be used. Negligible systemic absorption.

Common dosage range

Adult dose

MDI/DPI: 100–250 micrograms twice daily; up to 1,000 micrograms daily in severe persistent asthma.

Nebules: 2 mg twice daily.

Paediatric dose

MDI/DPI: >1 year, 50–100 micrograms twice daily; up to 500 micrograms daily in severe persistent asthma.

Nebules: >4 years, 1 mg twice daily for up to 7 days.

Monitor development and growth carefully in children on long-term therapy.

fluvastatin

HMG-CoA reductase inhibitor

Notes

- Take with food in the evening.
- If muscle pain, tenderness or weakness is experienced, seek medical advice.
- Increased risk of adverse effects in combination with gemfibrozil.
- Important to continue to follow a low-fat diet and other measures such as exercise and weight control.

Renal and hepatic impairment (mild–moderate): Caution, limited data available. Monitor clinically. Initiate at low dose and titrate carefully.

Renal and hepatic impairment (severe): Contraindicated.

Pregnancy: D. Lipid-lowering therapy not recommended during pregnancy.

Breastfeeding: Use not recommended as limited data available. Excreted in breast milk.

Common dosage range

Adult dose

20–40 mg daily in the evening. Maximum dose 80 mg daily (in 1 or 2 doses).

fluvoxamine

selective serotonin reuptake inhibitor, antidepressant

Cautionary advisory labels: 5, 9, 12, A*

Notes

- Medicine-free interval may be required when switching to/from any other antidepressants. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- May increase the anticoagulant response to warfarin. Monitor INR.
- Indications other than depression include obsessive compulsive disorder, anxiety, panic and eating disorders.
- SSRIs inhibit the cytochrome P450 enzymes (citalopram, escitalopram and sertraline the least—see Table D.1, Section D).
- Usually given as a morning dose due to activating effects (occasionally may cause somnolence and be taken at night).
- Full benefit may not be seen for several weeks but adverse effects may occur from start of treatment.
- The efficacy and safety of fluvoxamine for the treatment of major depressive disorder has not been established in individuals aged less than 18 years.

Changes to urinary system: May induce or aggravate urge/functional incontinence due to enhanced detrusor activity (instability), sedation or impairment of mobility.

Elderly: Hyponatraemia (SIADH) may occur.

Hepatic impairment (moderate): Caution. Monitor clinically. Initiate at low dose and titrate carefully.

Hepatic impairment (severe): Caution. Dose reduction necessary. Halve the usual dose.

Renal impairment: Caution. Monitor clinically. Initiate at low dose and titrate carefully.

Pregnancy: C. Use when clinically indicated if it is the drug of choice. There is increased risk of reversible withdrawal symptoms, not congenital malformations.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. sedation, restlessness, irritability, poor feeding) in infant. Avoid feeds for 5–8 hours following a dose.

Common dosage range

Adult dose

50–300 mg daily.

Paediatric dose

>8 years, 25 mg daily initially, increasing weekly by 25 mg to maximum 200 mg daily in two doses.

folic acid

B group vitamin, haematinic

Notes

- May be used to reduce mucosal and gastrointestinal side effects of methotrexate therapy at a dose of 5–10 mg per week, taken as a single dose or split doses, generally not on the day the methotrexate dose is taken.

Pregnancy: A

Breastfeeding: May be used.

Common dosage range

Adult dose

Prophylaxis during pregnancy and lactation (low risk): 0.5 mg daily.

Megaloblastic anaemia: 1–5 mg daily.

Paediatric dose

Megaloblastic anaemia: infants, 50 micrograms daily; >1 year, 1 mg daily; maintenance, 0.1–0.5 mg daily.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

fosamprenavir

antiretroviral protease inhibitor

Cautionary advisory labels: 5, 3a (liquid)

Notes

- Does not cure HIV or eliminate risk of transmission.
- May interact with many medicines (see Table D.1, Section D).
- Should be taken in combination with other antiretrovirals.
- Sulfonamide: caution allergies.

Hepatic impairment (mild): Caution. Limited data available, dose reduction may be necessary.

Hepatic impairment (moderate–severe): Contraindicated.

Renal impairment: Caution. Limited data available.

Pregnancy: B3. Previously commenced therapy should be continued and advice sought from an infectious diseases specialist.

Breastfeeding: Expected to be excreted into breast milk, but no safety data on drug in infants. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

700 mg twice daily or 1,400 mg once daily.

Paediatric dose

>6 years, 18 mg/kg (maximum 700 mg) twice daily.

fosinopril

angiotensin-converting enzyme inhibitor

Cautionary advisory labels: 11, 12†, 16†

Notes

- Monitor renal function and potassium concentration.
- Caution if the patient is taking NSAIDs (including COX-2 inhibitors) or lithium.
- Provide advice on avoiding foods and drugs with high potassium content.
- Blood pressure should be closely monitored during initiation of therapy.
- Can cause cough (cough can also be a symptom of heart failure). Establish if cough is productive or unproductive.
- May cause metallic taste or lack of taste.
- If persistent dry cough or swelling of face, lips or tongue is experienced, seek medical advice.
- A combination product of fosinopril with a diuretic is also available. Check that patient knows which product is being taken.

Changes to urinary system: May induce or aggravate stress incontinence due to cough-induced sphincter weakness.

Hepatic impairment: Caution. Dose reduction may be necessary. Start at 10 mg daily, titrate dose carefully.

Renal impairment: Caution. Dose reduction may be necessary.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as possible if pregnancy is suspected.

Breastfeeding: Use not recommended. Excreted in breast milk, but no safety data on drug in infants. If an ACE inhibitor is required, captopril or enalapril is preferred.

Common dosage range

Adult dose

10–40 mg once daily.

frusemide

loop diuretic

Cautionary advisory labels: 16

Notes

- Time dose to suit lifestyle—usually in the morning to avoid diuresis interfering with sleep.
- Caution with use in gout, prostatic obstruction.
- Care with NSAIDs, lithium, thiazide diuretics, digoxin.
- Can cause orthostatic hypotension. Ask about dizziness on standing and counsel about rising slowly and cautiously.
- Monitor electrolytes particularly for hypokalaemia and hyponatraemia.
- Tinnitus, reversible or permanent hearing impairment, has occurred following rapid IV administration.
- Sulfonamide: caution allergies.

Changes to urinary system: May induce or aggravate urge incontinence due to polyuria, constipation or frequency.

Elderly: Impaired glucose tolerance, hyperuricaemia, orthostatic hypotension leading to falls and fractures. Counsel about rising slowly and cautiously.

Renal and hepatic impairment (moderate): Caution. Monitor clinically. Measure electrolytes and creatinine.

Renal and hepatic impairment (severe): Contraindicated.

Pregnancy: C. Use not recommended.

† Most appropriate during initial treatment or when dosage is increased.

Breastfeeding: Use not recommended. Excreted in breast milk. Potential for adverse effects (e.g. electrolyte disturbances, diuresis) but none reported. May suppress lactation.

Common dosage range

Adult dose

Oral, 20–40 mg once or twice daily. May be gradually increased up to 400 mg daily. For patients with severe renal impairment, doses up to 1,000 mg daily may be required.

IV, 20–40 mg every 1–2 hours.

Paediatric dose

Oral, 1–2 mg/kg once or twice daily; maximum dose 6 mg/kg.

IM/IV, 0.5–1 mg/kg every 6–12 hours. Maximum dose 6 mg/kg.

gabapentin

antiepileptic, analgesic (neuropathic pain)

Cautionary advisory labels: 1, 9

Notes

Renal impairment: Caution. Dose reduction necessary. Refer to approved Product Information.

Pregnancy: B1. Consider risk of congenital malformation against dangers of uncontrolled epilepsy. Consider folic acid (5 mg) and vitamin K supplementation.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

900–3,600 mg daily in three doses.

Paediatric dose

3–12 years: 10 mg/kg on day 1; increase by 10 mg/kg a day up to 25–35 mg/kg daily in three doses; up to 60 mg/kg daily may be given if necessary.

galantamine

cholinesterase inhibitor

Cautionary advisory labels: 5, 12, A*, B

Notes

- If treatment is interrupted for several days, re-titrate dose to minimise adverse effects, e.g. nausea and vomiting.
- Can be given in the morning if vivid dreams occur at night.
- Avoid anticholinergics due to antagonistic effects.

Changes to urinary system: May induce or aggravate urge incontinence due to enhanced cholinergic effect, detrusor instability, frequency, or urgency.

Hepatic impairment (moderate): Caution. Dose reduction necessary.

Initial dose 8 mg every 48 hours (for 7 days), increased to 8 mg daily (for four weeks) to a maximum 16 mg daily.

Hepatic impairment (severe): Contraindicated where Child–Pugh score >9.

Renal impairment (moderate): Caution. Monitor clinically.

Renal and hepatic impairment (severe): Contraindicated when Cl_{cr} <9 mL/min.

Pregnancy: B1. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

8–24 mg once daily.

ganciclovir

antiviral

Notes

- Male patients should avoid fathering children during treatment and within 90 days of ceasing therapy.

Renal impairment: Caution. Dose reduction necessary. See approved Product Information.

Pregnancy: D. Use contraindicated.

Breastfeeding: Use contraindicated. Potential for serious adverse effects in infants. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

CMV retinitis

Induction: IV, 5 mg/kg infused over 1 hour every 12 hours for 14–21 days.

Maintenance: 6 mg/kg once daily for 5 days/week; or 10 mg/kg once daily for 3 days each week; or 5 mg/kg once daily every day.

Intravitreal implant 4.5 mg: 1 microgram/hr over 6–8 months.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

gemfibrozil

fibric acid derivative

Cautionary advisory labels: 3b

Notes

- If muscle pain, tenderness or weakness is experienced, seek medical advice.
- Increased risk of adverse effects in combination with a 'statin'.
- Important to follow low-fat diet and other measures such as exercise and weight control.

Renal and hepatic impairment (severe): Contraindicated.

Pregnancy: B3. Lipid-lowering therapy not recommended during pregnancy.

Breastfeeding: Use not recommended. Excretion in breast milk expected. Potential for adverse effects in infants.

Common dosage range

Adult dose

600 mg twice daily.

gentamicin

aminoglycoside antibacterial

Notes

- Plasma concentration monitoring is advisable, especially in patients with renal insufficiency and in neonates.
- Monitor for ototoxicity and nephrotoxicity—possible adverse effect.

Renal impairment: Caution. Dose reduction necessary. See approved Product Information.

Therapeutic monitoring: Several strategies have been proposed for monitoring extended dosing interval aminoglycoside therapy, including a nomogram and area-under-the-curve targeting. See to 'Optimal medicine concentration ranges', Section D.

Pregnancy: D. Use not recommended, except for severe or life-threatening infections where safer drugs are inappropriate.

Breastfeeding: May be used, although caution with premature neonates. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

IM/IV, 3–5 mg/kg daily; up to 8 mg/kg daily in severe or life-threatening infections.

Paediatric dose

IM/IV, 3–7.5 mg/kg daily in 2–3 doses.

glibenclamide

sulfonylurea antidiabetic agent

Cautionary advisory labels: 10a, B

Notes

- Advise patients of the signs of hypoglycaemia (i.e. sweating, hunger, faintness, palpitations, tremor, headache, visual disturbance) and its management. Administration with/after food minimises the risk of hypoglycaemia.
- Monitor and record blood sugar levels as prescribed. Advise/demonstrate use of testing kits.
- Adhere to diabetic diet and alcohol limitations.
- Start at low dose and increase weekly until control achieved.
- Increasing dose above recommended range generally has little additional hypoglycaemic effect. Consider combination or alternative therapy.
- Replace with insulin during pregnancy and breastfeeding.

Elderly: Use a shorter acting sulfonylurea, e.g. gliclazide.

Hepatic impairment (severe): Contraindicated.

Renal impairment: Caution. Dose reduction necessary. Monitor for signs of hypoglycaemia.

Renal and hepatic impairment (severe): Contraindicated.

Pregnancy: C. Oral hypoglycaemic agents usually replaced with insulin.

Breastfeeding: Use not recommended. Small amounts excreted in breast milk. Potential for hypoglycaemia in infant. Diet or insulin control preferred.

Common dosage range

Adult dose

2.5–20 mg daily in 1 or 2 doses.

gliclazide

sulfonylurea antidiabetic agent

Cautionary advisory labels: 10a, A*, B

Notes

- Advise patients of signs of hypoglycaemia (i.e. sweating, hunger, faintness, palpitations, tremor, headache, visual disturbance) and its management. Administration with/after food minimises the risk of hypoglycaemia.
- Monitor and record blood sugar levels as prescribed. Advise/demonstrate use of testing kits.
- Adhere to diabetic diet and alcohol limitations.
- Start at low dose and increase weekly until control achieved.
- Increasing dose above recommended range generally has little additional hypoglycaemic effect. Consider combination or alternative therapy.

Renal and hepatic impairment (mild–moderate): Caution. Dose reduction may be necessary. Monitor for signs of hypoglycaemia.

Renal and hepatic impairment (severe): Contraindicated.

Pregnancy: C. Oral hypoglycaemic agents usually replaced with insulin.

Breastfeeding: Use not recommended. Excretion in breast milk expected. Potential for hypoglycaemia in infant. Diet or insulin control preferred.

Common dosage range

Adult dose

40–320 mg daily; up to 160 mg may be taken as a single dose.

Controlled-release formulation: 30–120 mg once daily.

glimepiride

sulfonylurea antidiabetic agent

Cautionary advisory labels: 10a, F (or add 'with a meal')

Notes

- Advise patients of signs of hypoglycaemia (i.e. sweating, hunger, faintness, palpitations, tremor, headache, visual disturbance) and its management. Administration with/after food minimises the risk of hypoglycaemia.
- Monitor and record blood sugar levels as prescribed. Advise/demonstrate use of testing kits.
- Adhere to diabetic diet and alcohol limitations.
- Start low dose and increase weekly until control achieved.
- Increasing dose above recommended range generally has little additional hypoglycaemic effect. Consider combination or alternative therapy.

Renal and hepatic impairment (mild–moderate): Caution. Dose reduction may be necessary. Monitor for signs of hypoglycaemia.

Renal and hepatic impairment (severe): Contraindicated.

Pregnancy: C. Oral hypoglycaemic agents usually replaced with insulin.

Breastfeeding: Use not recommended. Excretion in breast milk expected. Potential for hypoglycaemia in infant. Diet or insulin control preferred.

Common dosage range

Adult dose

1–4 mg once daily.

glipizide

sulfonylurea antidiabetic agent

Cautionary advisory labels: 10a, B

Notes

- Advise patients of signs of hypoglycaemia (i.e. sweating, hunger, faintness, palpitations, tremor, headache, visual disturbance) and its management. Administration with/after food minimises the risk of hypoglycaemia.
- Monitor and record blood sugar levels as prescribed. Advise/demonstrate use of testing kits.
- Adhere to diabetic diet and alcohol limitations.
- Start at low dose and increase weekly until control achieved.
- Increasing dose above recommended range generally has little additional hypoglycaemic effect. Consider combination or alternative therapy.

Renal and hepatic impairment (mild–moderate): Caution. Dose reduction may be necessary. Monitor for signs of hypoglycaemia.

Renal and hepatic impairment (severe): Contraindicated.

Pregnancy: C. Oral hypoglycaemic agents usually replaced with insulin.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Breastfeeding: Use not recommended. Excreted in breast milk. Potential for hypoglycaemia in infant. Diet or insulin control preferred.

Common dosage range

Adult dose

2.5–40 mg daily in 1–2 doses. Use divided doses for doses >15 mg.

glucagon

hyperglycaemic pancreatic hormone

Notes

- Glucagon will have little or no effect when the patient is fasting or when hypoglycaemia is induced by alcohol.
- Oral carbohydrates (e.g. a sandwich or a glass of milk) should be given once the patient has responded to the treatment to prevent the occurrence of secondary hypoglycaemia.

Pregnancy: B2. May be used.

Breastfeeding: May be used in medical emergency.

Common dosage range

Adult dose

SC/IM/IV, 1 mg.

Paediatric dose

SC/IM/IV, ≥25 kg: 1 mg; <25 kg: 0.5 mg.

glyceryl trinitrate

nitrate, anti-anginal

Cautionary Advisory Labels:

Tablets: 7b, 13, 16

Patches: 13, 16, 21

Spray: 16

Notes

Sublingual tablets and spray

- Use during episodes of angina or before an activity expected to precipitate angina.
- Sit or lie down before use: the drug may cause orthostatic hypotension.
- Prime spray 5 times before first use, then spray under tongue.
- Place the tablet under the tongue, but do not swallow. Once angina has been relieved, spit out what is left of the tablet to avoid adverse effects such as headache.
- If 2 tablets or 2 sprays over 15 minutes do not relieve pain, advise patient to seek immediate medical assistance.
- Common adverse effects include headache, flushing, palpitations and hypotension.
- Store tablets in a glass container and protect from moisture, light and heat; do not carry close to the body; discard unused tablets 3 months after opening the bottle.

Patch

- Ensure a nitrate-free period of 10–12 hours each day.
- This form of glyceryl trinitrate will not relieve an acute attack; use sublingual tablets or spray.

Changes to urinary system: Brown–black discolouration of urine.

Renal and hepatic impairment (severe): Caution. Monitor clinically.

Pregnancy: B2. Consider alternatives. Use minimum effective dose if required in acute situation.

Breastfeeding: Use with caution, particularly infusions and sustained-release preparations. Excretion in breast milk unknown. Monitor for adverse effects in infants.

Common Dose Range

Adult dose

Acute angina: Sublingual tablet, 300–900 micrograms; sublingual spray, 400–800 micrograms (1–2 sprays).

Prevention of chronic angina: Patch, 5–15 mg for up to 14 hours daily.

Other indications: See approved Product Information.

granisetron

$5HT_3$ antagonist antiemetic

Cautionary advisory labels: 12

Notes

- Inquire if other medicine has been lost due to vomiting.

Renal and hepatic impairment: Safe to use.

Pregnancy: B1. Consider alternatives first. If a $5HT_3$ antagonist is required, ondansetron is preferred.

Breastfeeding: Use not recommended: limited data available. If a $5HT_3$ antagonist is required, ondansetron is preferred.

Common dosage range

Adult dose

Cancer chemotherapy–induced nausea/vomiting
Prevention: Oral, 2 mg one hour before chemotherapy, or IV, 3 mg 30 minutes before chemotherapy.

Maintenance: 2 mg daily for up to one week following chemotherapy.

Treatment: IV, 1 mg every 10 minutes. Maximum 9 mg in 24 hours.

Paediatric dose

>2 years: IV, 20–40 micrograms/kg (up to 3 mg) 30 minutes before chemotherapy.

griseofulvin

antifungal agent

Cautionary advisory labels: 2, 8, 12, B, D

Notes

- Duration of treatment depends on thickness of keratin layer. Usually 4–6 weeks for superficial infections but may be prolonged depending on the site of infection and species of fungus involved.
- Absorption is increased when taken with a high-fat meal. Take with food or milk.

Hepatic impairment (severe): Contraindicated.

Pregnancy: B3. Use not recommended during, and for four weeks after ceasing, therapy. Men also not to father children during and within six months of ceasing therapy.

Breastfeeding: Use not recommended. Significant amounts excreted in breast milk but no safety data on drug in infants.

Common dosage range

Adult dose

500–1,000 mg daily.

Paediatric dose

10 mg/kg daily in divided doses.

haloperidol

conventional antipsychotic agent

Cautionary advisory labels: 1, 16

Notes

Antinauseant: dopamine antagonists

- Do not take more than the recommended dose.
- Can cause dystonic reactions, particularly at higher doses.
- Inquire if other medicine been lost due to vomiting.
- May cause depression.

Psychotropic: conventional

- May cause anticholinergic, hypotensive and extrapyramidal effects (dystonia, akathisia, parkinsonism, tardive dyskinesia).
- Compliance may be a problem.
- Avoid concurrent use of more than one antipsychotic.

Changes to urinary system: May induce or aggravate overflow/functional/stress incontinence due to constipation, sedation, confusion or parkinsonism.

Elderly: Reduce dose in hepatic impairment and in the elderly to reduce risk of extrapyramidal effects, dizziness, confusion.

Hepatic impairment: Caution. Dose reduction necessary. Halve dose in severe impairment.

Renal impairment: Caution. Dose reduction may be necessary. Monitor when giving large doses.

Pregnancy: C. Use only if drug of choice. Use minimal effective dose.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. sedation, other central nervous system effects) in infant.

Common dosage range

Adult dose

Chronic psychoses: Oral, 1–15 mg daily in divided doses.

Acute psychoses: IM/IV, initially 2–10 mg every hour as needed. Maximum total daily dose, 100 mg.

Paediatric dose

>5 years: initially 0.25–0.5 mg once daily, increasing weekly according to indication:

- Tourette's syndrome, severe aggression: 0.075 mg/kg daily. Maximum 5 mg.
- Psychotic disorders: 0.15 mg/kg daily. Maximum 5 mg.

heparin sodium

heparin

Notes

Changes to faeces: Pink, red or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Renal and hepatic impairment: Caution. Monitor clinically.

Renal and hepatic impairment (severe): Contraindicated.

Pregnancy: C. May be used.

Breastfeeding: May be used. No excretion in breast milk. Rare reports of rapid development of severe osteoporosis and vertebral collapse in mother.

Common dosage range

Adult dose

Treatment: IV, 5,000 units initially, then 20,000–40,000 units over 24 hours.

Prophylaxis: SC, 5,000 units every 8–12 hours.

Paediatric dose

Load IV, 75–100 units/kg then 20–30 units/kg/hour.

hexamine hippurate

urinary antibacterial

Notes

- Avoid concomitant use of urinary alkaliniser.

Renal impairment (severe): Contraindicated. Ineffective in renal impairment because of inadequate concentrations in renal tubules (also risk of hippurate crystalluria in severe impairment).

Hepatic impairment (severe): Contraindicated.

Pregnancy: A

Breastfeeding: Use with caution. Small amounts expected to be excreted in breast milk, peaking within one hour of dose. Monitor for adverse effects in infant.

Common dosage range

Adult dose

1 g twice daily.

Paediatric dose

6–12 years, 0.5–1 g twice daily.

hormone replacement therapy

oestrogen or oestrogen/progestogen

Notes

- Used to relieve the symptoms of oestrogen deficiency—e.g. hot flushes, vaginal dryness.
- Oestrogen plus progestogen required unless post-hysterectomy.
- HRT does not provide contraceptive protection. If contraception during perimenopause is required seek medical advice.
- When stopping HRT, withdraw slowly to minimise symptom reappearance.
- For each woman considering use of HRT it is necessary that the benefits be weighed against the several risks that have been observed, including that of coronary heart disease within one year and breast cancer after one year of therapy.
- HRT is effective short-term (up to five years) treatment for menopausal symptoms, but it should not be used for long-term prevention of diseases. Review need for treatment annually.
- Although the risks are strongest for combination HRT involving use of an oral oestrogen and progestogen, data show use of any HRT, including oestrogen alone or transdermal preparations, is associated with some increase in risk, including that for breast cancer.
- Contraindicated when there is unexplained uterine bleeding, a previous thromboembolic disorder, severe liver disease, breast cancer or other oestrogen-dependent tumour, or cerebrovascular or coronary artery disease

Transdermal patches:

- Allows for smaller doses of oestrogen, which may reduce incidence of adverse effects.
- Apply patch to clean, dry, intact skin below waist or on upper buttock. Use different site each time to avoid irritation.
- Consider a topical oestrogen for urogenital symptoms.

Oral tablets:

- Oestrogen taken every day. Progestogen may be sequential or continuous. If sequential, bleeding likely in progesterone-free period. If continuous, bleeding may still occur but likely to stop after 6–12 months of therapy.
- To reduce nausea, take with food or use an alternative such as a patch.

Hepatic impairment (severe): Caution. Dose adjustment may be necessary. Monitor clinically for signs of jaundice.

Pregnancy: D. Use not recommended. Previously commenced therapy should be discontinued as soon as pregnancy is suspected.

Breastfeeding: Use contraindicated in lactating women. Excreted in breast milk. May suppress lactation.

Common dosage range

Adult dose

Various products available. See approved Product Information.

hydralazine

vasodilator

Cautionary advisory labels: 12, 16

Notes

Changes to faeces: Black discolouration.

Renal and hepatic impairment: Caution. Dose reduction may be necessary. Monitor clinically. Start at low dose, careful titration of dose.

Pregnancy: C. Use only in acute treatment of hypertensive emergencies.

Breastfeeding: Use with caution: limited data available. Small amounts excreted in breast milk.

Common dosage range

Adult dose

Oral, 25–100 mg twice daily.

IV, 5–10 mg by slow injection or infusion (repeat after 20–30 minutes if necessary).

Paediatric dose

Oral, initially 0.75 mg/kg daily in 2–4 divided doses, increasing over three weeks to 7.5 mg/kg daily; maximum 200 mg daily.

IV, 0.1–0.2 mg/kg (maximum 20 mg) as a single dose, then 4–6 micrograms/kg/minute.

hydrochlorothiazide

thiazide diuretic

Cautionary advisory labels: 16

Notes

- Monitor electrolytes, particularly for hypokalaemia, hyponatraemia, and hypomagnesaemia.
- Caution if patient suffers from diabetes, gout or dyslipidaemia (metabolic disturbances mainly associated with high dose).
- Contraindicated in persons with allergy to sulfonamides.

Changes to urinary system: May induce or aggravate urge incontinence due to polyuria, constipation or frequency.

Elderly: Orthostatic hypotension leading to falls and fractures, hypokalaemia, impaired glucose tolerance, hyperuricaemia. Counsel about rising slowly and cautiously.

Hepatic impairment: Caution. Dose reduction may be necessary. Monitor clinically.

Renal impairment: Caution. Where Cl_{cr} is below 30 mL/min, thiazide diuretics lose much of their diuretic efficacy, although vasodilatory action can still modestly contribute to blood pressure reduction. Loop diuretics are the drug of choice for maintenance of volume balance. Dose reduction may be necessary. Monitor clinically for signs of azotaemia and oliguria.

Pregnancy: C. Use not recommended.

Breastfeeding: Use with caution in low doses only. Small amounts excreted in breast milk. May suppress lactation.

Common dosage range

Adult dose

Hypertension: 12.5–100 mg daily.

Paediatric dose

<6 months: up to 1.75 mg/kg twice daily.

>6 months: 1.25 mg/kg twice daily.

hydrocortisone

corticosteroid

Cautionary advisory labels: 9, B (oral)

Notes

Changes to faeces: Pink, red or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Renal and hepatic impairment: Caution.

Pregnancy: A. Monitor maternal blood glucose: risk of hyperglycaemia.

Breastfeeding: Safe to use topically provided breast area is free of corticosteroid before breastfeeding. Use with caution systemically. Monitor infant if high or repeated doses are required.

Common dosage range

Adult dose

Adrenal insufficiency: Oral, 30 mg/day in divided doses (20 mg in morning, 10 mg late afternoon).

Paediatric dose

Anti-inflammatory: IV/IM, 2–4 mg/kg six-hourly.

Other indications: See approved Product Information.

Monitor growth and development in prolonged use.

hydromorphone

opioid analgesic

Cautionary advisory labels: 1, A*

Notes

- Constipation may be a problem with chronic use. Start treatment with stimulant or osmotic laxative (see 'Prevention and treatment of opioid-induced constipation', Section D).
- May cause nausea or vomiting.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to inhibition of the voiding reflex, constipation, confusion, reduced detrusor activity or urinary retention.

Renal and hepatic impairment: Caution. Dose reduction may be necessary. Use of an alternative opioid may be necessary. Monitor clinically for signs of drowsiness and respiratory depression.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Pregnancy: C. Use only if drug of choice. High doses or prolonged use at or near term may cause respiratory depression and withdrawal in newborn.

Breastfeeding: Use with caution: limited data available. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. sedation) in infant.

Common dosage range

Adult dose

Oral, 2–4 mg every four hours. SC/IM, 1–2 mg every 2 hours.

IV, 0.5–1 mg over 2–3 minutes. Infusions, up to 0.3 mg/hour.

Paediatric dose

>6 months: IV, 15 micrograms/kg every 2–4 hours; oral, 60 micrograms/kg every 3–4 hours.

hydroxychloroquine

quinoline, antimalarial, antirheumatic

Cautionary advisory labels: 8 (delete the word skin), 13, B

Notes

- Wear sunglasses when in bright sunlight.

Renal and hepatic impairment: Caution. Dose reduction may be necessary. Monitor clinically.

Pregnancy: May be used with caution. Seek specialist advice.

Breastfeeding: May be used for prophylaxis. Small amounts excreted in breast milk, which are unlikely to cause harm nor confer any benefit. Treatment doses not recommended as potential for severe adverse effects in high doses.

Common dosage range

Adult dose

Prophylaxis of malaria: 400 mg once weekly.

Rheumatoid arthritis: 400–600 mg daily in divided doses; maintenance, 200–400 mg daily.

Paediatric dose

Rheumatoid arthritis, systemic lupus erythematosus: >6 years, 5 mg/kg daily.

hydroxyurea

antimetabolite cytotoxic agent

Modification of oral formulation

Avoid crushing or altering capsule due to occupational health and safety risks.

Cautionary advisory labels: 21, B

Notes

Renal impairment: Caution. Dose reduction may be necessary.

Pregnancy: D. Use contraindicated.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

Initially 80 mg/kg as a single dose every third day or 20–30 mg/kg daily as a single dose. Further doses depend on response and toxicity; consult specialist protocols.

hyoscine

anticholinergic agent

Cautionary advisory labels: 12

Notes

- Common adverse effects include dry mouth, thirst, blurred vision, constipation, urinary retention.

Changes to urinary system: May induce or aggravate overflow incontinence due to reduced detrusor activity, voiding difficulty, urinary retention or constipation.

Renal and hepatic impairment: Caution. Dose reduction may be necessary. Monitor for signs of central nervous system effects.

Pregnancy: B2. Use not recommended in first trimester. If drug of choice, use with caution in second and third trimesters.

Breastfeeding: Use with caution. Minimal amounts excreted in breast milk. Monitor for adverse (i.e. anticholinergic) effects in infant.

Dosage range

Adult dose

GI spasm: Hyoscine butylbromide, IM or slow IV, 20–40 mg as needed. Maximum 100 mg daily.

Oral, 20 mg four times a day.

Premedication: hyoscine hydrobromide, SC/IM/IV, 300–600 micrograms.

Prevention of motion sickness: hyoscine hydrobromide, oral 0.3–0.6 mg 30 minutes before travelling, repeated as necessary every 4–6 hours. Maximum dose 1.2 mg/24 hours.

Paediatric dose

Antispasmodic: hyoscine butylbromide, IV, 0.5 mg/kg/dose every 6–8 hours.

>6 years, hyoscine butylbromide, oral, 10 mg every 8 hours.

Prevention of motion sickness: hyoscine hydrobromide, oral, 2–7 years: 75 micrograms/dose. Maximum 0.3 mg per 24 hours. >7 years 0.15–0.3 mg/dose. Maximum 0.6 mg per 24 hours.

hyoscyamine

anticholinergic agent

Cautionary advisory labels: 12

Notes

- Common adverse effects include dry mouth, thirst, blurred vision, constipation, urinary retention.
- More potent central nervous system and peripheral effects than found with atropine.

Changes to urinary system: May induce or aggravate overflow incontinence due to reduced detrusor activity, voiding difficulty, urinary retention or constipation.

Renal and hepatic impairment: Caution. Dose reduction may be necessary. Monitor for signs of central nervous system effects.

Pregnancy: B2. Use not recommended in first trimester. If drug of choice, use with caution in second and third trimesters.

Breastfeeding: Use with caution. Trace amounts excreted in breast milk. Monitor for adverse (i.e. anticholinergic) effects in infant.

Common dosage range

Adult dose

Hyoscyamine sulfate, 0.125–0.25 mg every four hours as needed. Maximum 1.5 mg per 24 hours.

ibuprofen

NSAID

Modification of oral formulation

Before crushing or otherwise altering tablets or capsules, consider unacceptable/undisguisable taste.

Cautionary advisory labels: 10a, 12†, B

Notes

- Maximum response should be seen in 1–3 weeks.
- Caution if taking warfarin or other anticoagulants.
- To lessen gastrointestinal complications, use lowest effective dose and take paracetamol as an alternative analgesic.
- Check use of over-the-counter NSAIDs.
- Caution with diabetes, hypertension, heart failure, asthma or peptic ulcer.
- Consider stopping 2–3 days before planned surgery; seek medical advice.

Changes to faeces: Pink, red, or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Hepatic impairment (severe): Caution. Dose reduction may be necessary. Monitor clinically.

Renal impairment (moderate–severe): Caution. Dose reduction may be necessary. Monitor clinically.

Pregnancy: C. Alternatives to NSAIDs should be considered for analgesia. Use not recommended during third trimester.

Breastfeeding: May be used. Not detected in breast milk in doses up to 2.4 g daily. Diclofenac and ibuprofen are the NSAIDs of choice in breastfeeding mothers.

Common dosage range

Adult dose

200–400 mg 3–4 times daily. Maximum 2,400 mg daily.

Paediatric dose

Fever, 5–10 mg/kg/dose 6–8 hourly as needed.

Anti-inflammatory, 10 mg/kg/dose 3–4 times a day.

idarubicin

cytotoxic anthracycline agent

Modification of oral formulation

Avoid crushing or altering capsule due to occupational health and safety risks.

Cautionary advisory labels: 21, A*, B

Notes

Renal and hepatic impairment (mild–moderate): Caution. Monitor clinically.

Renal and hepatic impairment (severe): Contraindicated.

Pregnancy: D. Use contraindicated.

Breastfeeding: Use contraindicated.

Common dosage range

See approved Product Information and specialist protocols.

Maximum cumulative dose

Adult: should not exceed 400 mg/m^2 orally and 160 mg/m^2 by IV route.

Child: should not exceed 90 mg/m^2 by IV route.

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

imatinib

tyrosine kinase inhibitor

Modification of oral formulation

Avoid crushing or altering capsule due to occupational health and safety risks.

Cautionary advisory labels: B

Notes

Renal and hepatic impairment: Caution. Monitor clinically. Dose adjustment may be necessary. Refer to approved Product Information.

Pregnancy: D. Use not recommended. Previously commenced therapy should be discontinued as soon as pregnancy is suspected.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

Initially, 400 mg daily in 1 or 2 doses; adjust according to response and toxicity.

Paediatric dose

≥3 yrs: chronic phase CML, 260 mg/m^2 daily. Maximum 400 mg. Advanced phase CML: 340 mg/m^2 daily. Maximum 600 mg.

imipramine

tricyclic antidepressant

Cautionary advisory labels: 1, 9, 13, 16

Notes

Psychotropics: tricyclic antidepressants

- Orthostatic hypotension may occur when rising quickly. Advise about rising slowly from sitting or lying down.
- Full therapeutic response may not be seen for 2–4 weeks, but adverse effects may occur from start of treatment.
- Anticholinergic adverse effects are common—dry mouth, constipation, blurred vision, difficulty in passing urine. Other adverse effects include hypotension and sedation.
- Medicine-free interval may be required when switching to/from another antidepressant. See NPS information on changeover of therapy at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- For antidepressant use, best taken as a single dose at night.
- Indications other than depression may include pain, obsessive compulsive disorder, anxiety and panic and eating disorders.
- If withdrawing treatment do so gradually.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to anticholinergic urinary retention, voiding difficulty, constipation, sedation or impairment of mobility.

Elderly: Avoid use for sedation due to adverse effects, such as constipation, urinary retention, confusion and orthostatic hypotension, which may lead to falls and fractures. Counsel about slowly from sitting or lying down.

Hepatic impairment: Caution. Dosage adjustment necessary. Give half normal dose. Monitor clinically. Consider using a tricyclic antidepressant that has serum levels that can be measured. (e.g. nortriptyline)

Renal impairment (severe): Caution. Monitor clinically.

Therapeutic monitoring: Therapeutic range is 100–300 micrograms/L (350–1,000 nanomol/L).

Toxicity: Both the parent drug and the active metabolite (desipramine) are effective and levels should be interpreted by considering the combined levels.

Pregnancy: C. Use when clinically indicated if it is the drug of choice. There is increased risk of reversible withdrawal symptoms, not congenital malformations.

Breastfeeding: Use with caution. Small amounts excreted into breast milk. If needed, preferably taken as a single dose. Monitor for adverse effects (e.g. sedation) in infant.

Dosage range

Adult dose

25–150 mg daily.

Maximum daily dose 300 mg.

Paediatric dose

ADHD: >5 years, 1mg/kg daily, increasing to a maximum of 2 mg/kg daily in 1–4 doses. ECG monitoring is recommended.

Nocturnal enuresis: 7–10 years, 10–20 mg 30–60 minutes before to bed.

>10 years, 25–50 mg 30–60 minutes before to bed.

indapamide

thiazide-like diuretic

Modification of oral formulation

Crushing or otherwise altering sustained-release tablet will alter absorption characteristics.

Cautionary advisory labels: 16

Notes

- Monitor electrolytes, particularly for hypokalaemia, hyponatraemia and hypomagnesaemia.

- Combination with a diuretic agent may lead to significant electrolyte disturbances and is not recommended.
- Caution if patient suffers from diabetes, gout or dyslipidaemia (metabolic disturbances mainly associated with high dose).
- Avoid NSAIDs, including COX-2 inhibitors, unless taken on medical advice.
- Contraindicated in persons with allergy to sulfonamides.

Hepatic impairment: Caution. Monitor clinically.

Renal impairment: Caution. Monitor clinically.

Renal and hepatic impairment (severe): Contraindicated if suffering from azotaemia and oliguria or electrolyte imbalance.

Pregnancy: C. Use not recommended.

Breastfeeding: Use not recommended: no data available. May suppress lactation.

Common dosage range

Adult dose

1.25–2.5 mg daily. Higher doses not recommended.

indinavir

antiretroviral protease inhibitor

Cautionary advisory labels: 3b, 5, 12

Notes

- Does not cure HIV or eliminate risk of transmission.
- Should be taken in combination with other antiretrovirals.
- Numerous medicine interactions (see Table D.1, Section D).
- Ensure adequate hydration (1.5–2 L/day).

Hepatic impairment (mild–moderate): Caution. Monitor clinically. Dosage adjustment necessary. Give 600 mg 8 hourly. No studies in severe impairment.

Pregnancy: B3. Previously commenced therapy should be continued and advice sought from an infectious diseases specialist.

Breastfeeding: Expected to be excreted into breast milk, but no safety data on drug in infants. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

800 mg every eight hours.

Combination therapy: See approved Product Information.

Paediatric dose

>3 years, 500 mg/m^2 (maximum 800 mg) every eight hours.

Also refer to dosage table in approved Product Information.

indomethacin

NSAID

Cautionary advisory labels: 10a, 12†, A*, B

Notes

- Maximum response should be seen in 1–3 weeks.
- Caution if taking warfarin or other anticoagulants.
- To lessen gastrointestinal complications, use lowest effective dose and take paracetamol as an alternative analgesic.
- Check use of over-the-counter NSAIDs.
- Caution with diabetes, hypertension, heart failure, asthma or peptic ulcer.
- Consider stopping 2–3 days before planned surgery; seek medical advice.

Changes to urinary system: Green discolouration of urine.

Changes to faeces: Green, pink, red or black. These colours may indicate medicine-induced gastrointestinal bleeding.

Elderly: May cause increased risk of gastric ulceration, renal dysfunction, dizziness, sodium and water retention, heart failure, and exacerbation of hypertension.

Hepatic impairment (severe): Caution. Dose reduction may be necessary. Monitor clinically.

Renal impairment (moderate–severe): Caution. Dose reduction may be necessary. Monitor clinically.

Pregnancy: C. Alternatives to NSAIDs should be considered for analgesia. Use not recommended during third trimester.

Breastfeeding: May be used short term. Small amounts excreted in breast milk. Diclofenac and ibuprofen are the NSAIDs of choice in breastfeeding mothers.

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Common dosage range

Adult dose

Oral, 50–200 mg daily in 2–4 doses.

Rectal, 100 mg once or twice daily.

Paediatric dose

Oral, 1–4 mg/kg daily in 2–4 doses.

interferon alfa

interferon

Cautionary advisory labels: 6, 12

Notes

- Warm by holding in hand for a few minutes or leave at room temperature for 30 minutes before injecting.

Hepatic impairment (severe): Caution. Monitor clinically. May worsen impairment.

Renal impairment (severe): Caution. Monitor clinically. Dose reduction may be necessary.

Pregnancy: B3. May be used with caution. Seek specialist advice.

Breastfeeding: Use not recommended: no data available.

iodine

topical anti-infective, inhibits thyroid hormone release

Notes

Changes to faeces: Black discolouration.

Pregnancy: Use not recommended. Even with topical use by mother, there is a risk of fetal hypothyroidism.

Breastfeeding: Use not recommended (including regular topical use). Excreted as iodide in breast milk and concentrates. Potential for hypothyroidism in infant.

Common dosage range

Varies according to condition being treated. See approved Product Information and specialist protocols.

ipecacuanha

gastrointestinal decontaminant

Notes

- Always contact a poisons information centre (phone 13 11 26) BEFORE administration. Not recommended if more than one hour has elapsed since ingestion of poison.

Pregnancy: Use only if it is the drug of choice in the management of poisoning.

Breastfeeding: Use only if it is the drug of choice in the management of poisoning.

Common dosage range

Adult dose

30 mL/dose (6% mixture); follow with a glass of water. May repeat once in 30 minutes if vomiting has not occurred.

Paediatric dose

15 mL/dose (6% mixture); follow with a glass of water. May repeat once in 30 minutes if vomiting has not occurred.

ipratropium

anticholinergic bronchodilator

Notes

- Dry mouth common.
- If using salbutamol or terbutaline, ipratropium and steroid inhalers, use in that order.
- Not for immediate relief of symptoms.
- Can be mixed with other beta$_2$ agonists for nebulised therapy.
- Inquire about eye and vision problems as some may be caused by leakage from mask.

Changes to urinary system: May induce or aggravate overflow incontinence (occasionally with nebulised therapy) due to reduced detrusor activity, voiding difficulty, urinary retention, constipation.

Pregnancy: B1. May be used.

Breastfeeding: May be used. Insignificant amounts excreted in breast milk and insignificant absorption by infant expected.

Common dosage range

Adult dose

MDI, 40–80 micrograms, repeat 3–4 times daily as necessary.

Nebuliser, 250–500 micrograms up to 3–4 times daily.

Nasal spray, 42–84 micrograms into each nostril 2–3 times daily.

Paediatric dose

MDI, <6 years, 20 micrograms three times daily;

6–12 years, 20–40 micrograms 3–4 times daily.

Nebuliser, 250 micrograms, diluted to 2–3 mL, four times daily.

irbesartan

angiotensin II receptor antagonist

Cautionary advisory labels: 11, 12†, 16†

Notes

- Blood pressure should be closely monitored during initiation.
- Monitor renal function and potassium concentration.
- Caution if the patient is taking NSAIDs (including COX-2 inhibitors) or lithium.
- Provide advice on foods and drugs with high potassium content.
- Can cause cough (cough can also be a symptom of heart failure). Establish nature of cough, productive or unproductive; incidence less than with ACE inhibitors.
- If swelling of face, lips or tongue is experienced, seek medical advice.
- A combination product of irbesartan with a diuretic is also available. Check that patient knows which product is being taken.

Elderly: Renal impairment, hyperkalaemia more common.

Renal and hepatic impairment (severe): Caution. Monitor clinically. Dose reduction may be necessary.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as possible if pregnancy is suspected.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

150–300 mg once daily.

isoniazid

tuberculosis antibacterial

Cautionary advisory labels: 3b

Notes

- Concurrent use of pyridoxine 25 mg daily is recommended to reduce risk of peripheral neuropathy.
- If signs of hepatic toxicity occur, such as persistent nausea and vomiting, malaise or jaundice, seek medical advice.
- Isoniazid may be used in daily or intermittent treatment regimens as part of a multi-drug regimen.

Hepatic impairment (mild–moderate): Caution. Monitor clinically.

Hepatic impairment (severe): Contraindicated.

Renal impairment (severe): Caution. Monitor clinically.

Pregnancy: A

Breastfeeding: May be used. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. vitamin B_6 deficiency, jaundice) in infant. Consider vitamin B_6 supplementation in mother and infant to reduce risk of toxicity.

Common dosage range

Adult dose

Treatment: (as part of multi-drug regimen) 5–10 mg/kg daily (maximum 300 mg) or 15 mg/kg (maximum 900 mg) 2–3 times a week.

Prophylaxis: (latent TB), oral 300 mg daily.

Paediatric dose

Treatment: (as part of multi-drug regimen) 10–20 mg/kg daily (maximum 300 mg); or 20–40 mg/kg (maximum 900 mg) 2–3 times a week.

Prophylaxis: 10 mg/kg (maximum 300 mg) once daily.

isosorbide dinitrate

nitrate, anti-anginal

Cautionary advisory labels: 16

Notes

- Sublingual tablets: use during episodes of angina or before an activity expected to precipitate angina.
- Call an ambulance if two sublingual tablets over 15 minutes do not relieve pain.
- Check nitrate-free interval: should be 10–12 hours per day.
- Common adverse effects include headaches, flushing, palpitations and hypotension.
- Angina treatment requires patient counselling.

Changes to urinary system: Brown–black discolouration of urine.

Renal and hepatic impairment: Caution. Dose reduction may be necessary. Monitor clinically.

Pregnancy: B1. Not recommended in first trimester. Consider alternatives before using in second and third trimesters.

Breastfeeding: Use with caution: no data available.

† Most appropriate during initial treatment or when dosage is increased.

Common dosage range

Adult dose

Oral, 30–160 mg daily in 3–4 divided doses.

Acute angina, sublingual, 5–10 mg.

isosorbide mononitrate

nitrate

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets may alter absorption characteristics. Check approved Product Information as some products may be cut in half.

Cautionary advisory labels: 16, A*

Notes

- Common adverse effects include headaches, flushing, palpitations and hypotension.
- Total daily dose to be taken as single dose.
- This form of nitrate will not relieve an acute attack.
- Take at the time of the day when angina is most frequent, e.g. at night for nocturnal angina or in the morning for daytime angina.
- Possible additive effect if other nitrates are used concurrently.

Changes to urinary system: Brown–black discolouration of urine.

Renal and hepatic impairment: Caution. Dose reduction may be necessary. Monitor clinically.

Pregnancy: B2. Not recommended in first trimester. Consider alternatives before using in second and third trimesters.

Breastfeeding: Use with caution: no data available.

Common dosage range

Adult dose

Controlled-release tablets, 30–120 mg daily as a single dose.

isotretinoin

oral retinoid

Modification of oral formulation

Avoid crushing or altering capsule due to occupational health and safety risks.

Cautionary advisory labels: 8, B, D

Notes

- Contraindicated in pregnancy. Women must use contraceptive measures for 1 month before, during and for 1 month after treatment.
- A mild disease flare is seen on initiation of therapy.
- Inform patient of relevance of frequent monitoring and blood tests.
- Monitor for signs of depression.
- Avoid vitamin A supplements.
- Adverse effects can be minimised by use of lip balm, lubricating eye drops, sunscreen and protective clothing.
- Do not give blood during treatment and for 1 month after stopping treatment.

Renal impairment: Caution. Dose adjustment may be necessary. Monitor clinically. Start at low dose, careful titration of dose.

Hepatic impairment (mild–moderate): Caution. Monitor clinically.

Hepatic impairment (severe): Contraindicated.

Pregnancy: X (oral), D (topical). Avoid pregnancy during and for at least one month after ceasing therapy. Unless contraindicated, a combined oral contraceptive with a non-androgenic progestogen is preferred, plus a barrier method.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

0.5–1 mg/kg daily in 1–2 doses. Maximum accumulated dose is 120–150 mg/kg over 4–6 months.

ispaghula husk

bulking laxative

Notes

- Chronic management may require combination treatment.
- Opioid induced—use a stool softener/stimulant and hyperosmotic. See 'Prevention and treatment of opioid-induced constipation', Section D.
- Faecal impaction may present as faecal soiling or diarrhoea.
- Give with extra fluid; first-line treatment in acute and chronic constipation. Contraindicated in intestinal obstruction and faecal impaction.

Pregnancy: May be used.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Breastfeeding: May be used. Oral absorption not expected.

Common dosage range

Adult dose

3.5 g in a glass of water twice daily.

Paediatric dose

>6 years: 1.75 g in a glass of water twice daily.

itraconazole

antifungal

Cautionary advisory labels: 5, B, D and 5, C (1 hour) and D for the solution

Notes

- Continue treatment for at least 2 weeks after symptoms subside.
- Report any signs indicative of hepatic damage. If fatigue, jaundice, dark urine, pale faeces, nausea or vomiting occurs, seek medical advice.
- Potential for significant medicine interactions (see Table D.1, Section D).
- Requires acidic environment for optimal absorption; avoid antacids, H_2 antagonists or proton pump inhibitors.

Hepatic impairment: Caution. Dose adjustment may be necessary. Monitor clinically.

Renal impairment: Caution. Dose adjustment may be necessary.

Pregnancy: B3. Use contraindicated in first trimester. Seek advice from infectious diseases specialist for use in second or third trimesters.

Breastfeeding: Use not recommended. Varying amounts excreted in breast milk, and no safety data on drug in infants.

Common dosage range

Adult dose

100–400 mg daily.

Specific indications: See approved Product Information.

Paediatric dose

Oral liquid, 3–5 mg/kg (rounded to the nearest 50 mg) daily in 1–2 doses.

Capsules, 5–7.5 mg/kg (rounded to the nearest 100 mg) daily in 1–2 doses.

ivabradine

inhibitor of cardiac pacemaker (I_f current)

Cautionary advisory labels: 5, 13, 18, B

Notes

- Caution with concomitant use with other drugs causing a reduction in heart rate—e.g. verapamil, diltiazem.
- Visual disturbances common.
- Drug must be ceased if the heart rate decreases to less than 50 beats per minute or if patient experiences symptoms related to bradycardia.

Renal impairment: Dosage adjustment required only if Cl_{cr} <15 mL/min.

Pregnancy: D.

Breastfeeding: Contraindicated.

Common dosage range

Adult dose

5 mg twice daily. Dose must be reduced if severe bradycardia occurs.

ivermectin

anthelmintic

Notes

Renal and hepatic impairment: Caution. Limited data available.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended. Excreted in breast milk, and no safety data on drug in infants.

Common dosage range

Adult dose

0.15–0.2 mg/kg single dose. Further doses may be needed. See approved Product Information

Paediatric dose

>15kg, as for adult dose.

ketoconazole

antifungal

Cautionary advisory labels: 4 (delete iron and calcium), 5, B, D, E (dermal)

Notes

- Continue treatment for at least 2 weeks after symptoms subside (dermal).
- Report any signs indicative of hepatic damage. If fatigue, jaundice, dark urine, pale faeces, nausea or vomiting occurs, seek medical advice.

- Requires acidic environment for optimal absorption; avoid antacids H_2 antagonists or proton pump inhibitors.
- Potential for significant medicine interactions (see Table D.1, Section D).

Hepatic impairment (mild–moderate): Caution. Dose adjustment may be necessary. Monitor clinically.

Hepatic impairment (severe): Contraindicated

Pregnancy: B3. Use not recommended.

Breastfeeding: Oral use not recommended. Excreted in breast milk, and no safety data on drug in infants. Use with caution topically.

Common dosage range

Adult dose

200–400 mg daily.

Paediatric dose

5–10 mg/kg daily in 1–2 doses.

ketoprofen

NSAID

Cautionary advisory labels: 10a, 12†, A*, B

Notes

- Maximum response should be seen in 1–3 weeks.
- Caution if taking warfarin or other anticoagulants.
- To lessen gastrointestinal complications, use lowest effective dose and take paracetamol as an alternative analgesic.
- Check use of over-the-counter NSAIDs.
- Use with care in diabetes, hypertension, heart failure, asthma or peptic ulcer.
- Consider stopping 2–3 days before planned surgery; seek medical advice.

Changes to faeces: Pink, red, black discolouration may indicate medicine-induced gastrointestinal bleeding.

Elderly: Increased risk of gastric ulceration, renal dysfunction, dizziness, sodium and water retention, exacerbation of hypertension and heart failure.

Renal and hepatic impairment (mild–moderate): Caution. Dose adjustment may be necessary. Monitor clinically.

Renal and hepatic impairment (severe): Contraindicated.

Pregnancy: C. Alternatives to NSAIDs should be considered for analgesia. Use not recommended during third trimester.

Breastfeeding: May be used. Avoid sustained-release preparations. Trace amounts excreted in breast milk. Diclofenac and ibuprofen are the NSAIDs of choice in breastfeeding mothers.

Common dosage range

Adult dose

100–200 mg once daily.

ketorolac

NSAID

Cautionary advisory labels: 10a, 12†, A*, B

Notes

- Maximum response should be seen in 1–3 weeks.
- Caution if taking warfarin or other anticoagulants.
- To lessen gastrointestinal complications, use lowest effective dose and take paracetamol as an alternative analgesic.
- Check use of over-the-counter NSAIDs.
- Use with care in diabetes, hypertension, heart failure, asthma or peptic ulcer.
- Consider stopping 2–3 days before planned surgery; seek medical advice.

Changes to faeces: Pink, red or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Elderly: Reduce dose. Increased risk of gastric ulceration, renal dysfunction, dizziness, sodium and water retention, exacerbation of hypertension, heart failure.

Hepatic impairment: Caution. Dose adjustment may be necessary. Monitor clinically.

Renal impairment (mild): Caution. Monitor clinically.

Renal impairment (moderate–severe): Contraindicated.

Pregnancy: C. Alternatives to NSAIDs should be considered for analgesia. Use not recommended during third trimester.

Breastfeeding: Use with caution. Small amounts expected to be excreted in breast milk. Diclofenac and ibuprofen are the NSAIDs of choice in breastfeeding mothers.

† Most appropriate during initial treatment or when dosage is increased.

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Common dosage range

Adult dose

IM, IV, initially 10 mg, followed by 10–30 mg every 4–6 hours (maximum 90 mg daily). Change to oral route as soon as possible

Oral, 10 mg every 4–6 hours. Maximum dose 40 mg daily.

labetalol

beta-blocker with alpha-blocker effect

Cautionary advisory labels: 9, 12†, 16

Notes

- If patient has a history of asthma or other lung disease, seek medical advice before dispensing.
- Caution if patient suffers from diabetes (can mask hypoglycaemic attack), hyperlipidaemia, peripheral vascular disease, hyperthyroidism, uncontrolled heart failure, asthma, chronic obstructive pulmonary disease.

Pregnancy: C. First-line antihypertensive agent in pregnancy. Monitor for hypoglycaemia in newborn.

Breastfeeding: May be used. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. bradycardia) in infant.

Common dosage range

Adult dose

Initially, 100–200 mg twice daily, increasing at weekly intervals to maintenance dose of 200–2,400 mg daily in 1–4 doses.

Paediatric dose

4 mg/kg daily in two doses. Higher doses may be needed, up to maximum 40 mg/kg daily in 1–4 doses.

lactulose

osmotic laxative

Notes

- Advise on use of fibre, increased fluid intake and exercise.
- Chronic constipation may require combination treatment.
- Opioid-induced constipation, use a stool softener/stimulant and hyperosmotic (see 'Prevention and treatment of opioid-induced constipation', Section D).
- Faecal impaction may present as faecal soiling or diarrhoea.

Pregnancy: May be used.

Breastfeeding: May be used. Minimal absorption by mother.

Common dosage range

Adult dose

Constipation: initially, 15–30 mL daily in 1–2 doses; maintenance 10–25 mL daily.

Hepatic encephalopathy: initially 30–45 mL every 1–2 hours, reducing to 3–4 times daily when laxative effect has been achieved.

Paediatric dose

Constipation: oral dose given once daily: <1 year, 3–5 mL; 1–6 years, 5–10mL; 7–14 years, 10–15mL.

lamivudine

antiviral, nucleoside reverse transcriptase inhibitor

Cautionary advisory labels: 12

Notes

Renal impairment (moderate–severe): Caution. Dose reduction required:

HIV maintenance dose:

Cl_{cr} 30–49 mL/min, 150 mg once daily.
Cl_{cr} 15–29 mL/min, 100 mg once daily.
Cl_{cr} 5–14 mL/min, 50 mg once daily.
Cl_{cr} <5 mL/min, 25 mg once daily.

Chronic hepatitis B maintenance dose:

Cl_{cr} 30–49 mL/min, 50 mg once daily.
Cl_{cr} 15–29 mL/min, 25 mg once daily.
Cl_{cr} 5–14 mL/min, 15 mg once daily.
Cl_{cr} <5 mL/min, 10 mg once daily.

Pregnancy: B3. Previously commenced therapy should be continued and advice sought from an infectious diseases specialist.

Breastfeeding: Expected to be excreted into breast milk, but no safety data on drug in infants. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

HIV: 300 mg daily in 1–2 doses.

Chronic hepatitis B: 100 mg once daily.

Paediatric dose

HIV: 3 months to 12 years, 4 mg/kg twice daily. Maximum 300 mg daily.

Chronic hepatitis B: >2 years, 3 mg/kg once daily. Maximum 100 mg daily.

† Most appropriate during initial treatment or when dosage is increased.

lamotrigine

antiepileptic, mood stabiliser

Cautionary advisory labels: 1, 9

Notes

- Severe skin reactions can occur. Risk increases with rapid dose escalation of lamotrigine or if taken with valproate.
- Seek medical advice immediately if rash occurs.
- If administered with valproate, lower doses of lamotrigine are required (see 'Common dosage range').

Hepatic impairment (moderate–severe): Caution. Initial, escalation and maintenance doses require reduction; see approved Product Information.

Renal impairment (severe): Caution. Dose reduction may be required.

Pregnancy: D. Consider risk of congenital malformation against dangers of uncontrolled epilepsy. Consider folic acid (5 mg) and vitamin K supplementation.

Breastfeeding: Use with caution. Small amounts excreted in breast milk, but no safety data on drug in infants. Therapeutic levels in infant may be reached.

Common dosage range

Adult dose

Monotherapy: maintenance, 100–200 mg daily in two doses.

Adjunctive therapy
With valproate: maintenance, 100–200 mg daily in 1–2 doses.

Without valproate: maintenance, 200–400 mg daily in two doses (up to 500–700 mg daily in some patients).

Paediatric dose

With valproate: initially, 0.15 mg/kg once daily, slowly increasing every two weeks to 1–5 mg/kg daily in 1–2 doses. Maximum 200 mg daily.

Without valproate: initially, 0.6 mg/kg daily in two doses, slowly increasing every two weeks to 5–15 mg/kg daily. Maximum 400 mg daily.

lansoprazole

proton pump inhibitor

Modification of oral formulation

Before crushing or otherwise altering enteric-coated capsules, consider the risk of altering medicine stability.

Cautionary advisory labels: A*

Notes

- Raised gastric pH can reduce bioavailability of ketoconazole, itraconazole (capsule form), iron salts and digoxin.
- Generally well tolerated.
- See doctor immediately if nausea, severe vomiting, epigastric pain, or diarrhoea with blood-stained stools during or after treatment is experienced.

Pregnancy: B3. May be used when treatment with antacids and H_2 antagonists has failed. If a proton pump inhibitor is required, omeprazole is preferred.

Breastfeeding: Use not recommended: limited data available. H_2 antagonists preferred.

Common dosage range

Adult dose

15–60 mg daily.

Zollinger Elllison syndrome: maintenance, up to 180 mg daily in two doses.

Paediatric dose

GORD: >1 year, ≤30 kg, 15 mg daily;
>30 kg, 30 mg daily.

lanthanum

phosphate-binding agent

Cautionary advisory labels: 5, B

Notes

- Increases gastric pH. May interact with drugs requiring an acidic environment for dissolution—e.g. ketoconazole.
- May reduce absorption of some drugs due to complexation—e.g. tetracyclines, quinolones. Separate doses by 2 hours.

Pregnancy: B3.

Breastfeeding: Avoid. Can be excreted in breast milk.

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Common dosage range

Adult dose

Initial dose depends on serum phosphate levels.

Phosphate levels:

>1.8 and <2.4 mmol/L, 250 mg three times daily.

>2.4 and <2.9 mmol/L, 500 mg three times daily.

>2.9 mmol/L, 750 mg three times daily.

lapatinib

kinase inhibitor

Cautionary advisory labels: 3b, 5, 12, 18

Notes

- Used in combination with capecitabine.
- Diarrhoea is common. Monitor for dehydration.
- Skin rashes common.
- Left ventricular ejection fraction should be measured prior to and during therapy.
- Signs of cardiac failure or lung inflammation (e.g. shortness of breath, cough) must be reported.

Pregnancy: B3.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

1,250 mg daily.

latanoprost

ocular prostaglandin analogue

Cautionary advisory labels: 7b

Notes

- May affect iris colour.
- Use in the evening for best effect.
- Minimise systemic absorption by applying pressure to tear duct after administration.
- Separate from use of other drops by 5 minutes.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use with caution. Excreted in breast milk, but levels undetectable 1–2 hours after dose. Dosing immediately after a breastfeed recommended (so next feed is at least two hours after administration).

Common dosage range

Adult dose

Instil 1 drop in affected eye(s) daily (1.5 micrograms latanoprost).

leflunomide

immunosuppressant for rheumatoid arthritis

Cautionary advisory labels: A

Notes

- Regular blood counts and hepatic function tests required.
- Concomitant administration of oral contraceptive required in women of child-bearing age during and for two years after stopping treatment.
- Increased adverse reaction if administered with methotrexate.

Hepatic impairment: Contraindicated.

Renal impairment: Caution.

Pregnancy: X. Use contraindicated.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

Maintenance dose, 10–20 mg daily.

Paediatric dose

>3 years: <20 kg, 10 mg once daily on alternate days.
20–40 kg, 10 mg once daily.

40 kg, 20 mg once daily.

lenalidomide

immunomodulating agent

Cautionary advisory labels: 12, A

Notes

- Dexamethasone is given as part of the therapeutic regimen.
- Women of child-bearing age should use an appropriate contraception method during treatment.
- Male subjects taking lenalidomide should use a barrier method of contraception if their partner is of child-bearing age.
- Monitor patients for signs of thromboembolism, e.g. shortness of breath, chest pain, arm or leg swelling.

Renal impairment: No formal studies, but the drug is extensively renally cleared and toxicity is expected to be greater in patients with renal impairment.

Pregnancy: D.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

25 mg daily on days 1–21 of repeated 28-day cycles. Dosage adjustments are recommended to manage neutropenia and thrombocytopenia.

lercanidipine

dihydropyridine calcium channel blocker

Cautionary advisory labels: 9, 12†, 18, C

Notes

- Dihydropyridines can cause peripheral oedema.

Renal or hepatic impairment (mild–moderate): Caution.

Renal or hepatic impairment (severe): Contraindicated.

Pregnancy: C. Consider alternative therapy first. Use not recommended in first trimester. More experience with nifedipine and felodipine in second and third trimesters.

Breastfeeding: Use with caution: limited data available. If a calcium channel blocker is required, nifedipine is preferred.

Common dosage range

Adult dose

10 mg daily, increasing to 20 mg daily if necessary.

letrozole

antineoplastic, aromatase inhibitor

Cautionary advisory labels: 12

Notes

- For postmenopausal women only.
- Treatment continues until tumour progression evident.
- Take after food if nausea or gastric irritation occurs.
- Monitor bone mineral density before and during treatment.

Renal or hepatic impairment: Caution.

Pregnancy: D. Use not recommended.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

2.5 mg daily.

levetiracetam

antiepileptic

Cautionary advisory labels: 1, 9

Notes

Hepatic impairment: Caution. Dose reduction may be required, depending on renal function. For example, severe hepatic impairment with Cl_{cr} <70 mL/min, reduce maintenance dose by half.

Renal impairment: Caution. Dose reduction required.

Cl_{cr} 30–49 mL/min, 250–750 mg twice daily.

Cl_{cr} <30 mL/min, 250–500 mg twice daily.

Pregnancy: B3. Consider risk of congenital malformation against dangers of uncontrolled epilepsy. Consider folic acid (5 mg) and vitamin K supplementation.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

500–1,500 mg twice daily (see above).

Paediatric dose

>4 years, <50 kg: initially 10 mg/kg twice daily, slowly increasing to 30 mg/kg twice daily.

>50kg: as per adult dose.

levodopa with decarboxylase inhibitor

dopamine precursor

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets or capsules will alter absorption characteristics.

Cautionary advisory labels: 9, 16

Notes

- Doses should be taken at the same time each day and consistently in relation to food.

Changes to faeces: Black discolouration.

Changes to urinary system: Red discolouration on voiding, which darkens on standing if in contact with hypochlorite toilet bleach.

Elderly: Confusion, psychoses, orthostatic hypotension, which may increase risk of falls and fractures.

Renal or hepatic impairment: Caution.

† Most appropriate during initial treatment or when dosage is increased.

Pregnancy: B3. Seek specialist advice.

Breastfeeding: Use not recommended. Excreted in breast milk. May suppress lactation.

Dosage range

Adult dose

Initially, 300 mg daily in three doses, increasing gradually according to response and tolerance.

Maintenance: 300–800 mg daily. Maximum 2 g daily.

lincomycin

antibacterial

Notes

- IV doses of lincomycin should be infused at a rate not exceeding 1 g/hour and in a concentration of less than 10 mg/mL. Rapid infusion may cause cardiac arrest.
- Discontinue if significant diarrhoea occurs. Seek medical advice.

Renal or hepatic impairment: Caution. Dose adjustment may be necessary.

Pregnancy: A.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

IM, 600 mg 12-hourly.

IV, 600–1,000 mg every 8–12 hours. Maximum 8 g daily.

Paediatric dose

IV, 15 mg/kg (maximum 1.2 g) 8-hourly.

linezolid

antibacterial

Cautionary advisory labels: D, I

Notes

- Linezolid is a weak MAOI and is contraindicated with concurrent (or within 2 weeks of stopping) MAOI therapy.
- Avoid foods rich in tyramine while taking this medicine.
- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible.
- Common adverse effects—nausea, diarrhoea, gastric upset.

Renal impairment: Caution. Thrombocytopenia and anaemia may be more frequent; monitor full blood count each week.

Pregnancy: B3. Seek advice from infectious diseases specialist.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

Oral, IV, 400–600 mg twice daily.

Paediatric dose

Oral, IV, 10 mg/kg 8-hourly.

lisinopril

angiotensin-converting enzyme inhibitor

Cautionary advisory labels: 11, 12†, 16†

Notes

- Blood pressure should be closely monitored during initiation of therapy.
- Monitor renal function and potassium concentration.
- Caution if the patient is taking NSAIDs (including COX-2 inhibitors) or lithium.
- Provide advice on foods and drugs with high potassium content.
- Can cause cough (cough can also be a symptom of heart failure). Establish if cough is productive or unproductive.
- If swelling of face, lips or tongue is experienced, seek medical advice.
- May cause metallic taste or lack of taste.

Changes to urinary system: May induce or aggravate stress incontinence due to cough-induced sphincter weakness.

Renal or hepatic impairment: Caution. Lower starting dose recommended.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as possible if pregnancy is suspected.

Breastfeeding: Use not recommended. Excreted in breast milk, but no safety data on drug in infants. If an ACE inhibitor is required, captopril or enalapril are preferred.

Common dosage range

Adult dose

2.5–20 mg daily as a single dose. Maximum 40 mg daily.

Paediatric dose

0.1–0.2 mg/kg (up to 1 mg/kg) once daily.

† Most appropriate during initial treatment or when dosage is increased.

lithium carbonate

mood stabiliser

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets will alter absorption characteristics.

Cautionary advisory labels: 5, 13, B

Notes

- Onset of action may be delayed for 6–10 days.
- Be aware of signs of lithium toxicity—thirst, frequent urination, nausea and vomiting.
- Inadequate intake or excessive excretion of sodium may precipitate toxicity. Maintain normal diet with adequate salt and fluid intake, particularly in hot weather. Avoid products with sodium bicarbonate.
- Therapeutic concentration monitoring recommended. Monitor more frequently during illness.
- Monitor renal and thyroid function.
- ACE inhibitors, NSAIDs and diuretics can reduce lithium clearance and increase the risk of toxicity (monitor lithium concentration).

Changes to urinary system: May induce or aggravate functional incontinence due to polydipsia, nocturia or frequency.

Elderly: In addition to age-related decline in renal function, older people are more sensitive to toxic effects. Use lower doses and monitor more frequently.

Renal impairment (mild–moderate): Caution. Dosage adjustment necessary.

Renal impairment (severe): Contraindicated.

Therapeutic monitoring: Therapeutic range:

Acute mania, 0.8–1.2 mmol/L. Prophylaxis, 0.4–1.0 mmol/L. Time to steady state, 5–7 days.

Toxicity: Monitor frequently when renal function is unstable, signs of toxicity may include nausea and flu-like symptoms.

Pregnancy: D. Contraindicated in first trimester. Seek specialist obstetric and psychiatric advice for use.

Breastfeeding: Use contraindicated. Acute toxicity in infant likely.

Common dosage range

Adult dose

Acute mania: initially 750–1,000 mg daily in divided doses; increase by 250–500 mg daily (depending on serum concentration) until symptoms resolve. Maximum 2,500 mg daily.

Prophylaxis: 250–1,000 mg daily for 2 weeks, then adjust dose according to serum concentration.

Paediatric dose

<12 years: use non-SR formulation; initially 15–20 mg/kg daily in 2–3 doses; adjust at weekly intervals, based on serum lithium concentrations (maximum 60mg/kg/day).

lomustine

antineoplastic cytotoxic agent

Cautionary advisory labels: 2, 3b, 21

Notes

Renal impairment (severe): Caution. Dose reduction may be required.

Pregnancy: D. Use contraindicated.

Breastfeeding: Use contraindicated.

Common dosage range

Initially, 130 mg/m^2 as a single dose; patients with compromised bone marrow function, 100 mg/m^2. Adjust according to haematologic response; see approved Product Information.

loperamide

opioid antidiarrhoeal

Notes

- Seek medical advice if there is no improvement after 48 hours or if unable to maintain adequate fluid intake.
- If fever or bloody diarrhoea occurs seek medical advice.
- Contraindicated for acute diarrhoea in children <12 years.

Hepatic impairment: Caution. Monitor for signs of central nervous system toxicity.

Pregnancy: B3. Not recommended in first trimester. Poorly absorbed from gastrointestinal tract; one or two doses may be used in second and third trimesters.

Breastfeeding: May be used short term. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. constipation) in infant.

Common dosage range

Adult dose

Initially 4 mg, then 2 mg after each loose bowel action. Maximum daily dose 16 mg.

Paediatric dose

1 month to 1 year: 0.1–0.2 mg/kg twice daily (maximum 2 mg/kg daily).

>1 year: 0.1–0.2 mg/kg (maximum 2 mg/dose) 3–4 times daily, up to 1.25 mg/kg daily in divided doses. Maximum 16 mg daily.

lopinavir with ritonavir

antiretroviral protease inhibitors

Cautionary advisory labels: 5, 6, B

Notes

- Does not cure HIV or eliminate risk of transmission.
- Potential for significant medicine interactions (see Table D.1, Section D).

Pregnancy: B3. Previously commenced therapy should be continued and advice sought from an infectious diseases specialist.

Breastfeeding: Expected to be excreted into breast milk, but no safety data on drug in infants. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

400 mg/100 mg lopinavir/ritonavir twice daily.

Paediatric dose

>2 years, <40 kg: 230/57.5 mg/m^2 (maximum dose 400 mg/100 mg) twice daily.

With efavirenz, nevirapine: 300/75 mg/m^2 twice daily.

>40 kg: 400 mg/100 mg lopinavir/ritonavir twice daily.

loratadine

less-sedating antihistamine

Notes

Hepatic impairment (severe): Caution. Halve usual initial dose.

Pregnancy: B1. Use not recommended. Consider use of sedating antihistamines first. If less-sedating antihistamine required, loratadine is preferred.

Breastfeeding: Small amounts excreted in breast milk. Consider use of sedating antihistamines first. If less-sedating antihistamine required, loratadine is preferred.

Common dosage range

Adult dose

10 mg daily.

Paediatric dose

1–2 years, 2.5 mg once daily.

>2 years, <30 kg 5 mg once daily.

>2 years, >30 kg 10 mg once daily.

lorazepam

benzodiazepine

Cautionary advisory labels: 1 or 1a, 9

Notes

- Regular use for more than 2–4 weeks may result in dependence and tolerance.
- Monitor patient for physical and psychological dependence and tolerance (check intervals between prescription refills).
- Beware sudden discontinuation of long-term treatment.
- May cause a 'morning-after' hangover effect.
- Caution with respiratory disease or sleep apnoea: reduced respiratory drive may cause hypoxaemia.

Changes to urinary system: May induce or aggravate functional incontinence due to sedation or impairment of mobility.

Elderly: Over-sedation, confusion, memory impairment, poor muscle coordination leading to falls and fractures. A low dose of a short-acting benzodiazepine (e.g. temazepam or oxazepam) is preferable for insomnia.

Renal or hepatic impairment: Caution.

Pregnancy: C. Use should be avoided if possible, especially during first trimester. If lorazepam is required, use the lowest effective dose for the shortest duration.

Breastfeeding: Use with caution. Excreted into breast milk, with concentrations increasing with time. Adverse effects (e.g. sedation, poor feeding) may be experienced by infant. Avoid long-term use, large doses or frequent dosing. If a benzodiazepine is required, a shorter acting one is preferred.

Common dosage range

Adult dose

Anxiety: 2–3 mg daily in 1–3 doses; range 1–10 mg.

Insomnia: 1–2 mg at night.

Premedication: 2–4 mg the night before and/or 1–2 hours before procedure.

Paediatric dose

Premedication: 0.05 mg/kg/dose.

losartan

angiotensin II receptor antagonist

Cautionary advisory labels: 11, 12†, 16†

Notes

- Blood pressure should be closely monitored during initiation of therapy.
- Monitor renal function and potassium concentration.
- Caution if the patient is taking NSAIDs (including COX-2 inhibitors) or lithium.
- Provide advice on foods and drugs with high potassium content.
- Can cause cough (cough can also be a symptom of heart failure). Establish if cough is productive or unproductive; incidence less than with ACE inhibitors.
- If swelling of face, lips or tongue is experienced, seek medical advice.

Elderly: Renal impairment, hyperkalaemia more common.

Hepatic impairment (severe): Caution. Dose reduction may be required.

Renal impairment: Caution. Hyperkalaemia more common.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as possible if pregnancy is suspected.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

25–100 mg daily in 1–2 doses.

magnesium hydroxide

antacid

Notes

- For symptomatic relief of upper gastrointestinal discomfort.
- Avoid precipitating factors—e.g. chocolate, fat, spices, large meals, alcohol, eating at bedtime, smoking.
- Dose best taken between meals and at bedtime as this is when acid levels at highest—i.e. 1–3 hours after meals.
- May interact with some medications. Separate by at least two hours.
- Most preparations are safe in pregnancy and breastfeeding; consult individual product monographs for detailed information.

Pregnancy: A

Breastfeeding: May be used. Poor systemic absorption. Excretion in breast milk unlikely.

Common dosage range

Adult dose

240–480 mg when required.

mebendazole

anthelmintic

Pregnancy: B3. Use not recommended in first trimester. Consider alternatives before using in second or third trimesters.

Breastfeeding: May be used. 2–10% of oral dose absorbed and minimal excretion in breast milk expected.

Common dosage range

Adult dose

Threadworm: 100 mg as a single dose; may repeat after 2–4 weeks.

Hookworm, roundworm, whipworm: 100 mg 12-hourly for three days.

Paediatric dose

Threadworm: >6 months and <10 kg, 50 mg as a single dose; may repeat after 2–4 weeks. >10 kg, adult dose.

Hookworm, roundworm, whipworm: >6 months and <10 kg, 50 mg twice daily for three days.

>10 kg, adult dose.

medroxyprogesterone

progestogen

Cautionary advisory labels: 12†

Notes

Contraceptive use

- Depot may be inappropriate if pregnancy is planned within one year.

Hormone replacement therapy

- Does not provide contraceptive cover during perimenopause.
- Irregular or atypical bleeding may indicate endometrial pathology; seek medical advice.
- Patient often needs information about benefits and risks of hormone replacement therapy.

Changes to faeces: Green discolouration.

Hepatic impairment (severe): Contraindicated.

† Most appropriate during initial treatment or when dosage is increased.

Pregnancy: D (oral). Previously commenced therapy should be discontinued as soon as pregnancy is suspected.

Breastfeeding: May be used IM. Very small amounts excreted in breast milk. Use larger oral doses only when no alternative available: no safety data on drug in infants.

Common dosage range

Adult dose

HRT: 5–10 mg daily for 10–14 days/month with continuous oestrogen, or 1.25–5 mg daily with continuous oestrogen.

Contraception: 150 mg IM every 3 months.

Other indications: See approved Product Information.

mefenamic acid

NSAID

Cautionary advisory labels: 10a, 12†, B

Notes

- Maximum response should be seen in 1–3 weeks.
- Alert patient to signs of gastrointestinal bleeding, (black stools or dark coffee-coloured vomit).
- Caution if taking warfarin or other anticoagulants.
- To lessen gastrointestinal complications, use lowest effective dose and take paracetamol as an alternative analgesic.
- Caution with diabetes, hypertension or heart failure, asthma or peptic ulcer.
- Consider stopping 2–3 days before planned surgery; seek medical advice.

Changes to faeces: Pink, red or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Elderly: Gastric ulceration, renal dysfunction, dizziness, sodium and water retention, exacerbation of hypertension and heart failure.

Hepatic impairment: Caution. Has been associated with adverse hepatic reactions.

Renal impairment (severe): Contraindicated.

Pregnancy: C. Alternatives to NSAIDs should be considered for analgesia. Use not recommended during third trimester.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Diclofenac and ibuprofen are the NSAIDs of choice in breastfeeding mothers.

Common dosage range

Adult dose

500 mg three times daily.

mefloquine

antimalarial

Cautionary advisory labels: 12

Notes

- Contraindicated in patients with neuropsychiatric disorders, epilepsy or cardiac conduction defects.
- For malaria prophylaxis, take regularly, at the same time and on the same day each week. Start taking preferably 2–3 weeks before entering and continue for 2–4 weeks after leaving an endemic area.

Hepatic impairment (severe): Contraindicated.

Renal impairment: Contraindicated.

Pregnancy: B3. May be used for prophylaxis in second and third trimesters if it is the drug of first choice and travel to areas of risk cannot be postponed. For use in first trimester, seek advice from an infectious diseases specialist.

Breastfeeding: Use with caution. Small amounts excreted in breast milk but may accumulate. Monitor for adverse effects in infant.

Common dosage range

Adults, children >45 kg

Prophylaxis: 250 mg once weekly on the same day each week.

Treatment of uncomplicated P. falciparum malaria: 750 mg, followed by 500 mg after 6–8 hours.

Paediatric dose

Prophylaxis: >3 months, 5 mg/kg (maximum 250 mg) weekly. Round dose to nearest quarter tablet.

Treatment of uncomplicated P. falciparum malaria: >3 months, 15 mg/kg (maximum 750 mg), followed by 10 mg/kg (maximum 500 mg) after 6–8 hours. Round dose to nearest quarter tablet.

megestrol

hormonal antineoplastic agent

Cautionary advisory labels: 12

Pregnancy: D. Use not recommended.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Potential for serious adverse effects in infants.

Common dosage range

Adult dose

160 mg daily in single or divided doses.

† Most appropriate during initial treatment or when dosage is increased.

meloxicam

NSAID

Cautionary advisory labels: 10a , 12†, A*, B

Notes

- Use with caution in patients with history of ischaemic heart disease, peripheral vascular disease and/or cerebrovascular disease.
- Maximum response should be seen in 1–3 weeks.
- Alert patient to signs of gastrointestinal bleeding, (black stools or dark coffee-coloured vomit).
- Caution if taking warfarin or other anticoagulants.
- To lessen gastrointestinal complications, use lowest effective dose and take paracetamol as an alternative analgesic.
- Check use of over-the-counter NSAIDs.
- Does the patient suffer from diabetes, hypertension, heart failure, asthma or peptic ulcer?
- Consider stopping 2–3 days before planned surgery; seek medical advice.

Changes to faeces: Pink, red or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Elderly: Gastric ulceration, renal dysfunction, dizziness, sodium and water retention, exacerbation of hypertension and heart failure.

Hepatic impairment: Caution. Has been associated with adverse hepatic reactions.

Renal impairment: Contraindicated if Clcr <20 mL/min. Maximum dose for patients on haemodialysis, 7.5 mg daily.

Pregnancy: C. Alternatives to NSAIDs should be considered for analgesia. Use not recommended during third trimester.

Breastfeeding: Use not recommended. Excretion in breast milk expected and potential for accumulation. Diclofenac and ibuprofen are the NSAIDs of choice in breastfeeding mothers.

Common dosage range

Adult dose

7.5–15 mg daily.

melphalan

cytotoxic alkylating agent

Modification of oral formulation

Avoid crushing or altering tablet due to occupational health and safety risks.

Cautionary advisory labels: 3b, 6, 21

Notes

Renal impairment (moderate–severe): May require dosage reduction by up to 50%.

Pregnancy: D. Use contraindicated.

Breastfeeding: Use contraindicated.

Common dosage range

See approved Product Information.

memantine

NMDA antagonist for Alzheimer's disease

Cautionary advisory labels: 12†

Notes

- Increasing urinary pH decreases clearance (e.g. urinary alkalinisers, drastic changes in diet, certain urinary tract infections).
- Actively secreted into renal tubule; clearance may be reduced by cimetidine and ranitidine.

Renal impairment: Contraindicated if Cl_{cr} <50 mL/min.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

Initially, 5 mg daily; maintenance, 10 mg twice daily.

mercaptopurine

cytotoxic, immunosuppressant, antimetabolite

Modification of oral formulation

Avoid crushing or altering tablet due to occupational health and safety risks.

Cautionary advisory labels: 3b, 8 , 21

Notes

- Caution: significant interaction with allopurinol. When administered with allopurinol, dosage should be reduced to one-quarter.
- Regular blood tests required.

Renal or hepatic impairment: Caution. Dose adjustment may be required.

Pregnancy: D. Use contraindicated.

Breastfeeding: Use contraindicated.

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Common dosage range

Adult dose

Antineoplastic: 2.5 mg/kg daily.

Inflammatory bowel disease: 1.5 mg/kg daily.

mesalazine

used in inflammatory large bowel disease

Modification of oral formulation

Before crushing or otherwise altering enteric-coated tablets, consider risk of failure to reach site of action.

Cautionary advisory labels: 3b*, 13, A*

Notes

- Some products are enteric coated, do not take indigestion remedies at the same time.
- Seek medical advice if sore throat, mouth ulcers, bruising, fever, malaise, rash or non-specific illness occurs.
- Different formulations are not directly interchangeable.

Changes to faeces: Black discolouration.

Changes to urinary system: Red discolouration to urine on contact with hypochlorite bleach in toilet.

Renal impairment (severe): Contraindicated

Pregnancy: C. May be used at minimum effective dose.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea) in infant.

Common dosage range

Adult dose

Treatment: oral, 500 mg three times daily; rectal foam/enema, 2–4 g once daily; suppository, 1 g once daily.

Maintenance: oral, 250 mg three times daily.

Paediatric dose

Oral, initially 15–20 mg/kg three times daily, reducing to 10 mg/kg 2–3 times daily.

metformin

biguanide antidiabetic agent

Cautionary advisory labels: 10a, A*, B

Notes

- Metformin has a slow onset of effect and may take two weeks to see maximum effects.
- Limit alcohol intake.
- If loss of appetite, nausea, vomiting, abdominal pain or weight loss occurs, seek medical advice.
- No risk of hypoglycaemia when used as a single treatment.
- Drug of choice for the obese patient.
- Caution risk of lactic acidosis (anorexia, nausea, vomiting, abdominal pain, cramps, malaise, weight loss) with high doses or if patient is renally impaired or at risk of hypoxic situations (e.g. heart failure, surgery).
- Metformin therapy should be temporarily stopped in patients undergoing surgery and procedures involving iodinated contrast media.

Elderly: Those on high doses and prolonged treatment are at increased risk of vitamin B_{12} deficiency.

Hepatic impairment (severe): Contraindicated.

Renal impairment (mild–moderate): Caution. Dosage modification required. Suggested maximum doses:

Cl_{cr} 60–90 mL/min, 2 g daily.

Cl_{cr} 30–60 mL/min, 1 g daily.

Renal impairment (severe): Contraindicated if Cl_{cr} <30 mL/min.

Pregnancy: C. Oral hypoglycaemic agents usually replaced with insulin.

Breastfeeding: Use with caution. Modest amount excreted in breast milk.

Common dosage range

Adult dose

Conventional tablet: 500–3,000 mg daily in 2–3 doses.

Controlled-release tablet: 500–2,000 mg once daily.

Paediatric dose

>10 years, conventional tablet, initially 500–850 mg once daily; maximum daily dose 2 g in 2–3 doses.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

methadone

opioid analgesic

Cautionary advisory labels: 1

Notes

- See also 'Opioid substitution therapy', Section A.
- Constipation may be a problem with chronic use. Consider treatment with stimulant or osmotic laxative (see 'Prevention and treatment of opioid-induced constipation', Section D).
- May cause nausea or vomiting.
- Long half-life means it may take a few days to gain the full effect of a dose change.
- Maintenance doses may need to be increased during pregnancy due to increased metabolism.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to inhibition of the voiding reflex, constipation, confusion, reduced detrusor activity or urinary retention.

Hepatic impairment (severe): Contraindicated

Renal impairment: Caution.

Cl_{cr} 10–50 mL/min, minimum dosage interval 8-hourly.

Cl_{cr} <10 mL/min, minimum dosage interval 12-hourly.

Pregnancy: C. May be used. Methadone substitution is treatment of choice for opioid dependence.

Breastfeeding: Use with caution. Varying amounts excreted in breast milk. Monitor for adverse effects (e.g. sedation, poor feeding) in infant. When ceasing breastfeeding, reduce gradually to minimise infant withdrawal.

Common dosage range

Adult dose

Analgesic: oral, IM, initially 5–10 mg 6–8 hourly.

Opioid dependence: initially 10–20 mg daily, adjusting gradually until stabilisation has occurred (usually 30–50 mg daily). Maximum recommended 80 mg daily.

Paediatric dose

Neonatal abstinence syndrome: initial dose, 100 micrograms/kg, increased by 50 micrograms/kg 6-hourly until symptoms controlled.

methotrexate

folic acid antagonist, antimetabolite, immunosuppressant

Modification of oral formulation

Avoid crushing or altering tablet due to occupational health and safety risks.

Cautionary advisory labels: 8, 10a, 20, 21

Notes

- Dose once weekly, check dosage with prescriber if methotrexate is prescribed more than once weekly for psoriasis or rheumatoid arthritis.
- NSAIDs, including COX-2 inhibitors, sulfonamides, probenecid, trimethoprim and pyrimethamine must be used with caution; usually not a clinical issue with once-weekly doses.
- Regular blood tests required.
- Ensure adequate hydration.

Changes to faeces: Black discolouration.

Renal impairment (mild–moderate): Caution. Dose reduction may be required.

Renal or hepatic impairment (severe): Contraindicated.

Pregnancy: D. Use contraindicated.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

Arthritis/dermatology: 5–25 mg once weekly (may be divided into 3 separate doses and taken at 0, 12 and 24 hours).

Antineoplastic: See approved Product Information and specialist protocols.

Paediatric dose

Arthritis: oral/IM/SC, 0.3–0.6 mg/kg once weekly.

methoxsalen

photosensitiser

Cautionary advisory labels: 8

Notes

- Following oral administration, wear wrap-around sunglasses during daylight hours for 24 hours, and avoid exposure to sunlight, even through glass and cloud cover, for at least 8 hours.
- Following topical administration, avoid exposure of treated areas to sunlight for at least 12–48 hours.
- If exposure to sunlight cannot be avoided, protective clothing should be worn and sunscreens applied to all areas that may be exposed, including lips.

Renal impairment (mild–moderate): Caution. Dose reduction may be required.

Hepatic impairment: Contraindicated.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use contraindicated. Most of maternal dose is cleared within 24 hours. Expressing and discarding milk during this time is recommended.

Common dosage range

Adult dose

Oral, 0.6 mg/kg (usual adult dose 20 mg) taken with milk or after food two hours before UV light exposure.

Topical, apply a 1:10 dilution of the 1% lotion (i.e. 0.1%) to the affected areas 30 minutes before UV light exposure.

methyldopa

centrally acting antihypertensive

Cautionary advisory labels: 12†, 16

Notes

- If a fever occurs seek medical advice.

Changes to urinary system: Urine darkens on standing if in contact with hypochlorite toilet bleach.

Hepatic impairment: Contraindicated (active hepatic disease).

Pregnancy: A

Breastfeeding: May be used. Small amounts excreted in breast milk.

Common dosage range

Adult dose

125–500 mg 2–4 times daily (maximum adult dose 3 g daily).

Paediatric dose

Initial dose, 10 mg/kg daily in 2–4 doses; maximum daily dose 65 mg/kg or 3 g, whichever is less.

methylphenidate

psychostimulant

Cautionary advisory labels: 12, 13, A*

Hepatic impairment (severe): Caution. Halve dose.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended. Excretion in breast milk expected, but no safety data on drug in infants.

Common dosage range

Adult dose

10–60 mg daily in 2–3 doses.

Paediatric dose

≥6 years: initially, 5 mg once or twice daily (usually morning and early afternoon); increase by 5–10 mg weekly. Maximum 60 mg daily.

Controlled release, 18–54 mg once daily.

methylprednisolone

corticosteroid

Notes

- Indication determines formulation. Acetate is for depot IM/intra-articular administration; sodium succinate is soluble and may be administered IV/IM only.

Changes to faeces: Pink, red or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Pregnancy: C. Monitor for neonatal hypo-adrenalism if used chronically.

Breastfeeding: Safe to use topically provided breast area is free of corticosteroid before breastfeeding. Use with caution systemically. If a corticosteroid is required, prednisolone is preferred.

Common dosage range

Adult dose

IV, 40–1,000 mg daily. Intra-articular, 4–80 mg.

Doses highly variable depending on indication; see approved Product Information.

Paediatric dose

Anti-inflammatory, immunosuppressive: IV, 1 mg/kg every 6–12 hours for 24 hours then review.

Other indications: See approved Product Information.

methysergide

antimigraine agent

Cautionary advisory labels: B

Notes

- Maximum continuous administration 6 months, followed by drug-free interval of 2–3 weeks.

Renal or hepatic impairment: Contraindicated.

Pregnancy: C. Use not recommended.

Breastfeeding: Use not recommended: no data available. Potential for metabolite to accumulate.

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Common dosage range

Adult dose

2–6 mg daily in 2–3 doses.

metoclopramide

dopamine antagonist, prokinetic agent

Cautionary advisory labels: 12

Notes

- Do not take more than the recommended dose. Can cause dystonic reactions, particularly at higher doses or in children and young adults.
- Higher doses may be used for nausea due to chemotherapy.
- Inquire if any other medicine been lost due to vomiting.
- Seek medical advice if involuntary eye, facial or limb movement occurs.
- Caution: may cause depression.

Elderly: Reduce dose to reduce risk of extrapyramidal effects, dizziness, confusion.

Renal or hepatic impairment (moderate–severe): Caution. Initiate at half the normal dose; subsequent dose will depend on creatinine clearance and individual response.

Cl_{cr} 40–50 mL/min use 75% of normal dose.

Cl_{cr} 10–40 mL/min use 50% of normal dose.

Cl_{cr} <10 mL/min use 25–50% of normal dose.

Pregnancy: A

Breastfeeding: May be used short term (up to 10–14 days) in doses up to 45 mg daily. Excreted in breast milk and may accumulate. May be used to promote lactation.

Common dosage range

Adult dose

Nausea and vomiting: 10 mg three times daily. Maximum 0.5 mg/kg daily.

Other indications: See approved Product Information.

Paediatric dose

Nausea and vomiting:

15–20 years: 5–10 mg three times daily.

5–14 years: 2.5–5 mg three times daily.

3–5 years: 2 mg 2–3 times daily.

1–3 years: 1 mg 2–3 times daily.

<1 year: 1 mg twice daily.

Vomiting associated with cancer chemotherapy: 1–2 mg/kg four-hourly. Maximum 10 mg/kg daily.

metoprolol

beta-blocker

Modification of oral formulation

Controlled-release tablet may be broken in half but not crushed or chewed.

Cautionary advisory labels: 9, 12†, A*

Notes

- Caution if patient suffers from diabetes (can mask hypoglycaemic attack), hyperlipidaemia, peripheral vascular disease, hyperthyroidism, uncontrolled heart failure, asthma or other lung disease.
- Doses below 150 mg may be given once daily.

When used for heart failure

- Counsel on the need for monitoring of heart rate, blood pressure, and clinical signs of heart failure weekly during dose titration.
- Report increased tiredness, breathlessness or wheezing, swollen feet or ankles, difficulty with exercise or a swollen abdomen to your doctor.
- Weigh yourself daily and consult your doctor if there is a weight gain of >1.5 kg in 24 hours.

Hepatic impairment: Caution. Lower dose may be required.

Pregnancy: C. If a cardioselective beta-blocker is required, metoprolol is preferred. Use with caution.

Breastfeeding: May be used. Small amounts excreted in breast milk and may concentrate. Although unlikely, monitor for adverse effects (e.g. hypotension, bradycardia, fatigue, nausea, diarrhoea) in infant.

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Common dosage range

Adult dose

Hypertension: oral, 50–100 mg once or twice daily. Maximum 400 mg daily.

Angina: oral, 25–100 mg 2–3 times daily.

Other indications: See approved Product Information.

Paediatric dose

IV, 0.1 mg/kg/dose; may be repeated twice if needed, then 1–5 micrograms/kg/minute. Oral, 1–2 mg/kg/dose 6–12 hourly.

metronidazole

anti-infective agent

Modification of oral formulation

Before crushing or otherwise altering tablets, consider unacceptable/undisguisable taste.

Cautionary advisory labels: 2, 5, B, D and for suspension use 2, 3b, D

Notes

- Avoid alcohol for 48 hours following completion of treatment.
- If numbness, tingling or pain in extremities occurs, seek medical advice.
- Confirm appropriate antibiotic and dose regimen.
- Common adverse effects—nausea, diarrhoea, gastric upset.
- If a skin rash develops, seek medical advice.
- Significant interaction with warfarin.

Changes to urinary system: Dark–brown discolouration of urine.

Hepatic impairment (severe): Caution. Dose reduction may be necessary.

Pregnancy: B2 (systemic and topical). May be used if drug of choice.

Breastfeeding: May be used in usual doses. Avoid high single-dose therapy or withhold feeds for 12–24 hours if necessary. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant. May cause temporary change to taste of milk.

Common dosage range

Adult dose

Oral, 200–400 mg every 8–12 hours, up to 4 g daily.

Rectal, 1 g every 8–12 hours.

Severe infections: IV, 500 mg every 8–12 hours. Maximum 4 g daily.

Giardiasis: 2 g daily for three days.

Other indications: See approved Product Information.

Paediatric dose

Oral/IV, 7.5 mg/kg eight-hourly.

Rectal, 1–5 years, 250 mg three times daily.

6–12 years, 500 mg three times daily.

Specific indications: see approved Product Information.

mexiletine

antiarrhythmic agent

Cautionary advisory labels: 12, 13

Notes

- Antiarrhythmic choice dictated by arrhythmia type and co-existing medical conditions.
- Mexiletine has serious adverse effects, including the potential to worsen arrhythmia.
- Caution with medicines that prolong the QT interval.
- Take capsules with a full glass of water to avoid oesophageal ulceration; do not lie down immediately after the dose.

Renal or hepatic impairment (moderate–severe): Caution. May require dosage adjustment.

Therapeutic monitoring: Therapeutic range is 0.5–2.5 mg/L (2.8–14 micromol/L).

Time to steady state: 2 days.

Pregnancy: B1. Not recommended in first trimester. Use with caution in second and third trimesters as risk of fetal bradycardia.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. hypotension, bradycardia) in infant.

Common dosage range

Adult dose

Ventricular arrhythmia: loading dose, 400 mg; maintenance, 300–800 mg daily in divided doses (commencing two hours after the loading dose).

Paediatric dose

Loading dose, 8 mg/kg (maximum 400 mg); maintenance, 4–8 mg/kg/dose (maximum 400 mg) three times a day, beginning 2 hours after loading dose.

mianserin

alpha2-adrenoceptor antagonist antidepressant

Cautionary advisory labels: 1, 9, 13, 16

Notes

- Medicine-free interval may be required when switching to/from another antidepressant. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.

- Full benefit may not be seen for several weeks however adverse effects may occur from start of treatment.
- Usually sedating; take dose in the evening unless insomnia occurs.
- If fever, sore throat or other signs of infection occur, seek medical advice.
- Regular full blood examinations are recommended early in treatment.
- Combination of antihistaminic (sedation) and alpha-adrenergic (hypotensive) effects.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to anticholinergic-reduced detrusor activity, urinary retention, voiding difficulty, constipation, sedation, or impairment of mobility.

Elderly: Avoid use for sedation due to adverse effects such as constipation, urinary retention, confusion, orthostatic hypotension, which may lead to falls and fractures. Counsel to rise slowly from sitting or lying down. Initiate therapy at low doses.

Renal or hepatic impairment: Caution. Increased risk of LFT abnormalities.

Pregnancy: B2. Consider switching to an SSRI. Use at minimum effective dose if drug of choice. There is increased risk of reversible withdrawal symptoms but not congenital malformations.

Breastfeeding: Use not recommended: limited data available. Consider TCAs or SSRIs first.

Common dosage range

Adult dose

60–90 mg daily in divided doses or a single dose at night. Maximum 120 mg daily.

miconazole

antifungal

Cautionary advisory labels: D, E (dermal)

Notes

- It is best to use the oral gel after (rather than before) a meal or drink.
- Interaction with warfarin may increase INR.
- Not recommended in children <6 months.

Pregnancy: A

Breastfeeding: May be used. Minimal systemic absorption, so unlikely to be excreted in breast milk.

Common dosage range

Adult dose

Half a measuring spoon four times a day.

Paediatric dose

6 months to 2 years: quarter of a measuring spoon four times a day.

>2 years: half a measuring spoon four times a day.

midazolam

benzodiazepine

Cautionary advisory labels: 1 or 1a

Notes

Elderly: Use smaller doses.

Hepatic impairment (severe): Contraindicated.

Renal impairment (severe): Caution. Halve usual dose.

Pregnancy: C. Use should be avoided if possible, especially during first trimester. If midazolam is required, use the lowest effective dose for the shortest duration.

Breastfeeding: May be used as single dose (e.g. pre-surgery). Withhold feeds for four hours after dose. Long-term use not recommended.

Common dosage range

Adult dose

Pre-operative sedation: IM, 0.07–0.08 mg/kg one hour before surgery.

Conscious sedation: IV, 1–5 mg; titrate slowly to desired effect.

Induction of anaesthesia: IV, 0.15–0.35 mg/kg slowly over 30 seconds.

Paediatric dose

Seizures: IV, 0.15 mg/kg stat then 2 micrograms/kg/minute, increasing by 2 micrograms/kg/minute until seizures cease; maximum 24 micrograms/kg/minute.

Premedication: oral, 0.4–0.6 mg/kg. Maximum 15 mg.

Intranasal, 0.2–0.4 mg/kg (maximum 10 mg). Dose should be dropped into alternate nostrils over 15 seconds.

minocycline

tetracycline anti-infective

Cautionary advisory labels: 4 (delete dairy products), 8, 12, B, D

Notes

- Do not lie down for at least one hour after taking medication.
- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible.
- Common adverse effects—nausea, diarrhoea, gastric upset, dizziness, headache.
- Seek medical advice if a skin rash develops, severe headache with visual disturbances or severe nausea occurs.

Hepatic impairment: Caution. Hepatotoxicity more likely.

Renal impairment: Caution. Dosage may require reduction.

Pregnancy: D. Use contraindicated in second and third trimesters due to effects on fetal teeth and bone growth.

Breastfeeding: May be used short-term (7–10 days), although consider alternatives with neonates. Small amounts excreted in breast milk.

Common dosage range

Adult dose

Initial dose 200 mg, then 100 mg 12-hourly. Maximum 400 mg daily.

Acne: 100 mg daily in 1–2 doses.

Paediatric dose

>8 years, initial dose 4 mg/kg, then 2 mg/kg (maximum 100 mg) twice daily.

minoxidil

systemic-vasodilator antihypertensive; topical-alopecia

Cautionary advisory labels: 16

Notes

- Hair loss may continue after topical treatment is stopped.

Pregnancy: C. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Hypertension: 5–40 mg daily in 1–2 doses. Maximum 100 mg daily.

Alopecia: apply 1 mL twice daily.

mirtazapine

SNRI antidepressant

Cautionary advisory labels: 1, 9, A (not chewed)

Notes

- Full benefit may not be seen for several weeks, but adverse effects may occur from start of treatment.
- Medicine-free interval may be required when switching to/from another antidepressant. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- More sedating at lower doses than higher doses.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to anticholinergic-reduced detrusor activity, urinary retention, voiding difficulty, constipation, sedation or impairment of mobility.

Pregnancy: B3. Continue previously commenced therapy if it is the drug of choice. There is increased risk of reversible withdrawal symptoms, not congenital malformations. For initiating treatment, consider an SSRI first.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

15–60 mg daily.

misoprostol

prostaglandin analogue

Cautionary advisory labels: B

Notes

- Antacids may decrease misoprostol effectiveness.
- Take with meals to minimise risk of diarrhoea.

Renal impairment: Caution. Half-life is increased, although dose adjustment usually unnecessay.

Pregnancy: X.

Breastfeeding: Use with caution, especially prolonged treatment. Excretion of parent compound in breast milk unlikely, but metabolite excretion unknown. Monitor for adverse effects (e.g. diarrhoea, abdominal symptoms) in infant.

Common dosage range

Adult dose

400–800 micrograms daily in 2–4 doses.

moclobemide

reversible MAOI antidepressant

Cautionary advisory labels: 9, 12, B

Notes

- Full benefit may not be seen for several weeks but adverse effects may occur from start of treatment.
- Medicine-free interval may be required when switching to/from another antidepressant. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- May cause insomnia if dose is taken after 2 pm.
- Avoid use in acute confusional states.

Changes to urinary system: May induce or aggravate urge/functional incontinence due to enhanced detrusor activity (instability), sedation or impairment of mobility.

Hepatic impairment (severe): Caution. Halve usual dose.

Pregnancy: B3. Consider switching to an SSRI. MAOIs are not drug of choice: they increase the risk of hypertensive crisis during pregnancy.

Breastfeeding: Use not recommended. Small amounts excreted in breast milk, but no safety data on drug in infants. May suppress lactation.

Common dosage range

Adult dose

300–600 mg daily in 1–2 doses.

Paediatric dose

4–12 mg/kg daily in 2–4 doses.

modafinil

non-amphetamine psychostimulant

Cautionary advisory labels: 12

Notes

- Give as a single dose in the morning or as 2 divided doses in the morning and at noon.

Hepatic impairment (severe): Caution. Halve dose.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

200–400 mg daily.

montelukast

leukotriene receptor antagonist for asthma

Notes

- Not for immediate relief of asthma symptoms or an acute attack.
- Avoid abrupt substitution for oral and inhaled corticosteroids.
- Several days of treatment required before therapeutic effect evident.
- The 5 mg and 10 mg tablets are not bioequivalent and so not interchangeable.

Pregnancy: B1. Use not recommended.

Breastfeeding: Use not recommended. Excretion in breast milk expected, but no safety data on drug in infants.

Common dosage range

Adult dose

10 mg at night.

Paediatric dose

2–5 years, 4 mg at night. 6–14 years, 5 mg at night. 15 years and over, 10 mg at night.

morphine

opioid analgesic

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets or capsules may alter absorption characteristics.

Cautionary advisory labels: 1, A*

Notes

- Dose according to response: required dose varies widely. Recommend a pain chart.
- Nausea and vomiting may occur.
- Constipation almost universal. Treatment with stimulant or osmotic laxative should be commenced at beginning of therapy (see 'Prevention and treatment of opioid-induced constipation', Section D).
- Onset of action varies with preparation prescribed. Advise accordingly, especially if controlled-release preparation dispensed for the first time.
- Naloxone may be used to reverse morphine-induced respiratory depression.
- Metabolites have a longer half-life and accumulate in the elderly and in renal impairment to cause respiratory depression and delirium.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to inhibition of the voiding reflex, constipation, confusion, reduced detrusor activity, or urinary retention.

Hepatic impairment (severe): Contraindicated.

Renal impairment (moderate): Caution. Lower doses required in chronic use.

Renal impairment (severe): Caution. Reduce dose; avoid chronic use.

Pregnancy: C. Use only if drug of choice. High doses or prolonged use at or near term may cause respiratory depression and withdrawal in newborn.

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Breastfeeding: Use with caution. Trace amounts excreted in breast milk. Therapeutic concentrations may be reached with repeated doses or long-term use. Monitor for adverse effects (e.g. sedation, respiratory depression) in infants.

Common dosage range

Adult dose

Oral, initially 10–30 mg four-hourly. Controlled release, 30–60 mg 12-hourly.

SC, IM injection, 2.0–12.5 mg. Higher doses are common, particularly in palliative care.

Paediatric dose

Oral, 0.2–0.5 mg/kg every 4–6 hours; titrate according to response. Controlled release, 0.3–0.6 mg/kg 12-hourly.

IM, SC, 0.1–0.2 mg/kg four-hourly.

IV, 0.05–0.1 mg/kg/dose four-hourly.

moxifloxacin

quinolone antibacterial

Cautionary advisory labels: 4 (delete dairy products and calcium), 12†, D

Notes

- Can be taken with or without meals.
- May prolong QT interval; ask about palpitations or fainting spells.
- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible.
- Common adverse effects—nausea, diarrhoea, gastric upset.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended. Excretion in breast milk expected. Potential for serious adverse effects (e.g. arthropathies) in infant.

Common dosage range

Adult dose

400 mg daily.

moxonidine

antihypertensive

Cautionary advisory labels: 9, 12

Notes

- May cause drowsiness, dry mouth, constipation, headache or fatigue.

Renal impairment (moderate): Caution. Maximum dose 0.2 mg, maximum daily dose 0.4 mg.

Renal impairment (severe): Contraindicated.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended. Excretion in breast milk expected and no safety data on drug in infants.

Common dosage range

Adult dose

0.2–0.6 mg daily.

mycophenolate

immunosuppressant

Cautionary advisory labels: 8, 9, A

Notes

- Regular blood tests required.

Renal impairment (severe): Caution. Dose reduction may be necessary.

Pregnancy: D. Use not recommended. Avoid pregnancy during and for at least six weeks after ceasing therapy.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

1–1.5 g twice daily.

Paediatric dose

Renal transplant: oral, 600 mg/m^2 twice daily. Maximum 2 g daily.

naltrexone

opioid antagonist

Cautionary advisory labels: 12

Notes

Hepatic impairment (severe): Contraindicated.

Renal impairment: Caution. May require dosage adjustment.

Pregnancy: B3. Use not recommended. Methadone substitution is treatment of choice for opioid dependence.

Breastfeeding: Use not recommended except in acute situation.

Common dosage range

Adult dose

50 mg daily.

† Most appropriate during initial treatment or when dosage is increased.

naproxen

NSAID

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets will alter absorption characteristics.

Cautionary advisory labels: 10a, 12†, A*, B

Notes

- Maximum response should be seen in 1–3 weeks.
- Alert patient to signs of gastrointestinal bleeding, (black stools or dark coffee-coloured vomit).
- Caution if taking warfarin or other anticoagulants.
- To lessen gastrointestinal complications, use lowest effective dose and take paracetamol as an alternative analgesic.
- Check use of over-the-counter NSAIDs.
- Caution with diabetes, hypertension, heart failure, asthma or peptic ulcer.
- Consider stopping 2–3 days before planned surgery; seek medical advice.

Changes to faeces: Pink, red or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Elderly: Increased risk of gastric ulceration, renal dysfunction, dizziness, sodium and water retention, exacerbation of hypertension and heart failure.

Hepatic impairment: Caution. May require dose reduction.

Renal impairment: Caution. May require dose reduction.

Pregnancy: C. Alternatives to NSAIDs should be considered for analgesia. Use not recommended during third trimester.

Breastfeeding: May be used for occasional doses. Very small amounts excreted in breast milk but may accumulate. Diclofenac and ibuprofen are the NSAIDs of choice in breastfeeding mothers.

Common dosage range

Doses refer to naproxen. Naproxen sodium is used in some formulations. 500 mg naproxen = 550 mg naproxen sodium.

Adult dose

250–1,250 mg daily in 2–4 doses. Controlled-release formulation, 750–1,000 mg once daily.

Paediatric dose

Juvenile rheumatoid arthritis: 10–15 mg/kg daily in two doses.

naratriptan

$5HT_1$ agonist, for acute migraine

Cautionary advisory labels: 12

Notes

- Seek medical advice if no relief occurs or if headaches are increasing in frequency or severity.
- If shortness of breath, difficulty breathing (anaphylactic-type reactions) or chest pain or tightness is experienced, seek medical advice. Should not be taken within 24 hours of ergotamine.
- Separate doses of different triptans by at least 12–24 hours.

Renal and hepatic impairment (mild–moderate): Caution. May require dose reduction.

Renal and hepatic impairment (severe): Contraindicated

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

2.5 mg as soon as headache occurs; repeat in not less than four hours if headache recurs. Total daily dose should not exceed 5 mg.

nedocromil

mast cell stabiliser

Notes

- Requires regular use.
- Not for acute asthma relief.
- Paradoxical bronchospasm may occur. If it does, seek medical advice.
- First-line treatment in children.
- Need 4-week therapeutic trial.
- With regular dosage may be able to reduce corticosteroid.

Pregnancy: B1. May be used, but cromoglycate is preferred.

Breastfeeding: May be used. Limited maternal absorption and negligible excretion in to breast milk expected.

† Most appropriate during initial treatment or when dosage is increased.

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Common dosage range

Adult dose

MDI, 4 mg four times daily or 15 minutes before exercise; reduce to twice daily when stabilised.

Paediatric dose

>2 years: 4 mg three times daily; reduce to twice daily when stabilised.

nelfinavir

antiviral (HIV) protease inhibitor

Cautionary advisory labels: 5, B

Notes

- Does not cure HIV or eliminate risk of transmission.
- Should be taken in combination with other antiretrovirals.
- May interact with many medicines (see Table D.1, Section D).

Pregnancy: B2. Previously commenced therapy should be continued and advice sought from an infectious diseases specialist.

Breastfeeding: Expected to be excreted in breast milk, but no safety data on drug in infants. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

750 mg three times daily or 1,250 mg every 12 hours.

Paediatric dose

2–13 years: 25–30 mg/kg three times daily.

nevirapine

antiretroviral non-nucleoside reverse transcriptase inhibitor

Cautionary advisory labels: 5

Notes

- Does not cure HIV or eliminate risk of transmission.
- May interact with many medicines (see Table D.1, Section D).
- Should be taken in combination with other antiretrovirals.
- Regular LFTs required during therapy.

Hepatic impairment (severe): Contraindicated.

Renal impairment (severe): Caution. May require dose adjustment.

Pregnancy: B3. Previously commenced therapy should be continued and advice sought from an infectious diseases specialist.

Breastfeeding: Excreted in breast milk, but no safety data on drug in infants. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

200 mg daily for 14 days, then 200 mg twice daily.

Paediatric dose

2 months to 8 years: 4 mg/kg once daily for 14 days then 7 mg/kg twice daily. Maximum 400 mg daily.

8–16 years: 4 mg/kg once daily for 14 days then 4 mg/kg twice daily. Maximum 400 mg daily.

nicorandil

antianginal agent

Cautionary advisory labels: 9, 12

Notes

Hepatic impairment (severe): Caution. Lower dose may be required.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

5 mg twice daily, increasing after 7 days to 10–20 mg twice daily.

nicotinic acid

hypolipidaemic agent, vasodilator

Cautionary advisory labels: B

Notes

Hepatic impairment: Caution. May exacerbate hepatic impairment.

Renal impairment (moderate–severe): Caution. Dose reduction may be required (hyperlipidaemia doses).

Pregnancy: B2. Lipid-lowering therapy not recommended during pregnancy. Previously commenced therapy should be discontinued as soon as pregnancy is suspected.

Breastfeeding: May be used for supplementation when dietary intake is insufficient. Use not recommended for hyperlipidaemia: limited data available.

Common dosage range

Adult dose

Hyperlipidaemia: 750–4,500 mg daily in three doses.

nifedipine

dihydropyridine calcium channel blocker

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets will alter absorption characteristics. Consider medicine stability issues before crushing or altering any nifedipine products.

Cautionary advisory labels: 9, 12†, 18, A*

Notes

- Dihydropyridines can cause peripheral oedema (swollen ankles).
- Potential for medicine interactions (see Table D.1, Section D).

Elderly: More susceptible to peripheral oedema.

Hepatic impairment: Caution. May require dose reduction.

Pregnancy: C. Consider alternative therapy first. If drug of choice, use with caution: maternal hypotension may produce fetal hypoxia.

Breastfeeding: May be used. <5% excreted in breast milk. Although unlikely, monitor for adverse effects (e.g. hypotension) in infant.

Common dosage range

Adult dose

Tablets, 10–40 mg twice daily. Controlled release tablets, 20–120 mg daily.

Paediatric dose

Hypertensive crisis: <2 years, 2.5 mg; >2 years, 5 mg. Check blood pressure after 20 minutes and redose if needed.

nilotinib

Bcr-Abl tyrosine kinase inhibitor

Cautionary advisory labels: 4, 5, 18, A

Notes

- Food should not be consumed for at least two hours before and one hour after each dose.
- Women of child-bearing age should use appropriate contraception.

Pregnancy: D.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

400 mg twice daily one hour before food. Dosage adjustments/interruption may be necessary to manage haematological toxicity.

nitrazepam

benzodiazepine

Cautionary advisory labels: 1 or 1a, 9

Notes

- Regular use for more than 2–4 weeks may result in dependence and tolerance.
- Monitor patient for physical and psychological dependence and tolerance. Check intervals between prescription refills.
- May cause a 'morning-after' hangover effect.
- Caution with respiratory disease or sleep apnoea: reduced respiratory drive may cause hypoxaemia.
- May exacerbate nightmares (common with nitrazepam).

Changes to urinary system: May induce or aggravate functional incontinence due to sedation or impairment of mobility.

Elderly: A low dose of a short- to medium-acting benzodiazepine is preferred for sedation.

Over-sedation, confusion, memory impairment, poor muscle coordination may lead to falls and fractures.

Hepatic impairment (severe): Contraindicated.

Renal impairment (severe): Caution. May require initial dose reduction.

Pregnancy: C. Use should be avoided if possible, especially during first trimester. If nitrazepam is required, use the lowest effective dose for the shortest duration.

Breastfeeding: Use with caution. Excreted in breast milk, with concentrations increasing with time. Adverse effects (e.g. sedation, poor feeding) may be experienced by infant. Avoid long-term use, large doses or frequent dosing. If a benzodiazepine is required, a shorter acting one is preferred.

Common dosage range

Adult dose

5–10 mg. Maximum dose 20 mg.

Paediatric dose

Anticonvulsant: 0.125–0.5 mg/kg twice daily.

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

nitrofurantoin

antibacterial

Modification of oral formulation

Before crushing or otherwise altering capsules, consider the increased risk of local gastrointestinal irritant effect.

Cautionary advisory labels: 12, B, D

Notes

- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible.
- Common adverse effects—nausea, diarrhoea, gastric upset.
- Antibacterial activity is lost if urine pH is >8; avoid excessive alkalinisation of urine.

Changes to urinary system: Rust yellow, brown discolouration of urine.

Elderly: Peripheral polyneuropathy and chronic pulmonary toxicity more comon.

Renal impairment (moderate–severe): Contraindicated.

Pregnancy: A (short course). Avoid at or near term.

Breastfeeding: May be used (except with neonates, or infants who are G6PD deficient). Small amounts excreted in breast milk. Monitor for adverse effects (e.g. haemolysis, jaundice) in infant.

Common dosage range

Adult dose

Treatment: 50–100 mg four times daily.

Prophylaxis: 50–100 mg at night.

Paediatric dose

Treatment: 5–7 mg/kg daily in four doses. Maximum 400 mg daily.

Prophylaxis: 1–2 mg/kg at night. Not recommended for use in infants <1 month of age.

nizatidine

H_2 antagonist

Notes

- Question long-term use without investigation.
- If symptoms do not improve after 2 weeks of treatment, seek medical advice.
- If nausea, severe vomiting, epigastric pain or black or blood-stained stools are experienced during or after treatment, seek medical advice.

Renal impairment: Caution. Dose reduction required.

Cl_{cr} 20–50 mL/min, 150 mg/day.

Cl_{cr} <20 mL/min, 150 mg every two days.

Pregnancy: B3. May be used when conservative treatment with antacids has failed. If an H_2 antagonist is required, ranitidine and famotidine are preferred.

Breastfeeding: May be used. Small amount excreted in breast milk. Dosing after a breastfeed to minimise infant exposure is recommended.

Common dosage range

Adult dose

150–300 mg daily in 1–2 doses.

norethisterone

progestogen

Notes

Hormone replacement therapy

- Patient needs information about benefits and risks of HRT.
- If withdrawal bleeding occurs, reduce oestrogen.
- If bleeding occurs during progestogen therapy, increase progestogen dose.

Oral contraceptives

- Beware of reduced efficacy resulting from concurrent use with antiepileptic and antibacterial medicines.
- Caution if patient suffers from vomiting or diarrhoea: contraceptive cover may have been compromised.
- See 'Managing missed doses of oral contraceptives', Section D.

Hepatic impairment (severe): Contraindicated.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as pregnancy is suspected.

Breastfeeding: May be used in low doses (e.g. progestogen-only contraceptives). Avoid larger doses: may affect milk production and composition.

Common dosage range

Adult dose

Contraception: 350 micrograms daily.

HRT: 1.25 mg daily for 10–14 days/month.

Other indications: 5–15 mg daily (see approved Product Information).

norfloxacin

quinolone antibacterial

Cautionary advisory labels: 3b, 4, 8, 12, D

Notes

- Confirm appropriate antibiotic and dose regimen.
- Maintain good fluid intake (1.5–2 L/day).
- Controversy remains over the possibility of quinolones causing arthropathy in children. Caution with use in prepubertal children.

- May cause tenderness of Achilles tendon.
- Space doses as evenly as possible.
- Common adverse effects—nausea, diarrhoea, gastric upset.
- Avoid concomitant urinary alkalinisers.

Renal impairment (severe): Caution.
Cl_{cr} <30 mL/min, maximum dose 400 mg daily.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended. Excretion in breast milk expected. Potential for serious adverse effects (e.g. arthropathies) in infant.

Common dosage range

Adult dose

Oral, 400 mg 12-hourly.

Paediatric dose

10 mg/kg 12-hourly.

nortriptyline

tricyclic antidepressant

Cautionary advisory labels: 1, 9, 13, 16

Notes

- Full antidepressant benefit may not be seen for several weeks, but adverse effects may occur from start of treatment.
- Anticholinergic adverse effects are common—dry mouth, constipation, blurred vision, difficulty in passing urine; other adverse effects include hypotension and sedation.
- Orthostatic hypotension may occur when rising quickly. Advise about getting up slowly from sitting or lying down.
- Sips of water, sugarless gum or sweets may help relieve dry mouth.
- Start with a low dose and titrate upwards
- Medicine-free interval may be required when switching to/from another antidepressant. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- For antidepressant use best taken as a single dose at night.
- Indications other than depression may include pain, enuresis and urge incontinence.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to anticholinergic-reduced detrusor activity, urinary retention, voiding difficulty, constipation, sedation or impairment of mobility.

Elderly: Avoid use for sedation due to adverse effects such as constipation, urinary retention, confusion, orthostatic hypotension, which may lead to falls and fractures. Counsel to rise slowly from sitting or lying down.

Hepatic impairment (severe): Caution. Dose reduction may be required.

Therapeutic monitoring: Therapeutic range is 50–170 micrograms/L (200–650 nanomol/L).

Pregnancy: C. Use when clinically indicated if it is the drug of choice. There is increased risk of reversible withdrawal symptoms, not congenital malformations.

Breastfeeding: Use with caution. Small amounts excreted into breast milk. If needed, preferably taken as a single dose. Monitor for adverse effects (e.g. sedation) in infant.

Common dosage range

Adult dose

Major depression: 25–100 mg daily.

Urinary urge incontinence: 10–25 mg 1–3 times daily.

Paediatric dose

Nocturnal enuresis: 7–10 years, 10–20 mg 30–60 minutes before bedtime.

>10 years, 25–50 mg 30–60 minutes before bedtime.

nystatin

antifungal

Cautionary advisory labels: B*, D, E (dermal)

Pregnancy: A

Breastfeeding: May be used.

Common dosage range

Adult dose

Oropharyngeal candidiasis: 100,000 units four times daily.

Intestinal candidiasis: 500,000 to 1 million units three times daily.

Paediatric dose

100,000 units four times daily.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

olanzapine

atypical antipsychotic

Cautionary advisory labels: 1, 8, 16

Notes

- It takes 1–2 weeks for a measurable response and 2–3 months for a full trial.
- Check glucose tolerance in patients who gain weight.
- Metabolism induced by smoking; dose adjustment may be required if patient's smoking status changes.

Changes to urinary system: May induce or aggravate overflow/functional/stress incontinence due to constipation, confusion, sedation or parkinsonism.

Elderly: Lower initial dose recommended.

Renal or hepatic impairment: Caution. Lower initial dose recommended.

Pregnancy: B3. Refer to psychiatrist to consider withdrawal. Use only if drug of choice.

Breastfeeding: Use with caution. Excreted in breast milk. Use minimum effective dose and monitor for adverse effects (e.g. sedation, jaundice, hypotonia) in infant.

Common dosage range

Adult Dose

5–20 mg daily.

olmesartan

angiotensin II receptor antagonist

Cautionary advisory labels: 11, 12†, 16†

Notes

- Blood pressure should be closely monitored during initiation of therapy.
- Monitor renal function and potassium concentration.
- Caution if the patient is taking NSAIDs (including COX-2 inhibitors) or lithium.
- Provide advice on foods and drugs with high potassium content.
- Can cause cough (cough can also be a symptom of heart failure). Establish if cough is productive or unproductive; incidence less than with ACE inhibitors.
- If swelling of face, lips or tongue is experienced, seek medical advice.
- A combination product of olmesartan with a diuretic is also available. Check that patient knows which product is being taken.

Elderly: Renal impairment, hyperkalaemia more common. Starting dose of 10 mg once daily recommended.

Hepatic impairment (severe): Caution. Limited data available.

Renal impairment (mild–moderate): Caution. Cl_{cr} 20–60 mL/min, maximum daily dose 20 mg.

Renal impairment (severe): Contraindicated.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as possible if pregnancy is suspected.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

10–40 mg once daily.

olsalazine

used in inflammatory large bowel disease

Modification of oral formulation

Crushing or otherwise altering tablets or capsules may alter absorption characteristics.

Cautionary advisory labels: B

Notes

- If sore throat, mouth ulcers, bruising, fever, malaise, rash, watery diarrhoea or non-specific illness occurs, seek medical advice.

Changes to faeces: Black.

Changes to urinary system: Red discolouration of urine on contact with hypochlorite bleach in toilet.

Pregnancy: B2. May be used at minimum effective dose.

Breastfeeding: May be used. Minimal amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea) in infant.

Common dosage range

Adult dose

500–1,000 mg twice daily. Maximum daily dose 3 g daily, maximum single dose 1,000 mg.

† Most appropriate during initial treatment or when dosage is increased.

omeprazole

proton pump inhibitor

Modification of oral formulation

Before crushing or otherwise altering enteric-coated tablets or capsules, consider risk of altering medicine stability.

Cautionary advisory labels: 13, A*

Notes

- Swallow capsules whole with a glass of water or sprinkle contents onto soft food.
- Tablets may be dispersed in water; the pellets must not be chewed or crushed.
- Raised gastric pH can reduce bioavailability of ketoconazole, itraconazole (capsule form), iron salts and digoxin.
- Generally well tolerated.
- See doctor immediately if nausea, severe vomiting, epigastric pain, or diarrhoea with blood-stained stools during or after treatment is experienced.
- Omeprazole is an inhibitor of cytochrome P450 system (see Table D.1, Section D).

Pregnancy: B3. May be used when treatment with antacids and H_2 antagonists has failed. If a proton pump inhibitor is required, omeprazole is preferred.

Breastfeeding: Use with caution. Minimal excretion in breast milk expected. Likely to be destroyed in infant's stomach, but no safety data on drug in infants. H_2 antagonists preferred.

Common dosage range

Adult dose

10–40 mg daily.

Zollinger–Ellison syndrome: 20–120 mg daily; maximum single dose 80 mg.

Paediatric dose

<10 kg, 5 mg once daily.

10–20 kg, 10 mg once daily; maximum 20 mg daily.

>20 kg, 20 mg once daily; maximum 40 mg daily.

ondansetron

$5HT_3$ antagonist antiemetic

Notes

- Confirm that no other medicine has been lost due to vomiting.

Hepatic impairment (moderate–severe): Caution. Maximum daily dose 8 mg.

Pregnancy: B1. Consider non-$5HT_3$ alternatives first. If a $5HT_3$ antagonist is required, ondansetron is the drug of choice.

Breastfeeding: Use not recommended: limited data available. If occasional doses needed, monitor for adverse effects (e.g. constipation, diarrhoea, abdominal pain) in infant.

Common dosage range

Adult dose

Oral, IV, rectal, 4–16 mg; maximum 32 mg/24 hours.

Paediatric dose

Post-operative nausea and vomiting: >2 years, IV, 0.1 mg/kg/dose (up to 4 mg).

Cancer chemotherapy: >1 year, IV, 5 mg/m^2 (maximum 8 mg) every 8–12 hours or oral 4 mg every 8–12 hours.

orlistat

lipase inhibitor

Cautionary advisory labels: B

Notes

- Caloric restriction, exercise and modification of diet should accompany treatment.
- Commonly causes headache, flatulence, faecal urgency and fatty or oily stools.
- May reduce absorption of fat soluble vitamins; take a multivitamin vitamin preparation at least 2 hours apart from orlistat.

Pregnancy: B1. Use not recommended. Previously commenced therapy should be discontinued as soon as pregnancy is suspected.

Breastfeeding: Use not recommended: limited data available. Limited maternal absorption, but effect on absorption of fat-soluble vitamins may be a concern.

Common dosage range

Adult dose

120 mg with (or up to 1 hour after) each main meal; maximum three doses/day.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

orphenadrine

anticholinergic agent

Cautionary advisory labels: 1, 13

Notes

- Anticholinergic adverse effects are common—dry mouth, constipation, blurred vision, difficulty in passing urine; other adverse effects include hypotension and sedation.

Changes to urinary system: May induce or aggravate overflow incontinence due to reduced detrusor activity, voiding difficulty, urinary retention or constipation.

Elderly: Anticholinergic adverse effects such as constipation, urinary retention and confusion are more common.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

200–300 mg daily in divided doses.

oseltamivir

antiviral (influenza A and B)

Cautionary advisory labels: A*, D

Notes

Renal impairment (moderate): Caution. Reduce dose. For Cl_{cr} 10–30 mL/min:
prevention, 75 mg on alternate days;
treatment, 75mg once daily.

Renal impairment (severe): Contraindicated if Cl_{cr} <10 mL/min.

Pregnancy: B1. Use not recommended.

Breastfeeding: Use not recommended.

Common dosage range

Adult dose

Prevention: 75 mg once daily

Treatment: 75 mg twice daily

Paediatric dose

>40 kg, use adult dose;

<40 kg, see approved Product Information.

oxazepam

benzodiazepine

Cautionary advisory labels: 1 or 1a, 9 (long-term regular therapy)

Notes

- Regular use for more than 2–4 weeks may result in dependence and tolerance.
- Monitor patient for physical and psychological dependence and tolerance (check intervals between prescription refills).
- Beware sudden discontinuation of long-term treatment.
- May cause a 'morning-after' hangover effect.
- Caution with respiratory disease or sleep apnoea: reduced respiratory drive may cause hypoxaemia.

Changes to urinary system: May induce or aggravate functional incontinence due to sedation or impairment of mobility.

Elderly: Over-sedation, confusion, memory impairment, poor muscle coordination leading to falls and fractures. Lower doses should be used.

Renal or hepatic impairment: Caution. Dose reduction may be necessary.

Pregnancy: C. Use should be avoided if possible, especially during first trimester. If oxazepam is required, use the lowest effective dose for the shortest duration.

Breastfeeding: Use with caution. Excreted into breast milk, with concentrations increasing with time. Adverse effects (e.g. sedation, poor feeding) may be experienced by infant. Avoid long-term use, large doses or frequent dosing. If a benzodiazepine is required, oxazepam is one of the preferred agents.

Common dosage range

Adult dose

15–120 mg daily in divided doses.

oxcarbazepine

anticonvulsant

Cautionary advisory labels: 5, 9, 12, 13

Notes

- Tell your doctor immediately if rash, sore throat, fever, mouth ulcers, bleeding or bruising occur.
- Cross-sensitivity to carbamazepine is high; avoid use in patients allergic to carbamazepine.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

- Hyponatremia may occur; monitor sodium concentration after 2 weeks and then each month for 3 months.

Hepatic impairment (severe): Caution. Limited data available.

Renal impairment (moderate–severe): Caution. Cl_{cr} <30 mL/min, initiate therapy at half usual dose.

Pregnancy: D. Consider risk of congenital malformation against dangers of uncontrolled epilepsy. Consider folic acid (5 mg) and vitamin K supplementation.

Breastfeeding: Use with caution. Excreted in breast milk. Monitor for adverse effects in infant and consider infant serum level monitoring.

Common dosage range

Adult dose

300–1,200 mg twice daily.

Paediatric dose

>1 month, initially, 8–10 mg/kg daily in two doses , increasing by 10 mg/kg each week to 30 mg/kg daily. Maximum 60 mg/kg daily.

oxpentifylline

xanthine derivative for peripheral vascular disease

Cautionary advisory labels: A, B

Notes

Hepatic impairment (severe): Caution. Use not recommended.

Renal impairment (severe): Caution. Dose reduction of 30–50% may be necessary.

Pregnancy: B1. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

400 mg 2–3 times daily.

oxprenolol

beta-blocker

Cautionary advisory labels: 9, 12†, A

Notes

- Caution if patient suffers from diabetes (can mask hypoglycaemic attack), hyperlipidaemia, peripheral vascular disease, hyperthyroidism, uncontrolled heart failure, asthma, chronic obstructive pulmonary disease.
- If patient has history of asthma or other lung disease, seek medical advice before dispensing.

Renal impairment (severe): Caution. Dose reduction may be necessary.

Pregnancy: C. First-line antihypertensive agent in pregnancy. Monitor for hypoglycaemia in newborn.

Breastfeeding: May be used. Insiginificant amounts excreted in breast milk. Monitor for adverse effects (e.g. bradycardia) in infant.

Common dosage range

Adult dose

20–40 mg 2–3 times a day. Maximum 320 mg daily.

oxybutynin

anticholinergic used in urinary incontinence

Cautionary advisory labels: 12

Notes

- Anticholinergic adverse effects are common—dry mouth, constipation, blurred vision, difficulty in passing urine.
- Start with a low dose and titrate upwards.
- Assess efficacy and cease if ineffective after 4 weeks.
- Avoid applying the patch to the same site within seven days.

Changes to urinary system: May induce or aggravate overflow incontinence due to reduced detrusor activity, voiding difficulty, urinary retention, or constipation.

Elderly: Over-sedation, confusion, memory impairment, poor muscle coordination leading to falls and fractures. Lower doses should be used.

Pregnancy: B1. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Oral, 2.5–5 mg 2–3 times daily. Maximum 20 mg daily.

Patch, (3.9 mg/24 hours): 1 patch applied every 3–4 days.

Paediatric dose

<5 years: 0.2 mg/kg 2–3 times daily.

>5 years: 2.5–5mg 2–3 times daily.

† Most appropriate during initial treatment or when dosage is increased.

oxycodone

opioid analgesic

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets will alter absorption characteristics.

Cautionary advisory labels: 1, A*

Notes

- Constipation may be a problem with chronic use. Commence treatment with stimulant or osmotic laxative (see 'Prevention and treatment of opioid-induced constipation', Section D).
- Dose required varies widely, adjust dose according to response. Recommend a pain chart.
- Nausea and vomiting may occur.
- Onset of action and duration of effect vary with preparation prescribed. Advise accordingly, especially if controlled-release preparation dispensed for the first time.
- Naloxone may be used to reverse oxycodone-induced respiratory depression.
- Inappropriate intravenous use of oxycodone products has been reported.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to inhibition of the voiding reflex, constipation, confusion, reduced detrusor activity, or urinary retention.

Elderly: Caution. Initiate therapy at one-third to one-half of normal dose.

Renal or hepatic impairment: Caution. Initiate therapy at one-third to one-half of normal dose.

Pregnancy: C. Use only if drug of choice. High doses or prolonged use at or near term may cause respiratory depression and withdrawal in newborn.

Breastfeeding: May be used for occasional or short-term dosing. Excreted in breast milk. Monitor for adverse effects (e.g. sedation, gastrointestinal effects) in infant. Long-term use not recommended.

Common dosage range

Adult dose

Conventional formulation: initially, 5–15 mg every 4–6 hours.

Controlled release: initially, 10 mg 12-hourly. Titrate doses according to response. Doses in excess of 400 mg daily have been used.

Paediatric dose

>1 month, initially 0.2 mg/kg (maximum 5 mg) every 4–6 hours. Titrate dose according to response.

paclitaxel

cytotoxic taxane

Cautionary advisory labels: 21

Notes

- Regular blood counts required.
- Advise patients on signs of neutropenia.
- Peripheral neuropathy is common adverse effect; dose dependent, requires reduction in dose.
- Arthralgia and myalgia are common, usually occurring 2–3 days after treatment and lasting only a few days.
- Nausea and vomiting common.
- Severe abdominal pain requires exclusion of bowel perforation.
- Alopecia occurs in almost all patients; reversible on discontinuation.
- Metabolised by the liver, care with concurrent administration of enzyme inhibitors, e.g. ketoconazole.
- Premedication with dexamethasone required to prevent severe hypersensitivity reactions.
- *Taxol*® brand contains dehydrated alcohol—possible central nervous system effects.

Hepatic impairment (moderate–severe): Caution. Clearance reduced, increased incidence of adverse effects. Avoid use or consider reduction of dose.

Pregnancy: D. Use contraindicated.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

See approved Product Information or specialist protocols.

paliperidone

antipsychotic

Cautionary advisory labels: 1, 16, A

Notes

- Possesses alpha-adrenergic blocking activity. Postural hypotension possible.
- Osmotic drug delivery system. The tablet shell may be passed intact in faeces.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Renal impairment: If creatinine clearance <50 mL/ min the recommended dose is 3 mg daily.

Pregnancy: B3.

Breastfeeding: Breastfeeding not recommended while undergoing treatment.

Common dosage range

Adult dose

6 mg once daily. Maximum recommended daily dose 12 mg.

pancreatin

pancreatic enzyme supplement

Cautionary advisory labels: A*, B

Pregnancy: Not absorbed from gastrointestinal tract so expected to be safe to use.

Breastfeeding: Not absorbed from gastrointestinal tract so expected to be safe to use.

Common dosage range

Adult dose

855–1,710 mg daily in divided doses.

pancrelipase

pancreatic enzyme supplement

Cautionary advisory labels: F

Notes

- Do not take with antacids: they may break down the enteric coating.
- Avoid taking this medicine with hot food or liquid: heat can destroy it.
- Capsules can be broken open to allow sprinkling of pellets. Pellets must not be crushed or chewed. In addition, if granules are to be mixed with food—DO NOT MIX WITH DAIRY PRODUCTS—it is important they are taken immediately otherwise dissolution of the enteric coat may occur.

Pregnancy: B2. May be used.

Breastfeeding: Not absorbed from gastrointestinal tract so expected to be safe to use.

Common dosage range

Adult dose

1–2 capsules with each meal, and one capsule with any between-meal snack. Maximum daily dose for most patients, lipase 10,000 BP units/kg.

pantoprazole

proton pump inhibitor

Modification of oral formulation

Before crushing or otherwise altering enteric-coated tablets, consider risk of altering medicine stability.

Cautionary advisory labels: A

Notes

- Raised gastric pH can reduce bioavailability of ketoconazole, itraconazole (capsule form), iron salts and digoxin.
- Generally well tolerated.
- See doctor immediately if nausea, severe vomiting, epigastric pain, or diarrhoea with blood-stained stools during or after treatment is experienced.

Hepatic impairment (moderate): Reduce initial dose.

Hepatic impairment (severe): Contraindicated.

Pregnancy: B3. May be used when treatment with antacids and H_2 antagonists has failed. If a proton pump inhibitor is required, omeprazole is preferred.

Breastfeeding: Use not recommended: limited data available. Minimal excretion in breast milk expected. Likely to be destroyed in infant's stomach, but no safety data on drug in infants. H_2 antagonists preferred.

Common dosage range

Adult dose

20–80 mg daily.

Zollinger–Ellison syndrome: 80–120 mg twice daily or 80 mg three times daily.

paracetamol

analgesic, antipyretic agent

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets will alter absorption characteristics.

Cautionary advisory labels: For all products containing paracetamol: 13, 19, A*

Notes

- Confirm the patient is not taking more than one product containing paracetamol. Calculate total daily dose where necessary. Maximum daily adult dose is 4 g.
- Consider a pain management plan.
- Caution regarding excessive alcohol use.
- Counsel if taking warfarin: large fluctuations in paracetamol doses may affect INR.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

- Consider additional topical and non-drug options—e.g. hot packs, relaxation and physiotherapy.
- Prolonged and frequent dosing should not be extended beyond 24–48 hours without medical review.

Changes to urinary system: In overdosage, dark brown urine discolouration may occur.

Therapeutic monitoring: Therapeutic range is 10–30 micrograms/L (66–99 micromol/L). Time to steady state: 10–20 hours.

Pregnancy: A

Breastfeeding: May be used. Small amounts excreted in breast milk. If infant also requires paracetamol, recommended dose does not need altering.

Common dosage range

Adult dose

Oral/rectal: 500–1,000 mg 3–4 hourly. Maximum 4 g daily.

Controlled release: 665–1,330 mg every 6–8 hours. Maximum 3,990 mg daily.

Paediatric dose

Oral: 15 mg/kg every 4–6 hours; maximum daily dose, 60 mg/kg (up to 4 g); up to 90 mg/kg daily may be given under medical supervision.

Rectal: 20–40 mg/kg as a single dose.

paraffin

stool softener

Notes

- Consider increased fibre, fluid intake and exercise.
- Chronic constipation management: may require combination treatment.
- Opioid-induced constipation: use a stool softener/stimulant and hyperosmotic (see 'Prevention and treatment of opioid-induced constipation', Section D).
- Faecal impaction may present as faecal soiling or diarrhoea.
- Absorption of fat-soluble vitamins (A,D,E,K) may be reduced.
- To minimise aspiration risk, remain upright for >2 hours following administration, avoid in patients with gastro-oesophageal reflux and avoid oral administration at bedtime.

Pregnancy: B2. Occasional doses may be used. Avoid chronic use due to impaired maternal gastrointestinal absorption of food and vitamins.

Breastfeeding: May be used short term. Not recommended long term due to affect on maternal absorption of fat-soluble vitamins.

Common dosage range

Dosing varies depending on the formulation. See approved Product Information.

Adult dose

Oral, 50% emulsion: 40 mL once daily. Increase or decrease by 5 mL if necessary to produce one soft motion with no oil leakage.

Paediatric dose

Oral, 50% emulsion: 12 months to 6 years, 10–15 mL daily; 7–12 years, 20 mL daily.

paroxetine

selective serotonin reuptake inhibitor, antidepressant

Cautionary advisory labels: 5, 9, 12, B

Notes

- Medicine-free interval may be required when switching to/from another antidepressant. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- May increase the anticoagulant response to warfarin. Monitor INR.
- Indications other than depression include obsessive compulsive disorder, anxiety, panic and eating disorders.
- SSRIs inhibit the cytochrome P450 enzymes (citalopram, escitalopram and sertraline the least—see Table D.1, Section D).
- Usually given as a morning dose due to activating effects (occasionally may cause somnolence and be taken at night).
- Full benefit may not be seen for several weeks, but adverse effects may occur from start of treatment.
- The efficacy and safety of paroxetine for the treatment of major depressive disorder has not been established in individuals less than 18 years of age.

Changes to urinary system: May induce or aggravate urge/functional incontinence due to enhanced detrusor activity (instability), sedation or impairment of mobility.

Elderly: Hyponatraemia (SIADH) may occur. Do not exceed 40 mg daily.

Hepatic impairment (severe): Caution. Dose adjustment may be necessary.

Renal impairment (severe): Caution. Dose adjustment may be necessary.

Pregnancy: D. Use not recommended. Consider switching to a different SSRI.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Avoid feeds when levels are peaking in milk (4–8 hours after dose) if possible. Monitor for adverse effects (e.g. sedation, restlessness, irritability, poor feeding) in infant.

Common dosage range

Adult dose

10–60 mg daily.

Paediatric dose

>6 years, 0.4–1 mg/kg once daily.

penicillamine

antirheumatic agent

Cautionary advisory labels: 3a, 4

Notes

- All patients should remain under the close supervision of their doctor.
- Instruct patient to immediately report fever, sore throat, mouth ulcers, unusual tiredness, chills, rash, bruising or bleeding.
- Patients sensitive to penicillin may display cross-sensitivity.

Renal impairment (moderate–severe): Contraindicated.

Pregnancy: D. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

250–2,000 mg daily in 2–3 doses.

pergolide

dopamine agonist

Cautionary advisory labels: 9, 12†, 16†, B

Notes

- Do not stand up quickly from a sitting or lying position due to postural hypertension risk.

Renal or hepatic impairment: Caution. Safety not established.

Pregnancy: C. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Initially, 50 micrograms daily, increasing gradually until optimal response achieved. Usual maintenance dose, 1 mg three times daily. Maximum 5 mg daily.

perhexiline

antianginal

Cautionary advisory labels: 5, 12†

Notes

- Monitor for hepatotoxicity and peripheral neuropathy.
- Caution with use in slow metabolisers: increase in incidence of adverse effects.
- An option for some patients with refractory angina.
- May be involved in potentially serious interactions (see Table D.1, Section D).

Renal and hepatic impairment: Caution. Dose reduction may be necessary.

Therapeutic monitoring: Therapeutic range is 0.15–0.60 mg/L (0.5–2.0 mmol/L). May be increased to 1.2 mg/L for poor response.

Time to steady state: 30 hours for extensive metabolisers, longer in poor metabolisers.

Toxicity: Poor metabolisers have longer half-lives and greater risk of toxicity. Perhexiline has non-linear pharmacokinetics.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Initially, 200–300 mg once daily for 5–7 days and then reduce to 100 mg daily. Adjust at 2–4 week intervals according to perhexiline plasma concentration and patient response. Maximum daily dose 400 mg.

Slow metabolisers, 50–100 mg once weekly (adjust dose based on plasma concentration).

† Most appropriate during initial treatment or when dosage is increased.

pericyazine

conventional antipsychotic

Cautionary advisory labels: 1, 9 (long-term regular therapy), 16

Notes

- May cause anticholinergic, hypotensive and extrapyramidal effects (dystonia, akathisia, parkinsonism, tardive dyskinesia).
- Avoid concurrent use of more than one antipsychotic.
- Withdraw antipsychotics slowly if stopping the medication.

Changes to urinary system: Pink, red or red–brown discolouration of urine. May induce or aggravate overflow/functional incontinence due to anticholinergic-induced urinary retention and constipation, voiding difficulty, sedation, confusion, parkinsonism or impaired mobility.

Elderly: Adverse effects more common, orthostatic hypotension (may lead to falls and fractures), confusion, sedation, extrapyramidal adverse effects (e.g. parkinsonism), constipation, urinary retention, blurred vision.

Hepatic impairment: Caution. Dose adjustment may be necessary.

Renal impairment: Caution. Dose adjustment may be necessary.

Pregnancy: C. Use not recommended. Refer to psychiatrist to consider withdrawal.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

15–75 mg daily in 1–2 doses.

Elderly dose

2.5–10 mg at night or 10–30 mg daily in 1–2 doses.

Paediatric dose

>1 year, initially 0.5 mg/year of age; maximum 1 mg/year of age.

perindopril

angiotensin-converting enzyme inhibitor

Cautionary advisory labels: 11, 12†, 16†

Notes

- Blood pressure should be closely monitored during initiation of therapy.
- Monitor renal function and potassium concentration.
- Caution if the patient is taking NSAIDs (including COX-2 inhibitors) or lithium.
- Provide advice on foods and drugs with high potassium content.
- Can cause cough (cough can also be a symptom of heart failure). Establish if cough is productive or unproductive.
- If swelling of face, lips or tongue is experienced, seek medical advice.
- May cause metallic taste or lack of taste.
- A combination product of perindopril with a diuretic is also available. Check that patient knows which product is being taken.
- Two different formulations are available. Check which has been prescribed as doses are not directly equivalent. 2.5 mg of perindopril arginine is equivalent to 2 mg of perindopril erbumine.

Changes to urinary system: May induce or aggravate stress incontinence due to cough-induced sphincter weakness.

Elderly: 2–4 mg daily.

Renal impairment: Caution.

Cl_{cr} 30–60 mL/min, 2 mg daily.

Cl_{cr} 15–30 mL/min, 2 mg every second day.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as possible if pregnancy is suspected.

Breastfeeding: Use not recommended: limited data available. If an ACE inhibitor is required, captopril or enalapril are preferred.

Common dosage range

Adult dose

2–8 mg (erbumine formulation) once daily.

2.5–10 mg (arginine formulation) once daily.

† Most appropriate during initial treatment or when dosage is increased.

pethidine
opioid analgesic

Cautionary advisory labels: 1

Notes

- May cause constipation, nausea and vomiting.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to inhibition of the voiding reflex, constipation, confusion, reduced detrusor activity or urinary retention.

Elderly, renal impairment: Caution. Increased risk of norpethidine accumulation and toxicity.

Pregnancy: C. Use only if drug of choice. High doses or prolonged use near term may cause respiratory depression and withdrawal in newborn.

Breastfeeding: May be used for single doses. Small but potentially significant amounts excreted in breast milk and may accumulate. Monitor for adverse effects (e.g. sedation, gastrointestinal effects) in infant. Repeated doses and long-term use not recommended.

Common dosage range

Adult dose

SC/IM, 25–100 mg, 4-hourly. IV, 25–50 mg, 4-hourly.

Paediatric dose

IM,IV, SC, 0.5–2 mg/kg (up to 100 mg) 3–4 hourly; maximum 10 mg/kg daily. Caution in infants <12 months.

phenelzine
monoamine oxidase inhibitor antidepressant

Cautionary advisory labels: 1, 5, 6, 13, 16, I

Notes

- Significant medicine and food interactions may be important (check medicine history).
- Advise patient on foods to avoid while on this medicine (see 'MAOI advice card' in Section A).
- Avoid preparations containing ephedrine, pseudoephedrine, phenylephrine and dextromethorphan.
- If frequent or severe headaches, or palpitations occur, seek medical advice.
- Medicine-free interval may be required when switching to/from other antidepressants. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.

Pregnancy: B3. Use not recommended. Consider switching to an SSRI.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

15–30 mg three times daily. Maximum 90 mg daily.

phenindione
oral anticoagulant

Cautionary advisory labels: 10b

Notes

Changes to faeces: Pink, red, black. These colours may indicate medicine-induced gastrointestinal bleeding.

Changes to urinary system: Red discolouration of urine that disappears upon acidification of the urine (distinguishes it from haematuria).

Hepatic impairment (severe): Caution.

Renal impairment (severe): Caution.

Pregnancy: D. Use contraindicated.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

100 mg twice daily on day 1, 50 mg twice daily on day 2, then 12.5–50 mg twice daily according to INR. Usual maintenance dose 20–80 mg twice daily. Maximum dose 100 mg twice daily.

pheniramine
sedating antihistamine

Modification of Oral Formulation

Crushing or otherwise altering controlled-release tablets will alter absorption characteristics.

Cautionary advisory labels: 1, 13

Pregnancy: A

Breastfeeding: Use with caution. Avoid slow-release formulations. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. sedation, irritability) in infant.

Common dosage range

Adult dose

Initially 22.65 mg (half a tablet) 2–3 times daily up to 45.3 mg (1 tablet) three times daily.

Paediatric dose

Children 5–10 years; 22.65 mg (half a tablet) up to three times daily.

phenobarbitone

barbiturate, antiepileptic

Cautionary advisory labels: 1, 5, 9

Notes

- Available as base or sodium salt; check which has been prescribed.
- Barbiturates increase hepatic metabolism and reduce effectiveness of some medicines (see Table D.1, Section D).
- IV administration requires a diluted solution given at a rate not exceeding 60 mg/minute.
- Monitor vital functions during IV administration as respiratory depression and hypotension are common.

Renal and hepatic impairment, Elderly: Caution. Dose reduction may be required.

Therapeutic monitoring: Therapeutic range: Adult 10–40 mg/L (45–180 micromol/L).

Child 10–30 mg/L (45–135 micromol/L).

Time to steady state: 14–20 days.

Toxicity: Monitor seizure control and sedation.

Pregnancy: D. Use not recommended.

Breastfeeding: Use with caution. Avoid large doses. Excreted in breast milk and accumulation likely. Monitor for adverse effects (e.g. sedation, vomiting, poor feeding) in infant and consider infant serum level monitoring.

Common dosage range

Adult dose

Anticonvulsant: oral, 60–240 mg daily in 1–3 doses.

Status epilepticus: IV, 10–20 mg/kg, repeated if necessary to a total dose of 1–2 g.

Paediatric dose

Anticonvulsant: oral, 1–6 mg/kg daily in 1–3 doses.

Status epilepticus: IV, initially 15–20 mg/kg; repeat if necessary at 5–10 mg/kg every 20 minutes to a maximum total dose of 40 mg/kg.

phenoxybenzamine

nonselective alpha-blocker

Cautionary advisory labels: 12, 16

Pregnancy: B2. May be used when surgical intervention is not possible.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Phaeochromocytoma: initially, 10 mg twice daily; increase every four days until response achieved. Maintenance, 10–30 mg twice daily.

Urinary retention: due to neurogenic bladder, 10 mg twice daily.

Paediatric dose

Phaeochromocytoma: initially, 0.2 mg/kg (maximum 10 mg) once daily, gradually increasing to a maintenance dose of 0.4–1.2 mg/kg daily in 2–3 doses.

phenoxymethylpenicillin (penicillin V)

beta-lactamase labile penicillin

Cautionary advisory labels: 3a or 3b, D

Notes

- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible.
- Ask about an adverse effect or allergy to penicillin.
- Common adverse effects—nausea, diarrhoea, gastric upset.
- If a skin rash develops, seek medical advice.

Hepatic impairment (severe): Dose adjustment may be necessary.

Renal impairment (severe): Dose adjustment may be necessary.

Pregnancy: A

Breastfeeding: May be used. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

Oral, 250–500 mg 4–6 hourly.

Tonsilitis: 500 mg orally, 12-hourly for 10 days.

Rheumatic fever prophylaxis: 250 mg twice daily.

Paediatric dose

10–12.5 mg/kg (maximum 500 mg) six-hourly.

Tonsilitis: 10 mg/kg (maximum 500 mg) 12-hourly for 10 days.

Rheumatic fever prophylaxis: <5 years, 125 mg twice daily; >5 years, 250 mg twice daily.

phentolamine

non-selective alpha-blocker

Pregnancy: B1. Not recommended in first trimester. If used in second and third trimesters, monitor for maternal hypotension and fetal hypoxia.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Phaeochromocytoma: IV, 2–5 mg pre-operatively, repeated as necessary.

Erectile dysfunction: intracavernosal, 0.08–1.25 mg combined with papaverine or alprostadil.

Paediatric dose

Phaeochromocytoma: 0.1 mg/kg pre-operatively, then 5–50 micrograms/kg/minute.

phenytoin

antiepileptic

Modification of oral formulation

Crushing or otherwise altering capsules may alter absorption of phenytoin.

Cautionary advisory labels: 5, 9, 12†, 13

Notes

- Protect tablets from light.
- Seek medical advice if sore throat, mouth ulcers, bruising, fever, malaise, rash, slurred speech, nystagmus or any non-specific illness occurs.
- Regular therapeutic monitoring recommended.
- Encourage regular dental visits and good oral hygiene to reduce severity of gingival hyperplasia.
- Phenytoin is a medicine of low therapeutic index with non-linear pharmacokinetics and is involved in significant medicine interactions (see Table D.1, Section D).
- Alcohol ingestion may potentiate sedative adverse effects.
- Concomitant administration with nasogastric feeds or antacids may reduce the oral bioavailability of phenytoin.
- IV administration should not exceed 50 mg/min in adults; 1–3 mg/kg/min (maximum 50 mg/min) in children.
- IM administration is not recommended.

Changes to urinary system: Pink, red or red–brown discolouration of urine.

Hepatic impairment: Caution. May require dose reduction.

Therapeutic monitoring: Therapeutic range: 10–20 mg/L (total), 1–2 mg/L (unbound). 40–80 micromol/L (total). Time to steady state: 5–7 days.

Toxicity: Phenytoin has non-linear pharmacokinetics, so small dose changes can cause large changes in serum concentration.

Pregnancy: D. Consider risk of congenital malformation against dangers of uncontrolled epilepsy. Consider folic acid (5 mg) and vitamin K supplementation.

Breastfeeding: May be used. Small amounts excreted in breast milk. Ensure maternal serum level remains within therapeutic range. Monitor for adverse effects (e.g. sedation, decreased sucking) in infant and consider infant serum level monitoring.

Common dosage range

Adult dose

Anticonvulsant: oral, initially, 4–5 mg/kg daily (maximum 300 mg daily) in 2–3 doses. Adjust dosage according to plasma levels; usual maintenance dose 4–8 mg/kg daily. Maximum 600 mg day.

Status epilepticus: IV, 10–15 mg/kg.

Paediatric dose

Anticonvulsant: oral, initially 5 mg/kg/day 2–3 divided doses (maximum 300 mg daily). Adjust dosage according to plasma levels; usual maintenance dose 4–8 mg/kg day.

Status epilepticus: IV, 10–20 mg/kg.

pholcodine

opioid cough suppressant

Cautionary advisory labels: 1

Pregnancy: A

Breastfeeding: May be used. Small amounts excreted in breast milk.

Common dosage range

Adult dose

10–15 mg 3–4 times daily.

Paediatric dose

2–5 years, 2–2.5 mg three times daily;
6–12 years, 5–10 mg 3–4 times daily.

† Most appropriate during initial treatment or when dosage is increased.

phytomenadione

vitamin K

Notes

Elderly: May be more susceptible to reversal of anticoagulation; lower doses may be required.

Pregnancy: May be used if risk of deficiency, particularly in those on liver–enzyme inducing antiepileptics.

Breastfeeding: May be used short term. Use with caution if chronic dosing required.

Common dosage range

Adult dose

Oral, IV, 0.5–20 mg (maximum 40 mg daily), depending on INR and presence of minor or major bleeding.

Paediatric dose

Neonates: IM, 1 mg single dose. Oral, 2 mg at birth, and again at 3–5 days of age and at four weeks.

pindolol

beta-blocker

Cautionary advisory labels: 9, 12†

Notes

- If patient has history of asthma or other lung disease seek medical advice before dispensing.
- Caution if patient suffers from diabetes (can mask hypoglycaemic attack), hyperlipidaemia, peripheral vascular disease, hyperthyroidism, uncontrolled heart failure, asthma, chronic obstructive pulmonary disease.

Pregnancy: C. Use not recommended in first trimester. If drug of choice, use with caution in second and third trimesters.

Breastfeeding: Consider alternatives first. Small amounts excreted in breast milk. If used, monitor for adverse effects (e.g. bradycardia, hypotension) in infant.

Common dosage range

Adult dose

10–30 mg daily in 2–3 divided doses.

pioglitazone

thiazolidinedione

Cautionary advisory labels: 10a

Notes

- Hepatic function should be monitored every two months for first year of therapy and periodically thereafter.
- Advise patient to report to doctor any signs or symptoms of hepatic dysfunction (e.g. nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine, pale stools, yellow skin or eyes).
- Can increase plasma volume and may worsen heart failure. Advise patient to monitor for signs and symptoms (e.g. shortness of breath, swollen ankles, fatigue).
- Advise doctor if patient is, or is considering becoming, pregnant or breastfeeding.

Hepatic impairment: Caution. Clearance may be reduced in patients with hepatic disease, increase dose cautiously. Contraindicated in patients with baseline ALT >2.5 the upper limit of normal.

Pregnancy: B3. Oral hypoglycaemic agents usually replaced with insulin.

Breastfeeding: Use not recommended: limited data available. Consider short-term insulin therapy.

Common dosage range

Adult dose

15–45 mg daily.

piperacillin

antipseudomonal penicillin

Notes

- Available as a single product or in combination with tazobactam (beta-lactamase inhibitor); clarify which product has been prescribed.
- Sodium content may require consideration in certain patients.

Renal impairment (moderate–severe): Caution. Dose reduction required. See approved Product Information.

Pregnancy: B1. May be used only if drug of choice.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

† Most appropriate during initial treatment or when dosage is increased.

Common dosage range

Adult dose

3–4 g every 4–6 hours. Maximum 24 g daily.

Specific indications: see approved Product Information.

Paediatric dose

Moderate infections: 100–200 mg/kg daily in four doses.

Severe infections: 200–300 mg/kg daily in 3–4 doses. Administer via IV infusion over 30 minutes.

piroxicam

NSAID

Cautionary advisory labels: 10a, 12†, B

Notes

- Maximum response should be seen in 1–3 weeks.
- Alert patient to signs of gastrointestinal bleeding, (black stools or dark coffee-coloured vomit).
- Caution if taking warfarin or other anticoagulants.
- To lessen gastrointestinal complications, use lowest effective dose and take paracetamol as an alternative analgesic.
- Check use of over-the-counter NSAIDs.
- Caution with diabetes, hypertension, heart failure, asthma or peptic ulcer.
- Consider stopping 2–3 days before planned surgery; seek medical advice.

Changes to faeces: Pink, red or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Elderly: Increased risk of gastric ulceration, renal dysfunction, dizziness, sodium and water retention, heart failure, exacerbation of hypertension.

Renal impairment: Caution. Increased risk of further renal impairment and bleeding.

Pregnancy: C. Alternatives to NSAIDs should be considered for analgesia. Use not recommended during third trimester.

Breastfeeding: May be used for occasional doses. Small amounts excreted in breast milk but has potential to accumulate. Diclofenac and ibuprofen are the NSAIDs of choice in breastfeeding mothers.

Common dosage range

Adult dose

10–20 mg once daily.

Paediatric dose

0.2–0.3 mg/kg once daily. Maximum 15 mg daily.

pizotifen

antimigraine agent

Cautionary advisory labels: 1

Pregnancy: B1. Consider alternatives first. Use not recommended in first trimester.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Initially 0.5 mg daily, increasing to 1.5 mg daily in 1–2 doses. Maximum 3–4.5 mg daily in 2–3 doses.

Paediatric dose

Initially, 0.5 mg at night, then 0.5–1.5 mg daily in 1–2 doses. Maximum nightly dose 1 mg.

poloxamer

stool softener

Notes

- Consider increased fibre, fluid intake and exercise.
- Chronic management: may require combination treatment.
- Opioid-induced constipation: use a stool softener/stimulant and hyperosmotic (see 'Prevention and treatment of opioid-induced constipation', Section D).
- Faecal impaction may present as faecal soiling or diarrhoea.

Common dosage range

Paediatric dose

Oral drops (10%): <6 months, 10 drops; 6–18 months, 15 drops; 18–36 months, 25 drops. Give up to three times daily.

potassium chloride

electrolyte

Modification of oral formulation

Before crushing or otherwise altering tablets, consider the increased risk of local gastrointestinal irritant effect.

Cautionary advisory labels: A*, B

Notes

- Some slow-release matrix formulations may appear intact in the stools.
- Periodic blood tests are recommended.

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

- Provide advice on potassium-rich foods.
- Caution if combined with potassium-sparing agents.

Pregnancy: May be used.

Breastfeeding: May be used for supplementation. Keep maternal serum levels within the normal range.

Common dosage range

Adult dose

Oral, 600-1,200 mg 2–3 times daily

IV, 40–80 mmol/day; usual maximum, 200 mmol/24 hours.

Paediatric dose

Oral, 2–4 mmol/kg daily in 2–4 doses.

IV, initially, 0.6 mmol/kg over three hours; maintenance, 2–4 mmol/kg daily.

pramipexole

Parkinson's disease, restless legs syndrome

Cautionary advisory labels: 1, 9, 12, 16

Notes

- Somolence.
- Sudden onset of sleep during daily activities.
- Ability to drive or participate in dangerous activities may be impaired.
- Postural hypotension.
- For restless legs, the dose should be taken 2–3 hours before bedtime.

Renal impairment: Dosage adjustment required.

Pregnancy: B3.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

Parkinson's disease: 125 micrograms three times daily for one week, then 250 micrograms three times daily for one week, then 500 micrograms three times daily. May be increased gradually to a maximum of 4.5 mg daily.

Restless legs syndrome: 125 micrograms once daily at bedtime, increasing every 5–7 days if needed by 125 micrograms a day to a maximum of 750 micrograms daily.

pravastatin

HMG-CoA reductase inhibitor

Notes

- If muscle pain, tenderness or weakness is experienced, seek medical advice.
- Liver function tests recommended prior to starting and during therapy.
- Increased risk of adverse effects in combination with gemfibrozil.
- Important to follow a low-fat diet and other measures such as exercise and weight control.

Renal impairment: Caution. A lower starting dose recommended.

Pregnancy: D. Lipid-lowering therapy not recommended during pregnancy.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

10–80 mg daily as a single evening dose.

Paediatric dose

8–13 years, 20 mg once daily.

14–18 years, 40 mg once daily.

praziquantel

anthelmintic

Cautionary advisory labels: 12, B

Notes

Hepatic impairment (moderate–severe): Caution. Dose reduction may be required.

Pregnancy: B1. Use not recommended in first trimester. For use in second and third trimesters, seek advice from an infectious diseases specialist.

Breastfeeding: May be used for single-day treatment. For dosing over longer periods, withhold feeds until at least six hours after last dose.

Common dosage range

Adult and paediatric doses

Schistosomiasis: 20 mg/kg every four hours for three doses.

Intestinal tapeworm: 10 mg/kg single dose.

Other indications: See approved Product Information.

prazosin

selective alpha-blocker

Cautionary advisory labels: 12†, 16

Notes

- Treatment may be for benign prostatic hypertrophy (BPH) or hypertension.
- If no improvement in symptoms of BPH in 4–6 weeks, discontinue.
- Monitor for hypotension when used for BPH.
- May cause a 'first-dose' effect characterised by hypotension with dizziness or syncope 30–90 minutes after the initial dose. Initial dose should be administered at bedtime or to a recumbent patient.
- Dose should be gradually increased up to the maintenance dose according to response.
- Caution if taking diuretics or patient is volume depleted.

Changes to urinary system: May induce or aggravate stress incontinence due to sphincter relaxation or inadvertant dribbling of urine.

Elderly: Caution. Orthostatic hypotension more common and may lead to falls and fractures.

Hepatic impairment: Caution. May require dosage reduction.

Renal impairment: Caution. First-dose hypotension may be enhanced.

Pregnancy: B2. Use not recommended in first trimester. May be used in second and third trimesters when adequate blood pressure has not been achieved with first-line therapy.

Breastfeeding: Use with caution. Small amounts excreted in breast milk.

Common dosage range

Adult dose

Initially, 0.5 mg twice daily, increasing to 3–20 mg daily in 2–3 doses.

Paediatric dose

Initially, 5 micrograms/kg (maximum 500 micrograms) 6-hourly; increase slowly to 25 micrograms/kg 2–3 times daily. Maximum dose, 100 micrograms/kg.

prednisolone

corticosteroid

Cautionary advisory labels: Oral: 9 (except short courses), B

Notes

- Take in the morning if a once-daily dosing is ordered.
- May cause reduced wound healing.
- Seek prompt medical advice following close contact with someone with an infection, chickenpox or shingles.
- May cause mood swings (mental disturbances, psychosis, euphoria), osteoporosis, cushingoid effects (e.g. thin skin, moon face, buffalo hump, striae, acne), raised blood sugar levels and cataracts in high dose.
- Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Pregnancy: A. Monitor blood glucose levels.

Breastfeeding: May be used. For doses >20 mg daily, withhold feeds for 3–4 hours after each dose.

Common dosage range

Adult Dose

Acute asthma: oral, 40–50 mg once daily for at least 5 days.

Rheumatoid arthritis: oral, 5–10 mg once daily.

Other indications: See approved Product Information.

Paediatric dose

Acute asthma: oral, 1 mg/kg once daily for at least three days.

Croup: oral, 1 mg/kg 12-hourly for 1–2 doses.

Other indications: See approved Product Information.

prednisone

corticosteroid

Cautionary advisory labels: Oral: 9 (except short courses), B

Notes

- Take in the morning if a once-daily dosing is ordered.
- May cause reduced wound healing.
- Seek prompt medical advice following close contact with someone with an infection, chickenpox or shingles.

† Most appropriate during initial treatment or when dosage is increased.

- May cause mood swings (mental disturbances, psychosis, euphoria), osteoporosis, cushingoid effects (e.g. thin skin, moon face, buffalo hump, striae, acne), raised blood sugar levels and cataracts in high dose.

Hepatic impairment (severe): Caution. Hepatic conversion active form may be reduced.

Pregnancy: A. Monitor blood glucose levels.

Breastfeeding: Prednisolone is preferred to avoid 'double-peak'or parent drug and metabolite.

Common dosage range

Adult dose

5–60 mg daily in divided doses.

pregabalin

antiepileptic

Cautionary advisory labels: 1, 9

Notes

Renal impairment: Caution. Dose reduction required according to renal function.

Cl_{cr} 30–60 mL/min, 75–300 mg daily in 1–2 divided doses.

Cl_{cr} 15–30 mL/min, 25–150 mg daily in 1–2 divided doses.

Cl_{cr} <15 mL/min, 25–75 mg as a single daily dose.

Pregnancy: B3. Consider risk of congenital malformation against dangers of uncontrolled epilepsy. Consider folic acid (5 mg) and vitamin K supplementation.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

75–300 mg twice daily.

primaquine

antiprotozoal antimalarial

Cautionary advisory labels: B

Notes

Changes to urinary system: Rust yellow or brown urine discolouration.

Pregnancy: D. Use not recommended.

Breastfeeding: Use with caution: limited data available. Avoid if infant is G6PD deficient. Monitor for adverse effects (e.g. haemolysis, jaundice) in infants.

Common dosage range

Adult dose

15–30 mg daily for 14–21 days.

Elimination of P. falciparum gametocytes: 45 mg single dose.

Paediatric dose

0.3 mg/kg once daily for 14 days.

Elimination of P. falciparum gametocytes: 0.7–1 mg/kg single dose.

primidone

barbiturate antiepileptic agent

Cautionary advisory labels: 1, 5, 9

Notes

- Barbiturates increase hepatic metabolism and reduce effectiveness of some medicines (see Table D.1, Section D).

Renal or hepatic impairment: Caution. Dose reduction may be required.

Pregnancy: D. Consider risk of congenital malformation against dangers of uncontrolled epilepsy. Consider folic acid (5 mg) and vitamin K supplementation.

Breastfeeding: Use with caution. Excreted in breast milk. Monitor for adverse effects (e.g. sedation, poor feeding) in infant and consider infant serum level monitoring.

Common dosage range

Adult dose

Initially, 125 mg daily, increasing to a maximum of 750 mg twice daily.

Paediatric dose

Initially, 62.5 mg at bedtime for three nights; gradually increase to 20–30 mg/kg daily in two doses. Maximum 750 mg daily.

probenecid

uricosuric agent

Cautionary advisory labels: 10a, B

Notes

Renal impairment (moderate–severe): Caution. Efficacy may be significantly reduced.

Pregnancy: B2. Use not recommended in first trimester.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

0.5–2 g daily in 2–4 divided doses.

Paediatric dose

>2 years, initially 25 mg/kg, then 10 mg/kg (maximum 500 mg) 6-hourly.

procarbazine

cytotoxic, weak MAOI

Cautionary advisory labels: 2, 5, 21, I

Notes

Renal impairment (severe): Caution. Dose reduction may be required.

Pregnancy: D. Use contraindicated.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

Initially 50 mg, increasing by 50 mg each day to 250–300 mg daily. The daily dose may be divided if nausea is a problem.

prochlorperazine

phenothiazine, dopamine antagonist

Cautionary advisory labels: 1, 16

Notes

- If dystonic reaction occurs—jaw rigidity, eyes rolling backwards, spasm of the muscles of the face and neck—seek medical advice.
- Confirm other medicine has not been lost due to vomiting.
- Caution: may cause central nervous system depression.
- Reduce dose in renal impairment and in the elderly to avoid extrapyramidal effects.

Elderly: More susceptible to adverse effects, including orthostatic hypotension, drowsiness, confusion, extrapyramidal adverse effects (e.g. parkinsonism).

Changes to urinary system: May cause pink, red or red–brown urine discolouration.

Hepatic impairment: Caution. May require dose reduction.

Renal impairment: Caution. May require dose reduction according to renal function.

Pregnancy: C. May be used if first-line agents are ineffective. Avoid high doses near term.

Breastfeeding: Use with caution. Excretion in breast milk expected. Monitor for adverse effects (e.g. sedation) in infant.

Common dosage range

Adult dose

Oral, 5–10 mg 3–4 times daily. An initial 20 mg dose may be given for acute nausea and vomiting.

IV, 12.5 mg every 8 hours.

Rectal, 25 mg.

Paediatric dose

>2 years, >10kg: oral, 0.2 mg/kg 2–3 times a day.

proguanil

antimalarial

Cautionary advisory labels: 4 (delete milk, iron and calcium), B

Notes

- Start taking 1–2 days before entering and continue for four weeks after leaving an endemic area.

Renal impairment (moderate–severe): Caution. Dose reduction required.

Cl_{cr} 20–59 mL/min, 100 mg daily.

Cl_{cr} 10–19 mL/min, 50 mg every second day.

Cl_{cr} <10 mL/min, 50 mg once weekly.

Pregnancy: B2. May be used for prophylaxis if it is the drug of first choice and travel to areas of risk cannot be postponed. Consider supplementation with folic acid 5 mg daily.

Breastfeeding: May be used. Insignificant amounts excreted.

Common dosage range

Adult dose

200 mg daily with chloroquine.

Paediatric dose

Oral, 3.5 mg/kg daily (maximum 200 mg daily) with chloroquine.

promethazine

phenothiazine antihistamine

Cautionary advisory labels: 1

Notes

- Anticholinergic adverse effects may occur (dry mouth, constipation, dizziness, fatigue or blurred vision)—advise accordingly.

Elderly: More susceptible to adverse effects including orthostatic hypotension, drowsiness, confusion.

Pregnancy: C. May be used if first-line agents are ineffective. Avoid high doses near term.

Breastfeeding: Use with caution. Small amounts expected to be excreted in breast milk. Monitor for adverse effects (e.g. sedation) in infant. Avoid long-term dosing.

Common dosage range

Adult dose

Oral, 10–25 mg 2–4 times daily. Maximum 100 mg daily.

IM/IV, 12.5–50 mg 2–4 hourly. Maximum 150 mg daily.

Paediatric dose

Antihistamine: oral, 2–5 years, 5 mg 2–3 times daily; 6–12 years, 10 mg 2–3 times daily.

Antiemetic: ≥2 years, IM, 0.25–0.5 mg/kg every 4–6 hours as needed.

propantheline

anticholinergic

Modification of oral formulation

Before crushing or otherwise altering tablets, consider unacceptable/undisguisable taste.

Cautionary advisory labels: 9, 12

Notes

- Anticholinergic adverse effects are common—dry mouth, constipation, blurred vision, difficulty in passing urine.
- Assess efficacy and cease if ineffective after 4 weeks.
- Sips of water, sugarless gum or sweets may help relieve dry mouth.

Changes to urinary system: May induce or aggravate overflow incontinence due to reduced detrusor activity, voiding difficulty, urinary retention or constipation.

Elderly: Caution. More susceptible to adverse effects including orthostatic hypotension, drowsiness, confusion.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use with caution. Minimal excretion in breast milk expected. Monitor for adverse effects (e.g. sedation, anticholinergic effects) in infant.

Common dosage range

Adult dose

Peptic ulcer: 15 mg three times daily 30 minutes before meals and 30 mg at bedtime. Maximum 120 mg daily.

Other indications: 15–30 mg four times daily.

Paediatric dose

2 mg/kg daily in 2–6 doses.

propranolol

beta-blocker

Cautionary advisory labels: 9, 12†

Notes

- Do not stop taking suddenly: dose needs to be reduced over 4–8 days.
- If patient has history of asthma or other lung disease, seek medical advice before dispensing.
- Caution if patient suffers from diabetes (can mask hypoglycaemic attack), hyperlipidaemia, peripheral vascular disease, hyperthyroidism, uncontrolled heart failure, asthma, chronic obstructive pulmonary disease.

Pregnancy: C. Consider more selective beta-blockers first.

Breastfeeding: May be used. Small amounts excreted in breast milk. Although unlikely, monitor for adverse effects (e.g. hypotension, bradycardia, fatigue, nausea, diarrhoea) in infant. Consider withholding feeds until 2–3 hours after dose, particularly with neonates.

Common dosage range

Adult dose

Initially, 20–120 mg daily in divided doses, increasing to a maximum of 320 mg daily in 2–4 doses.

Paediatric dose

Arrhythmias: 0.25–0.5 mg/kg 3–4 times daily.

Migraine prophylaxis: >7 years, initially 10 mg once or twice daily, increasing to 2 mg/kg daily in 2–3 doses.

propylthiouracil

antithyroid agent

Notes

- Dose is initially taken in divided doses but may be taken once daily for maintenance therapy.
- If fever, mouth ulcer, sore throat, or skin rash occurs, seek medical advice.

Pregnancy: C. If drug of choice, use with caution with fetal thyroid gland monitored by ultrasound and monitoring of newborn thyroid function.

Breastfeeding: Antithyroid agent of choice during lactation. Small amounts excreted in breast milk. Monitor infant thyroid function periodically when used long term or in high doses.

† Most appropriate during initial treatment or when dosage is increased.

Common dosage range

Adult dose

Initially, 25–300 mg daily in 2–4 doses.

Maintenance, 50–800 mg daily in 2–4 doses.

Paediatric dose

Thyrotoxicosis: 5–7 mg/kg daily in three doses.

pseudoephedrine

oral sympathomimetic decongestant

Notes

- The effect on blood pressure may be accentuated in the elderly.

Changes to urinary system: May induce or aggravate overflow incontinence due to enhanced sphincter activity, urinary retention or voiding difficulty.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Potential for adverse effects (e.g. irritability, disturbed sleep) in infant. May suppress lactation.

Common dosage range

Adult dose

60 mg 4–6 hourly.

Paediatric dose

>2 years: 1 mg/kg 3–4 times daily.

pyrantel

anthelmintic

Notes

- Treat all contacts.
- Tablets may be crushed and mixed with jam.

Hepatic impairment: Caution. Contraindicated in acute hepatic disease.

Pregnancy: B2. May be used.

Breastfeeding: May be used. Minimal maternal absorption so negligible excretion in breast milk expected.

Common dosage range

Manufacturers recommend a single dose for all indications. The *Australian Medicines Handbook* 2008 suggests adult and paediatric dose be repeated after 2 weeks for threadworm and taken daily for 3 days for hookworm.

Adult and paediatric dose

10 mg/kg (maximum 750 mg) as single dose.

pyrazinamide

antitubercular agent

Notes

- Before treatment obtain full blood count, serum uric acid, creatinine, urea and liver transaminase concentrations.
- Interrupt treatment if transaminase concentrations increase to >5 times the normal upper limit or bilirubin concentration rises; reintroduce cautiously once liver function returns to normal.

Hepatic impairment (moderate–severe): Contraindicated.

Renal impairment (moderate–severe): Contraindicated.

Pregnancy: B2. May be used on advice of an infectious diseases specialist.

Breastfeeding: Use with caution. Small amounts excreted in breast milk but has potential to accumulate. Monitor for adverse effects (e.g. jaundice) in infant.

Common dosage range

Adult dose

20–35 mg/kg (maximum 1.5 g) daily or 50 mg/kg (maximum 3 g) three times a week.

Paediatric dose

15–30 mg/kg (maximum 1.5 g) daily or 50 mg/kg (maximum 2 g) three times a week.

pyridostigmine

anticholinesterase

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets will alter absorption characteristics.

Notes

Renal impairment: Caution. Dose reduction may be required.

Pregnancy: C. Benefits are likely to outweigh risks.

Breastfeeding: Use with caution. Excreted in breast milk. Monitor for adverse effects (i.e. anticholinergic effects) in infant.

Common dosage range

Adult dose

Conventional tablet: initially, 60 mg once daily, increasing to 300–720 mg daily in divided doses.

Controlled-release tablet: 180–540 mg once or twice daily.

Paediatric dose

Conventional tablet: increase gradually up to 7 mg/kg daily in 4–6 doses.

Controlled-release tablet: 90–180 mg at night.

pyridoxine

vitamin B_6

Pregnancy: May be used.

Breastfeeding: May be used for supplementation if maternal intake is deficient. Avoid large doses (>200 mg daily) as may suppress lactation.

Common dosage range

Adult dose

Prevention of isoniazid neuropathy, homocystinuria: 25 mg daily.

Sideroblastic anaemia: 100–200 mg daily.

Paediatric dose

Seizures due to congenital pyridoxine dependency: IV/oral/IM, 50–100 mg daily.

Prevention of isoniazid neuropathy: 25 mg daily.

quetiapine

atypical antipsychotic agent

Cautionary advisory labels: 1, 9, 12†, 16†

Notes

- Avoid combination with other medicines that also prolong the QT interval and increase risk of arrhythmia.
- It takes 1–2 weeks for a measurable response and 2–3 months for a full trial.
- Metabolism inhibited by some medicines (see Table D.1, Section D).

Changes to urinary system: May induce or aggravate overflow/functional/stress incontinence due to constipation, confusion, sedation or parkinsonism.

Elderly: Use with caution.

Hepatic impairment: Caution. Dosage adjustment necessary. Intitally, 25 mg daily, increasing in by 25–50 mg daily to an effective dose.

Pregnancy: B3. Use only if drug of choice. Refer to psychiatrist to consider if withdrawal is required.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Schizophrenia: initially, 25 mg twice daily, increasing gradually over three or more days to 150 mg twice daily; if required, may be increased to a total daily dose of 750 mg.

Acute mania: initially, 50 mg twice daily, increasing gradually over three days to 200 mg twice daily; if required, may be increased to a total daily dose of 800 mg.

quinapril

angiotensin-converting enzyme inhibitor

Cautionary advisory labels: 11, 12†, 16†

Notes

- Blood pressure should be closely monitored during initiation of therapy.
- Monitor renal function and potassium concentration.
- Caution if the patient is taking NSAIDs (including COX-2 inhibitors) or lithium.
- Provide advice on foods and drugs with high potassium content.
- Can cause cough (cough can also be a symptom of heart failure). Establish nature of cough, productive or unproductive.
- If swelling of face, lips or tongue is experienced, seek medical advice.
- May cause metallic taste or lack of taste.

Changes to urinary system: May induce or aggravate stress incontinence due to cough-induced sphincter weakness.

Renal impairment: Caution. Dosage adjustment necessary. Initial dose:

Cl_{cr} >30 mL/min 5 mg daily.

Cl_{cr} 10–30 mL/min 2.5 mg daily.

Cl_{cr} <10 mL/min use with caution.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as possible if pregnancy is suspected.

Breastfeeding: Use not recommended. Small amounts excreted in breast milk (detectable for about four hours), but no safety data on drug in infants. If an ACE inhibitor is required, captopril or enalapril is preferred.

Common dosage range

Adult dose

5–40 mg daily in 1–2 doses.

† Most appropriate during initial treatment or when dosage is increased.

quinine

antimalarial agent

Modification of oral formulation

Before crushing or otherwise altering tablets, consider unacceptable/undisguisable taste.

Cautionary advisory labels: 13

Notes

- If tinnitus or visual disturbance, headache, nausea or diarrhoea occurs, seek medical advice.
- Caution with medicines that prolong the QT interval.
- Reduces clearance of digoxin; halve digoxin dose and monitor plasma concentration.
- Not recommended for treatment or prophylaxis of leg cramp due to risk–benefit profile.
- Monitor blood glucose concentration, blood pressure and ECG during IV treatment.

Changes to urinary system: May discolour urine brown or black.

Pregnancy: D. Use not recommended.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. haemolysis, jaundice) in infants. Avoid in G6PD deficient infants.

Common dosage range

Adult dose

Malaria treatment: oral, 600 mg three times daily for 7–14 days.

Paediatric dose

Malaria treatment: oral, 10 mg/kg (maximum 600 mg) three times daily for 7–10 days.

rabeprazole

proton pump inhibitor

Modification of oral formulation

Before crushing or altering enteric-coated tablets consider medicine stability issues.

Cautionary advisory labels: A

Notes

- Raised gastric pH can reduce bioavailability of ketoconazole, itraconazole (capsule form), iron salts and digoxin.
- Generally well tolerated.
- See doctor immediately if nausea, severe vomiting, epigastric pain or diarrhoea with blood-stained stools during or after treatment is experienced.

Hepatic impairment (severe): Caution
Start at low dose, careful titration of dose.

Pregnancy: B1. May be used when treatment with antacids and H_2 antagonists has failed. If a proton pump inhibitor is required, omeprazole is preferred.

Breastfeeding: Use not recommended. Excretion in breast milk expected.

Common dosage range

Adult dose

20–40 mg daily in 1 or 2 doses.

raloxifene

selective oestrogen-receptor modulator

Notes

- Risk of thromboembolism if patient is immobile.
- Maintain adequate intake of calcium and vitamin D.

Hepatic impairment (severe): Contraindicated.
No data.

Pregnancy: X.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

60 mg daily.

raltegravir

HIV integrase strand transfer inhibitor

Cautionary advisory labels: 12

Pregnancy: B3.

Breastfeeding: Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

400 mg twice daily. Dosage should be increased if administered with phenytoin, rifampicin or barbiturates.

ramipril

angiotensin-converting enzyme inhibitor

Cautionary advisory labels: 11, 12†, 16†

Notes

- Blood pressure should be closely monitored during initiation of therapy.
- Monitor renal function and potassium concentration.
- Caution if the patient is taking NSAIDs (including COX-2 inhibitors) or lithium.

† Most appropriate during initial treatment or when dosage is increased.

- Provide advice on foods and drugs with high potassium content.
- Can cause cough (cough can also be a symptom of heart failure). Establish nature of cough, productive or unproductive.
- If swelling of face, lips or tongue is experienced, seek medical advice immediately.
- May cause metallic taste or lack of taste.

Changes to urinary system: May induce or aggravate stress incontinence due to cough-induced sphincter weakness.

Hepatic impairment: Caution. Dose adjustment may be necessary.

Renal impairment (mild–moderate): Caution. Dosage adjustment necessary. Monitor clinically. Initiate at 1.25 mg daily.

Renal impairment (severe): Contraindicated.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as possible if pregnancy is suspected.

Breastfeeding: Use not recommended. Small amounts excreted in breast milk, but no safety data on drug in infants. If an ACE inhibitor is required, captopril or enalapril is preferred.

Common dosage range

Adult dose

2.5–10 mg daily in 1 or 2 doses.

ranitidine

H_2 antagonist

Notes

- Question long-term use without investigation.
- If symptoms do not improve after 2 weeks of treatment, seek medical advice.
- If nausea, severe vomiting, epigastric pain, black or blood-stained stools are experienced during or after treatment, seek medical advice.
- Bradycardia has been reported with rapid IV administration. Ensure that ranitidine is given as a slow IV injection or as an infusion at a rate not exceeding 10 mg/minute.

Renal impairment (severe): Caution. Dose adjustment may be necessary.

Pregnancy: B1. May be used when conservative treatment with antacids has failed. If an H_2 antagonist is required, ranitidine and famotidine are preferred options.

Breastfeeding: Use with caution. Excreted in breast milk and accumulates. If an H_2 antagonist is required, famotidine and nizatidine is preferred.

Common dosage range

Adult dose

Oral, 150–300 mg daily in 1–2 doses.

IV, 50 mg over 5 minutes every 6–8 hours.

Paediatric dose

Oral, 2–4 mg/kg twice daily. Maximum 300 mg daily.
IV, 2–4 mg/kg daily in 3–4 divided doses.

reboxetine

selective noradrenaline reuptake inhibitor

Cautionary advisory labels: 9, 12†, 16

Notes

- Medicine-free interval may be required when switching to/from another antidepressant. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- Full benefit may not be seen for several weeks, but adverse effects may occur from start of treatment.
- Dry mouth and constipation are common.
- Not recommended in patients with narrow-angle glaucoma.
- Insomnia is a common adverse effect.
- Monitor blood pressure and heart rate.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to anticholinergic-reduced detrusor activity, urinary retention, voiding difficulty, constipation, sedation or impairment of mobility.

Elderly: Reduce initial dose in elderly, initially 2 mg twice daily, maximum 6 mg daily.

Renal and hepatic impairment (moderate–severe): Caution. Dosage adjustment necessary. Monitor clinically.

Pregnancy: B1. Use lowest effective dose if it is the drug of choice due to failure of other agents. There is increased risk of reversible withdrawal symptoms, not congenital malformations. For initiating treatment, consider SSRI first.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult Dose

4 mg twice daily. Increase if required after three weeks to 10 mg daily in divided doses. Maximum 12 mg daily.

† Most appropriate during initial treatment or when dosage is increased.

repaglinide

antidiabetic agent

Cautionary advisory labels: 13

Notes

- Take with a glass of water immediately before main meals.
- Withhold dose if a meal is skipped: hypoglycaemia could occur.
- Start with low dose (e.g. 0.5 mg daily) and increase every 1–2 weeks according to blood sugar levels.
- Advise patients of signs of hypoglycaemia (i.e. pale skin, sweating, hunger, faintness, palpitations, tremor, headache and visual disturbance) and its management.
- Home monitoring and recording of blood sugar levels as recommended by doctor. Advise/demonstrate use of testing kits.
- Avoid combination with sulfonylureas.

Renal and hepatic impairment (mild–moderate): Caution. Dosage adjustment necessary. Monitor clinically. Start at low dose; careful titration of dose.

Hepatic impairment (severe): Contraindicated.

Pregnancy: C. Oral hypoglycaemic agents usually replaced with insulin.

Breastfeeding: Use not recommended. Excretion in breast milk expected, but no safety data on drug in infants.

Common dosage range

Adult dose

0.5–4 mg immediately before each main meal. Maximum recommended single dose is 4 mg; maximum total daily dose 16 mg.

riboflavin

vitamin B_2

Notes

Changes to urinary system: Yellow discolouration of urine.

Pregnancy: May be used in usual doses.

Breastfeeding: May be used in usual doses.

Common dosage range

Adult and Paediatric dose

Vitamin B_2 Deficiency: 1–3 mg daily.

Glutaric aciduria: 50–300 mg daily in divided doses.

rifabutin

rifamycin anti-infective agent

Cautionary advisory labels: 5, D

Notes

- Urine, faeces, sweat, tears and possibly saliva may be coloured red or orange. Skin may also become yellow.
- Soft contact lenses may be discoloured permanently.
- Report any signs of hepatic damage (e.g. fatigue, jaundice, dark urine, pale faeces, nausea and vomiting).
- Non-hormonal forms of contraception should be used during treatment and for 4 weeks post-treatment.
- May induce the metabolism of other medicines (see Table D.1, Section D).

Changes to faeces: Red–orange discolouration.

Changes to urinary system: Red–orange discolouration.

Renal and hepatic impairment (mild–moderate): Caution. Monitor clinically.

Renal impairment (severe): Caution. Dosage adjustment necessary. If Cl_{cr} <30 mL/min give 50% of usual dose.

Pregnancy: C. Seek advice from infectious diseases specialist. Not recommended in second and third trimesters. Consider vitamin K supplementation if used late in pregnancy.

Breastfeeding: Contraindicated. Insufficient data in humans.

Common dosage range

Adult dose

150–600 mg once daily.

Paediatric dose

5 mg/kg once daily up to 300 mg.

rifampicin

rifamycin anti-infective agent

Cautionary advisory labels: 3b, 5, D

Notes

- Urine, faeces, sweat and tears may be coloured red or orange.
- Soft contact lenses may be discoloured.
- Report any signs of hepatic damage (e.g. fatigue, jaundice, dark urine, pale faeces, nausea and vomiting).

- Pre-existing hepatic disease and the use of other hepatotoxic drugs can increase the risk of jaundice occurring during therapy with rifampicin. Hepatic function should be monitored in these patients.
- Non-hormonal forms of contraception should be used during treatment and for 4 weeks post-treatment.
- May induce the metabolism of other medicines (see Table D.1, Section D).

Changes to faeces: Red–orange discolouration.

Changes to urinary system: Red–orange discolouration of urine.

Hepatic impairment: Caution. Dose adjustment may be necessary. Monitor clinically.

Pregnancy: C. Seek advice from infectious diseases specialist. Not recommended in second and third trimesters. Consider vitamin K supplementation if used late in pregnancy.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Oral/IV, 450–600 mg once daily or 15 mg/kg (maximum 600 mg) three times weekly.

Paediatric dose

Oral/IV, 10–20 mg/kg (maximum 600 mg) daily in 1–2 doses, or 15 mg/kg (maximum 600 mg) 3 times weekly.

riluzole

neurological agent for amyotrophic lateral sclerosis

Cautionary advisory labels: 12

Notes

- Do not take with a high-fat meal.
- Monitor hepatic function regularly.

Hepatic impairment: Contraindicated in patients with baseline serum transaminase levels >3 times upper limit of normal.

Renal impairment: Caution.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

50 mg twice daily.

risedronate

bisphosphonate

Modification of oral formulation

Before crushing or otherwise altering tablets, consider the increased risk of local gastrointestinal irritant effect.

Cautionary advisory labels: 20 (certain forms), A, C

Notes

- Take first thing in the morning with a full glass of water.
- Presence of food reduces absorption significantly.
- Remain upright for 30 minutes after the dose and until after the first meal of the day.
- Report signs of reflux, worsening indigestion, pain or difficulty swallowing.
- For osteoporosis, ensure adequate intake of calcium and vitamin D (taken at different time of day).

Renal impairment (severe): Contraindicated. If Cl_{cr} <30 mL/minute.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended. Excretion in breast milk expected. Potential for serious adverse effects in infant.

Common dosage range

Adult dose

Osteoporosis: 5 mg once daily or 35 mg once a week.

Paget's disease: 30 mg once daily for two months.

risperidone

atypical antipsychotic agent

Cautionary advisory labels: 1, 16

Notes

- Increased risk of cerebrovascular events—e.g. stroke, transient ischaemic attack.
- Response occurs in 1–2 weeks; need to allow 2–3 months for full effect.
- May lower seizure threshold.
- Metabolism inhibited by some medicines (see Table D.1, Section D).
- Daily doses greater than 4 mg increase the risk of extrapyramidal effects.

Changes to urinary system: May induce or aggravate overflow/functional/stress incontinence due to constipation, confusion, sedation or parkinsonism.

Renal and hepatic impairment: Caution. Limited data available. Dosage adjustment necessary. Give 50% of usual dose.

Elderly: Reduce dose.

Pregnancy: B3. Use only if drug of choice. Refer to psychiatrist to consider if withdrawal is required.

Breastfeeding: Use with caution; low doses only. Excreted in breast milk. Monitor for adverse effects (e.g. drowsiness) in infant.

Common dosage range

Adult dose

0.5–3 mg twice daily; maximum 5 mg twice daily.

Paediatric dose

0.02–0.08 mg/kg (maximum 4 mg) daily in two doses.

ritonavir

antiretroviral protease inhibitor

Cautionary advisory labels: 5, B

Notes

- Does not cure HIV or eliminate risk of transmission.
- May interact with many medicines (see Table D.1, Section D).
- Should be taken in combination with other antiretrovirals.

Hepatic impairment: Caution. Dose adjustment may be necessary. Monitor clinically.

Pregnancy: Previously commenced therapy should be continued and advice sought from an infectious diseases specialist.

Breastfeeding: Expected to be excreted into breast milk but no safety data on drug in infants. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

300 mg twice daily increasing within two weeks to 600 mg twice daily.

Paediatric dose

>1 month, initially, 250 mg/m^2 twice daily; increase by 50 mg/m^2/dose every 2–3 days to 350–400 mg/m^2 (maximum 600 mg) twice daily; consider alternative treatment if dose of 400 mg/m^2 is not tolerated.

rivastigmine

anticholinesterase

Cautionary advisory labels: 12, B

Notes

- If treatment is interrupted for several days, re-titrate dose to minimise adverse effects—e.g. nausea and vomiting.
- Avoid anticholinergics due to antagonistic effects.

Changes to urinary system: May induce or aggravate urge incontinence due to enhanced cholinergic effect, detrusor instability, frequency, or urgency.

Renal and hepatic impairment (mild–moderate): Caution. Limited data available. Start at low dose, careful titration of dose.

Hepatic impairment (severe): Contraindicated. No data.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Initial, 1.5 mg twice daily; maintenance dose, 1.5–6 mg daily. Maxiumum 6 mg twice daily.

ropinirole

dopamine agonist

Cautionary advisory labels: 12

Notes

- Ropinirole is metabolised by CYP1A2 and has potential to be involved in medicine interactions (see Table D.1, Section D).

Elderly: Alteration in mental alertness and/or coordination may increase risk of falls and fractures.

Renal and hepatic impairment: Contraindicated. No data.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended. May suppress lactation.

Common dosage range

Adult dose

0.25 mg daily for two days. If tolerated, increase by 0.5 mg per week; usual dose 2 mg daily. Maximum 4 mg daily.

rosiglitazone

thiazolidinedione

Cautionary advisory labels: 10a, A

Notes

- Hepatic function tests should be monitored every two months for first year of therapy.
- Advise patient to report to doctor any signs or symptoms of hepatic dysfunction (e.g. nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine, pale stools, yellow skin or eyes).

- Can increase plasma volume and may worsen heart failure. Advise patient to monitor for signs and symptoms (e.g. shortness of breath, swollen ankles, fatigue).

Hepatic impairment (moderate–severe): Contraindicated. Limited data available.

Pregnancy: B3. Oral hypoglycaemic agents usually replaced with insulin.

Breastfeeding: Use not recommended: limited data available. Consider insulin short term.

Common dosage range

Adult dose

Initially, 4 mg daily; may increase to 8 mg daily in 1–2 doses.

rosuvastatin

HMG-CoA reductase inhibitor

Notes

- Important to follow a low-fat diet and other measures such as exercise and weight control.
- If muscle pain, tenderness or weakness is experienced, seek medical advice.
- Increased risk of adverse effects in combination with gemfibrozil.
- Japanese and Chinese patients may need lower doses (always start at 5 mg).
- May be taken at any time of day.

Hepatic impairment: Caution. Start at low dose; careful titration of dose. Monitor clinically. Contraindicated in active liver disease or if patient has unexplained and persisitent elevations in serum transaminases.

Hepatic impairment (severe): Initiate on 10 mg once daily.

Renal impairment: Caution. Start at low dose; careful titration upwards is needed. If Cl_{cr} <30 mL/min, initiate on 5 mg once daily.

Pregnancy: D. Lipid-lowering therapy not recommended during pregnancy.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

Initially, 5–10 mg once daily; usual range, 5–20 mg once daily. Maximum 40 mg once daily.

rotigotine

non-ergot dopamine receptor agonist

Cautionary advisory labels: 1, 9, 12, 13, 16

Notes

- After use fold adhesive side inwards and dispose appropriately.
- Do not apply the patch to red, irritated or damaged skin.
- Application site should be rotated daily.
- Do not use the same site within 14 days.
- Excessive heat should not be applied to the area of the patch.
- Somnolence and/or sudden sleep episodes have been reported.
- The patch should not be cut into pieces.
- Regular opthalmological examinations are recommended.
- Multiple patches may be required to obtain the appropriate dose in a patient.

Pregnancy: B3.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

2–16 mg/24 hours depending upon the stage of the Parkinson's disease. Start at lower strength and titrate upwards as needed at weekly intervals.

roxithromycin

macrolide antibacterial

Cautionary advisory labels: 3b, D

Notes

- Confirm appropriate antibiotic and dose regimen.
- If nausea occurs, take with food.
- Notify prescriber if patient has experienced an adverse effect or allergy previously with macrolide antibacterials.
- Adverse effects—nausea, diarrhoea, gastric upset.

Renal and hepatic impairment: Caution. Limited data available. Dose adjustment may be necessary.

Hepatic impairment (severe): Contraindicated.

Pregnancy: B1. May be used.

Breastfeeding: May be used. Very small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

150 mg twice daily or 300 mg once daily.

Paediatric dose

2.5–4 mg/kg twice daily.

salbutamol

beta$_2$ agonist, short acting

Cautionary advisory labels: 22 (capsules and nebules), 7b (foil wrapping)

Notes

- Reliever for asthma: can be used to treat an acute attack.
- Inhalation devices should be primed before first use and again if device not used for two weeks.
- If using salbutamol, ipratropium (or eformoterol or salmeterol) and steroid inhalers, use in that order.
- Can cause tachycardia, tremor and electrolyte disturbances.
- Encourage the development of an asthma management plan.
- If previously effective dose fails to provide at least three hours' relief, seek medical advice.
- Counsel on technique (spacer, face mask, nebuliser).
- Increasing use to control symptoms indicates deterioration of asthma control; treatment should be re-assessed.
- 0.9% sodium chloride should be used as a diluent with nebuliser solution if required.
- Nebuliser solution is stable for one hour once mixed with sodium cromoglycate or ipratropium.

Pregnancy: A

Breastfeeding: May be used. Excreted in breast milk. Monitor for adverse effects (e.g. tremor, agitation) in infant when large doses are taken orally.

Common dosage range

Adult dose

DPI, 200–400 micrograms 3–4 times daily as required or 5–15 minutes before exercise.

MDI, 100–200 micrograms 3–4 times daily as required or 5–15 minutes before exercise.

Nebuliser, 2.5–5 mg; repeat 3–4 times daily.

Oral, 2–4mg 3–4 times per day.

SC/IM, 500 micrograms every 3–4 hours.

IV, 200–300 micrograms over 1 minute. May be repeated after 15 minutes.

Paediatric dose

MDI, 100–200 micrograms every 4–6 hours.

Nebuliser, <2 years, 0.1 mg/kg up to 2.5 mg; repeat 3–4 times daily as required.

>2 years, 2.5–5 mg; repeat 3–4 times daily as required.

Oral, 0.15 mg/kg/dose; repeat up to every six hours as required; maximum single dose, 4 mg.

IM, >2 years, 10–20 micrograms/kg; repeat every four hours if necessary.

IV, <2 years, 5 micrograms/kg over 5 minutes as a single dose.

>2 years, 15 micrograms/kg (maximum 250 micrograms) over 5 minutes as a single dose.

salcatonin

calcitonin, salmon origin

Cautionary advisory labels: 6

Notes

- A scratch test should be performed prior to administration.

Hepatic impairment: No information available.

Renal impairment: Dose reduction may be required.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use not recommended: limited data available. May suppress lactation.

Common dosage range

Adult dose

Hypercalcaemia: 5–10 international units (IU) per kg daily by slow IV infusion, or by slow IV injection in 2–4 doses.

Paget's Disease: SC/IM, 80 to 100 IU daily.

salmeterol

beta$_2$ agonist, long acting

Notes

- Do not use to treat an acute asthma attack.
- Use regularly, usually twice a day or at least 30 minutes before exercise.
- Encourage the development of an asthma management plan.
- Increased reliance on short-acting beta-agonists indicates deterioration of asthma control; treatment should be re-assessed.
- Can cause tachycardia and tremor.
- Provide advice on inhaler/accuhaler technique.
- Recommend use of a spacer with an inhaler.

Pregnancy: B3. May be used.

Breastfeeding: May be used. Monitor for adverse effects (e.g. tremor, agitation) in infant.

Common dosage range

Adult dose

MDI/DPI, 50–100 micrograms twice daily.

Paediatric dose

≥ 4 years: MDI/DPI, 50 micrograms twice daily.

saquinavir

antiretroviral protease inhibitor

Cautionary advisory labels: 5, 18, B

Notes

- Capsules should be refrigerated in the pharmacy. Patients can store at room temperature for up to 90 days.
- Does not cure HIV or eliminate risk of transmission.
- Least potent inhibitor of hepatic enzymes of protease inhibitors, many potential medicine interactions (see Table D.1, Section D).
- Should be taken in combination with other antiretrovirals.
- Indicated only in combination with ritonavir.

Hepatic impairment (mild–moderate): Caution. Dose adjustment may be necessary.

Hepatic impairment (severe): Contraindicated.

Pregnancy: B1. Previously commenced therapy should be continued and advice sought from an Infectious Diseases specialist.

Breastfeeding: Expected to be excreted into breast milk, but no safety data on drug in infants. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

1,000 mg every 12 hours .

selegiline

dopaminergic agent and inhibitor of MAO type B

Cautionary advisory labels: 5, 12, B

Notes

- Do not start antidepressants or other medicines with serotonergic effects within 2 weeks of stopping selegiline. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- Dietary restrictions required if used with moclobemide.
- Best taken at breakfast and lunch to minimise sleep disturbance.

Elderly: Confusion, hallucinations, orthostatic hypotension, which may increase risk of falls and fractures.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use not recommended. Excretion in breast milk expected. Metabolised to amphetamine.

Common dosage range

Adult dose

2.5 mg daily, increasing to 5 mg twice daily.

senna

stimulant laxative

Notes

- Advise increased fibre, fluid intake and exercise.
- Chronic management: may require combination treatment.
- Opioid-induced constipation: use a stool softener/stimulant and hyperosmotic (see 'Prevention and treatment of opioid-induced constipation', Section D).
- Faecal impaction may present as faecal soiling or diarrhoea.

Changes to faeces: Yellow, green discolouration

Changes to urinary system: Yellow, red, red–brown discolouration.

Pregnancy: A. Occasional doses may be used. Large doses or prolonged use should be avoided.

Breastfeeding: May be used in the recommended dose. Avoid large doses or chronic use.

Common dosage range

Adult dose

7.5–30 mg at bedtime.

Paediatric dose

2–6 years, 3.75–7.5 mg at bedtime.

6–12 years, 7.5–15 mg at bedtime.

One 5 mL teaspoon of granules contains approximately 15 mg of senna.

sertraline

selective serotonin reuptake inhibitor

Cautionary advisory labels: 5, 9, 12

Notes

- Medicine-free interval may be required when switching to/from another antidepressant. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.

- May increase the anticoagulant response to warfarin. Monitor INR.
- Indications other than depression may include obsessive compulsive disorder, anxiety, panic and eating disorders.
- SSRIs inhibit the cytochrome P450 enzymes (citalopram, escitalopram and sertraline the least; see Table D.1, Section D).
- Usually given as a morning dose due to activating effects (occasionally may cause somnolence and be taken at night).
- Full benefit may not be seen for several weeks, but adverse effects may occur from start of treatment.
- The efficacy and safety of sertraline has not been established in individuals aged less than 18 years.

Changes to urinary system: May induce or aggravate urge/functional incontinence due to enhanced detrusor activity (instability), sedation or impairment of mobility.

Elderly: Hyponatraemia (SIADH) may occur.

Hepatic impairment (mild–moderate): Caution. Dose adjustment may be necessary.

Pregnancy: C. Use when clinically indicated if it is the drug of choice. There is increased risk of reversible withdrawal symptoms, not congenital malformations.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. sedation, restlessness, irritability, poor feeding) in infant.

Common dosage range

Adult dose

Initially, 50 mg daily. Maximum 200 mg daily.

Paediatric dose

>6 years: initially, 25 mg daily increasing as necessary each week to 1–2 mg/kg daily.

sevelamer

phosphate binder

Cautionary advisory labels: 13, A, B

Notes

- Tablets must not be crushed, chewed or broken: sevelamer swells in contact with water.
- Ciprofloxacin absorption is decreased by 50% if administered with sevelamer.
- Administer oral dose of other drugs one hour before or three hours after sevelamer.
- Use sevelamer with caution in patients with dysphagia or severe gastrointestinal motility disorders.
- Carefully monitor patients with severe constipation while being treated with sevelamer.
- Sevelamer reduces LDL and total cholesterol by increasing the faecal excretion of bile acids.

Pregnancy: B3.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

800–2,400 mg with each meal depending on serum phosphate level.

sibutramine

serotonin/noradrenaline reuptake inhibitor, anti-obesity

Cautionary advisory labels: 5, 12

Notes

- Sibutramine increases blood pressure and heart rate.
- Sibutramine is contraindicated in many patients including those with psychiatric illness, cardiovascular and cerebrovascular disease and uncontrolled hypertension.
- Co-administration with drugs with serotonergic activity may result in serotonin syndrome.
- Drugs in cough/cold preparations that may raise blood pressure (e.g. pseudoephedrine) should be used with caution.
- Sibutramine must be used in conjunction with a reduced-calorie diet.

Pregnancy: C.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

10–15 mg daily.

sildenafil

phosphodiesterase inhibitor

Cautionary advisory labels: 5, 16

Notes

- Contraindicated in patients using any form of nitrate.
- Cardiovascular risk associated with sexual activity should be individually assessed.
- Additive antihypertensive effect in patients taking antihypertensive agents.
- Report visual disturbances immediately.
- Flushing is common.
- If headache, blurred vision, chest pain or shortness of breath occurs, seek medical advice.
- Not indicated for use in women.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: not indicated for use in women.

Common dosage range

Adult dose

Erectile dysfunction: 25–100 mg at a maximum recommended dosing frequency of once daily, about one hour before sexual activity.

simvastatin

HMG-CoA reductase inhibitor

Cautionary advisory labels: 18

Notes

- Take in the evening.
- Important to follow a low-fat diet and other measures such as exercise and weight control.
- If muscle pain, tenderness or weakness is experienced, seek medical advice.
- Increased risk of adverse effects in combination with gemfibrozil.

Pregnancy: D. Lipid-lowering therapy not recommended during pregnancy.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

10–80 mg once daily in the evening.

Paediatric dose

2–10 years, 5–20 mg once daily.

>10 years, 10–80 mg once daily.

sirolimus

immunosuppressant

Cautionary advisory labels: 5, 8, 18 and for solution add 6, 7b

Notes

- Take consistently with or without food.
- It is recommended that sirolimus be taken four hours after cyclosporin.
- Oral solution can be mixed with water or orange juice.
- If solution develops a slight haze on refrigeration allow to stand at room temperature and shake gently until haze disappears.
- Avoid use of live vaccines.
- Clinically significant medicine interactions may occur (see Table D.1, Section D).
- Risk of nephrotoxicity.

Hepatic impairment: Reduce maintenance dose by one-third. No change recommended to loading dose.

Renal Function: Monitor.

Therapeutic monitoring: Whole blood trough concentration monitoring should be performed in all patients. Therapeutic range:

With calcineurin inhibitor, 6–15 micrograms/L.

Without calcineurin inhibitor, up to 20 micrograms/L.

Time to steady state: 14 days.

Toxicity: Minimise calcineurin inhibitor 2–4 months post-transplant due to synergistic nephrotoxicity.

Pregnancy: C. Consider alternative therapy. Avoid pregnancy during and for at least 12 weeks after ceasing therapy.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

Without calcineurin inhibitor or patients with high risk of rejection: loading dose 15 mg, then 5 mg daily.

With calcineurin inhibitor: loading dose 6 mg, then 2 mg daily.

Paediatric dose

>13 years and <40 kg, loading dose 3 mg/m^2, then 1 mg/m^2 daily.

sitagliptin

antidiabetic

Notes

- Combined with other antidiabetic agents in type 2 diabetes
- Lower doses of sulphonylureas may be required to avoid hypoglycaemic events.

Renal impairment: Reduce dose to 50 mg if creatinine clearance is between 30 and 50 mL/min and to 25 mg if <30 mL/min.

Pregnancy: B3.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

100 mg daily.

sitaxentan

endothelin receptor antagonist

Cautionary Advisory Labels: 5

Notes

- Teratogenic agent.
- Women of child-bearing age must use appropriate contraception. Monthly pregnancy tests recommended.

- Contraindicated in mild to severe hepatic impairment.
- Seek medical advice if any incidence of a bleeding event occurs.

Renal impairment: No dosage adjustment required.

Pregnancy: X.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

100 mg daily.

sodium fusidate

antibacterial

Cautionary advisory labels: A*, B, D

Notes

- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible.
- Common adverse effects—nausea, diarrhoea, gastric upset.
- 175 mg sodium fusidate is therapeutically equivalent to fusidic acid 250 mg oral liquid.
- Use in combination with another antibiotic.
- Reduce dose in hepatic impairment.
- Monitor hepatic function tests in people taking high doses, in prolonged treatment, or if there is pre-existing hepatic disease.

Hepatic impairment: Avoid use if possible.

Pregnancy: C. Seek advice from infectious diseases specialist.

Breastfeeding: Use with caution: limited data available. Monitor for adverse effects in infant.

Common dosage range

Adult dose

Oral, 0.5–1 g every 8–12 hours.

IV infusion, 0.5 g every 8 hours.

Paediatric dose

Oral, <1 year, 50 mg/kg daily in three doses.

1–5 years, 250 mg three times a day.

6–12 years, 500 mg three times a day.

IV infusion, 6.5 mg/kg every 8 hours.

somatropin

synthetic human growth hormone

Cautionary advisory labels: 6

Notes

- Rotate injection site
- Do not use if solution appears cloudy or contains particulate matter.
- Perform thyroid function tests periodically.
- Patients should report severe recurrent headaches, visual problems, nausea and vomiting.

Elderly: Experience with patients over 60 years is lacking.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

SC, 0.04 mg/kg (0.125 IU/kg) weekly; gradually increase according to patient requirements to a maximum of 0.08 mg/kg (0.25 IU/kg) weekly.

Paediatric dose

SC, 0.177–0.255 mg/kg weekly (maximum 0.26 mg/kg), in 3, 6 or 7 equally divided doses.

sorafenib

multiple kinase inhibitor

Cautionary advisory labels: 3b, 5

Notes

- Hand-foot skin reaction.
- Elevated lipase and amylase levels common.
- Hypophosphataemia common.

Renal impairment: No dose adjustment necessary in mild to moderate renal impairment.

Pregnancy: D.

Breastfeeding: Breastfeeding should be discontinued during sorafenib therapy.

Common dosage range

Adult dose

400 mg twice daily.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

sorbitol

osmotic laxative

Notes

- Counsel on increased fibre, fluid intake and exercise treatment options.
- Chronic management: may require combination treatment.
- Opioid-induced constipation: use a stool softener/stimulant and hyperosmotic (see also 'Prevention and treatment of opioid-induced constipation', Section D).
- Faecal impaction may present as faecal soiling or diarrhoea.
- May take 2–3 days for onset of action

Pregnancy: May be used.

Breastfeeding: May be used.

Common dosage range

Adult dose

20 mL daily, increasing to 20 mL three times daily if necessary according to response.

sotalol

beta-blocker

Cautionary advisory labels: 4 (delete antacids and iron), 9, 12†, C (1–2 hours)

Notes

- Take tablets on an empty stomach.
- If arrhythmias worsen, especially in first week of treatment, seek medical advice.
- Caution with medicines that prolong the QT interval.
- Caution if patient suffers from diabetes (can mask hypoglycaemic attack), hyperlipidaemia, peripheral vascular disease, hyperthyroidism, uncontrolled heart failure, asthma, chronic obstructive pulmonary disease.

Renal impairment: Dose adjustment may be necessary

Pregnancy: C. May be considered in certain arrhythmias. Observe fetus and newborn for signs of beta-blockade.

Breastfeeding: Use with caution. Large amounts excreted in breast milk and concentrates. Monitor for adverse effects (e.g. bradycardia) in infant.

Common dosage range

Adult dose

Oral, initially 40–80 mg twice daily; increase according to response to 160 mg twice daily; maximum 640 mg daily.

IV, 0.5–1.5 mg/kg (maximum 120 mg) over 10 minutes, six-hourly, or infuse 80–160 mg over 12 hours.

Paediatric dose

Oral, 2–5 mg/kg daily in two doses; increase if necessary to 12 mg/kg daily. Give doses >5 mg/kg daily in 3 doses.

IV, 0.5–1.5 mg/kg six-hourly.

spironolactone

aldosterone antagonist, potassium-sparing diuretic

Cautionary advisory labels: 11, 12†, 16

Notes

- Provide advice on food and drugs with high potassium contents.
- Risk of hyperkalaemia; caution if used in combination with ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, potassium supplements, cyclosporin.
- Caution in patients with renal disease.
- May take up to 2 weeks to exert maximum effect.

Elderly: More susceptible to orthostatic hypotension, hyperkalaemia and urinary incontinence.

Renal impairment (mild–moderate): Caution. Increases risk of severe hyperkalaemia.

Renal impairment (severe): Contraindicated.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use with caution. Small amounts of metabolite excreted in breast milk. Potential for electrolyte disturbances in infant. May suppress lactation.

Common dosage range

Adult dose

25–200 mg daily as a single dose or divided doses.

Paediatric dose

1–3 mg/kg daily in 1–3 doses.

strontium ranelate

use: osteoporosis

Cautionary advisory labels: 4

Notes

- Best taken at bedtime at least 2 hours after eating.
- Contents of one sachet should be mixed with a minimum of 30 mL water.

† Most appropriate during initial treatment or when dosage is increased.

- Take constituted product immediately after preparation.
- BMD is overestimated in patients taking strontium.
- Calcium and vitamin D supplements are recommended if dietary intake is insufficient.

Renal impairment (severe): Not recommended if Cl_{cr} is <30 mL/min.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

2 g daily, preferably at bedtime.

sucralfate

cytoprotective agent

Cautionary advisory labels: 3b, 5

Notes

- Do not take antacids half an hour before or after sucralfate.
- If symptoms do not improve after 2 weeks of treatment, seek medical advice.
- If nausea, severe vomiting, epigastric pain, black or blood-stained stools are experienced during or after treatment, seek medical advice.
- Tablets may be dispersed in water.

Renal impairment (mild–moderate): Caution. Long-term use not recommended.

Renal impairment (severe): Contraindicated.

Pregnancy: B1. May be used: intestinal absorption is limited.

Breastfeeding: May be used: minimal maternal absorption.

Common dosage range

Adult dose

Acute, 1 g four times daily. Maintenance, 1 g twice daily.

Paediatric dose

10–20 mg/kg/dose four times daily.

sulfadoxine with pyrimethamine

combination antimalarial agent

Cautionary advisory labels: 8, B

Notes

- Contraindicated in individuals allergic to sulfonamides.
- Not routinely used for malaria prophylaxis unless all other alternatives are contraindicated or not available.

Pregnancy: C. Seek advice from infectious diseases specialist.

Breastfeeding: Use with caution. Excretion in breast milk expected. Avoid with infants who are premature or G6PD deficient.

Common dosage range

Adult dose

Treatment of uncomplicated chloroquine-resistant *P. falciparum* malaria:
Give on day 3 or 4 of treatment with oral quinine. Three tablets (75 mg/1,500 mg) or 7.5 mL IM.

Paediatric dose

Doses are based on 1.25 mg pyrimethamine with 25 mg sulfadoxine/kg. Do not give less than this as treatment failure has resulted from underdosing.

>45 kg, 3 tablets.

31–45 kg, 2 tablets.

21–30 kg, 1.5 tablets.

11–20 kg, 1 tablet.

5–10 kg, half a tablet.

sulfasalazine

sulfonamide anti-inflammatory

Modification of oral formulation

Before crushing or otherwise altering enteric-coated tablets, consider risk of failure to reach site of action.

Cautionary advisory labels: A*, B

Notes

- Contraindicated in individuals with allergy to sulfonamides or salicylates.

Changes to urinary system: May cause orange or yellow discolouration (in alkaline urine).

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Hepatic impairment (severe): Caution.

Renal impairment (severe): Caution.

Pregnancy: A. Consider supplementation with folic acid 5 mg daily.

Breastfeeding: May be used in low to moderate doses. Small amounts of parent and metabolite excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea) in infant. Avoid in G6PD deficient infants.

Common dosage range

Adult dose

Ulcerative colitis: acute, 1 g 2–4 times daily; maintenance, 0.5 g four times daily.

Rheumatoid arthritis: 2–3g daily in 2–3 doses.

Paediatric dose

Ulcerative colitis: acute, 10–15 mg/kg (maximum 1 g) 4–6 times daily (maximum 60 mg/kg daily); maintenance, 5–7.5 mg/kg (maximum 500 mg) four times daily.

Rheumatoid arthritis: 20–30 mg/kg (maximum 2 g) daily in 2–3 doses.

sulindac

NSAID

Cautionary advisory labels: 10a, 12†, B

Notes

- Maximum response should be seen in 1–3 weeks.
- To lessen gastrointestinal complications, use lowest effective dose and take paracetamol as an alternative analgesic.
- Caution if taking warfarin or other anticoagulants.
- Check use of over-the-counter NSAIDs.
- Consider stopping 2–3 days before planned surgery; seek medical advice.

Changes to faeces: Pink, red or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Elderly: Increased risk of gastric ulceration, renal dysfunction, dizziness, sodium and water retention, exacerbation of hypertension and heart failure.

Pregnancy: C. Alternatives to NSAIDs should be considered for analgesia. Use not recommended during third trimester.

Breastfeeding: Use not recommended. Excretion in breast milk expected. Diclofenac and ibuprofen are the NSAIDs of choice in breastfeeding mothers.

Common dosage range

Adult dose

200–400 mg daily in 1 or 2 doses.

sumatriptan

$5HT_1$ agonist

Cautionary advisory labels: 12

Notes

- Seek medical advice if no relief occurs, or if headaches are increasing in frequency or severity.
- If shortness of breath, difficulty breathing (anaphylactic-type reactions) or chest pain/tightness is experienced, seek medical advice.
- Should not be taken within 24 hours of ergotamine.
- Separate doses of different triptans by at least 12–24 hours.

Tablets:

- Swallow whole as soon as possible after the onset of the migraine.
- Dose may be repeated if migraine recurs but not if unresponsive to initial dose.

Injection:

- Inject one dose as soon as possible after the onset of the migraine.
- Dose may be repeated, after not less than 1 hour if migraine recurs but not if unresponsive to initial dose.

Nasal spray:

- Spray one spray into one nostril as soon as possible after the onset of the migraine.

Hepatic impairment (severe): Contraindicated.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use with caution. Small amounts excreted but no safety data on drug in infants. If used, express and discard milk for eight hours after dose.

Common dosage range

Adult dose

Oral, 50–100 mg. May be repeated after at least two hours; maximum dose 300 mg/24 hours.

Intranasal, 10–20 mg into one nostril, repeat once after two hours if needed. Maximum 40 mg daily.

SC, 6 mg. May be repeated after at least one hour; maximum daily dose 12 mg.

Paediatric dose

<12 years: not recommended.

12–17 years: intranasal, 10–20 mg in one nostril as a single dose.

† Most appropriate during initial treatment or when dosage is increased.

sunitinib

multiple receptor tyrosine kinase inhibitor

Cautionary advisory labels: 5, 12

Notes

- Skin discolouration is common (30% of patients).
- Monitor patients for signs of cardiac failure and of hypothyroidism.
- Baseline and periodic evaluation of left ventricular ejection fraction should be considered.
- Women of child-bearing age should use appropriate contraception during treatment and for at least 4 weeks after ceasing therapy.

Renal impairment: No formal studies.

Pregnancy: D.

Breastfeeding: Not recommended.

Common dosage range

Adult dose

50 mg daily for 4 consecutive weeks followed by 2 weeks off. Constitutes one cycle of treatment.

tacrolimus

calcineurin inhibitor

Cautionary advisory labels: 3b, 5, 8, 12, 13, 18

Notes

- Significant medicine interaction potential (see Table D.1, Section D). Blood level monitoring is essential.

Renal impairment: No dosage adjustment required.

Therapeutic monitoring: Therapeutic range:

Kidney transplant, 10–20 micrograms/L (0–3 months), 5–15 micrograms/L (4–12 months).

Liver transplant, 2–15 micrograms/L. Heart transplant, 10–15 micrograms/L.

Pregnancy: C. Seek specialist advice.

Breastfeeding: Use not recommended. Small amounts excreted in breast milk. Potential for serious adverse effects (e.g. immunosuppression) in infant.

Common dosage range

Adult dose

Oral, 75–300 micrograms/kg daily.

IV, approximately one-third of oral dose.

Paediatric dose

Oral, 100–300 micrograms/kg daily in two doses.

Specific indications: see approved Product Information.

tadalafil

phosphodiesterase inhibitor

Cautionary advisory labels: 5, 16

Notes

- Contraindicated in patients using any form of nitrate.
- Additive antihypertensive effect in patients taking antihypertensive agents.
- Flushing is common.
- If headache, blurred vision, chest pain or shortness of breath occurs, seek medical advice.
- Many drug interactions: care is needed (see Table D.1, Section D).
- Not indicated for use in women.

Renal impairment (severe): Caution. Maximum dose 10 mg daily.

Pregnancy: B1. Use not recommended.

Breastfeeding: Use not recommended. Not indicated for use in women.

Common dosage range

Adult dose

10–20 mg 30 minutes to 12 hours before sexual activity. Maximum dosing frequency is once daily.

tamoxifen

anti-oestrogen

Cautionary advisory labels: 12†

Notes

- If vaginal bleeding or discharge, blurred vision or bone pain occur, seek medical advice.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended.

Common dosage range

Adult dose

20–40 mg daily.

tamsulosin

selective alpha-blocker for BPH

Cautionary advisory labels: 12, 16, A

Notes

- If no improvement in symptoms of BPH after 4–6 weeks, discontinue tamsulosin.
- Not indicated for use in women.

† Most appropriate during initial treatment or when dosage is increased.

Changes to urinary system: May induce or aggravate stress incontinence due to sphincter relaxation or unconscious dribbling of urine.

Hepatic impairment (severe): Contraindicated.

Renal impairment: Caution. Contraindicated in Cl_{cr} <10 ml/min.

Pregnancy: B2. Use not recommended. Potential for severe adverse effects in infant. May suppress lactation.

Breastfeeding: Contraindicated.

Common dosage range

Adult dose

400 micrograms once daily in the morning.

teicoplanin

glycopeptide antibacterial

Notes

Renal impairment: Caution. Dose reduction required. Reduction usually not required until fourth day of treatment. Cl_{cr} 40–60 mL/min, halve normal dose or double dosage interval.

Cl_{cr} <40 mL/min, give one-third of normal dose or triple the dosage interval.

Therapeutic monitoring: Therapeutic range: Trough concentration when treating serious infections should be >10 mg/L (>20 mg/L for infections such as septic arthritis, *S. aureus* endocarditis).

Pregnancy: B3. Seek advice from infectious diseases specialist.

Breastfeeding: Use with caution. Excretion in breast milk expected. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

IV, 6–12 mg/kg (up to 800 mg) every 12 hours for three doses, then 6 mg/kg (up to 400 mg) once daily.

Paediatric dose

Neonate: IV, loading dose 16 mg/kg, then 8 mg/kg once daily.

>2 months: IV, 10mg/kg (maximum 800 mg) 12-hourly for 3 doses, then 6–10 mg/kg once daily.

telbivudine

thymidine nucleoside analogue

Cautionary advisory labels: 12

Notes

- Myalgia occurs; patients presenting with such symptoms should be monitored for myopathy with measurement of creatine kinase levels.

Renal impairment: Dose adjustment required if creatinine clearance is <50 mL/min.

Pregnancy: B1.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

600 mg once daily.

telmisartan

angiotensin II receptor antagonist

Cautionary advisory labels: 11, 12†, 16†

Notes

- Blood pressure should be closely monitored during initiation of therapy.
- Monitor renal function and potassium concentration.
- Caution if the patient is taking NSAIDs (including COX-2 inhibitors) or lithium.
- Provide advice on foods and drugs with high potassium content.
- Can cause cough (cough can also be a symptom of heart failure). Establish if cough is productive or unproductive; incidence less than with ACE inhibitors.
- If swelling of face, lips or tongue is experienced, seek medical advice.
- A combination product of telmisartan with a diuretic is also available. Check that patient knows which product is being taken.

Hepatic impairment (severe or biliary obstruction): Contraindicated.

Renal impairment: Hyperkalaemia more common.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as possible if pregnancy is suspected.

Breastfeeding: Use not recommended: limited data available.

† Most appropriate during initial treatment or when dosage is increased.

Common dosage range

Adult dose

20–40 mg once daily. Maximum 80 mg daily.

temazepam

benzodiazepine

Cautionary advisory labels: 1 or 1a, 9 (long-term regular therapy)

Notes

- Regular use for more than 2–4 weeks may result in dependence and tolerance.
- Monitor patient for physical and psychological dependence and tolerance (check intervals between prescription refills).
- Beware sudden discontinuation of long-term treatment.
- May cause a 'morning-after' hangover effect.
- Caution with respiratory disease or sleep apnoea: reduced respiratory drive may cause hypoxaemia.

Changes to urinary system: May induce or aggravate functional incontinence due to sedation or impairment of mobility.

Elderly: Over-sedation, confusion, memory impairment, poor muscle coordination leading to falls and fractures.

Renal impairment (severe): Caution. Increased sensitivity to central nervous system effects; lower initial dose recommended.

Pregnancy: C. Use should be avoided if possible, especially during first trimester. If temazepam is required, use the lowest effective dose for the shortest duration.

Breastfeeding: Use with caution. Excreted into breast milk, with concentrations increasing with time. Adverse effects (e.g. sedation, poor feeding) may be experienced by infant. Avoid long-term use, large doses or frequent dosing. If a benzodiazepine is required, a short acting one is preferred.

Common dosage range

Adult dose

5–30 mg.

Paediatric dose

Premedication: 0.3 mg/kg at least half an hour before procedure.

temozolomide

cytotoxic alkylating agent

Modification of oral formulation

Avoid crushing or altering capsule due to occupational health and safety risks.

Cautionary advisory labels: 21, C (1 hour)

Pregnancy: D. Use contraindicated.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

150–200 mg/m^2 once daily for 5 days/28-day cycle.

Specific indications: see approved Product Information.

Paediatric dose

≥3 years: 150–200 mg/m^2 once daily for 5 days/28-day cycle.

Specific indications: see approved Product Information.

terazosin

selective alpha-blocker for BPH

Cautionary advisory labels: 12†, 16

Notes

- May be used for benign prostatic hypertrophy (BPH) or hypertension.
- If no improvement in symptoms of BPH after 4–6 weeks, discontinue.
- Monitor for hypotension when used for BPH.
- Give initial dose before bedtime to minimise first-dose hypotension.
- Caution if taking diuretics or the patient is volume depleted.

Changes to urinary system: May induce or aggravate stress incontinence due to sphincter relaxation or unconscious dribbling of urine.

Elderly: Caution: orthostatic hypotension more common and may lead to falls and fractures.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Benign prostatic hyperplasia: initially, 1 mg at bedtime for four days, then 1 mg in morning for three days; 2 mg in morning for 7 days, then 5 mg in morning for 7 days; maintenance: 5–10 mg in the morning.

† Most appropriate during initial treatment or when dosage is increased.

Hypertension: Initially, 1 mg at bedtime; maintenance, 1–20 mg once daily in the morning.

terbinafine

antifungal agent

Cautionary advisory labels: D

Notes

Hepatic impairment: Caution. Contraindicated in active liver disease

Renal impairment: Caution.

Cl_{cr} 20–50 mL/min, halve normal dose.

Cl_{cr} <20 mL/min, no data. Avoid use.

Pregnancy: B1. Oral use not recommended. May be used topically in second and third trimesters.

Breastfeeding: Use with caution topically. Use not recommended orally. Excreted in breast milk but no safety data on drug in infants.

Common dosage range

Adult Dose

250 mg once daily.

Paediatric Dose

<20 kg, 62.5 mg once daily; 20–40 kg, 125 mg once daily.

terbutaline

$beta_2$ agonist, short acting

Notes

- Reliever for asthma or chronic obstructive pulmonary disease; can be used to treat an acute attack.
- If using terbutaline, ipratropium (or eformoterol, salmeterol) and steroid inhalers, use in that order.
- Can cause tachycardia, tremor and electrolyte disturbances.
- Encourage the development of an asthma plan.
- If previously effective dose fails to provide at least three hours' relief, seek medical advice.
- Counsel on device/inhaler technique, cleaning and disposal.
- Review technique (spacer, face mask, nebuliser).
- Increased reliance on short-acting beta-agonists indicates deterioration of asthma control; treatment should be reassessed.

Pregnancy: A

Breastfeeding: May be used. Monitor for adverse effects (e.g. tremor, agitation) in infant when larger doses are taken orally.

Common dosage range

Adult dose

DPI, 500 micrograms every 4–6 hours.

Oral, 3–4.5 mg three times daily.

Nebuliser, 2.5–5 mg six-hourly; up to 10 mg in severe cases.

SC, 0.25 mg every 6 hours.

Paediatric dose

DPI, 500 micrograms every 4–6 hours.

Oral, 0.075 mg/kg every six hours.

Nebuliser, 0.2 mg/kg, repeated every four hours as needed.

SC, 5 micrograms/kg, repeated every six hours as needed.

teriparatide

recombinant human parathyroid hormone

Cautionary advisory labels: 6, 7b

Notes

- Give calcium and vitamin D supplements to patients with low intake of these nutrients.
- Lifetime maximum duration of 18 months' therapy is recommended.
- Appropriate aseptic technique, site rotation and disposal of needles and syringes.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

SC, 20 micrograms daily.

tetrabenazine

CNS-amine depleting agent for movement disorders

Cautionary advisory labels: 1

Pregnancy: B2. Use not recommended.

Breastfeeding: Use with caution: limited data available. Monitor for adverse effects in infant.

Common dosage range

Adult dose

25 mg twice daily, increasing to 200 mg daily if necessary.

Paediatric dose

12.5 mg twice daily with increments of 12.5 mg every 3–4 days, to a maximum of 100 mg or 3 mg/kg daily.

thalidomide

immunomodulator, antiangiogenic agent

Cautionary advisory labels: 1, 16

Notes

- Counsel about effective contraception requirements. Considered teratogenic in females and males.
- Ensure product is safely stored to avoid inadvertent ingestion by women of child-bearing age.

Pregnancy: X.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

50–800 mg daily.

Specific indications: see approved Product Information.

theophylline

bronchodilator

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets will alter absorption characteristics.

Cautionary advisory labels: 5, A*, B

Notes

- Monitoring of plasma theophylline concentration is advisable, particularly in neonates and patients showing signs of toxicity or not responding to therapy. If nausea, palpitations, insomnia, headache or gastrointestinal upsets are experienced, seek medical advice.
- Theophylline is a medicine of low therapeutic index and is involved in significant medicine interactions (see Table D.1, Section D).
- Smokers (cigarettes and/or marijuana) may require larger doses.

Changes to faeces: Black discolouration.

Elderly: May require dosage adjustment due to reduced clearance (clearance in 65 years+ is 25% lower than healthy young adult).

Renal and hepatic impairment: Caution. Toxicity possible due to reduced clearance and low therapeutic index. In suspected toxicity monitor theophylline and reduce dose.

Therapeutic monitoring: Therapeutic range: Adult 10–20 mg/L (55–110 micromol/L). Neonate 38–85 micromol/L.

Time to steady state: 1–7 days.

Toxicity: Monitor for adverse effects. Toxic doses of theophylline may cause nausea, vomiting, tachycardia and convulsions.

Pharmacokinetics are influenced by smoking, heart failure, hepatic disease and medicines.

Pregnancy: A

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Use minimum effective dose. Monitor for adverse effects (e.g. irritability) in infant and consider infant serum level monitoring.

Common dosage range

Adult dose

10–16 mg/kg daily; maximum maintenance dose 900 mg daily. Sustained-release preparations are given every 12 hours; conventional preparations are given every six hours.

Paediatric dose

Sustained release preparations: 1–7 years, 10 mg/kg 12-hourly; 8–16 years, 8 mg/kg 12-hourly.

Syrup: >2 years, 1 mL (5.3 mg)/kg (max. 25 mL) every 6 hours.

thiamine

vitamin B_1

Notes

- IV injection has caused anaphylaxis. Parenteral administration is rarely indicated.

Pregnancy: A.

Breastfeeding: May be used for supplementation.

Common dosage range

Adult dose

50–100 mg daily.

Paediatric dose

Oral, therapeutic, 10–100 mg daily.

thyroxine

thyroid hormone replacement therapy

Cautionary advisory labels: 3b, 4, 6

Notes

- Periodic blood tests recommended.
- Doses should be taken at the same time each day and consistently in relation to food (absorption is greater on an empty stomach).

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

- Ask about symptoms suggestive of hypothyroidism or hyperthyroidism.
- If tachycardia, nervousness, tremor, headache, flushing, excessive weight loss, shortness of breath or chest pain occurs, seek medical advice.
- Monitor TSH.
- Warfarin interaction—monitor INR.
- Tablets are stable for 40 days out of the fridge.

Pregnancy: A. Monitor thyroid dose in each trimester and adjust dose as necessary.

Breastfeeding: May be used. Small amounts excreted in breast milk. Consider baseline and periodic thyroid function monitoring of infant.

Common dosage range

Adult dose

Initially, 50 micrograms daily, increasing by 25–50 micrograms every 6–8 weeks according to TSH.

Maintenance, 100–200 micrograms daily.

Paediatric dose

Initially, 25 micrograms daily, increased as necessary.

<6 months, 8–10 micrograms/kg daily.

7–12 months, 6–8 micrograms/kg daily.

1–5 years, 5–6 micrograms/kg daily.

6–12 years, 4–5 micrograms/kg daily.

>12 years, approximately 2 micrograms/kg daily.

tiagabine

antiepileptic agent

Cautionary advisory labels: 1, 9, B

Notes

Hepatic impairment (mild–moderate): May require dosage reduction.

Hepatic impairment (severe): Contraindicated.

Pregnancy: B3. Consider risk of congenital malformation against dangers of uncontrolled epilepsy. Consider folic acid (5 mg) and vitamin K supplementation.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Initially 7.5–15 mg daily in three doses; increase weekly by 5–15 mg daily; maintenance 15–30 mg daily in people not taking hepatic enzyme–inducing drugs; 30–50 mg in people taking hepatic enzyme–inducing drugs.

tiaprofenic acid

NSAID

Cautionary advisory labels: 10a, 12†, B

Notes

- Maximum response should be seen in 1–3 weeks.
- Alert patient to signs of gastrointestinal bleeding (black stools or dark coffee-coloured vomit).
- Caution if taking warfarin or other anticoagulants.
- To lessen gastrointestinal complications, use lowest effective dose and take paracetamol as an alternative analgesic.
- Check use of over-the-counter NSAIDs.
- Caution with diabetes, hypertension, heart failure asthma or peptic ulcer.
- Confirm a clear indication for treatment.
- Consider stopping 2–3 days before planned surgery; seek medical advice.

Changes to faeces: Pink, red or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Changes to urinary system: May induce or aggravate urge incontinence, cystitis-like symptoms due to enhanced detrusor activity, frequency, urgency.

Elderly: Gastric ulceration, renal dysfunction, dizziness, sodium and water retention, heart failure and exacerbation of hypertension are more common.

Hepatic impairment (severe): Caution. Increased risk of bleeding.

Renal impairment (moderate–severe): Avoid use: increased risk of further renal impairment and bleeding.

Pregnancy: C. Alternatives to NSAIDs should be considered for analgesia. Use not recommended during third trimester.

Breastfeeding: Use not recommended. Small amounts excreted in breast milk. Diclofenac and ibuprofen are the NSAIDs of choice in breastfeeding mothers.

Common dosage range

Adult dose

300–600 mg daily in divided doses.

ticarcillin with clavulanic acid

antipseudomonal penicillin antibacterial

Notes

- Confirm appropriate antibiotic and dose regimen.
- Space doses as evenly as possible.
- Ask about any previous reaction or allergy to penicillin.

† Most appropriate during initial treatment or when dosage is increased.

- Common adverse effects—nausea, diarrhoea, gastric upset.
- If a skin rash develops, seek medical advice (more common in cystic fibrosis patients).
- Contains 15.6 mmol (360 mg) sodium per 3 g ticarcillin with 100 mg clavulanic acid.

Renal and hepatic impairment: Caution. May require dosage reduction.

Pregnancy: B2. Use only if drug of choice.

Breastfeeding: May be used. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

IV infusion, 3 g/0.1 g every 4–6 hours over 30 minutes. Maximum daily dose 18 g/0.6 g.

Paediatric dose

Doses expressed as ticarcillin.

Moderate infections: 50 mg/kg six-hourly.

Severe infections: 50 mg/kg 4–6 hourly.

Cystic fibrosis: 100 mg/kg (maximum 6 g) eight-hourly.

ticlopidine

thienopyridine antiplatelet agent

Cautionary advisory labels: 10b, A, B

Notes

- If fevers, chills, sore throat, mouth ulcers, bleeding or bruising develop, seek medical attention.

Renal or hepatic impairment (severe): Contraindicated.

Pregnancy: B1. Use not recommended.

Breastfeeding: Use not recommended. Excretion and accumulation in breast milk expected.

Common dosage range

Adult dose

250 mg twice daily.

tiludronate

bisphosphonate

Cautionary advisory labels: 4, A, C (2 hours)

Notes

- Presence of food reduces absorption significantly. Should not be taken within 2 hours of food.
- Take in the morning with a full glass of water.
- Treatment for Paget's disease is generally for three months.
- Ensure adequate intake of calcium and vitamin D (taken at different time of day).
- Treatment course may be repeated after 6 months in case of relapse.

Renal impairment (mild–moderate): Caution. Dose reduction may be required.

Renal impairment (severe): Contraindicated.

Pregnancy: B2. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

400 mg daily for three months.

tinidazole

nitroimidazole antibacterial

Cautionary advisory labels: 2, B, D (multiple dosing)

Notes

- May cause a metallic taste.
- Avoid alcohol due to the risk of disulfiram-like reaction.
- Confirm appropriate antibiotic and dose regimen.
- Common adverse effects—nausea, diarrhoea, gastric upset.
- If a skin rash develops, seek medical advice.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended. Metronidazole is preferred. If used, avoid breastfeeding for 72 hours after a single dose.

Common dosage range

Adult dose

Giardiasis, Trichomoniasis: 2 g as a single dose.

Acute intestinal amoebiasis: 2 g daily for three days.

Other indications: See approved Product Information.

Paediatric dose

Giardiasis: 50 mg/kg (maximum 2 g) as a single dose; may be repeated after 24–48 hours.

Acute intestinal amoebiasis: 50 mg/kg (maximum 2 g) daily for three days.

tiotropium

anticholinergic bronchodilator

Cautionary advisory labels: 22 (capsules for inhalation)

Notes

- Use within 5 days of opening each blister strip of 5 capsules.
- Dry mouth is a common adverse effect.
- Caution in patients with prostatic hypertrophy.
- Avoid eye contact with powder.
- Not for immediate relief of symptoms.
- Ensure patient can manage *HandiHaler*.

Pregnancy: B1. May be used.

Breastfeeding: May be used. Small amounts expected to be excreted in breast milk.

Common dosage range

Adult dose

18 micrograms once daily by inhalation.

tobramycin

aminoglycoside antibacterial

Notes

- Plasma concentration monitoring is advisable, especially in patients with renal impairment and in neonates.
- Ototoxicity and nephrotoxicity may occur.

Therapeutic monitoring: Several strategies have been proposed for monitoring extended dosing interval aminoglycoside therapy, including a nomogram and area-under-the-curve targeting. See the approved Product Information.

Pregnancy: D. Use not recommended.

Breastfeeding: May be used. Small amounts excreted in breast milk. Potential for accumulation with prolonged dosing.

Common dosage range

Adult dose

IM/IV, 2–5 mg/kg (maximum 8 mg/kg) daily; once-daily regimen appears to be at least as efficacious as divided doses and there is evidence that it may cause less nephrotoxicity.

Paediatric dose

1 month to 10 years: IM/IV, 7.5 mg/kg once daily or 1.5–2.5 mg/kg 8-hourly.

>10 years: IM/IV, 6 mg/kg once daily or 1–2 mg/kg 8-hourly.

Cystic fibrosis: IV, >5 years, initially 10 mg/kg (maximum 660 mg) once daily.

tolterodine

urinary anticholinergic agent

Cautionary advisory labels: 12, 16

Notes

Changes to urinary system: May induce or aggravate overflow incontinence due to reduced detrusor activity, voiding difficulty, urinary retention or constipation.

Elderly: Elderly are more sensitive to anticholinergic adverse effects (e.g. dry mouth, constipation, dry eyes, tachycardia, urinary retention); start with a low dose and titrate upwards.

Hepatic impairment: Maximum dosage 1 mg twice daily.

Renal impairment: Caution. Cl_{cr} <30 mL/min, maximum dosage 1 mg twice daily.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

1–2 mg twice daily.

topiramate

antiepileptic

Modification of oral formulation

Before crushing or otherwise altering tablets, consider unacceptable/undisguisable taste.

Cautionary advisory labels: 1, 9, 12, A*

Notes

- If visual acuity is affected or ocular pain occurs seek medical advice.
- Doses greater than or equal to 50 mg should be taken in two divided doses.

Renal impairment: Caution. Reduced maintenance dose and a longer interval between dose adjustments may be required; increased risk of metabolic acidosis.

Pregnancy: B3. Consider risk of congenital malformation against dangers of uncontrolled epilepsy. Consider folic acid (5 mg) and vitamin K supplementation.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Breastfeeding: Use with caution. Small amounts expected to be excreted in breast milk. Monitor for adverse effects (e.g. sedation) in infant.

Common dosage range

Adult dose

Initially, 25–50 mg once daily; maintenance, 25–200 mg twice daily. Maximum 1 g/day.

Specific indications: see approved Product Information.

Paediatric dose

>2 years: initially, 0.5–1 mg/kg once daily; increase by 1–3 mg/kg daily; maintenance, 3–9 mg/kg daily. Usual maximum 10 mg daily but higher doses (up to 30 mg/kg daily) have been used.

tramadol

opioid analgesic agent

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets will alter absorption characteristics.

Cautionary advisory labels: 1, 5, A*

Notes

- Dizziness, nausea, vomiting and constipation common.
- Tramadol has serotonergic effects; caution with other serotonergic medicines.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to inhibition of the voiding reflex, constipation, confusion, reduced detrusor activity or urinary retention.

Hepatic impairment: Caution. Dose reduction may be required in cirrhosis; avoid sustained-release preparations.

Renal impairment: Caution.
If Cl_{cr} 10–30 mL/min:

IV/IM/oral (conventional formulation), 50–100mg every 12 hours.

Oral (controlled-release formulation), 100–200 mg every 24 hours.

If Cl_{cr} <10 mL/min avoid use.

Pregnancy: C. Use only if drug of choice. High doses or prolonged use at or near term may cause respiratory depression and withdrawal effects in the newborn.

Breastfeeding: Use with caution. Small amounts of parent drug and metabolite excreted in breast milk but no safety data on drug in infants. Monitor for adverse effects (e.g. sedation) in infant, particularly with repeat or high doses.

Common dosage range

Adult dose

Oral (conventional formulation), 50–100 mg every 4–6 hours. Maximum 400 mg daily.

Oral (controlled-release formulation), 100–200 mg every 12 hours. Maximum 400 mg daily.

IM/IV, 50–100 mg every 4–6 hours. Maximum 600 mg daily.

Paediatric dose

Oral, 1–2 mg/kg four times daily. Maximum 400 mg daily.

trandolapril

angiotensin-converting enzyme inhibitor

Cautionary advisory labels: 11, 12†, 16†

Notes

- Blood pressure should be closely monitored during initiation of therapy.
- Monitor renal function and potassium concentration.
- Caution if the patient is taking NSAIDs (including COX-2 inhibitors) or lithium.
- Provide advice on foods and drugs with high potassium content.
- Can cause cough (cough can also be a symptom of heart failure). Establish if cough is productive or unproductive.
- If swelling of face, lips or tongue is experienced, seek medical advice.
- May cause metallic taste or lack of taste.

Changes to urinary system: May induce or aggravate stress incontinence due to cough-induced sphincter weakness.

Renal or hepatic impairment: Caution. Lower starting dose recommended.

Pregnancy: D. Previously commenced therapy should be discontinued as soon as possible if pregnancy is suspected.

Breastfeeding: Use not recommended. Excreted in breast milk, but no safety data on drug in infants. If an ACE inhibitor is required, captopril or enalapril is preferred option.

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Common dosage range

Adult dose

0.5–4 mg daily as a single dose.

tranexamic acid

antifibrinolytic agent

Notes

Renal impairment: Dose reduction may be required.

Pregnancy: B1. Use not recommended in first trimester. Use only if drug of choice in second and third trimesters.

Breastfeeding: Use with caution. Minimal amounts excreted in breast milk but no safety data on drug in infants.

Common dosage range

Adult dose

Oral, 1–1.5 g 2–3 times daily.

Specific indications: see approved Product Information.

Paediatric dose

>1 month: oral, 15–25 mg/kg (maximum 1.5 g) 2–3 times a day.

IV, 10 mg/kg (maximum 1 g) 2–3 times a day.

triamterene

potassium-sparing diuretic

Cautionary advisory labels: 11, B

Notes

- Risk of hyperkalaemia; caution if used in combination with ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, potassium supplements, cyclosporin.

Changes to faeces: Black discolouration.

Changes to urinary system: May cause blue discolouration of the urine.

Elderly: More susceptible to orthostatic hypotension, hyperkalaemia and incontinence.

Renal or hepatic impairment: Caution. Increased risk of electrolyte imbalance; avoid use.

Pregnancy: C. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Only available in combination with hydrochlorothiazide (triamterene 50 mg/hydrochlorothiazide 25 mg).

Initially, 1 tablet daily. Maximum four tablets daily.

triazolam

benzodiazepine

Cautionary advisory labels: 1 or 1a, 9 (long-term regular therapy), 18

Notes

- Regular use for more than 2–4 weeks may result in dependence and tolerance.
- Monitor patient for physical and psychological dependence and tolerance (check intervals between prescription refills).
- Beware sudden discontinuation of long-term treatment.
- May cause a 'morning-after' hangover effect.
- Caution with respiratory disease or sleep apnoea: reduced respiratory drive may cause hypoxaemia.
- Caution with drugs that inhibit CYP3A4 (see Table D.1, Section D).

Changes to urinary system: May induce or aggravate functional incontinence due to sedation or impairment of mobility.

Elderly: Over-sedation, confusion, memory impairment, poor muscle coordination leading to falls and fractures.

Renal or hepatic impairment: Caution. Lower doses should be used.

Pregnancy: C. Use should be avoided if possible, especially during first trimester. If triazolam is required, use the lowest effective dose for the shortest duration.

Breastfeeding: Use not recommended: limited data available. Adverse effects (e.g. sedation, poor feeding) may be experienced by infant. Avoid long-term use, large doses or frequent dosing. If a benzodiazepine is required, a shorter acting one is preferred.

Common dosage range

Adult dose

0.125–0.5 mg at night.

trifluoperazine

conventional antipsychotic agent

Cautionary advisory labels: 1, 8, 9 (long-term regular therapy), 16

Notes

- May cause anticholinergic, hypotensive and extrapyramidal effects (dystonia, akathisia, parkinsonism, tardive dyskinesia).
- Avoid concurrent use of more than one antipsychotic.
- Withdraw antipsychotics slowly if stopping the medication.

Changes to urinary system: May discolour urine pink, red or red–brown. May induce or aggravate overflow/functional incontinence due to anticholinergic-urinary retention and constipation, voiding difficulty, sedation, confusion, parkinsonism or impaired mobility.

Elderly: Adverse effects more common—orthostatic hypotension (may lead to falls and fractures), confusion, sedation, extrapyramidal adverse effects (e.g. parkinsonism), constipation, urinary retention, blurred vision.

Renal impairment: Caution. Cl_{cr} <50 mL/min: lower doses may be required.

Pregnancy: C. Use only if drug of choice. Use minimal effective dose.

Breastfeeding: Use with caution. Avoid large doses. Excreted in breast milk. Monitor for adverse effects in infant.

Common dosage range

Adult dose

1–2 mg twice daily. If necessary, dosage may be increased to 6 mg daily.

Paediatric dose

3–5 years: up to 1 mg daily in divided doses.

>5 years: 0.025–0.1 mg/kg 12-hourly.

trimeprazine

phenothiazine, sedating antihistamine

Cautionary advisory labels: 1, 13

Notes

- Anticholinergic adverse effects may occur (dry mouth, constipation, dizziness, fatigue or blurred vision); advise accordingly.
- Use cautiously in the elderly: they are more sensitive to adverse effects.

Pregnancy: C.

Breastfeeding: May be used for occasional doses. Small amounts excreted in breast milk. Dose after feeds. Monitor for adverse effects (e.g. sedation) in infant.

Common dosage range

Adult dose

10 mg 3–4 times daily. Maximum 100 mg daily.

Paediatric dose

>2 years

Allergy: 0.1–0.25 mg/kg six-hourly. Maximum 6.25 mg/dose.

Sedation: 1–2 mg/kg (maximum 50 mg) at night.

trimethoprim

antibacterial

Cautionary advisory labels: D

Notes

- Single daily doses should be taken at bedtime to maximise urinary concentration.
- Confirm appropriate antibiotic and dose regimen.
- Common adverse effects—nausea, diarrhoea, gastric upset.
- If a skin rash develops, seek medical advice.
- Monitor FBC and folate status during prolonged or high-dose treatment.

Hepatic impairment: Caution. Increased risk of toxicity.

Renal impairment: Caution. Increased risk of hyperkalaemia. Halve usual dose in moderate impairment. Use not recommended if Cl_{cr} <10mL/min.

Pregnancy: B3. Use not recommended in first trimester. Consider supplementation with folic acid 5 mg daily if used in second or third trimesters.

Breastfeeding: May be used in usual doses. Small amounts excreted in breast milk.

Common dosage range

Adult dose

Treatment: 300 mg daily.

Prophylaxis: 150 mg daily.

Paediatric dose

Treatment: 4 mg/kg (maximum 150 mg) 12-hourly.

Prophylaxis: 2 mg/kg at night.

trimethoprim with sulfamethoxazole

antibacterial, also known as co-trimoxazole

Cautionary advisory labels: 8, B, D

Notes

- Confirm appropriate antibiotic and dose regimen.
- Maintain a high fluid intake.
- Contraindicated with allergy to sulfonamides.
- Common adverse effects—nausea, diarrhoea, gastric upset.
- If a skin rash develops, seek medical advice.
- If multiple daily doses, space doses as evenly as possible.
- IV doses of co-trimoxazole should be well diluted and given as an infusion over 1 hour.
- Monitor FBC and folate status during prolonged or high-dose treatment.

- Not recommended for use in premature babies or during the first few weeks of life. Theoretically, sulfonamides may displace bilirubin from protein-binding sites in newborns. Caution with glucose-6-phosphate dehydrogenase deficient infants; monitor infant for haemolysis or jaundice.

Changes to urinary system: May cause rust yellow or brown discolouration of urine.

Elderly: Severe skin reactions and blood dyscrasias are more common.

Hepatic impairment: Caution. Increased risk of toxicity.

Renal impairment: Caution. Increased risk of hyperkalaemia. Reduce dose in moderate impairment. Use not recommend if Cl_{cr} <15 mL/min.

Pregnancy: B3. Use not recommended in first trimester. Consider supplementation with folic acid 5 mg daily if used in second or third trimesters.

Breastfeeding: Use with caution, particularly with neonates and infants that are G6PD deficient.

Common dosage range

Adult dose

Doses are expressed as trimethoprim/sulfamethoxazole.

Mild–moderate infections: oral, 80/400–160/800 mg every 12 hours.

Severe infections: IV, 160/800–320/1,600 mg every 12 hours.

Maximum: Oral/IV, 20/100 mg/kg daily in divided doses (in P. jirovecii pneumonia).

Paediatric dose

Mild–moderate infections: oral, 4/20 mg/kg every 12 hours.

Severe infections: IV, 5/25 mg/kg every 12 hours.

trimipramine

tricyclic antidepressant

Cautionary advisory labels: 1, 9, 13, 16

Notes

- Full benefit may not be seen for several weeks, but adverse effects may occur from start of treatment.
- Anticholinergic adverse effects are common—dry mouth, constipation, blurred vision, difficulty in passing urine; other adverse effects include hypotension and sedation.
- Medicine-free interval may be required when switching to/from another antidepressant. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- For antidepressant use, best taken as a single dose at night.
- Indications other than depression may include pain, obsessive compulsive disorder, anxiety, and panic and eating disorders.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to anticholinergic-reduced detrusor activity, urinary retention, voiding difficulty, constipation, sedation or impairment of mobility.

Elderly: Avoid use for sedation due to adverse effects such as constipation, urinary retention, confusion, orthostatic hypotension, which may lead to falls and fractures. Counsel to rise slowly from sitting or lying down.

Pregnancy: C. Use when clinically indicated if it is the drug of choice. There is increased risk of reversible withdrawal symptoms, not congenital malformations.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

50–300 mg daily.

tropisetron

$5HT_3$ antagonist

Cautionary advisory labels: 12, C (1 hour)

Notes

- Confirm other medicines have not been lost due to vomiting.

Pregnancy: B3. Consider alternatives first. If a $5HT_3$ antagonist is required, ondansetron is the preferred choice.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

Chemotherapy-induced vomiting: IV, 5 mg before chemotherapy followed by oral 5 mg daily for 5 days.

Postoperative-nausea and vomiting: IV, 2 mg daily.

Paediatric dose

Chemotherapy-induced vomiting: >2 years, IV, 0.2 mg/kg (up to 5 mg) before chemotherapy followed by oral/IV, 0.2 mg/kg once daily (up to 5 mg) for up to 5 days.

Postoperative-nausea and vomiting: >2 years, IV/oral, 0.05–0.2 mg/kg once or twice daily (maximum 2 mg daily).

ursodeoxycholic acid

bile acid modifier

Pregnancy: B3. May be used for cholestasis when other treatments have failed.

Breastfeeding: Use with caution. Minimal maternal absorption. Monitor for nausea or vomiting in infants.

Common dosage range

Adult dose

Oral, 10–20 mg/kg daily in 2–4 divided doses.

Paediatric dose

Oral, 15–20 mg/kg daily in 2–3 divided doses.

valaciclovir

guanine analogue, antiviral

Cautionary advisory labels: D—some packaging contains more units than for the treatment for one episode, e.g. episodic treatment of recurrent disease

Notes

- Take at regular intervals.
- Ensure adequate fluid intake (1.5–2 L/day).

Renal impairment: Caution. Reduce dose and/or dosage interval depending on renal function (increased risk of neurological adverse effects).

Pregnancy: B3. More experience with aciclovir in pregnancy. Seek advice from an infectious diseases specialist.

Breastfeeding: Use not recommended: limited data available. Aciclovir preferred.

Common dosage range

Adult dose

Genital herpes: 500 mg twice daily.

Shingles: 1 g three times daily.

Paediatric dose

20 mg/kg three times a day.

valganciclovir

guanine analogue, antiviral

Cautionary advisory labels: 12†, 13, 21, A, B

Notes

- Monitor complete blood profile, electrolytes, renal function and hepatic enzymes. Neutropenia is dose dependent.

Renal impairment: Dose reduction required in patients with Cl_{cr} <60 mL/min.

Pregnancy: D. Use contraindicated.

Breastfeeding: No data available. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

CMV retinitis: Induction, 900 mg twice each day for 21 days; maintenance, 900 mg daily.

Prevention of CMV disease after transplant: 900 mg once daily.

valproate

antiepileptic

Modification of oral formulation

Before crushing or otherwise altering enteric-coated tablets, consider the possibility of altered absorption characteristics.

Cautionary advisory labels: 9, 10a, 12†, 13, A*, B

Notes

- Take regularly and space dose evenly throughout the day: try to take at the same time each day.
- Periodic blood tests will be required to monitor hepatic function.
- If nausea and vomiting, malaise, jaundice, epigastric pain, sore throat, mouth ulcers, bruising, fever rash or non-specific illness occurs, seek medical advice.
- Monitoring plasma valproate concentrations is advisable in patients receiving high doses.
- Valproate concentrations may be decreased when given with carbamazepine, phenobarbitone or primidone. Plasma phenobarbitone concentration may be increased when given concurrently with sodium valproate.

Hepatic impairment (severe): Avoid use in impairment.

Therapeutic monitoring: Therapeutic range is 50–100 mg/L (350–700 micromol/L). Measure as trough concentration. Time to steady state: 3–5 days.

Toxicity: There is a poor correlation between concentration and effect. Up to 150 mg/L may be necessary in some patients. Monitoring may be useful to confirm toxicity or assess compliance.

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Pregnancy: D. Consider risk of congenital malformation against dangers of uncontrolled epilepsy. Consider folic acid (5 mg) and vitamin K supplementation.

Breastfeeding: May be used. Small amounts excreted in breast milk. Use minimum effective dose. Monitor for adverse effects (e.g. jaundice, petechial rash) in infants.

Common dosage range

Adult dose

Epilepsy: initially, 15 mg/kg daily in 1–2 doses, increasing by 200 mg daily every two weeks.

Maintenance, oral/IV, 20–30 mg/kg daily; maximum 2.5 g daily.

Prevention of migraine: oral, 200–400 mg twice daily.

Paediatric dose

Initially, 10 mg/kg/day in two doses, increasing at weekly intervals to 20–60 mg/kg daily in 2–3 doses.

vancomycin

glycopeptide antibacterial

Cautionary advisory labels: D

Notes

- Establish bacterial sensitivity, confirm appropriate antibiotic and dose regimen.
- Plasma concentration monitoring may be indicated with IV administration, especially in patients with renal impairment and in neonates.
- Dose modification is required in renal impairment.
- Ototoxicity and nephrotoxicity may occur.

Elderly: Risk of adverse effects is higher in the elderly.

Renal impairment: Dose and dose interval adjustment required. Use trough concentration monitoring to guide dosage interval.

Therapeutic monitoring: Therapeutic range is 10–20 mg/L for most indications and dosage regimens.

Toxicity: Therapeutic range applies to a trough level during once- or twice-daily dosing.

Pregnancy: B2. Seek advice from infectious diseases specialist.

Breastfeeding: May be used. Trace amounts excreted in breast milk. Monitor for adverse effects (e.g. diarrhoea, thrush) in infant.

Common dosage range

Adult dose

IV, 500 mg six-hourly or 1 g 12-hourly.

Pseudomembranous colitis: oral, 250–500 mg six-hourly.

Paediatric dose

IV, 10-15 mg/kg six-hourly.

Pseudomembranous colitis: oral, 5–10 mg/kg six-hourly.

vardenafil

phosphodiesterase inhibitor

Cautionary advisory labels: 5, 16

Notes

- Contraindicated in patients using any form of nitrate.
- Additive antihypertensive effect in patients taking antihypertensive agents.
- Flushing is common.
- If headache, blurred vision, chest pain or shortness of breath occurs, seek medical advice.
- Not indicated for use in women.

Elderly: Lower starting dose recommended.

Hepatic impairment (moderate): Reduce initial dose to 5 mg. Maximum dose 10 mg.

Hepatic impairment (severe): Contraindicated.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended. Not indicated for use in women.

Common dosage range

Adult dose

5–20 mg 25–60 minutes before sexual activity. Maximum of once per day.

varenicline

anti-smoking agent

Cautionary advisory labels: 12, 13, A, B

Notes

- Use in combination with an anti-smoking support program.
- Monitor patient for signs of depression and suicidal ideation.
- Sleep disturbances/anxiety are common.

Renal impairment: No adjustment required in mild to moderate renal impairment. In severe impairment the dose is reduced to 1 mg daily.

Pregnancy: B3.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

1 mg twice daily following an 8-day titration dose schedule.

venlafaxine

SNRI antidepressant

Modification of oral formulation

Crushing or otherwise altering controlled-release capsules will alter absorption characteristics.

Cautionary advisory labels: 5, 9, 12, B

Notes

- Full benefit may not be seen for several weeks, but adverse effects may occur from start of treatment.
- Medicine-free interval may be required when switching to/from another antidepressant. See NPS switching chart at www.nps.org.au/__data/assets/pdf_file/0015/22830/Depression2004ClinicalAuditPack.pdf.
- May increase the anticoagulant response to warfarin: monitor INR.
- Monitor for dose-related hypertension.
- Used for depression and generalised anxiety disorders.

Changes to urinary system: May induce or aggravate urge/functional incontinence due to enhanced detrusor activity (instability), sedation, impairment of mobility.

Renal or hepatic impairment: Caution. Dose adjustment necessary. Starting doses should be halved in patients with renal and/or hepatic impairment.

Pregnancy: B2. Continue previously commenced therapy if it is the drug of choice. There is increased risk of reversible withdrawal symptoms, not congenital malformations. For initiating treatment, consider suitable SSRI first.

Breastfeeding: Use with caution. Excreted in breast milk. Potential for adverse effects (e.g. insomnia, restlessness) in infants.

Common dosage range

Adult dose

Usual range 75–225 mg daily.

verapamil

calcium channel blocker

Modification of oral formulation

Crushing or otherwise altering controlled-release tablets or capsules will alter absorption characteristics.

Cautionary advisory labels: 9, 12, 13, 18, A*, B*

Notes

- Constipation is common; advise accordingly.
- Caution with other antiarrhythmics—increased risk of heart failure, bradycardia and proarrhythmic effect.
- Significant interaction potential (see Table D.1, Section D).

Changes to urinary system: May induce or aggravate overflow incontinence due to reduced detrusor activity or constipation.

Pregnancy: C. Consider alternative therapy first. If drug of choice, use with caution: maternal hypotension may produce fetal hypoxia.

Breastfeeding: Use with caution: limited data available. Small amounts excreted in breast milk.

Common dosage range

Adult dose

80–160 mg 2–3 times daily.

Sustained-release forms, 120–240 mg once or twice daily. Maximum daily dose 480 mg.

Paediatric dose

Oral (non-SR formulation), 1–3 mg/kg/dose three times daily.

vigabatrin

antiepileptic

Cautionary advisory labels: 9, 12†

Notes

- Monitor and test for visual field defects.

Renal impairment: Caution. Lower starting doses may be required.

Pregnancy: D. Consider risk of congenital malformation against dangers of uncontrolled epilepsy. Consider folic acid (5 mg) and vitamin K supplementation.

Breastfeeding: Use not recommended unless maternal benefits far outweight risk to infant. Small amounts excreted in breast milk but no safety data on drug in infants.

Common dosage range

Adult dose

2–4g daily in 1–2 doses.

† Most appropriate during initial treatment or when dosage is increased.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Paediatric dose

Oral, 40 mg/kg daily in 1–2 doses, increasing to 100 mg/kg (150 mg/kg in infants) daily if needed.

vinblastine

cytotoxic vinca alkaloid

Cautionary advisory labels: 21

Notes

- Fatal if given intrathecally.
- Do not extravasate.

Pregnancy: D. Use contraindicated.

Breastfeeding: Use contraindicated.

Common dosage range

Adult dose

Initially, IV, single dose of 3.7 mg/m^2. Thereafter white blood cell counts should be made to determine the patient's sensitivity. See approved Product Information for dosing schedule.

Paediatric dose

See approved Product Information for dosing schedule.

vincristine

cytotoxic vinca alkaloid

Cautionary advisory labels: 21

Notes

- Fatal if given intrathecally.
- Do not extravasate.

Pregnancy: D. Use contraindicated.

Breastfeeding: Use contraindicated

Common dosage range

Adult dose

0.4–1.4 mg/m^2. See approved Product Information for dosing schedule.

Paediatric dose

≥10 kg, 1.5–2.0 mg/m^2; <10 kg or BSA <1 m^2, 0.05 mg/kg weekly. See approved Product Information for dosing schedule.

voriconazole

triazole antifungal agent

Cautionary advisory labels: 5, 8, 12, C, D

Notes

- Warn patient that vision may be blurred (visual abnormalities appear to be dose related).
- Contraindicated in combination with other drugs that prolong the QT interval.

Hepatic impairment: Caution. Maintenance dose halved in mild-to-moderate hepatic cirrhosis.

Renal impairment: Caution. In Cl_{cr} <50 mL/min, IV solvent accumulates. Oral therapy preferred.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: no data available.

Common dosage range

Adult dose

IV, 6 mg/kg every 12 hours for two doses, then 3–4 mg/kg every 12 hours.

Oral, 200–400 mg every 12 hours for two doses then 100–200 mg every 12 hours.

Paediatric dose

≥2 years: IV or oral, 6 mg/kg/dose 12-hourly for two doses, then 4 mg/kg/dose 12-hourly.

warfarin

anticoagulant

Cautionary advisory labels: 5, 10b

Notes

- Counsel to ensure patient understanding.
- Encourage patient to take dose at the same time each day.
- Ensure patient consistently takes the same brand.
- Advise about maintaining a stable vitamin K dietary intake, and to report signs of over-anticoagulation (bleeding gums, haematuria, melaena, nose bleeds, excessive bruising).
- Inform about the importance of regular INR monitoring.
- Warfarin is a medicine of low therapeutic index and is involved in significant medicine interactions. Check regimen and advise accordingly (see Table D.1, Section D).
- Dental and surgical caution: encourage close liaison between patient, doctors and dentists. An option is to cease warfarin 5 days prior to surgery. Bridging therapy with heparin may be indicated. Warfarin may be continued if operative site is limited and accessible to allow effective local procedures for haemostasis.

Changes to faeces: Pink, red or black discolouration may indicate medicine-induced gastrointestinal bleeding.

Changes to urinary system: May discolour urine orange/yellow.

Elderly: Increased risk of bleeding.

Hepatic impairment: Response to warfarin may be increased; dose reductions may be necessary, as determined by INR.

Therapeutic monitoring: Although clinical benefit is yet to be established, selected laboratories may measure warfarin concentration (1–3 mg/L to confirm resistance to therapy). Target INR range usually 2–3.

Pregnancy: D. Use contraindicated.

Breastfeeding: May be used. Insignificant excretion in breast milk. Monitor for adverse effects (e.g. easy bruising, prolonged bleeding) in infants. Consider monitoring infant INR if doses >12 mg daily are required.

Common dosage range

Adult dose

Initially, 5–10 mg daily; maintenance dose, 1–10 mg daily in accordance with INR.

Paediatric dose

Initially, 0.1–0.2 mg/kg daily, then adjust depending on INR.

zafirlukast

leukotriene-receptor antagonist

Cautionary advisory labels: 3b

Notes

- Not for immediate relief of symptoms or an acute asthma attack.
- Avoid abrupt substitution for oral and inhaled corticosteroids.
- Several days of treatment required before therapeutic effect evident.
- Report immediately any nausea, vomiting, abdominal pain, fatigue, loss of appetite, dark urine or jaundice.

Hepatic impairment: Contraindicated.

Pregnancy: B1. Use not recommended.

Breastfeeding: Use not recommended.

Common dosage range

Adult dose

20-40 mg twice daily.

Paediatric dose

>7 years, 10 mg twice daily.

zidovudine

antiretroviral nucleoside reverse transcriptase inhibitor

Cautionary advisory labels: 12

Notes

- Report fever, nausea, vomiting, diarrhoea, rash, tiredness, difficulty breathing, sore throat or cough.
- If hypersensitivity reactions occur, stop drug and do not rechallenge.
- Drug does not cure HIV or reduce risk of transmission.
- Should be taken in combination with other antiretrovirals.

Renal or hepatic impairment: Accumulation may occur; dose reduction may be necessary.

Pregnancy: B3. Previously commenced therapy should be continued and advice sought from an infectious diseases specialist.

Breastfeeding: Excreted in breast milk but no safety data on drug in infants. Breastfeeding is not recommended in women with HIV because of the risk of viral transmission to the infant.

Common dosage range

Adult dose

500–600 mg daily in 2–5 divided doses.

Paediatric dose

3 months to 12 years: 90–180 mg/m^2 every 6–8 hours.

zinc sulfate

mineral

Cautionary advisory labels: B

Common dosage range

Adult dose

50 mg (elemental zinc) 1–3 times daily.

Paediatric dose

Deficiency: 1 mg (elemental zinc)/kg daily in 1–3 doses.

Acrodermatitis enteropathica: 50 mg (elemental zinc) daily in 1–3 doses.

zolmitriptan

5HT$_1$ agonist for migraine

Cautionary advisory labels: 12

Notes

- Seek medical advice if no relief occurs or if headaches are increasing in frequency or severity.
- If shortness of breath, difficulty breathing (anaphylactic-type reactions) or chest pain or tightness is experienced, seek medical advice.
- Should not be taken within 24 hours of ergotamine.
- Separate doses of different triptans by at least 12 to 24 hours.

Hepatic impairment: Maximum dose 5 mg/24h.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

2.5 mg. Dose may be repeated after at least two hours if symptoms persist. Maximum 10 mg/24 hours.

zolpidem

non-benzodiazepine hypnotic agent

Cautionary advisory labels: 1 or 1a, A*

Notes

- Effects potentiated by cytochrome P450 3A4 inhibitors (see Table D.1, Section D).
- Potential for dependence.
- Used for minimum required period only.

Hepatic impairment (moderate): Starting dose of 5 mg.

Hepatic impairment (severe): Contraindicated.

Pregnancy: B3. Use not recommended.

Breastfeeding: Use with caution. Small amounts excreted in breast milk. Monitor for adverse effects (e.g. sedation, poor feeding) in infant.

Common dosage range

Adult dose

Immediate-release formulation: 10 mg at night (5 mg for elderly patients).

Controlled-release formulation: 12.5 mg at night (6.25 mg for elderly patients).

zonisamide

antiepileptic

Cautionary advisory labels: 1, 5, 9

Notes

- Must be added to existing therapy.
- Gradual withdrawal if discontinuing therapy.
- Women of child-bearing potential should use adequate contraception.

Renal impairment: Clearance is correlated with creatinine clearance.

Pregnancy: D.

Breastfeeding: Excreted in milk at the same concentration in plasma. Breastfeeding should not resume until after one month after ceasing zonisamide therapy.

Common dosage range

Adult dose

Initial dose 50 mg daily in divided doses. May be increased to 100 mg daily after one week and then titrated to 300–500 mg daily in increments of 100 mg.

zopiclone

non-benzodiazepine hypnotic agent

Cautionary advisory labels: 1 or 1a

Notes

- Effects potentiated by cytochrome P450 3A4 inhibitors (see Table D.1, Section D).
- Potential for dependence.

Elderly, renal or hepatic impairment: Recommended starting dose is 3.75 mg.

Pregnancy: C. Use not recommended.

Breastfeeding: Use not recommended: limited data available.

Common dosage range

Adult dose

3.75–7.5 mg before bedtime.

zuclopenthixol

conventional antipsychotic agent

Cautionary advisory labels: 1, 8, 13, 16

Notes

- May cause anticholinergic, hypotensive and extrapyramidal effects (dystonia, akathisia, parkinsonism, tardive dyskinesia).
- Avoid concurrent use of more than one antipsychotic.
- Withdraw antipsychotics slowly if stopping the medication.

Changes to urinary system: May induce or aggravate overflow/functional incontinence due to anticholinergic-urinary retention and constipation, voiding difficulty, sedation, confusion, parkinsonism, or impaired mobility.

Elderly: Adverse effects more common, orthostatic hypotension (may lead to falls and fractures), confusion, sedation, extrapyramidal adverse effects (e.g. parkinsonism), constipation, urinary retention, blurred vision.

Hepatic impairment: Halve recommended initial dose.

* Some products have specific indications or specialised formulations or coatings which give rise to instructions different from those applicable generally to the conventional dose form. In cases of doubt concerning specific products with specialised formulations or coatings, reference should be made to the recommendations contained in the manufacturer's information.

Pregnancy: C. Use only if drug of choice. Use minimal effective dose.

Breastfeeding: Use with caution. Excreted in breast milk. Monitor for adverse effects (e.g. sedation) in infant.

Common dosage range

Adult dose

Zuclopenthixol acetate: IM, 50–150 mg every 2–3 days.

Zuclopenthixol decanoate: IM, 200–400 mg every 2–4 weeks. Zuclopenthixol dihydrochloride, oral, 10–50 mg (75 mg in severe cases) daily.

Section C

Complementary medicines monographs

Complementary medicines monographs

This section contains information to help pharmacists provide evidence-based information for the safe, effective and appropriate use of complementary and alternative medicines (CAMs) of herbal and non-herbal origin, also known as complementary medicines.

Definition

In Australia, medicinal products containing herbs, vitamins, minerals, and nutritional supplements, homoeopathic medicines and certain aromatherapy products are referred to as 'complementary medicines'. The term also includes traditional medicines, such as traditional Chinese medicines (TCMs), Ayurvedic medicines and Australian indigenous medicines. Complementary medicines have also been referred to as 'alternative medicines', 'natural medicines' or 'holistic medicines'.

Complementary medicines are defined by the *Therapeutics Goods Act 1989* (the Act) and may be used in a therapeutic regimen for the maintenance of health, or the prevention or alleviation of a disease or ailment. They do not necessarily rely on evidence of efficacy based on western medical practice or philosophy. The use and preparation of CAMs may be entirely, or in some part, based on traditional knowledge.

TGA regulations

CAMs are commonly regulated as non-prescription medicines in Australia. Like other marketed medicines, those that make therapeutic claims must be included in the Australian Register of Therapeutic Goods (ARTG). CAMs included in the ARTG are evaluated using a risk-based pre-market assessment to determine whether they should be 'listed' or 'registered'.[1]

Listed medicines

Most complementary medicines included in the ARTG are listed medicines. CAMs that are listed contain unscheduled substances, present a low-level risk, and make low-level therapeutic claims (www.tga.gov.au/docs/html/tgaccevi.htm). Evidence supporting safety and efficacy of individual listed medicines must be made available to the TGA on request. The TGA may accept 'traditional use' as supporting evidence, and products are generally not permitted to refer to the treatment, cure or prevention of a disease, disorder or condition. CAMs 'listed' with the TGA include an 'AUST L' number on the label, e.g. AUST L 67974.

The form and dose of the active constituents in listed medicines can vary, and individual sponsors identify an effective therapeutic dose for the intended use. Processing methods, plant quality and the part utilised vary considerably and will influence the effective dose of particular constituents for each product. Pharmacists need to be aware of comparative doses and dose forms and of like-named listed medicines. Careful reading of the label will identify the plant part or process used and the dose or dry-weight-equivalent dose (for herbal products).

Registered medicines

CAMs deemed to present a higher therapeutic risk or make higher level therapeutic claims are classified by the TGA as registered medicines. Registered complementary medicines may be non-prescription, over-the-counter medicines or medicines available only on prescription. Data supporting safety, quality and efficacy must be submitted to the TGA for evaluation prior to marketing. Registered medicines have an 'AUST R' number on the product label.

Global guidelines

Different cultural groups and countries have differing levels of CAM use and regulatory controls. The World Health Organisation aims to enhance global quality control and the monitoring of safety of CAMs with guidelines for the standardisation of consumer information, pharmacovigilance, and collection practices for botanicals.[2]

Quality assurance

Herbal ingredients contain constituents with levels that may vary depending on the part of the plant used, stage of ripeness, geographic area where the plant is grown, and storage conditions. Different extraction and manufacturing processes can also cause therapeutic differences between products. Ingredients may be 'standardised' to an accepted concentration of an identified constituent and provide batch-to-batch reproducibility of an identified constituent. Products of St John's wort (*Hypericum perforatum*), for example, may be labelled as containing 300 mg of a standardised herb extract containing 0.3% hypericin per dose. Standardisation is not a measure or guarantee of efficacy or potency of the product. Full product

standardisation requires the application of quality standards to the growing, harvesting, processing and manufacturing stages.

Herbal preparations are considered therapeutically equivalent if they have, or would be reasonably likely to have, comparable therapeutic effects when used at the recommended doses. To establish this, it is necessary to show that the preparations contain a similar range and concentration of constituents, including any known active constituents, or have a similar therapeutic action on the body. For example, a *Ginkgo biloba* leaf extract prepared by a process different from one for which clinical efficacy in the treatment of dementia has been demonstrated must be proven to be therapeutically equivalent before it can be used in a similar manner.

All manufacturers of CAMs must be licensed and comply with the principles of good manufacturing practice. The TGA undertakes inspections and audits to identify issues such as the substitution of plant species and heavy metal adulteration.

Labelling

CAMs must be labelled in English, showing the therapeutically active ingredients and the plant part used, the dose or dry-weight-equivalent dose, and any warnings or cautionary statements necessary for correct and safe use.

Marketing

The *Therapeutic Goods Act* gives effect to the Therapeutic Goods Advertising Code, which aims to ensure that all marketing and advertising of therapeutic goods to consumers embraces the quality use of therapeutic goods, is socially responsible and does not mislead or deceive the consumer. Advertising should not encourage consumers to self-medicate for conditions that require expert advice. Promotion of CAMs for the treatment or prevention of serious diseases such as AIDS, gastric, peptic or duodenal ulcers and neoplastic diseases is restricted by the Therapeutic Goods Advertising Code. Prior approval of the TGA is required for the advertising of the treatment or prevention of other serious forms of diseases.

Marketing intended exclusively for healthcare professionals is governed by industry codes of practice and not subject to the Therapeutic Goods Advertising Code.

Purpose and content of the CAM monographs

The following pages describe a selection of CAMs commonly available from Australian community pharmacies. Individuals may take these medicines as part of a prescription from a naturopath or herbalist or as a product purchased over-the-counter.

The information included in these monographs provide evidence-based information so that pharmacists can advise patients about the safety, efficacy and standardisation of CAMs. The information contained in this section may extend beyond that which is approved for use in Australia (refer to the ARTG at www.tga.gov.au/docs/html/artg.htm). Pharmacists are advised to consult specialist CAM references for more detailed information or use evidence-based information sources such as those referred to in 'Information from the world wide web', Section F.

The monographs are in the following format.

Name

Each monograph gives the common and botanical names of the herb and, where appropriate, the part of the plant used medicinally. A CAM may have multiple 'common' names not included in this text, and pharmacists should be aware that some common names can refer to several species with differing therapeutic activity (e.g. skullcap).

Common uses

A summary of scientific evidence grouped by some common indications has been sourced from systematic reviews or meta-analyses of randomised-controlled trials (RCT), or well-conducted trials. Reviews of numerous (often small) well-conducted trials may also be included. Traditional use of CAMs often combines different ingredients for an additive or synergistic effect, and evidence from rigorous scientific trials on isolated constituents is generally limited. There are, however, increasing numbers of well-designed clinical studies being undertaken. Evidence-based reviews of studies made available since the release of this publication can be found in sources such as the Cochrane Library (see 'Information from the world wide web', Section F).

Other reported uses

Under this heading is a sample of both traditional and modern uses of the CAM. Despite widespread community use, there is often limited scientific evidence to support the use of a particular CAM for a specific indication.

Notes

This is a brief listing of additional information to be used by pharmacists providing CAMs.

Pharmacists should evaluate and consider the risk to individuals wishing to take CAMs, particularly those:

- taking medications with a narrow therapeutic index
- taking multiple medications
- who are elderly
- who are children
- diagnosed with a chronic or severe medical condition
- with impaired liver or kidney function.

These individuals are at higher risk of adverse events when CAMs are co-administered with prescription medicines, and this should be carefully explained.

Information on adverse effects has been derived from traditional use, clinical trials and post-marketing surveillance. Pharmacists have an important role in the recognition and reporting of adverse reactions to the Adverse Drug Reactions Advisory Committee (see 'Clinical monographs', Section B).

CAMs that have anticoagulant or antiplatelet effects or potentiate or prolong sedation should generally be ceased one to two weeks prior to surgery.[3] Some CAMs, however, should not be discontinued abruptly.[4] Valerian, for example, has been associated with withdrawal symptoms similar to those of benzodiazepine withdrawal. Where possible, doses should be tapered or, if this is not possible, valerian should be continued until surgery and benzodiazepines should be used to treat any withdrawal symptoms.[5] The following CAMs should be used with caution in individuals on anticoagulants or antiplatelet therapy:

- artichoke
- bilberry
- celery
- chamomile (German)
- coenzyme Q10
- cranberry
- devil's claw
- dong quai
- evening primrose oil
- feverfew
- fish oil
- garlic
- ginger
- ginkgo
- glucosamine
- grape seed
- green tea
- horse chestnut
- kelp
- licorice
- pau d'arco
- red clover
- saw palmetto
- willow bark.

Studies have identified a high rate of CAM use by patients undergoing treatment for cancer. These patients should be encouraged to openly discuss any use of CAMs with their medical practitioner(s) *prior* to commencing treatment in order to avoid drug interactions, adverse reactions or diminished efficacy. Information from sources such as the Cancer Council of Australia or the National Center for Complementary and Alternative Medicine (NCCAM) can provide valuable assistance for both pharmacists and patients.[6,7]

Pregnancy and breastfeeding

The reported level of CAM use during pregnancy in Australia is between 10 and 56% and increasing.[8]

Pharmacists should be aware of the common herbal supplements used by women during pregnancy, and of the evidence regarding potential benefits or harm.

Few scientific trials have studied the safe use of conventional medicines in pregnancy and breastfeeding, and significantly fewer have addressed CAMs.

Women considering CAM use during pregnancy or breastfeeding should be given detailed advice on both the potential harms and benefits, so they can make an informed decision, particularly where limited data are noted. No medicine, either conventional or complementary, should be taken during pregnancy or breastfeeding unless the benefit is greater than the risk to the mother or infant. For the majority of CAMs, there is no evidence suggesting they cause birth defects, but there is also very little direct evidence that they are safe for use in pregnancy.

The Royal Women's Hospital Drug Information Centre has published a list of CAMs to avoid during pregnancy and breastfeeding.[9] Pharmacists may consult a specialised information service for guidance on CAM use in pregnancy or lactation, since recommendations may change as further safety data becomes available. See 'Specialist medicines information centres' in 'Medicines and breastfeeding', Section D.

Contraindications

Systematic studies and evidence-based information in this area are limited. Pharmacists should consider individual patient characteristics to assess potential clinical relevance.

Interactions

Drug interactions represent one of the greatest safety risks with the use of CAMs. This section presents a summary of some of the available case reports and theoretical concerns of potentially clinically significant interactions. Available data vary widely in quality and reliability. The included interactions have been reported in pharmacological profiles, case reports, preliminary studies in animals, and human clinical trials. The list of included interactions is not exhaustive.

Common dosage ranges

Recommended doses are based on traditional use or, where possible, those used in clinical trials. Unless otherwise specified, doses are for adult use. CAMs may be administered in a range of different forms, such as:

- *Tea.* An infusion made by adding boiling water to fresh or dried botanicals.
- *Decoction.* Some roots, bark and berries must be simmered in boiling water for a lengthy period.
- *Tincture.* Made by soaking a botanical in a solution of alcohol and water. Tinctures are available in various concentrations expressed as botanical to extract ratios (the weight of the dried botanical to the volume or weight of the finished product).
- *Liquid extract.* Made by soaking the botanical in a liquid to capture the desired constituent. It may be used in this liquid form or be further evaporated to make a 'dry extract' for use in capsules or tablets.

Botanical products may vary between manufacturers, batches and formulations. Where identification of the active constituent has not occurred, standardisation of individual doses is difficult and the clinical effect of different batches and brands may not be comparable.

Pharmacists' role

When responding to inquiries about CAMs, pharmacists should:

- appreciate consumers' cultural and social beliefs regarding the use of CAMs and their desire to take control and responsibility for their own treatment
- recognise a product's potential to interact with conventional pharmacotherapy or other CAMs
- be aware some products may influence pathology laboratory results
- assume a non-judgmental role and provide the same level of evidence-based advice while promoting the quality use of CAMs, as would be provided with any other medicine
- remain up-to-date with information, research and publications pertaining to CAMs
- be aware of the evidence to support safety and efficacy claims and have some insight into the quality of that evidence
- be aware of the clinically relevant standardisation and quality process required for products to meet relevant TGA standards
- take an active role in the recognition and reporting of adverse reactions and interactions to both the Adverse Drug Reactions Advisory Committee and the product's sponsor.

Informed ethical recommendations

At times a pharmacist may be required to respond to a request for a CAM which presents an ethical dilemma. For example, a customer may insist on purchasing a CAM for which there is no supporting scientific evidence for the intended use and that has the potential to precipitate an adverse event. There is often no definitive answer to such situations, and the pharmacist should provide the best advice possible under the circumstances. The most appropriate response must be guided by the Pharmaceutical Society of Australia's *Code of Professional Conduct*:

- Principle ONE: *The primary concern of the pharmacist must be the health and wellbeing of both clients and the community.*
- Principle EIGHT: *A pharmacist must respect the client's autonomy and dignity and their right to make informed decisions relating to their treatment.*[10]

Ultimately, if the pharmacist has provided the best available information on current evidence (or lack there of) for efficacy, potential adverse effects, contraindications, or drug-herb interactions and has encouraged the patient to inform their medical practitioner(s), the patient has the right to make the final decision about his or her own treatment.[11]

CAM monographs

The following CAM monographs include evidence-based information for the safe, effective and appropriate use of CAMs of herbal and non-herbal origin.

artichoke

Cynara scolymus (leaf)

Common uses

Dyspepsia

Evidence: A double-blind RCT with 244 participants and an open RCT with 454 participants, found artichoke leaf extract provided moderate relief of symptoms such as nausea, vomiting, flatulence, and abdominal pain in functional dyspepsia or dyspepsia associated with biliary disease.[12,13]

Hyperlipidaemia

Evidence: A 2002 Cochrane systematic review found few studies had rigorously researched use in individuals with raised cholesterol levels. Analysis of two RCTs involving 167 participants found some beneficial effects, but the evidence was not considered compelling.[14]

Other reported uses: Alcohol-induced hangover symptoms and irritable bowel syndrome.[3]

Notes

- *Cynara scolymus* should not be confused with Jerusalem artichoke *(Helianthus tuberosus)*.
- Increased bile flow may worsen bile duct obstruction or symptoms of gall stones.[15]
- Nephrotoxicity has been reported.[16]

Pregnancy and breastfeeding

Insufficient reliable data.

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and *NSAIDs (e.g. ibuprofen):* Artichoke extract has caused reduced platelet aggregation (both spontaneous and ADP-induced) and increased risk of bleeding.[16] Monitor for signs of bleeding and possible increase in INR if taking warfarin.

Common dosage ranges[16]

Optimal doses for efficacy and safety have not been established. Some products are standardised to 15% chlorogenic acid, 2–5% cynarin per dose, or 1% caffeyol acid derivatives.

Tablets/capsules (dried leaf extract): 250–750 mg of cynarin or 1,800–1,900 mg dried leaf extract daily have been used in trials. 320–640 mg dried leaf extract daily has been used for dyspepsia. For dyslipidaemia, 320 mg standardised dried leaf extract four to six times daily for a minimum of six weeks.

Liquid extract (1:2): 3–8 mL daily.

astragalus

Astragalus membranosus (root)

Common uses

Immune system stimulant

Evidence: A 2005 Cochrane systematic review of four clinical trials in a total of 342 colorectal cancer patients undergoing chemotherapy found a decoction of *Astragalus* spp. *Huangqi* provided minor stimulation of immunocompetent cells and reduced the number of patients experiencing chemotherapy-induced nausea and vomiting. Trials were considered to have methodological limitations, however, and further research is needed.[17]

Other reported uses: The common cold, upper respiratory infections and hepatitis.

Notes

- The intended use of CAMs by individuals undergoing chemotherapy should be discussed with their medical practitioner(s) and be medically supervised. For further information, refer to the 'Notes' section under 'Purpose and content of the CAM monographs'.
- Astragalus is commonly used in combination with other traditional Chinese medicine herbs.
- Anecdotal reports suggest it may cause mild diuresis and reduction in blood pressure.[16]
- Avoid use during acute infections.

Pregnancy and breastfeeding

Insufficient reliable data.

Interactions

Many anecdotal and theoretical interactions have been reported, with uncertain clinical importance.[16]

Immunosuppressant agents (e.g. corticosteroids, cyclosporin): Theoretically, the immunostimulating properties of astragalus may reduce the efficacy of immunosuppressants.

Common dosage ranges

Tablets/capsules: 500–1,000 mg of the dried root three times daily has been used.[16]

Powder: 1–30 g daily. 4–7 g daily is commonly used for prevention of the common cold.[18]

bilberry

Vaccinium myrtillus (fruit)

Common use

Effect on night vision

Evidence: A systematic review of 30 clinical trials (12 placebo-controlled, five RCT, seven non-RCT and six non–placebo controlled trials) found no improvement in night vision attributable to bilberry extract, although it was noted there was a wide variation in doses used.[19]

Other reported uses: Circulatory problems and diabetic retinopathy.

Notes

- May cause mild gastrointestinal upset.

Pregnancy and breastfeeding

Insufficient reliable data about use in therapeutic doses.

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): Bilberry inhibits platelet aggregation, and it potentially has an anticoagulant effect.[15,16] Monitor for signs of bleeding and possible increase in INR if taking warfarin.

Iron: Theoretically, the tannins in bilberry may reduce iron absorption. Separate doses by two hours.[3]

Common dosage ranges

Bilberry VMA (*Vaccinium myrtillus* anthocyanoside) may be standardised to contain 25% anthocyanidin. The optimal efficacious and safe dose has not been determined.

Dried extract: 50–288 mg anthrocyanins daily.[3] 80–480 mg bilberry VMA daily in two or three divided doses has been used for circulatory and ophthalmologic problems.[16]

black cohosh

Cimicifuga racemosa (rhizome and root)

Common use

Menopausal symptoms

Evidence: Many trials have studied the safety and effectiveness of black cohosh[16], although few have been well-designed RCTs with large numbers of participants or have been conducted for longer than six months.[20] Some black cohosh extracts have been modestly effective in reducing menopausal symptoms such as hot flushes, although some trials also found improvement in 50% of the participants receiving placebo.[15] The most consistent positive evidence refers to the product *Remifemin*.[18]

There are contradictory findings for efficacy in managing chemically induced hot flushes such a those induced by tamoxifen.[3,16]

Other reported uses: Premenstrual syndrome, dysmenorrhoea and osteoporosis.

Notes

- Until further information is available, avoid use in patients with oestrogen-dependent tumours (e.g. certain breast or ovarian cancers), due to possible oestrogenic activity.[20]
- The TGA require the labels of black cohosh products to contain a 'black box'—"Warning: Black cohosh may harm the liver in some individuals. Use under the supervision of a healthcare professional". Monitor for signs of liver toxicity (e.g. nausea, fatigue, loss of appetite, itchy skin, pale stools, dark urine, jaundice or elevated liver function tests).
- Theoretically, taking black cohosh with other hepatotoxic drugs may increase the risk of liver damage.[18]
- Reported side effects include hypotension, nausea, vomiting, dizziness, headache, tremors, mastalgia and weight gain.
- Four to 12 weeks' continuous use may be required for symptom relief.

Pregnancy

Avoid use due to purported uterine stimulant effects.[9]

Breastfeeding

Insufficient reliable data.

Contraindications

- Patients with previous or existing liver disease should avoid use.[20] Black cohosh has been associated with case reports of liver failure and auto-immune hepatitis, although, considering the widespread use, the incidence appears to be low.[21]
- Patients receiving chemotherapy or anti-oestrogenic treatment should consult their medical practitioner prior to use.

Interactions

Chemotherapeutic agents: An in-vitro study demonstrated that black cohosh might alter the efficacy and toxicity of various chemotherapeutic agents on breast cancer cells. The clinical significance is, however, currently unclear.[22]

Cytochrome P450 substrates: A clinical trial found a reduction in CYP2D6 enzyme activity but no effect on CYP3A4, CYP1A2 or CYP2E1 enzymes.[23] Patients receiving medications metabolised by CYP2D6 should be monitored for drug efficacy and adverse effects. See Table D.1, Section D.

Oral contraceptives, HRT, clomiphene: Contradictory advice exists for safety of use with black cohosh, and it is unclear how (or if) black cohosh acts on oestrogen receptors.[16] Patients taking this combination should do so under strict medical supervision.

Tamoxifen: Contradictory advice exists for the combination.[16] It is unclear how (or if) black cohosh acts on oestrogen receptors. Patients taking this combination should do so under strict medical supervision.

Common dosage ranges

Many trials have used products standardised to triterpenes, calculated as 27-deoxyactein *(Remifemin)*, or the component CR BNO 1055, marketed as *Klimadynon*.[3] The manufacturing process and dosing recommendations for *Remifemin* have changed over the past 20 years, and the results found in earlier trials or those with different constituents are not necessarily comparable.[16]

Tablets/capsules: 1–2 mg of 27-deoxyactein twice daily or 40 mg CR BNO 1055 daily for menopausal symptoms.[16,18]

capsicum/capsaicin

Capsicum frutescens and *C.annuum* (fruit)

Common use

External analgesia and counter-irritant

Evidence: A meta-analysis of six double-blind placebo-controlled trials (total 656 patients with chronic neuropathic pain) found topical capsaicin had moderate to poor efficacy in relieving chronic musculoskeletal or neuropathic pain, although it may be useful as an adjunct or sole therapy for patients who are unresponsive to other treatments.[24]

Other reported uses: (orally) Dyspepsia, flatulence, colic, toothache, poor circulation and osteoarthritis.

Notes

- Topical formulations should be applied as a thin film and massaged into the affected area three to four times daily. Initial application may cause burning, but pain relief will increase as substance P depletion increases. Wash hands after application to avoid contact with mucous membranes and eyes.
- Intensity of adverse reactions is dose and concentration dependent. May cause extreme burning pain in nose, sneezing and serous nasal discharge, gastrointestinal discomfort, transient bronchoconstriction and skin irritation. Gastroenteritis or liver or kidney damage may result from excessive ingestion.
- Avoid in patients sensitive to capsicum or chilli pepper products.
- Avoid in asthmatics (bronchoconstrictive) and oral use in ulcer and reflux disease.
- Avoid contact with mucous membranes and open wounds.

Pregnancy and breastfeeding

Likely to be safe when used topically in recommended doses, but there are insufficient reliable data on the safety of oral use in therapeutic doses.[18]

Interactions

ACE inhibitor: One case report describes topical capsaicin-induced cough in a patient receiving an ACE inhibitor. Monitor incidence of cough during co-administration.[25] Clinical significance of this interaction is unclear.

Theophylline: A study found theophylline bioavailability increased with capsaicin co-administration. Monitor for adverse effects of theophylline toxicity.[25]

Common dosage ranges

Oleoresin: (oral) 1.2 mg in a single dose; maximum daily dose 1.8 mg.[20]

Ointment or cream: (external use) 0.025% capsaicinoids for arthritis; up to 0.075% for post herpetic pain and diabetic neuropathy.[26]

cascara sagrada

Rhamnus purshiana (aged bark)

Common use

Stimulant laxative

Evidence: Cascara is a mild stimulant laxative whose glycoside components increase the smooth muscle tone of the large intestine. The US Food and Drug Administration removed its designation as safe and effective in 2002 due to lack of supporting evidence.[18]

Notes

- May cause cramping, diarrhoea, cardiac disturbances, albuminuria, haematuria, long-term dependence, fluid and electrolyte imbalance, particularly potassium depletion.
- Large doses may result in nephritis.

- Long-term use may result in dependence.
- May discolour urine (pink, red, orange or yellow–brown).[18]

Contraindications

- Avoid in intestinal obstruction, ulcerative colitis, appendicitis, abdominal pain of unknown origin or irritable or spastic bowel associated with constipation.
- Avoid in children younger than 12 years of age.

Pregnancy

Insufficient reliable data; the use of bulk-forming or surfactant laxatives is preferred.

Breastfeeding

Cascara constituents are excreted into breast milk and may cause gastrointestinal upset or diarrhoea in the infant. Avoid use.[18]

Interactions

Corticosteroids: Prolonged use of cascara may compound diuretic-induced potassium loss.[18]

Digoxin and other cardiac glycosides: Prolonged use of cascara may cause potassium depletion and hypokalaemia, increasing the risk of digoxin toxicity. Restrict to use for short-term symptomatic relief; if long-term therapy is necessary, maintain adequate fluid intake and monitor potassium concentration to avoid potential adverse effects of digoxin.[20]

Stimulant laxatives: Concomitant use increases the risk of potassium depletion.[20]

Thiazide diuretics: Prolonged use of cascara may compound diuretic-induced potassium loss.[18]

Common dosage ranges

Preparations containing non-standardised anthraquinones may cause unpredictable effects and should be avoided. The appropriate amount of cascara is the smallest dose required to maintain soft stools.[20]

Tablets/capsules: equivalent of 20–30 mg hydroxyanthracene derivatives (calculated as cascaroside A) daily.

Infusion: 1.5–2 g daily of dried bark taken in 150 mL hot water.

celery

Apium graveolens (seed)

Common uses

Celery seed is often used to relieve arthritis, rheumatism, gout, urinary tract inflammation, nervousness and loss of appetite; however, there are currently no published clinical trials investigating efficacy.

Notes

- May cause central nervous system depression (large doses), dermatitis (allergic reaction), hypersensitivity reactions and phototoxicity (avoid large doses prior to ultraviolet radiation exposure).

Pregnancy

Celery seed oil is reputed to have a uterine stimulant, or abortifacient, action. Avoid high-dose preparations.[3,18,20]

Breastfeeding

Conflicting advice is found in many texts regarding safety of use. There are insufficient reliable data for a clear recommendation.

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): Celery constituents can theoretically exert an anticoagulant effect due to the naturally occurring coumarins.[3] Monitor INR if warfarin is used and for possible signs of bleeding (e.g. bruising).

Thyroxine: There are two Australian case reports of lowered T_4 levels in female patients taking thyroxine and celery seed tablets. Monitor thyroid function if this combination is taken.[27]

Common dosage ranges

Seed (fruit): 0.5–2 g of dried seed as a decoction (1:5) three times daily.[18,20]

Liquid extract (1:1 in 60% alcohol): 0.3–1.2 mL three times daily.[18]

chamomile, German

Matricaria recutita (flower heads)

Common uses

Topical anti-inflammatory

Evidence: A clinical trial comparing chamomile with hydrocortisone 0.5% cream found some improvement after two weeks, although both were only marginally better than placebo. The study was considered poorly designed and poorly reported.[15,16,28]

Insomnia

Evidence: Small, poor-quality studies report possible sedative properties, although results in animal studies have been favourable.[3] There have been no well-designed clinical trials in humans.[16]

Oral mucositis

Evidence: Conflicting results have been found with studies on oral mucositis caused by radiation therapy and chemotherapy. It is unclear if chamomile is beneficial for this condition.[16]

Other reported uses: Irritable and spasmodic conditions of the gastrointestinal tract, dysmenorrhoea and wound healing.

Notes

- May cause allergic dermatitis or aggravate symptoms in asthmatics.
- Oral use for two weeks or more may result in reduced urinary creatinine output.[18]

Pregnancy

Theoretically, chamomile could act as a uterine stimulant, or abortifacient. Avoid use.[16]

Breastfeeding

Insufficient reliable data to recommend safe use.[16,18]

Contraindications

Anaphylaxis has resulted from oral and rectal use in individuals hypersensitive to members of the daisy family (*Asteraceae*).

Interactions

Cytochrome P450 substrates: Preliminary animal research suggests German chamomile may inhibit CYP3A4 and CYP1A2 isoenzymes.[18,20] See Table D.1, Section D.

Common dosage ranges

Tea/infusion: 2–4 g of dried flower heads steeped in 150 mL hot water three or four times daily.

Topical: 3–10% applied up to four times daily has been used, although there is no standard concentration.

Mouthwash: 10–15 drops of liquid extract in 100 mL warm water has been used three times daily.

chaste tree/vitex agnus-castus

Vitex agnus-castus (fruit)

Common uses

Premenstrual syndrome

Evidence: A double-blind placebo-controlled RCT in 178 women using *agnus castus* dry extract daily for three consecutive cycles found reduced self-assessed symptoms of irritability, mood alteration, anger, headache, breast fullness, and other menstrual symptoms such as bloating. The treatment was well tolerated.[29]

Cyclic mastaglia

Evidence: A double-blind RCT in 160 women is reported to have found chaste tree more effective than placebo.[15,16]

Other reported uses: Amenorrhoea, oligomenorrhoea, and menopausal symptoms such as hot flushes.

Notes

- May cause gastrointestinal upset, headache, diarrhoea, nausea, rash, acne, insomnia, weight gain, and irregular menstrual bleeding.[18]
- Some manufacturers recommend it be taken each morning on an empty stomach for maximal effect.[3]

Pregnancy and breastfeeding

Chaste tree constituents lower prolactin levels and, although used historically as a galactagogue, it should be avoided by women who are pregnant or breastfeeding.[16] It is proposed that lower doses might increase prolactin levels and breast milk production, while higher doses may have the opposite effect.[30]

Interactions

Dopamine receptor antagonists (e.g. haloperidol, chlorpromazine, metoclopramide): Chaste tree constituents bind to dopamine-2 receptors and may impair dopamine receptor antagonist activity (i.e. antagonise the antipsychotic or anti-emetic effect).[16,31] This has not been confirmed by clinical trials.

Oral contraceptives, HRT, clomiphene: Theoretically, chaste tree constituents may indirectly affect hormone levels in a dose-dependent manner. Low doses have resulted in decreased oestrogen levels and increased progesterone levels. The mechanism of action has not been clarified and the clinical relevance is uncertain.[15,31,33]

Common dosage ranges

There is no universal standardisation of chaste tree products. Trials have used extracts standardised to 0.5% agnuside or 0.6% aucubin constituents. Doses used in trials for PMS include Ze 440 extract (*Prefemin*) 20 mg daily; 1.6–3.0 mg of dried fruit extract (6.7–12.5:1) twice daily (*Femicur*).

Dried fruit (or equivalent in tablets/capsules): 1.5–3 g in the morning.

coenzyme Q10/CoQ10/ ubiquinone/ubidecarenone

(derived from mammalian heart, liver, kidney and pancreatic extract)

Common uses

Congestive heart failure

Evidence: A meta-analysis of eight RCTs found adjunctive treatment of congestive heart failure (CHF) improved haemodynamic parameters.[32] Some trials, however, have found no benefit, suggesting the need for further prospective trials before routine supplementation can be recommended.[15,16]

Hypertension

Evidence: A systematic review of eight trials using various doses as adjuvant therapy for essential hypertension found a mean decrease in systolic and diastolic blood pressure of 16 and 10 mm Hg respectively.[33] However, the trials demonstrated confounding variables or low statistical power.

Treating adverse effects of cancer therapies

Evidence: A systematic review of six studies found that CoQ10 provided some protection against cardiotoxicity and liver toxicity during cancer treatment. Poor reporting and analysis and questionable validity of outcome measures for the individual trials, however, mean the results are not conclusive.[34]

Statin-induced myopathy

Evidence: A systematic review concluded there was insufficient evidence to recommend routine use of CoQ10 to treat fatigue and muscle pain associated with statin-associated myopathy, although some patients responded well to its use as a supplement.[35]

Other reported uses: Ischaemic heart disease, hypertension, reperfusion injury, improvement of athletic endurance and Parkinson's disease.

Notes

- Generally well tolerated but may cause anorexia, mild nausea, diarrhoea, epigastric discomfort and ischaemic tissue damage (during intense exercise).
- Beta-blockers, clonidine, hydralazine, methyldopa, diazoxide, sulphonylureas, phenothiazines, tricyclic antidepressants, gemfibrozil and thiazide diuretics have been reported to cause reduced CoQ10 levels.[3,15]

Pregnancy and breastfeeding

Insufficient reliable data.

Interactions

Warfarin: There are case reports of CoQ10 causing a decreased international normalised ratio (INR), but a placebo-controlled trial in patients on stabilised warfarin therapy, taking recommended CoQ10 doses for four weeks, found no clinical effect.[33] Close monitoring of the INR is advised for patients taking this combination.[3] A warning statement is required on all CoQ10 medicines.

Common dosage ranges

100–150 mg daily has been used for conditions such as CHF and hypertension, and is the listable ceiling dose approved in Australia. Higher doses such as 60–600 mg are reportedly used in angina, and 300 mg to 1200 mg daily has been suggested for the treatment of Parkinson's disease.[3]

cranberry

Vaccinium macrocarpon (fruit)

Common uses

Prevention of urinary tract infection (UTI)

Evidence: a systematic review of 10 studies (total 1049 participants) found that cranberry (juice or capsules) can decrease the number of symptomatic urinary tract infections (UTIs) over a 12-month period, particularly for women with recurrent UTIs. Effectiveness in elderly men and children, however, remains unclear. A large drop-out rate was noted, and the exact dosage form and dose of cranberry for optimal outcomes was not determined.[36]

Other reported uses: Reduction of urinary odour in incontinence and facilitation of urinary excretion of phencyclidine in drug overdose cases.

Notes

- Taking more than 3–4 L of cranberry juice daily may cause diarrhoea and gastrointestinal discomfort.
- Undiluted cranberry juice contains approximately 1.9 mg of oxalate per 30 mL[18] and should be used with caution in patients with a history of urinary calculi due to potential for increased urinary calcium oxalate levels.
- Cranberry juice contains salicylic acid and, theoretically, large amounts could trigger an allergic reaction in people with aspirin allergy or aspirin-sensitive asthma.
- Cranberry juice has been found to increase absorption of vitamin B_{12} in patients taking proton pump inhibitors.[16]

Pregnancy and breastfeeding

Insufficient reliable data.

Interactions

Warfarin: A controlled trial in healthy subjects published in 2008 found that, unlike some earlier evidence, cranberry juice extract can increase warfarin response.[16,20,37,38] Patients should be advised to avoid cranberry products whilst on anticoagulants (and possibly antiplatelet agents); monitor for signs of bleeding and possible increase in INR if commencing or ceasing these products.

Common dosage ranges[16,18,20]

There is no standardisation for cranberry juice constituents, although some preparations are standardised to 11 to 12% quinic acid per dose. Commercial cranberry 'drink' or cocktail is approximately 26–33% pure cranberry juice and is sweetened with

fructose or artificial sweetener. 1,500 g of fresh fruit equates to approximately 1 L of pure juice.

Juice: 300 mL of commercial drink daily (e.g. *Ocean Spray*) has been used for preventing UTIs. Recommended doses range from 90–480 mL of drink twice a day or 1–30 mL of unsweetened 100% juice. 100–200 mL of drink daily has been used as a urinary deodoriser in incontinent patients.

Cranberry juice extract powder: 300–400 mg capsules, one to six times daily, have been used.

devil's claw

Harpagophytum procumbens (root)

Common uses

Osteoarthritis and non-specific lower back pain

Evidence: A systematic review of five trials investigating use in osteoarthritis, four in low back pain and three in mixed pain found moderate evidence for use in osteoarthritis of the spine, hip and knee and in the treatment of acute exacerbations of chronic non-specific low back pain.[39] A systematic review of use in low back pain found strong evidence that doses standardised to 50 mg or 100 mg harpagoside daily were better than placebo for short-term improvements in pain and need for rescue medication. The trials were of moderate or high quality, but they were limited to short-term use (up to six weeks). The Cochrane review noted potential conflicts of interest in half of the reviewed studies.[40]

Musculoskeletal pain

Evidence: A randomised double-blind, placebo controlled trial in 65 patients taking the equivalent of 24 mg of harpagoside daily found an improvement in visual analogue scale (VAS) scores for muscle pain after four weeks' treatment for mild to moderate musculoskeletal pain.[20]

Other reported uses: Gout, myalgia, fibrositis, lumbago and pleurodynia.

Notes

- Increased stomach acidity may cause diarrhoea and gastrointestinal discomfort in sensitive patients. Avoid in patients with acid reflux or duodenal ulcer.
- May lower blood sugar levels.[16]
- Alteration in calcium influx regulation in smooth muscle may affect heart rhythm and rate. Use with caution in patients on anti-arrhythmic therapy.

Pregnancy and breastfeeding

Insufficient reliable data, although several sources refer to a report of ototoxicity[3,20], and others note it may stimulate uterine contractions.[41] Avoid use.

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): There is a theoretical increase in risk of bleeding. Monitor for signs of bleeding. An increase in INR may require adjustment of warfarin dose.[18]

Cytochrome P450 substrates: Devil's claw constituents may inhibit CYP2C9 and CYP3A4 isoenzymes, increasing levels of related substrates. See Table D.1, Section D.

H_2 antagonists and proton pump inhibitors: May have reduced effectiveness.

Common dosage ranges

Tablets/capsules: Clinical trials for the treatment of osteoarthritis frequently use the equivalent of 57 mg of the harpagoside constituent and 87 mg of total iridoid glycosides, although a range of 30–100 mg harpagoside has also been used. 50–100 mg harpagoside daily has been used for low back pain.[18,20]

Dried root: 1.5–3 g as a decoction three times daily (or equivalent aqueous or hydroalcoholic extract) has been suggested for painful arthritis.

dong quai/tang-kuei/dang gui

Radix angelicae sinensis (root)

Common use

Menopausal symptoms

Evidence: A double-blind placebo-controlled RCT in 71 postmenopausal women did not find a reduction in hot flushes, endometrial wall thickness or other menopausal symptoms, suggesting there is no oestrogenic effect. The trial, however, was small, and the extract used may not have been manufactured in the same way as other available products.[16,42]

Other reported uses: Gynaecological disorders, including irregular menstruation, dysmenorrhoea and premenstrual syndrome, and premature ejaculation.

Notes

- May cause mild gastrointestinal discomfort or an allergic rash.
- Theoretically, the furocoumarins in dong quai may cause photosensitivity. Do not take with other photosensitisers such as St John's wort. Recommend protection from direct sunlight and avoidance of sun lamps.[15,16]
- Avoid use in patients with diarrhoea or hypermenorrhagia.

Pregnancy and breastfeeding

Avoid use in pregnancy and lactation.[3,9,43]

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): Concomitant use increases the risk of bleeding. Dong quai is thought to have an anticoagulant effect and to inhibit platelet activation and aggregation.[18] Dong quai 565 mg once or twice daily for four weeks increased the INR to 4.9 in one case report. The INR normalised four weeks after discontinuation of dong quai.[44] Monitor for signs of bleeding and possible increase in INR if taking warfarin.

Common dosage ranges[3]

Dong quai is commonly used in various individualised doses and in combination with other traditional medicines.[16]

Liquid extract (1:2): 4.5–8.5 mL daily.

Dried root: 4.5–9 g as a decoction daily.[43]

echinacea

Echinacea purpurea, E.angustifolia or E.pallida (herb)

Common uses

Treatment & prevention of the common cold

Evidence: A 2007 meta-analysis of nine studies (total of 1356 participants) on the incidence of infection and seven studies (1639 participants) on the duration of symptoms found the incidence of cold episodes in 65% in the group given placebo and 45% of the echinacea treatment group and a decrease in duration of symptoms of 1.4 days with treatment. The finding that those who took echinacea were about 30% less likely to catch a cold than those who did not, was presented by the authors as a '58% reduction in odds' (1.88 cf 0.81) but has been represented in the media as meaning echinacea use will result in 58% fewer colds.[45,46]

Generally, collective analyses of trials of echinacea are difficult to conduct due to the wide variation in products chosen for testing. Rigorous clinical trials of sufficient sample sizes and evaluation of standardised dosage forms are required before definitive recommendations on effectiveness can be made.

Treating Herpes simplex virus

Evidence: A year-long double-blind placebo-controlled crossover trial in 50 patients using a specific *E. purpurea* extract (*Echinaforce* by Bioforce AG), 800 mg twice daily, did not prevent or reduce frequency or duration of recurrent genital herpes in patients with herpes simplex virus (HSV) type 1 or 2.[47]

Other reported uses: Wound healing and chronic infections of the respiratory tract.

Notes

- Not to be confused with andrographis (*Andrographis paniculata*) referred to as 'Indian echinacea'.
- Avoid in patients with hypersensitivity to plants of the daisy family (Asteraceae).
- Generally well tolerated but may cause allergic rash or bronchospasm in atopic patients.
- Cease use 10 days prior to surgery.
- Advise patients with auto-immune diseases such as multiple sclerosis, systemic lupus erythematosus (SLE) or rheumatoid arthritis, to avoid or use echinacea with caution as it theoretically may have disease-stimulating activity and exacerbate symptoms.[18]

Pregnancy

A 2006 systematic literature review of evidence on the use, safety, and pharmacology of echinacea in pregnancy and lactation found there was good evidence that oral use in recommended doses during the first trimester did not increase the risk for major malformations[48], although some references recommend avoiding use.[9]

Breastfeeding

There are insufficient reliable data and conflicting advice regarding safety in breastfeeding.[16,18]

Interactions

Cytochrome P450 substrates: Preliminary evidence suggests that echinacea constituents inhibit intestinal CYP3A4 and induce hepatic CYP3A4 enzymes. A 2007 study found mild inhibition of CYP2C19, CYP2D6 and CYP3A4 and equivocal outcomes for CYP1A2 with different products. An example of the clinical significance of this interaction is the recommendation to cease echinacea 10 days prior to surgery due to a reduction in the expected plasma concentrations of midazolam.[18] See Table D.1, Section D.

Immunosuppressants (e.g. cyclosporin, tacrolimus, azathioprine): Although there are no case reports or outcomes from clinical trials, there is a theoretical risk of reduced immunosuppressant effect due to immunostimulatory activity. The risk of organ rejection may be remote, but clinically serious, and the combination should be avoided.

Common dosage ranges

Some trials have found only certain preparations more effective than placebo. The greatest evidence for efficacy has been with *E. purpurea*. Commercial products contain various species and plant parts (leaves vs root) that provide different constituents. For example, traditionally the root of *E. pallida* is used but the leaves of *E. purpurea*. Doses used in clinical trials and those recommended for 'echinacea' products vary widely.

Some products are standardised to echinacoside 5%, or cichoric acid. The active ingredient has not been identified, however, and standardisation may not be relevant in predicting clinical effectiveness.[16]

Tablets/capsules (dried powdered herb): 500–1,000 mg three times daily for 5–7 days is commonly recommended for upper respiratory tract infections (URTIs).[16]

Liquid extract (1:2): 3–6 mL daily of either *E. angustifolia* or *E. purpurea*. Started at first sign of URTI symptoms and continued for 7–10 days; it may be increased to 10–20 mL daily in acute conditions.[3]

General therapeutic use:

- *root. E. purpurea* 900 mg as an infusion, three times daily. *E. angustifolia* 1 g as an infusion or decoction several times daily
- *pressed fresh juice (herb). E. purpurea* 6–9 mL daily or equivalent
- *hydroethanolic extract (root). E. pallida* 900 mg daily or equivalent.

evening primrose oil

Oenothera biennis (seed oil)

Common uses

Atopic eczema

Evidence: The evening primrose oil constituent gamma-linolenic acid (GLA) has been widely evaluated for the treatment of inflammatory skin conditions. Results have generally been inconclusive, and it has been withdrawn for this use in the United Kingdom. Large trials[49] and a systematic review[50] have found insufficient evidence to support use[51], while a 2006 meta-analysis concluded symptoms such as pruritus, crusting, oedema and redness improved after four to eight weeks of treatment. The authors noted the magnitude of effect may have been confounded by concurrent steroid use.[52]

Premenstrual syndrome

Evidence: A systematic review of seven double-blind placebo-controlled RCTs failed to show any reduction in symptoms.[53]

Breast cancer

Evidence: A study with 38 breast cancer patients found a faster clinical response to tamoxifen 20 mg combined with 2.8 g GLA per day than with tamoxifen 20 mg alone, at both six weeks and six months.[54]

Schizophrenia

Evidence: Various open and placebo-controlled trials have reported mixed results. Generally, the trials were small, of limited duration and failed to show any clear benefit.[20]

Mastalgia

Evidence: A 1985 review of RCTs and open studies in 291 participants found improvement in 45% of patients with cyclical mastalgia and 27% with non-cyclical mastalgia.[55] A 2007 meta-analysis, however, found there was no advantage in pain relief over placebo.[56]

Other reported uses: Psoriasis, multiple sclerosis, diabetic neuropathy, Sjögren's syndrome and attention deficit hyperactivity disorder.

Notes

- Generally well tolerated but may cause occasional mild gastrointestinal discomfort, indigestion, nausea, headache and softening of stools.
- Lowering of seizure threshold has previously been reported, generally in patients with a history of epilepsy or concurrently taking medications known to lower seizure threshold.[20,18] A 2007 review of the data from 1980, however, found evening primrose oil safe in patients with epilepsy and the warnings unnecessary.[57]
- Patients taking tamoxifen should discuss their intended use of evening primrose oil with their medical practitioner.

Pregnancy

Insufficient reliable data. GLA may increase prostaglandin E levels[15], and safe use cannot be recommended.[16,20]

Breastfeeding

Evening primrose oil produces high levels of GLA in breast milk, although the clinical effect and safe level are unknown since significant amounts are normally present.[18,20]

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): Some references report a theoretical increased risk of bleeding[3,18], while others make no mention of the interaction in people taking evening primrose oil.[15,16,20]

Phenothiazines (e.g. thioridazine and trifluoperazine): There have been a number of case reports of evening primrose oil causing an increased risk of seizures in patients using phenothiazines. Advise patient to monitor for risk of seizures.

Common dosage ranges

Evening primrose oil may be standardised to 70% linoleic acid and 9% GLA.

Capsules: 4–8 g oil daily in divided doses for atopic dermatitis. 3 g daily in divided doses for cyclic mastalgia.[16] 250–500 mg GLA daily is used in some standardised products.

feverfew

Tanacetum parthenium (leaf)

Common use

Migraine prophylaxis

Evidence: Evidence is conflicting. A systematic review of five RCTs (involving 343 participants) found mixed results that overall did not provide convincing evidence for use in migraine prevention. Only mild and transient adverse events were reported.[58]

Other reported uses: Treatment of chronic migraine, fever, menstrual disorders and arthritic conditions.

Notes

- Avoid in patients with hypersensitivity to other members of the daisy family (Asteraceae).
- Side effects are generally mild and transient and may include mouth ulcers, dry and sore tongue, swollen lips and mouth, loss of taste and gastric upset.
- May increase risk of photosensitivity.[16]

Pregnancy and breastfeeding

Insufficient reliable data, although some references say to avoid use.[9,15,16,18]

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): Theoretically, concomitant use may increase the risk of bleeding. Feverfew constituents are thought to inhibit platelet aggregation and have an anticoagulant effect.[18] There has been a case report of increased prothrombin time in a patient taking feverfew for six months. Monitor for signs of bleeding and possible increase in INR.

Common dosage ranges

In the United Kingdom and Canada, standardised products contain at least 0.2% parthenolide. The most effective form or dose of feverfew is currently unknown. Clinical trials have used 50–114 mg powdered leaves, or the equivalent of 0.5 mg parthenolide, daily.[16]

fish oil/omega-3

essential polyunsaturated fatty acids

Oil from cod or shark liver is a rich source of vitamins A and D. Oil derived from the body of oily fish such as tuna, salmon and cod is low in the vitamins, but both are a rich source of the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

Common uses

Secondary cardiovascular disease prevention

Evidence: Numerous epidemiological studies, case-control series and RCTs have demonstrated fish oil can reduce the risk of major cardiovascular events, including sudden cardiac death and all-cause mortality. A 2008 review of three large RCTs involving a total of 32,000 participants found fish oil reduced the incidence of secondary cardiovascular events by 19–45%, although some research found no additional cardiovascular benefit occurred when the diet already included fish oil.[59–61] Multiple mechanisms have been proposed, including reduced triglyceride levels, reduced inflammation, slightly lowered blood pressure, reduced blood clotting, reduced tendency for the heart to develop abnormal rhythms[62] and reduction in atherosclerotic plaques.[63,64]

Hypertriglyceridaemia

Evidence: Numerous studies have established that fish oil supplementation can lower triglycerides, either alone or in combination with statin therapy. 5–7 g fish oil (3–4 g of DHA and EPA) daily has been found to lower triglyceride levels by 30–50% in patients with raised levels. A further 23–29% reduction has been observed with concomitant statin therapy.[65]

Atrial fibrillation

Evidence: A 2008 review of the cumulative data found significant benefits for the use of DHA and EPA in atrial fibrillation.[62]

Joint pain in rheumatoid arthritis and osteoarthritis

Evidence: Several RCTs have found high doses of fish oil supplements significantly reduced morning stiffness, tender joint count, and the need for NSAID therapy in patients with rheumatoid arthritis.[66–68]

Attention deficit hyperactivity disorder

A 2007 RCT in Australian children taking six capsules daily of a product containing 400 mg fish oil and 100 mg evening primrose oil (*eye q*), found improved outcomes, according to parental reporting, in cognitive function, hyperactivity, inattentiveness, and behaviour in children aged 7–12 years.[69]

Other reported uses: Depression, asthma, dermatitis, schizophrenia, diabetes, arrhythmia, Crohn's disease, ulcerative colitis, migraine and dry eyes.

Notes

- Generally well tolerated but may cause a fishy aftertaste, or 'fishy burp', halitosis, heartburn, dyspepsia, nausea, loose stools and rash. Take with food to reduce the fishy aftertaste; it has been proposed that refrigerating or freezing the capsules may reduce the 'fishy burp'.[18]

- May increase LDL by 10–30 % when used in high doses to treat high triglyceride levels.[59,70]
- Separate doses of orlistat and fish oil by at least two hours.[18] Refer to orlistat under 'Interactions'.
- Anti-thrombotic and anti-arrhythmic effects occur from the first weeks of use, but the heart rate–, blood pressure– and triglyceride–lowering effects may require months to years of therapy.[59,62]

Pregnancy

Considered safe in amounts usually consumed in food. Maximum safe dose during pregnancy has not been established. Due to the potential for toxicity with high doses of vitamin A, it is recommended that therapeutic doses of cod liver oil be taken under medical supervision.[15,18]

Breastfeeding

Likely to be safe when used orally and in recommended doses.[71]

Contraindications

Theoretically, individuals allergic to fish might also be allergic to fish oil supplements, although there are no reliable data. Until more is known, advise patients allergic to fish to avoid fish oil supplements or use them with caution.

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): Fish oils decrease platelet aggregation, and doses over 3 g daily taken with drugs that increase clotting time or inhibit platelet function may increase the risk of bleeding, particularly in the elderly. Monitor for bruising and overt bleeding.[16,18]

Orlistat: Orlistat binds to lipase in the gastrointestinal tract, reducing fat absorption, and there is a theoretical risk that orlistat may also decrease absorption of fatty acids from fish oil.

Common dosage ranges

Dosing of products should be according to DHA and EPA content, rather than total fish oil.

Capsules: 3–4 g fish oil (900–1200 mg DHA and EPA) daily or two to three fish meals per week for secondary cardiovascular disease (CVD) prevention; 1–2 g fish oil (30–600 mg of DHA and EPA) daily, or one to two fish meals per week for primary CVD prevention; 2–4 g DHA plus EPA daily has been recommended for hypertriglyceridaemia.

Clinical trials have used a range of larger doses for rheumatoid arthritis, commonly between 3–5 g DHA and EPA[16] or 15 mL of bottled fish body oil daily. Cod liver oil should be used at this dose only if the vitamin A and D have been removed.[68,72]

garlic

Allium sativum (bulb; preparations include aged garlic extract, powder, oil)

Common uses

Hypercholesterolaemia

Evidence: Results from clinical studies examining the ability of garlic to reduce LDL have been inconsistent. Studies in the 1990s reported modest benefits, but they are considered low-quality trials. A 2007 RCT in 192 patients with moderately high LDL compared fresh garlic and two different proprietary supplements with placebo. None of the garlic treatments was found to affect the lipid parameters after six months' treatment.[73]

Hypertension

Evidence: A meta-analysis of eight RCTs using a dried garlic powder preparation (*Kwai*) in a total of 415 participants found a small but statistically significant decrease in blood pressure, which was possibly dose and product dependent. Only three of the trials were conducted in hypertensive patients, so it was considered that, although garlic powder preparation may be of benefit in mild hypertension, there was insufficient evidence to recommend routine use.[74]

Cancer prevention

Evidence: Numerous population studies report increased dietary garlic decreases the risk of developing various cancers, although there appears to be a high level of bias and confounding factors.[18,20] More rigorous RCT trials using garlic supplements have not found data to support the recommendation of using high-dose garlic intake to prevent cancer.[75,76]

Other reported uses: Gastrointestinal motility disorders and coronary artery disease.

Notes

- Generally considered non-toxic but may cause malodorous breath, body odour, nausea, diarrhoea and vomiting. Cases of contact dermatitis have been reported.
- To reduce potential for bleeding complications, advise patients to cease use for at least one week prior to undergoing surgery.
- 'Odourless' products are available, some of which may have limited amounts of active ingredient. Therapeutic doses of these products, however, still produce a garlic smell in up to 50% of users.[15]

- Enteric coating can be used to protect the active constituents from degradation by stomach acid.

Pregnancy

While dietary use is considered safe in amounts usually consumed in food, therapeutic doses may be unsafe as garlic is reported to be an abortifacient.[77]

Breastfeeding

Garlic is secreted into breast milk and may affect feeding due to changed flavour.

Contraindications

- Therapeutic doses of garlic with certain Cytochrome P450 substrates (e.g. protease inhibitors such as ritonavir, saquinavir and cyclosporin) should be avoided until further data are available regarding safe use (see below).[18]
- Some sources suggest high doses are unsafe in children.

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): Anticoagulant activity may be enhanced due to increased fibrinolysis and decreased platelet aggregation. Studies show contradictory findings and variation in outcomes may be related to differences in the garlic preparations tested. A 2006 RCT comparing aged garlic extract in 52 patients did not find a significantly increased INR or increased risk of bleeding events.[78]

Patients receiving anticoagulant therapy should be monitored for signs of bleeding and possible increase in INR. Avoid doses of greater than 4 g daily.

Cytochrome P450 substrates: Research has found garlic oil in therapeutic doses can inhibit the activity of CYP2E1 by 39%.[79] Drugs metabolised by CYP2E1 include theophylline and paracetamol.

It is thought that garlic may also cause induction of the CYP3A4 isoenzyme, causing enhanced metabolism of CYP3A4 substrates such as:

- *Saquinavir*. Garlic has been found to decrease peak levels by 54% and mean trough levels by 49%.[80]
- *Ritonavir*. A four-day trial in 10 patients, however, found no change in the single-dose pharmacokinetics of ritonavir. The effect of longer treatment is unknown.[81]
- *Cyclosporin*. Potential to cause transplant rejection.

Patients taking drugs metabolised by P450 enzymes should be monitored for drug efficacy and adverse effects. See Table D.1, Section D.

Common dosage ranges

Activity has been associated with the sulfur-containing constituent alliin, found in varying levels in different formulations and products. Recent research suggests the need for the presence of the associated enzyme allicin or that other constituents are responsible for activity.[15,20] Variations in manufacturing processes result in wide differences in constituent levels.

Most of the studies of therapeutic garlic have used a dried powdered form containing 1.3% alliin, taken at a dose of 900 mg daily, equivalent to 10 mg of alliin.[15]

ginger

Zingiber officinale (rhizome)

Common uses

Pregnancy-induced nausea and vomiting

Evidence: An RCT in 70 women taking 1 g for four days found improvement in nausea and vomiting in 28 of the 32 in the ginger group, compared with 10 of the 35 in the placebo group.[82] (See 'Use in pregnancy' below.)

Sea sickness

Evidence: An RCT with 80 men taking 1 g ginger, found greater reduction in vomiting and cold sweating than placebo but no statistical reduction of nausea and vertigo.[83]

Other reported uses: Prophylaxis and treatment of nausea from chemotherapy or surgery and osteoarthritis.

Notes

- Avoid large doses in patients on existing cardiac, antidiabetic or anticoagulant therapy.
- To reduce potential for bleeding complications, advise patients to cease use for at least one week prior to undergoing surgery.
- Common side effects include abdominal discomfort, heartburn, diarrhoea, and a pepper-like irritant effect in the mouth and throat.[18]

Pregnancy

The safety of therapeutic ginger in pregnancy is controversial and the maximum safe dose is unknown. Some references note a concern that high doses have been shown to have abortifacient and uterine stimulant activity in animals.[15,16,20]

Breastfeeding

Insufficient reliable data. Avoid using amounts greater than those found in foods.[18]

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): Theoretically, ginger may inhibit thromboxane synthetase and decrease platelet aggregation, increasing the risk of bleeding, although the mechanism is unclear and results in trials vary.[16,18] Monitor for signs of bleeding or increase in INR.

Common dosage ranges

Dried powdered root: 250 mg four times daily has been used for morning sickness. 1 g taken between 30 minutes and four hours before travel has been used for motion sickness, or 500 mg two to four times daily for longer journeys.[16,20] Safety with long-term use of therapeutic doses has not been established.

ginkgo

Ginkgo biloba (leaf)

Common uses

Dementia (Alzheimer's, vascular or mixed dementia)

Evidence: A 2007 Cochrane review of 29 RCTs reported that the positive findings of early small studies had not been confirmed in more recent trials and that the rigour with which RCTs are carried out had improved considerably.[84] The review considered use of ginkgo to be safe, although a separate RCT published in 2008, studying 118 patients, resulted in six strokes and one transient ischemic attack in the group treated with 240 mg standardised *Gingko biloba* extract three times daily, compared with none in the placebo group.[85] As with the Cochrane review, no statistical difference was found in effectiveness of treatment.

Tinnitus

Evidence: A Cochrane review in 2004 identified only three good-quality trials and found no evidence that gingko is effective for tinnitus in patients with cerebral insufficiency.[86]

Intermittent claudication

Evidence: A meta-analysis of eight RCTs found *Gingko biloba* extract 120–160 mg daily superior to placebo. The size of the overall treatment effect was modest, however, and of uncertain clinical relevance.[87]

Prevention of macular degeneration

Evidence: A 1999 Cochrane review identified two small, short RCTs (20 and 99 participants) with some positive results but found there was insufficient evidence to support use in the prevention of age-related macular degeneration.[88]

Other reported uses: Asthma, hearing loss and altitude sickness.

Notes

- May cause gastrointestinal upset, headache, bruising and bleeding including subarachnoid haemorrhages.[18]
- A minimum of three months' treatment has been recommended for maximum efficacy.[3,15,16]
- To reduce potential for bleeding complications, advise patients to cease use for at least one week prior to undergoing surgery.
- Preliminary research has found an increase in insulin and C-peptide blood levels.[16]

Pregnancy

Theoretically, ginkgo may adversely affect pregnancy due to changes in bleeding. Avoid use as there are insufficient reliable safety data.[3,9,15,18]

Breastfeeding

Insufficient reliable data. Some sources recommend avoiding use.[9,15,18]

Interactions

Alprazolam: Ginkgo has been reported to decrease the absorption of alprazolam but not its elimination half-life.[89]

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): Case reports suggest concurrent use with drugs that increase clotting time or inhibit platelet function may increase the risk of bleeding, particularly in the elderly. Monitor for bruising and overt bleeding.[3,16,18]

Anti-epileptics and seizure threshold–lowering drugs (e.g. prochlorperazine, chlorpromazine): Seizures have been reported in patients predisposed to seizures or on medications that lower the seizure threshold.[18]

Cytochrome P450 substrates: Studies suggest gingko may mildly inhibit CYP1A2, CYP2D6, CYP2E1 and CYP2C9 and induce CYP2C19. There are conflicting reports about the influence on CYP3A4.[18,20] Until more is known, patients taking drugs metabolised by P450 enzymes should be monitored for drug efficacy and adverse effects. See Table D.1, Section D.

Donepezil: A study in Alzheimer's patients taking ginkgo for at least five months showed no effect on the pharmacokinetics of donepezil.[90]

Haloperidol: A 2001 study of the addition of ginkgo to haloperidol therapy in treatment-resistant patients with

schizophrenia found increased effectiveness and reduced side effects of the antipsychotic.[91]

Common dosage ranges

Tablets/capsules: 80–240 mg of a 50:1 standardised leaf extract (containing 22–27% flavone glycosides and 5–7% terpene lactones) daily in two to three doses has been used in studies.[3,15,16]

ginseng, Asian and American

Panax ginseng (Asian or Korean ginseng), *Panax quinquefolius* (American ginseng) (root)

Ginsenosides are the active constituents found in extracts of *Panax ginseng* (e.g. ginsenosides Rh2 and Rg3) and have been extensively studied. American ginseng lacks the Rf ginsenoside found in Asian ginseng. Siberian ginseng (*Eleutherococcus senticosus*), often promoted as a cheaper alternative, does not contain ginsenosides.[16]

Common uses

Asian ginseng has been used to enhance physical performance, psychomotor performance and cognitive function, immunomodulation. It has been used in the treatment of Type 2 diabetes mellitus and herpes simplex type 2 infections.

Evidence: There are many clinical trials involving *Panax ginseng*, but few are considered rigorous. A systematic review of 16 RCTs[92] and a review of nine studies, assessing the possible impact of Asian ginseng on health-related quality of life[93], have not demonstrated a beneficial effect. The available evidence is not compelling for any of the reported uses.

Notes

- Not to be confused with Siberian ginseng (*Eleutherococcus senticosus*).
- Generally well tolerated in recommended daily dosages. May cause mild and transient headache, insomnia and gastrointestinal disorders. Less commonly, may cause mastalgia, vaginal bleeding, amenorrhea, tachycardia and palpitations, hypertension, hypotension, oedema, decreased appetite, diarrhea, hyperpyrexia, pruritus, rose spots, headache, vertigo, euphoria and mania.[18]
- Some references suggest a ginseng-free period of two to three weeks every 30–60 days.[15,16,20]

Pregnancy

Ginsenoside Rb1, an active constituent of American ginseng, may have teratogenic effects. Avoid use.[18,20]

Breastfeeding

Insufficient reliable data.[18,20]

Contraindications

- Avoid use in infants and children as there is a report of death in an infant.[18]
- Only use where potential benefit is not outweighed by the potential harm for patients with cardiac conditions, diabetes and hypertension or hypotension.

Interactions

Cytochrome P450 substrates: There is some evidence that *Panax ginseng* can mildly inhibit the cytochrome P450 CYP2D6 and CYP1A enzymes.[3,18] Eighteen days' treatment with ginseng resulted in a 53% increase in nifedipine plasma levels, suggesting the inhibition of CYP3A4 enzymes.[94] Until more is known, patients taking drugs metabolised by P450 enzymes should be monitored for drug efficacy and adverse effects. See Table D.1, Section D.

Digoxin: Depending on the assay technique used, Asian and American ginseng may cause an apparent alteration in serum digoxin levels.[95] Patients on digoxin should be warned of a potential to alter plasma digoxin test results. Monitor for any adverse effects if the combination is used.

Hypoglycaemic agents: A study found a single dose of *Panax ginseng* increased postprandial glucose levels, whereas *Panax quinquefolius* reduced postprandial glucose levels.[96,97] Monitor blood glucose levels as the dose of the hypoglycaemic agent may need to be adjusted.

Phenelzine: Two case reports of suspected interaction have been documented.[18,20] Theoretically, *Panax ginseng* may interfere with monoamine oxidase inhibitor therapy and potentially worsen depression. Avoid combination.

Warfarin: Reports are conflicting with some case reports of decreased INR[98], but a clinical study found no effect of *Panax ginseng* on warfarin pharmacokinetics, pharmacodynamics, or clotting status after seven days.[99] *Panax quinquefolius* decreased INR values and warfarin plasma concentrations in one study.[100] Monitor INR within three days of starting concomitant therapy and reassess need for concomitant use if INR altered.

Common dosage ranges

'White' ginseng is prepared by drying the raw root, while 'red' ginseng is steamed prior to drying, with the aim of increasing the ginsenoside concentration and potency. Doses used in clinical trials vary.

Tablets/capsules: 100–200 mg of standardised extract (G115—4% ginsenoside) once or twice daily for four to 12 weeks.[16,20]

Dried root: 0.5–2 g. Some references recommend a maximum of 1 g daily for long-term use.[15,16,20]

ginseng, Siberian

Eleutherococcus senticosus (root and rhizome)

Siberian ginseng is technically not a species of ginseng but is thought to have activity comparable to that of Asian and American ginseng.

Common use

Chronic fatigue syndrome

Evidence: An RCT in 96 participants using standardised extract of 2.24 mg eleutherosides (B and E) daily did not find evidence of efficacy.[101] Available evidence is not compelling for any of the reported uses.

Other reported uses: Herpes simplex virus type 2 and heart disease.

Notes

- May cause slight drowsiness, anxiety, irritability, melancholy, mastalgia and uterine bleeding.[18]
- Some literature recommends avoiding the use for patients with blood pressure higher than 180/90 mm Hg and use with coffee, antipsychotic drugs or hormonal treatments, although there is no supporting scientific research.[18,20]
- Some references suggest a ginseng-free period of two to three weeks every 30–60 days.[15,16,20]

Pregnancy and breastfeeding

Animal studies have not reported any teratogenic effects. In view of the many documented pharmacological actions, use during pregnancy and breastfeeding should be avoided.

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): Dihydroxybenzoic acid, a constituent of Siberian ginseng, may inhibit platelet aggregation.[102] Concomitant use may increase the risk of bleeding.

Cytochrome P450 substrates: A 14-day study using recommended doses found no effect on the activity of CYP3A4 or CYP2D6.[103] Preliminary evidence suggests that standardised extracts of Siberian ginseng might inhibit CYP2C9 and CYP1A2.[104] Until more is known, patients taking drugs metabolised by P450 enzymes should be monitored for drug efficacy and adverse effects. See Table D.1, Section D.

Digoxin: There is a case report of Siberian ginseng causing elevated serum digoxin levels, although a study found that constituents of Siberian ginseng may artificially raise serum digoxin levels depending on the assay method.[20,105] Patients on digoxin should be warned of a potential to alter plasma digoxin levels. Monitor for any adverse effects if the combination is used.

Common dosage ranges

Dried extract: Varying products and strengths are available and dose recommendations vary with formulation and constituent. For example, a daily dose may be 400 mg standardised to eleutheroside E 0.3%[18] or 2.24 mg of a standardised extract providing eleutherosides (B and E).[20]

Dried root: 0.6–3 g daily for up to one month has been recommended.

glucosamine

(chitosamine, glucosamine sulfate, and glucosamine hydrochloride)

Glucosamine is an amino sugar precursor of glycosaminoglycans, proteoglycans and glycolipids.

Common use

Osteoarthritis

Evidence: There is currently conflicting evidence about the effectiveness of glucosamine, with the early evidence generally supporting the use of the hydrochloride salt, primarily in a combination product containing glucosamine hydrochloride, chondroitin sulfate and manganese ascorbate.[16] An RCT with 1583 participants (the GAIT trial) found glucosamine alone or in combination with chondroitin sulfate did not reduce pain in osteoarthritis of the knee more effectively than placebo (which had a positive response rate of 60%).[106] A Cochrane review including recent high-quality trials pooled data from 20 RCTs in 2570 participants and found no evidence that pain improved with glucosamine over placebo when taken for two to three months.[107] A 2007 12-month RCT in 89 participants found a glucosamine–chondroitin combination was not superior to placebo in improving function, pain or mobility.[108]

Other reported uses: Back pain and glaucoma.

Notes

- Glucosamine is often derived from the exoskeletons of crustaceans. Many sources note a concern that use may precipitate an allergic reaction in people sensitive to shellfish, although the allergic reaction is caused by IgE antibodies to antigens in the meat of shellfish, not antigens in the shell. There are no documented reports of allergic reaction to glucosamine in shellfish-allergic patients.[18] Patients with severe allergy, however, may wish to use a form not derived from shellfish.[3]

- There is some evidence that patients with underlying impaired insulin sensitivity are at risk of glucosamine exacerbating insulin resistance[109], although clinical studies have not shown an adverse affect on HbA_{1C} in people with Type 2 diabetes.[110]
- May cause constipation, diarrhoea, drowsiness, epigastric pain and discomfort, headache, heartburn, nausea and rash.
- Use glucosamine hydrochloride with caution in renal impairment as it is renally excreted.[16]
- Products complexed with potassium chloride may raise potassium levels and should be used with caution in the elderly, people with renal impairment, and patients taking potassium-sparing diuretics, ACE inhibitors or potassium supplements or with existing raised potassium levels.[111]
- There is no consensus regarding the ability of glucosamine to slow disease progression. Advise patients to continue using standard analgesics for the initial four to six weeks of treatment because the onset of any pain relief may be delayed.[3]

Pregnancy and breastfeeding

Insufficient reliable data.

Interactions

Warfarin: Patients should be advised that the combination may cause an increase in INR and that they should inform their medical practitioner.[112,113] Check INR within three days of commencing glucosamine since warfarin dose may need to be adjusted. Monitor at regular intervals thereafter.

Common dosage ranges

The clinical equivalence of different dose forms and salts of glucosamine has not yet been established.

Tablets/capsules: 500 mg three times daily has been used alone, or in combination with chondroitin sulfate 400 mg three times daily.

goldenseal

Hydrastis canadensis (rhizome and rootstock)

Common uses

Oral—upper respiratory tract infections, nasal congestion, diarrhoea, gastritis, peptic ulcers, heart failure. Topical—mouthwash, conjunctivitis and earache.

Evidence: Rigorous clinical investigation of efficacy and safety is limited.[20] There is insufficient scientific evidence to support the use of goldenseal for any of the reported uses.[16]

Notes

- Berberine, an active alkaloid constituent of goldenseal, has been associated with ventricular tachycardia/torsades de pointes in patients with heart failure. Use with caution in cardiovascular disease and for those at risk of developing arrhythmias.[16]
- Avoid use in renal impairment due to decreased alkaloid excretion.[3]
- Berberine is generally well tolerated when used topically. Oral use may cause stomach upset and doses higher than 500 mg berberine may cause lethargy, dizziness and dyspnoea.[3] Toxic doses may result in convulsions, delirium, hyperreflexia and paralysis.[16]

Pregnancy

Berberine is thought to cross the placenta and may harm the fetus. Avoid use.[18,20]

Breastfeeding

Several cases of kernicterus and infant death have occurred when berberine has been ingested by a nursing mother.[114] Avoid use.

Contraindications

Berberine has been shown to displace bilirubin from albumin. Avoid use in newborns, infants with raised bilirubin levels and individuals with glucose-6-phosphate deficiency as fatalities have been reported.[16,18]

Interactions

Cytochrome P450 substrates: Goldenseal may inhibit CYP2D6. There are conflicting outcomes on the influence on CYP3A4.[16,115] Until more is known patients taking drugs metabolised by P450 enzymes should be monitored for drug efficacy and adverse effects. See Table D.1, Section D.

P-glycoprotein substrates: There is conflicting evidence about the effect of goldenseal on p-glycoprotein. A small 2007 study found goldenseal increased the $C_{(max)}$ of digoxin by about 14% but caused no other changes to the pharmacokinetics.[116]

Common dosage ranges[3]

Oral use:

- *tincture (1:3).* 2.0–4.5 mL daily or 15–30 mL per week.
- *dried root and rhizome.* 1.5–3 g daily by decoction.

gotu kola

Centella asiatica (whole herb)

Common use

Chronic venous insufficiency (varicose veins)

Evidence: Preliminary evidence from small trials has found a small to moderate benefit in capillary filtration rate and ankle oedema.[117] Other uses of gotu kola are not supported by scientific evidence.

Other reported uses: Chronic hepatic disorders, rheumatism, anxiety. Topically used for wound healing and reducing scarring.

Notes

- Topical use may cause a burning sensation or contact dermatitis.
- Oral use may cause gastric irritation, pruritus and nausea.
- May be hepatotoxic in some patients. Three cases of jaundice have occurred after 20, 30 and 60 days of use. All patients improved when gotu kola was discontinued.[118] Avoid use in patients with liver disease.

Pregnancy and breastfeeding

Insufficient reliable data.[16,18]

Interactions

Concomitant use with other potentially hepatotoxic products (including other CAMs such as comfrey, DHEA, germander, niacin, pennyroyal oil, red yeast) may theoretically increase the risk of liver damage.[18]

Common dosage ranges

Various dosage regimens have been used. A daily dose of 60–180 mg of gotu kola extract has been used for venous insufficiency.

grape seed

Vitis vinifera (seed and leaf)

Common use

Chronic venous insufficiency

Evidence: A 12-week RCT in 260 patients with chronic venous insufficiency using up to 720 mg daily of a specific grape leaf extract (AS 195), found oedema of the legs decreased after six weeks. Patients also reported decreases in subjective symptoms such as tired or heavy legs, tension, and tingling and pain.[119]

Other reported uses: Fluid retention, eye strain, gastric acidity, antioxidant for circulatory disorders, inflammatory conditions and varicose veins.

Notes

- Generally well tolerated.
- One study found that patients with hypertension and taking both vitamin C 500 mg and 1,000 mg grape seed polyphenols daily had significantly increased systolic and diastolic blood pressure.[120] The mechanism or clinical significance is uncertain.
- Cease use seven days prior to surgery.

Pregnancy and breastfeeding

Insufficient reliable data.

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): Theoretically, the tocopherol content of grape seed oil may increase the anticoagulant effect of warfarin and the risk of bleeding. Procynidin oligomers, an active constituent, are thought to inhibit platelet aggregation.[3,18] Use with caution; monitor for bleeding and any INR changes.

Cytochrome P450 substrates: Grape juice is thought to induce cytochrome CYP1A2 metabolism.[18] Until more is known, patients taking drugs metabolised by P450 enzymes should be monitored for drug efficacy and adverse effects. See Table D.1, Section D.

***Lactobacillus acidophilus*:** Grape anthocyanins may inhibit the growth of *Lactobacillus acidophilus*. Concurrent use may theoretically prevent *L.acidophilus* colonisation.[18] Avoid concurrent use.

Common dosage ranges

Tablets/capsules: 360–720 mg (standardised red vine grape extract AS 195) daily for chronic venous insufficiency. 75–300 mg (grape seed extract) daily for three weeks, followed by a maintenance dose of 40–80 mg daily, or proanthocyanidin 150–300 mg daily have also been used.[3,18]

green tea

Camellia sinensis (leaf)

Common uses

Prevention of cancer, dental caries, arthritis, asthma, hypercholesterolaemia and atherosclerosis and weight loss.

Evidence: Rigorous clinical investigation of efficacy is limited and there is insufficient scientific evidence to support the reported uses.[16]

Notes

- Green tea contains a significant quantity of caffeine, although less than black tea or coffee, and is a

source of the polyphenolic antioxidants known as catechins.

- Doses of more than 500 mg caffeine daily may cause anxiety, agitation or detrusor muscle instability (unstable bladder).[16]
- Caffeine increases urine and sodium loss, and the effect may be additive when taken with diuretics.[16]
- Use with caution in hepatic impairment due to increased risk of caffeine toxicity and reports of hepatotoxicity.[16,18]
- Green tea may increase liver function test findings including alkaline phosphatase, aspartic acid transaminase (AST, SGOT) alanine aminotransferase (ALT, SGPT), and bilirubin.[18,121]

Pregnancy

The use of caffeine during pregnancy is controversial. Caffeine crosses the placenta; moderate consumption is likely to be safe, although taking more than 200 mg daily is associated with an increased risk of miscarriage[122] and low birth weight.[16,18]

Breastfeeding

The caffeine in green tea is readily transferred to breast milk. Newborns metabolise caffeine very slowly, with a half-life of 97.5 hours compared with 2.6 hours in a 6-month-old. Maximum dose should be 300 mg daily, preferably timed for after feeding the infant.[123]

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): A case report found large doses of green tea reduced the effects of warfarin and INR levels, possibly due to vitamin K content.[124] Caffeine is, however, also reported to have antiplatelet properties and may increase the risk of bleeding.[18] Monitor INR closely if green tea is commenced in a patient taking warfarin.

Cytochrome P450 substrates: Caffeine is metabolised in the liver by CYP1A2. Receptor competition may cause increased caffeine blood levels or half-life.[16] Preliminary research shows green tea has no effect on CYP3A4 or CYP2D6.[125]

Lithium: Abrupt caffeine withdrawal can increase serum lithium levels.[18]

Theophylline: Caffeine may reduce metabolism and increase serum theophylline levels.

Common dosage ranges

Infusion: One cup of brewed tea (approximately one teaspoon of tea leaves in 250 mL boiling water) contains 50–60 mg caffeine and 80–100 mg polyphenols. Doses of green tea vary significantly, with one to three cups daily commonly recommended[15,18], although up to 10 cups have been used. Strength or cup size is not standardised.[16,18]

guarana

Paullinia cupana (seed)

Common uses

Psychostimulant

Evidence: Results from small studies are conflicting as to whether the primary activity of guarana is due solely to its high caffeine content. A 2007 trial in 26 participants found 37.5 mg and 75 mg of a standardised guarana extract (PC-102) produced more positive cognitive effects than doses of 150 mg and 300 mg, suggesting that the effects are not attributable solely to caffeine.[126]

Weight loss

Evidence: Clinical studies have generally investigated guarana in combination with other herbs, and more evidence is needed to evaluate guarana for use in weight loss.[3,18]

Other reported uses: Enhancing athletic performance, an adjunct in the treatment of headache, aphrodisiac and diuretic.

Notes

- Excessive consumption of energy drinks that contain guarana may contribute (alone or in combination with caffeine and taurine) to seizures.[127]
- Caffeine increases urine and sodium loss and the effect may be additive with diuretic use.[16]
- Doses of more than 500 mg caffeine daily may cause anxiety, agitation or detrusor muscle instability (unstable bladder).[16]
- Avoid high caffeine levels in patients with peptic ulcer disease, hypertension, angina or arrhythmias.
- Avoid or use cautiously in patients with cardiovascular disease, gastric ulcer, chronic headache or diabetes.

Pregnancy

Caffeine in guarana crosses the placenta, and the use of caffeine during pregnancy is controversial. Moderate consumption is likely to be safe, although taking more than 200 mg daily is associated with an increased risk of miscarriage[122] and low birth weight.[16,18]

Breastfeeding

The caffeine in guarana is readily transferred to breast milk. Newborns metabolise caffeine very slowly, with a half-life of 97.5 hours compared with 2.6 hours in a

six-month-old. Maximum consumption is 300 mg daily, preferably timed for after feeding the infant.[123]

Interactions

Antihypertensives: CNS stimulation may increase heart rate and blood pressure. Monitor blood pressure.

CNS depressants: Stimulant effects of xanthine constituents may reduce effectiveness of treatment.

Diuretics: There is a potential additive effect due to the xanthine content. Recommend adequate fluid intake.

Lithium: Abrupt caffeine withdrawal can increase serum lithium levels.[18]

Theophylline: Caffeine may reduce metabolism and increase serum theophylline levels.

Warfarin: Guarana aqueous extracts have decreased platelet aggregation, suggesting a theoretical increased risk of bleeding.[128] Monitor INR and for signs of bleeding.

Common dosage ranges

Dose is highly variable depending on the product. 800 mg guarana contains approximately 30 mg caffeine. Daily dose should not exceed 3 g guarana powder or equivalent.[41]

hawthorn

Crataegus laevigata, C. monogyna or C. folium (berry, flower or leaf)

Common use

Chronic heart failure

Evidence: A 2008 Cochrane review of pooled data from 10 RCTs (total of 855 chronic heart failure patients) found hawthorn extract significantly improved exercise tolerance, ejection fraction, shortness of breath and fatigue compared with placebo. The findings supported the combined use of hawthorn extract with conventional treatments for chronic heart failure.[129]

Other reported uses: Atherosclerosis, angina, rheumatism, hyperlipidaemia, hypertension, and orthostatic hypotension.

Notes

- Avoid in patients hypersensitive to members of the *Rosaceae* family.[16]
- Patients taking cardiovascular medications such as antihypertensives, vasodilators and cardiac glycosides should discuss the possible risk of harm when taking hawthorn supplements with their medical practitioner prior to use and be carefully monitored for drug efficacy and adverse effects.
- Generally well tolerated at recommended doses. May cause mild and transient nausea, dizziness and gastrointestinal complaints. High doses may cause hypotension, arrhythmias and sedation.
- Use cautiously in the elderly and individuals prone to hypotension.[16]

Pregnancy and breastfeeding

Insufficient reliable data, although it is thought that some hawthorn extracts may reduce the tone of uterine muscle.[20] Avoid use.[16,18]

Interactions

Antihypertensives, phosphodiesterase inhibitors and nitrates: Use may result in additive vasodilation and hypotension.[18] Monitor for signs of hypotension.

Beta-blockers and calcium channel blockers: Use may have additive effects on blood pressure and heart rate. Monitor for signs of hypotension.

Digoxin: Theoretically, hawthorn may potentiate the inotropic effects of cardiac glycosides, requiring a reduction in digoxin dose. One study, however, found the combination caused a slightly decreased AUC and peak concentration of digoxin that was not statistically significant.[130] Digoxin dose may need to be decreased if hawthorn is commenced, or conversely, increased if hawthorn is ceased.

Common dosage ranges

Standardised extract: Used for congestive heart failure, maximum effect may not be seen for six to 12 weeks of treatment.[18]

- WS 1442 (standardised to 18.75% oligomeric proanthocyanidins): 60 mg three time daily or 80 mg twice daily has been used in trials.[16]
- LI 132 (standardised to 2.2% flavinoids): 100–300 mg three times daily has been used in trials.[16]

horse chestnut

Aesculus hippocastanum (seed)

Common use

Chronic venous insufficiency (varicose veins)

Evidence: A 2006 Cochrane review of six RCTs (involving 543 participants) found that two to 16 weeks of treatment with horse chestnut seed extract reduced leg pain, volume and circumference, as well as oedema and pruritus.[131]

Other reported uses: Diarrhoea, fever, phlebitis, haemorrhoids and prostate gland enlargement.

Notes

- Avoid in patients hypersensitive to members of the Hippocastanaceae plant family.
- Avoid in patients with known bleeding disorders.
- Adverse events reported in clinical trials were usually mild and infrequent. Gastrointestinal irritation may occur with large doses.
- There have been isolated cases of renal and hepatic toxicity and anaphylactic reactions.[16]
- Cease 7 days prior to surgery.

Pregnancy and breastfeeding

Insufficient reliable data.[16,18]

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): Horse chestnut may inhibit platelet aggregation and concomitant use may increase the risk of bleeding. Monitor for signs of bruising or bleeding. Patients on warfarin should advise their medical practitioner and have INR closely monitored.[16,18]

Common dosage ranges

Products are normally standardised to contain 16–20% triterpene glycosides, calculated as escin content.

Seed extract: products containing 50–100 mg escin has been used twice daily.[3]

kava

Piper methysticum (rhizome and root)

Common uses

Anxiety

Evidence: While some trials have found kava was no more effective than placebo, other studies have found 60–240 mg kavalactones daily from WS-1490 standardised extract statistically superior to placebo in reducing anxiety. Seven RCTs in a 2003 Cochrane meta-analysis found a small but statistically significant reduction in anxiety using the Hamilton Anxiety (HAM-A) scale.[132] The risk of hepatotoxicity and the uncertainty of long-term safety may, however, outweigh any benefits.

Peri- and post-menopausal anxiety

Evidence: An RCT in 40 women using either 100 mg kava extract (55% kavain) with hormone replacement therapy or HRT plus placebo for six months, found HAM-A score reduced in all groups, with a significantly greater reduction in the kava group.[133] The risk of hepatotoxicity and the uncertainty of long-term safety may, however, outweigh any benefits.

Insomnia

Evidence: A 2005 RCT with 391 participants found those taking kava (100 mg kavalactone three times daily) or valerian (6.4 mg valerenic acid an hour before bedtime) for four weeks had no greater improvements in anxiety symptoms or sleep over placebo.[134]

Benzodiazepine withdrawal

Evidence: A well-conducted five-week RCT with 40 participants titrated kava extract WS-1490 upwards to 300 mg daily while reducing the benzodiazepine dose. Upwardly titrating kava over one week while tapering the benzodiazepine over two weeks produced fewer withdrawal symptoms and less anxiety than for those on placebo.[135]

Notes

- May cause headache, restlessness, tiredness, stomach complaints, disturbances of visual accommodation, tremor, and a hangover effect. Kava dermopathy (a reversible dry, scaly dermatitis) is associated with chronic high use.
- Long term traditional or ceremonial use of high doses has been associated with case reports of renal dysfunction, thrombocytopenia, neutropenia and pulmonary hypertension.
- High doses have caused isolated cases of acute urinary retention, parkinsonism, altered mental status and ataxia. Use with caution in peri-operative patients and those with renal disease.
- There are case reports of acute liver failure, liver transplant and death resulting from kava use.[136] It is thought that individuals with deficiency in the cytochrome P450 CYP2D6 isoenzyme (those known as 'poor metabolisers') may be at increased risk of hepatotoxicity.[18] Some references propose that the extraction methodology may be responsible, as the alcohol and acetone extracts have been linked to liver toxicity but not the aqueous extracts.[3,18] Advise patients to monitor for yellowing of the skin, fatigue and dark urine; to have liver function routinely monitored; and that symptoms have occurred after as little as three to four weeks of use.

Pregnancy and breastfeeding

There are insufficient reliable data, although there is concern that the hepatotoxic pyrone constituents in kava may cause loss of uterine tone or pass into breast milk. Avoid use.[16,18]

Contraindications

- Kava has been reported to antagonise the effect of dopamine and has caused severe, rapidly progressive, persistent extrapyramidal effects.[3,16,18] Avoid use in Parkinson's disease.

- Kava may exacerbate hepatitis in patients with a history of recurrent hepatitis.[18] Avoid use in hepatic impairment and concurrent use with other hepatotoxic drugs.
- There is concern that concomitant use of kava and alcohol may further increase the risk of hepatotoxicity.[18] High doses of kava may also potentiate the effect of alcohol on subjective measures of cognition, sedation, intoxication and willingness to drive, as well as measurable activities of attention, concentration and accuracy. Individuals taking kava should avoid alcohol if driving or carrying out other tasks requiring concentration and attention.[137]

Interactions

Anxiolytics (e.g. benzodiazepines): It is thought kava may potentiate central nervous system depression via a direct effect on GABA receptors. There has been a case report of the possible interaction between alprazolam and kava resulting in coma.[138] Avoid combination, monitor for signs of excessive CNS depression.

Cytochrome P450 substrates: Preliminary evidence suggests kava significantly inhibits cytochrome P450 CYP1A2, CYP2C19, CYP2C9, CYP2D69 and CYP2E1. There are contradictory results for the influence on CYP3A4 and CYP2D6.[16,18] The strength of the effect varies between products, with commercial products showing greater inhibition than traditional preparations.[20] Until more is known, patients taking drugs metabolised by P450 enzymes should be monitored for drug efficacy and adverse effects. See Table D.1, Section D.

Levodopa: Kava may reduce effectiveness via dopamine receptor antagonism.[139] Avoid combination as it may exacerbate Parkinson's disease or increase risk of dyskinesia.

P-glycoprotein substrates (e.g. ketoconazole, cimetidine, diltiazem, verapamil, corticosteroids, erythromycin): Theoretically, kava may inhibit the P-glycoprotein mediated drug efflux and potentially increase levels of drugs that are P-glycoprotein substrates. Until more is known, kava should be used cautiously in people taking P-glycoprotein substrates.

Common dosage ranges

Kava exists in numerous varieties and varying potencies, and only preparations standardised to kavalactone content should be used for therapeutic purposes, which generally should not exceed three months.

In August 2003, in response to concerns about hepatotoxicity, the Therapeutic Goods Administration limited the maximum amount of *Piper methysticum* permitted per dosage form in Australia. A single tablet or capsule may contain a maximum of 125 mg of the active consistuent kavalactones. Each tea bag is limited to 3 g of dried rhizome. All kava products, in any dosage form, must comply with a maximum daily dose of not more than 250 mg of kavalactones.[136] Kava is classified as a prohibited import under the Customs (Prohibited Imports) Regulations.

Tablets/capsules: standardised extract (70% kavalactone) 100 mg (70 mg kava-lactones) three times daily has been used in trials for anxiety disorders.[18]

kelp/kelpware/bladderwrack

Fucus vesiculosus

Laminaria, Fucus, Macrocystis and *Ascophyllum* species are referred to as brown seaweeds. The generic term 'kelps' technically refers to species of *Laminaria* and *Macrocystis*, although it is often also used in reference to *Fucus* species.

Common uses

Kelp (*Fucus vesiculosus*) has been used to treat underactive thyroid, hypertension and hyperglycaemia and as an anticoagulant and antirheumatic agent. The available evidence is not compelling for any of the reported uses.

Notes

- Contains up to 600 mircograms iodine per gram and use may induce or exacerbate hyperthyroidism.[16] Use with caution in patients with thyroid disorders.
- High doses of kelp have been shown to reduce T_3 levels, elevate TSH levels and increase TRH response after four weeks.[140]
- Avoid in renal impairment or heart failure due to the potentially high sodium content and heavy metal contamination.[16]
- Preliminary research suggests bladderwrack may impair fertility.[141] Avoid use in women trying to conceive.
- There have been case reports of abnormal erythropoiesis, acneiform eruptions, autoimmune thrombocytopenia and bleeding.[142,143]
- Not to be confused with bladderwort.
- Cease 7 days prior to surgery.

Pregnancy and breastfeeding

Avoid use due to the high iodine content and potential effect on the thyroid and possible contamination with toxic heavy metals.[9,16,18]

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): An increased risk of bruising and bleeding may occur due to heparin-like activity of its fucoidan component.[16,18]

Thyroxine: Patients receiving thyroid medication or with a thyroid condition should have thyroid function tests closely monitored if this combination is used.

Common dosage ranges

There are no data from high-quality human trials on the safety or efficacy of any specific dose. Not all products list the iodine content.

Tablets/capsules (alcohol extract): 200–600 mg daily has been used traditionally.[16]

Alcoholic liquid extract (1:1 in 25% alcohol): 4–8 mL three times daily.[20]

liquorice

Glycyrrhiza glabra (root and rhizome)

A wide range of pharmacological effects have been attributed to liquorice confectionery, which is frequently flavoured with anise oil and may contain minimal levels of the active constituent glycyrrhizin. A UK study found the glycyrrhizin content of confectionery products varied between 0.26 and 7.9 mg/g, while 'therapeutic products' such as those purchased in a community pharmacy contained 0.3 to 47.1 mg/g.[144] There is thus some overlap between confectionery and therapeutic products. This monograph refers to all products containing a therapeutic amount of glycyrrhizin.

Common uses

Therapeutic doses of liquorice have been used to treat bronchial catarrh, bronchitis, chronic gastritis, peptic ulcer, constipation, colic and primary adrenocorticoid insufficiency. The available evidence is not compelling for any of the reported uses.

Notes

- Avoid long-term use and large doses in patients with hypertension, hypokalaemia, arrhythmias and cardiovascular, renal or hepatic disease. Consumption, if necessary, should be carefully monitored.
- Liquorice can decrease serum testosterone and increase 17-hydroxyprogesterone, causing decreased male libido and sexual dysfunction.[145]
- Side effects are generally more likely with daily doses equivalent to glycyrrhizin greater than 100–400 mg and may include headache, lethargy, muscle pain and weakness, pseudoaldosteronism, asthma, heart failure, cardiac arrest, and ventricular tachycardia.[3]
- Electrolyte changes may include sodium and water retention, hypokalaemia and metabolic acidosis. Generalised oedema may cause hypertension.[16]
- Recommend that prescription medicines be taken an hour before, or two hours after, liquorice as it may increase absorption and side effects of some drugs (e.g. nitrofurantoin).[16]

Pregnancy

Avoid use due to mineralocorticoid action.[9] Consumption of 500 mg glycyrrhizic acid per week (about 250 g of liquorice) is related to reports of lower gestational age at birth.[15,18,146]

Breastfeeding

Insufficient reliable data.[15,16]

Contraindications

Due to potential symptoms of primary hyperaldosteronism (sodium and water retention) and hypokalaemia. Use should be avoided by individuals with existing coronary heart disease or congestive heart failure, and used cautiously in hypertension.[16,20]

Interactions

De-glycyrrhizinised liquorice may be involved in fewer interactions.

Antihypertensives: Glycyrrhizin constituent can cause pseudoaldosteronism (sodium and water retention), with a subsequent increase in blood pressure. Monitor blood pressure in hypertensive patients receiving medication. Avoid high doses for prolonged periods (more than four to six weeks).

Cytochrome P450 substrates: Preliminary studies propose that liquorice may inhibit CYP2B6 and CYP2E1 and induce CYP1A1[3,15]; and there are conflicting results for CYP3A4, CYP2C9.[18] Until more is known patients taking drugs metabolised by P450 enzymes should be monitored for drug efficacy and adverse effects. See Table D.1, Section D.

Digoxin and diuretics: Liquorice constituents may potentiate therapeutic action due to potassium depletion. Avoid combination or monitor digoxin and potassium concentrations closely.

Prednisolone: One study found reduced drug clearance and elevated plasma concentrations.[147] Theoretically, liquorice may also potentiate the effects of corticosteroids. Monitor for excessive corticosteroid adverse effects.

Common dosage ranges

As noted, there is a large variation in the glycyrrhizin content of liquorice preparations, typically around 2–3 mg/g (0.2–0.3% w/w). There is also variation in response to liquorice. Individuals with hypertension, heart disease, kidney disease or a high salt intake are more sensitive to its effects. The mineralocorticoid effect is a saturable process and is not dose dependent.

Liquorice extract (BPC 1973)[20]: 0.6–2.0 g.

Tablets (de-glycyrrhizinised liquorice): 380–1140 mg three times daily, 20 minutes before meals.

Dried root: 5–15 g (200–600 mg glycyrrhizin) daily. This is considered a large dose, and it is recommended treatment be limited to a maximum of one week when used for gastric and duodenal ulcers and gastritis.[15,16] 1.5–5 g (60–200 mg glycyrrhizin) daily has been used for treatment of bronchial catarrh and coughs.

milk thistle

Silybum marianum (seed), St Mary's thistle

Common use

Alcohol-induced and/or hepatitis B or C virus liver disease

Evidence: When combining all trials or high-quality RCTs, a 2007 Cochrane review could demonstrate no significant effect of milk thistle on mortality, or complications of liver disease in patients with alcoholic and/or hepatitis B or C liver diseases.[148]

Other reported uses: Gastric ulcer.

Notes

Use cautiously in patients with hypersensitivity to plants of the daisy family (*Asteraceae*), as anaphylaxis has been reported.[16]

May cause mild abdominal pain, fluid diarrhoea, sweating, nausea, vomiting, weakness.

Pregnancy and breastfeeding

Although used historically to improve lactation, there are insufficient reliable safety data.[16,18]

Interactions

Cytochrome P450 substrates: There are contradictory findings for the effect on CYP3A4 and CYP2C9 isoenzymes.[16,18] Evidence to date suggests there is no effect on CYP1A2, CYP2E1 and CYP2D6. Several studies have demonstrated milk thistle does not alter the pharmacokinetics of indinavir (a CYP3A4 substrate).[18,149] Until more is known, patients taking drugs metabolised by P450 enzymes should be monitored for drug efficacy and adverse effects. See Table D.1, Section D.

Metronidazole: A study in 12 individuals found increased clearance of metronidazole and its active metabolite, suggesting that the active constituent silymarin, may induce both intestinal P-glycoprotein and CYP3A4 with multiple dose administration.[150] Monitor for lack of drug efficacy or avoid combination.

P-glycoprotein substrates (e.g. ketoconazole, cimetidine, diltiazem, verapamil, corticosteroids, erythromycin): Preliminary research indicates a high affinity for direct binding to P-glycoprotein.[150]

Common dosage ranges

Milk thistle extract (*Legalon*): 280–420 mg (70–80% silymarin) daily has been used for hepatic cirrhosis.[16]

pau d'arco/lapacho/taheebo

Tabebuia impetiginosa, Tabebuia avellanedae (bark)

Common uses

Pau d'arco has been associated with the treatment of bacterial, fungal and viral infections and cancer therapy. The available evidence is not compelling for any of the reported uses. Serious toxicities such as uncontrolled bleeding, related to the hydroquinone content, have occurred with high doses, and its use should be considered with a degree of caution.[18,41]

Notes

- May cause nausea, vomiting, dizziness, anemia, bleeding, and discoloration of urine.[41,151]
- Increased risk of bleeding may occur with high doses.
- Cease 7 days prior to surgery.

Pregnancy and breastfeeding

Insufficient reliable data, although use should be avoided because of the known toxicity associated with hydroquinone constituents.[18]

Interactions

Warfarin: Daily doses of lapachol (a napthoquinine constituent) over 2 g have caused a reversible increase in prothrombin time.[152] Monitor INR and for signs of bleeding.

Common dosage ranges

Doses of pau d'arco providing greater than 1.5 g daily of the lapachol constituent have been associated with the greatest risk of toxicity.[18]

Tablets/capsules: Bark extract equivalent to 1–4 g daily in two to three doses has been used. One source warns that the product should not be used for more than seven days.[18,41]

Dried bark (tea): 1 tsp in 250 mL water and boiled for five to 15 minutes two to eight times daily has been recommended.[153]

peppermint

Mentha piperita (leaves and flowering tops; peppermint oil)

Common uses

Irritable bowel syndrome

Evidence: A 2008 Cochrane review considered the evidence for the use of peppermint oil in adults with

irritable bowel syndrome equivocal, while a small trial in children showed no benefit.[154] Overall, the trials were small and not well designed or reported. Peppermint oil may provide symptomatic relief in some patients, but longer well-designed studies are needed to demonstrate conclusive efficacy.

Tension headache

Evidence: An RCT with 41 participants used a 10 g topical application of 10% peppermint oil solution spread across forehead and temples, which was repeated at 15 and 30 minute intervals. Patients using a headache diary reported greater reduction in pain intensity than for placebo, an efficacy similar to 1,000 mg paracetamol.[155] Some doubts about the rigour of the study have been raised, questioning the evidence for effectiveness of treatment.

Other reported uses: Orally—dyspepsia, flatulence, colic, diarrhoea, inflammation of the gums and nausea. Topically—headache, myalgia, pruritus and as an inhalant for treating colds and influenza.

Notes

- Drugs that decrease stomach acid and raise gastric pH can cause premature dissolution of enteric-coated peppermint oil, increasing the risk of unabsorbed menthol contacting the anal mucosa and causing anal burning.[18]
- May cause mucosal ulceration; laryngeal or bronchial spasms (in infants and small children) or heartburn due to relaxation of lower oesophageal reflux sphincter and gastrointestinal smooth muscle.
- Allergic reactions and sensitisation can occur with internal or topical use.

Pregnancy and breastfeeding

Likely to be safe in amounts normally consumed in food, but there are insufficient reliable data on use at therapeutic doses to recommend safe use. Peppermint leaf tea should be used in preference to oil during pregnancy and lactation.

Contraindications

Contraindicated in liver damage, bile duct obstruction and inflammation of gall bladder.

Interactions

Cytochrome P450 substrates: Preliminary research indicates peppermint oil may inhibit CYP3A4, CYP1A2, CYP2C19 and CYP2C9 isoenzymes, particularly at high doses.[18] Preliminary studies suggest the possibility of potentially significant drug interactions with cyclosporin, felodipine and simvastatin.[3] Advise patients of the potential harm–benefit differential. Until more is known, patients taking drugs metabolised by P450 enzymes should be monitored for drug efficacy and adverse effects. See Table D.1, Section D.

Common dosage ranges[3,16]

Oral use:

- *essential oil*—0.2–0.4 mL three times daily, diluted, or as enteric-coated capsules, for intestinal disorders and irritable bowel syndrome.
- *dried herb (leaf)*—An infusion of 3–6 g of dried leaf is traditionally taken one to three times daily.

Topical use:

- *oil in ethanol solution (10%)*—10 g applied across the forehead and temples, repeated after 15 and 30 minutes, has been used for tension headaches.

phosphatidylserine

(also known as PS; formerly from bovine source, now from soya bean extract)

Phosphatidylserine is an endogenous human phospholipid that also occurs in small quantities in most foods.

Common uses

Most clinical studies have used PS sourced from bovine cortex, but currently available supplements use soy- or cabbage-derived PS. It is not known if PS from these sources is as effective as the bovine-derived.

Age-related cognitive impairment

Evidence: A 1999 double-blind trial in 494 elderly participants with moderate to severe cognitive decline found a statistically significant improvement in behaviour and cognition in the group receiving 300 mg phosphatidylserine (bovine-PS) daily for six months.[156]

Alzheimer's disease

Evidence: A small six-month RCT in 1994 found 400 mg PS daily improved neuropsychological testing, notably at eight and 16 weeks.[157] Other small RCTs of the era found similar effects.[18]

Other reported uses: Depression, overtraining syndrome in athletes, and attention deficit hyperactivity disorder (ADHD) in children.

Notes

- Generally well tolerated; rarely causing mild gastrointestinal upset.
- It is proposed that PS may work by increasing levels of acetylcholine and other neurotransmitters such as norepinephrine, serotonin and dopamine.[18]
- May be taken with or without meals.

Pregnancy and breastfeeding

Insufficient reliable data.

Contraindications

Safety has not been established in patients with liver or renal disease or in young children.

Interactions

Anticholinergic drugs: Theoretically, PS could increase acetylcholine levels and negate the anti-cholinergic action.[18]

Cholinergic drugs: Theoretically, PS could potentiate the cholinergic action due to increased acetylcholine levels.[18]

Heparin: Preliminary studies indicate synergistic anticoagulant effect with PS.[15] Monitor for signs of bleeding.

Common dosage ranges

100 mg three times daily has been used in clinical studies for Alzheimer's disease, senile dementia, and age-related cognitive or memory impairment.[18]

probiotics

(a diverse range of live micro-organisms, often sourced from cultured milk products)

Probiotics are used to suppress the growth of pathogenic bacteria, block epithelial attachment by pathogens, enhance mucosal function, and modulate immune responses of the host.

Common uses

Acute infectious diarrhoea (viral)

Evidence: Several Cochrane reviews and meta-analyses have found convincing evidence to support the effectiveness of probiotics, with the most supporting evidence for *Lactobacillus rhamnosus* GG (LGG) and *Saccharomyces boulardii*. A pooled estimate of one meta-analysis showed LGG reduced the duration of diarrhoea by 1.2 days. There is no evidence to support efficacy in diarrhoeal illness of bacterial origin.[158]

Prevention of antibiotic-associated diarrhoea

Evidence: An RCT of 269 children concluded that for every 10 patients receiving *S. boulardii* with antibiotic use one fewer would develop diarrhoea.[159] The findings have been supported by other trials and meta-analysis. Two systematic reviews have found no evidence to support the routine use of probiotics to treat or prevent *Clostridium difficile* induced diarrhoea.[158]

Travellers' diarrhoea

Evidence: A meta-analysis of 12 studies showed that probiotics decreased the risk of traveller's diarrhoea (RR, 0.85; 95% CI 0.79–0.91; P<0.001).[160]

Ulcerative colitis

Evidence: A 2007 Cochrane review of four RCTs comparing conventional therapy with combined conventional therapy and a probiotic did not find any improvement in overall remission rates in mild to moderate ulcerative colitis. There were significant variations in design between the trials, and all were considered to have methodological limitations.[161]

Other reported uses: Irritable bowel syndrome, necrotising enterocolitis, inflammatory bowel disease and atopy.

Notes

Probiotics are generally well tolerated.

Pregnancy and breastfeeding

Insufficient reliable data.

Contraindications

Avoid in immuno-compromised patients or those with severe underlying illnesses due to the risk of bacteraemia and fungaemia.

Interactions

None reported.

Common dosage ranges

There is significant variation in the number and strains of bacteria in available products. Optimum dose, frequency and duration of treatment of specific probiotics for specific conditions or in different populations have not been established.[162] Examples of other bacteria used are *Bacillus coagulans* and *Bifidobacteria*.

Acute infectious diarrhoea (viral): Effectiveness is increased if used early in the course of the illness, and at doses of at least 10 billion colony-forming units (CFU). LGG has been used in many of the trials.

Antibiotic-associated diarrhoea: LGG in doses of 10–20 CFU daily has been found beneficial. *Lactobacillus acidophilus, L. casei* and *S. boulardii* have also been used.[158]

propolis

(Bee glue)

Propolis is a resinous material used by bees to maintain their hives. Harvesting a pure product is difficult, and preparations may be contaminated with allergenic beehive by-products.

Common uses

Upper respiratory tract infection

Evidence: A case-control study using an aqueous nasal spray (*Nivcrisol*) in children with acute and chronic

rhinopharyngitis throughout the cold season found limited benefit from propolis.[163]

Periodontitis

Evidence: A study of 20 patients with chronic periodontitis using aqueous propolis extract as a subgingival irrigation (as an adjuvant to scaling and root planing) twice a week for two weeks showed reduced microbial burden.[164]

Minor burns

Evidence: A 2002 study compared the use of propolis cream with silver sulfadiazine cream on minor burns within 48 hours of injury. There was no significant difference in microbial colonisation, but burns treated with propolis appeared to have less inflammation and faster healing that those treated with silver sulphadiazine.[165]

Genital herpes

Evidence: An RCT compared propolis ointment with aciclovir and placebo ointments in 90 patients with recurrent genital herpes. Propolis ointment was superior to either topical acyclovir or placebo ointments in healing genital herpes lesions and reducing local symptoms.[166] However, there may have been some bias due to lack of subject blinding.[16]

Other reported uses: Asthma and as an antioxidant, anti-inflammatory and antihyperglycemic.

Notes

- Propolis is a known sensitising agent. Oral use can cause allergic reactions, oedema and acute oral mucositis.
- There are a large number of case reports of allergic contact dermatitis. May also cause laryngeal oedema or anaphylactic shock with either oral and topical use.[167]
- There has been one report of renal failure with oral use.[168]
- Patch-test topical products as there is a high risk of sensitisation. Use orally with caution in allergic asthmatics and children.[169]

Pregnancy and breastfeeding

Insufficient reliable data.

Contraindications

Avoid use in individuals hypersensitive to bee by-products (e.g. honey), conifers, poplars, Peru balsam, and salicylates.[18]

Interactions

None reported.

Common dosage ranges[16]

Tablets/capsules: 500 mg three times daily as an antibacterial.

Ethanol extract mouthwash: Rinse with 10 mL of a 0.2–10% solution for 60 to 90 seconds and spit out, once or twice daily.

Ointment: 3% ointment four times daily for 10 days has been used for genital herpes.

red clover

Trifolium pratense
(flower head, isolated isoflavone extracts)

Red clover isoflavones are believed to have oestrogen-like activity and are often referred to as 'phytoestrogens'. Robust clinical research is limited, and most trials have used proprietary products containing standardised isoflavone extracts.

Common uses

Menopausal symptoms

Evidence: A 2007 Cochrane review of phytoestrogens for vasomotor menopausal symptoms found many of the 30 identified RCTs to be of low quality and underpowered. A meta-analysis using pooled data from five suitable trials found no evidence of effectiveness for red clover extract (*Promensil*) in reducing the frequency or severity of hot flushes, with a placebo effect ranging from 1% to 59%. The majority of the trials used 50–100 mg isoflavones daily.[170]

Arterial stiffness

Evidence: An RCT in 80 postmenopausal women and normotensive men found using isoflavones (enriched with formononetin) for 6 to 10 weeks reduced arterial stiffness and total vascular resistance.[171]

Hyperlipdiaemia

Evidence: An RCT in 93 postmenopausal women with moderately elevated cholesterol and taking red clover extract isoflavones found no significant improvement in cholesterol or lipid profiles. The drop-out rate for the trial was 19.3%.[172]

Bone density

Most studies investigating isoflavones and bone metabolism have used soy products with a higher concentration of genistein and daidzein and potentially active ingredients other than red clover.

Evidence: The studies of red clover isoflavones in osteoporosis have not provided a clear answer to their role. Two RCTs have demonstrated a positive effect on bone mineral density and an increase in bone formation markers.[173] A third RCT examined bone resorption

markers and found no effect. Some investigators' conclusions conflict with the results of independent analysis. Although the evidence is limited, red clover isoflavones may have a positive effect on bone mineral density in peri- and post-menopausal women.[174]

Other reported uses: Benign prostatic hypertrophy, prostate cancer, cyclic mastalgia eczema and psoriasis.

Notes

- Generally well tolerated. High doses may produce oestrogen-like effects, including breast tenderness and enlargement, change in menses, weight gain and redistribution; infertility; and growth disorders.
- Patients with protein S deficiency may have an increased risk of thrombosis.[18]
- Cease 7 days prior to surgery.

Pregnancy and breastfeeding

There are insufficient reliable data, although oral use in therapeutic doses is not recommended due to potential oestrogenic effects.[18]

Contraindications

Red clover binds to intracellular oestrogen receptors. Avoid in individuals with oestrogen-sensitive cancer, endometrial hyperplasia or prostate cancer.

Interactions

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): Although data are limited, there may be an increased risk of bruising and bleeding due to coumarin content.[16,18]

Cytochrome P450 substrates: Preliminary evidence suggests red clover might inhibit CYP1A2, CYP2C19, CYP2C9 and CYP3A4.[16,18] Until more is known, patients taking drugs metabolised by P450 enzymes should be monitored for drug efficacy and adverse effects. See Table D.1, Section D.

Tamoxifen: There is preliminary evidence that genistein, a constituent of red clover, may have oestrogenic effects and antagonise the antitumor effects of tamoxifen. Patients intending to take tamoxifen should be advised to discuss the possible harms and benefits of isoflavone supplements with their medical practitioners.

Common dosage ranges

Tablets/capsules: 40–160 mg daily of a red clover isoflavone extract (*Promensil*) has been used for menopausal symptoms of hot flushes; 40 mg daily has been used for osteoporosis, and 40–80 mg daily for bone density.[16]

Liquid extract: 1.5–3 mL daily.[20]

Dried flowerhead: 4 g as an infusion three times daily.[20]

saw palmetto

Serenoa repens (berry)

Common use

Symptoms of benign prostatic hyperplasia

Evidence: A 2002 Cochrane review of 21 RCTs (18 of which were double-blinded) in a total of 3,139 patients with benign prostatic hyperplasia (BPH) using an average daily dose of 320 mg standardised lipido-sterolic extract over four to 48 weeks, found significant improvement in lower urinary tract symptoms and urinary flow measures compared with placebo. Efficacy was similar to 5-alpha-reductase inhibitors with fewer side effects.[175]

Although most research has shown effectiveness, some has not been so positive. A 2006 high-quality study found saw palmetto ineffective for reducing symptoms in men with moderate to severe symptoms of BPH after a year of treatment.[176]

Other reported uses: Inflammation of the male genitourinary tract, testicular atrophy, sex hormone disorders and alopecia. Has been marketed for enlarging female breasts and as an aphrodisiac for both sexes.

Notes

- Generally well tolerated, although high doses may cause gastrointestinal symptoms, headaches and diarrhoea. Male sexual dysfunction, including loss of libido and erectile dysfunction, has also been reported.
- Cease 7 days prior to surgery.

Pregnancy and breastfeeding

Although rarely used by women, and because of a lack of reliable data, most references recommend avoiding use due to the proposed inhibition of testosterone conversion to dihydrotestosterone and potential abnormalities of foetal male genitalia.

Interactions

5-alpha-reductase inhibitors (e.g. finasteride): There is a potential additive effect based on the proposed anti-androgenic activity of saw palmetto.

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): Saw palmetto is reported to prolong bleeding time and there are case reports of INR increases. Individuals should inform their medical practitioner of intended use. Check INR within three days of commencing saw palmetto: warfarin dose may need to be adjusted. Monitor at regular intervals thereafter.

Cytochrome P450 substrates: Preliminary studies have found recommended doses had no effect on

CYP3A4, CYP2D6, CYP1A2, CYP2E1 or CYP1A2 enzyme activity[16,20], although there are some conflicting results for CYP2D6 and CYP3A4.[18]

Oral contraceptives and hormone replacement therapy: The anti-androgenic and anti-oestrogenic effect of saw palmetto may potentially reduce effectiveness. Monitor for lack of efficacy, including mid-cycle spotting or breakthrough bleeding.

Common dosage ranges[16]

A standardised extract containing 80–95% sterols and fatty acids (liposterolic content) is available.

Standardised lipophilic extract: 320 mg daily in one or two doses has been used in trials for BPH.

Ground dried berries: 1–2 g daily

Tincture (1:4): 2–4 mL three times daily.

shark cartilage

Mainly composed of calcium, phosphorus, water, collagen and proteoglycans

Commercial shark cartilage is made up of the proteoglycan chondroitin sulphate, calcium, phosphorus and collagen. It contains up to 780 mg elemental calcium per daily dose. This monograph refers to sterilised and ground dried shark cartilage products, rather than processed chondroitin (possibly bovine sourced), which has been extensively studied for use in osteoarthritis.

Common uses

Cancer

Evidence: Use of shark cartilage was popularised in the 1980s after several poorly designed trials claimed it was a 'miracle cure'. The growth of new blood vessels (angiogenesis) is necessary for tumors to grow and metastasise. Early trials claimed shark cartilage had anti-angiogenic properties, although later studies have found no benefit in patients with advanced or previously treated cancer, including breast cancer; colorectal cancer; lung cancer; prostate cancer; brain cancer or non-Hodgkin's lymphoma.[177-179]

Some Phase II and III clinical trials studying *Neovastat*, a product containing shark cartilage derivative AE-941, did however, report positive anti-angiogenic effects in patients with solid tumours.[180,181]

Psoriasis

Evidence: A randomised dose comparison trial of 49 patients with plaque psoriasis taking *Neovastat* for 12 weeks found daily doses over 30 mL resulted in a statistically significant improvement in Psoriasis Area and Severity Index (PASI) score, severity of itch, and physician's global assessment.[182]

Other reported uses: Osteoporosis, Kaposi's sarcoma and macular degeneration and as an analgesic, anti-inflammatory agent, immunostimulant, antibiotic and antioxidant.

Notes

- Intended use of complementary medicines by individuals undergoing chemotherapy should be discussed with their medical practitioner(s) and be medically supervised. For further information see the 'Notes' section under 'Purpose and content of the CAM monographs'.
- Generally well tolerated, but may cause gastrointestinal symptoms of nausea, diarrhoea, vomiting, flatulence, constipation, possibly due to the high calcium content in some products. Other events reported include rash, acne and alteration in taste.[16]
- To maximise absorption, take on an empty stomach and not at the same time as acidic fruit juice.
- There are isolated case reports of hepatitis, hypercalcaemia, hypoglycaemia and asthma. Use with caution in renal or hepatic impairment or individuals with arrhythmias or taking calcium supplements (monitor calcium levels).[16]
- Discontinue use three weeks before surgery, and for six weeks post-surgery due to the anti-angiogenic effects.[3]

Pregnancy and breastfeeding

Insufficient reliable data, although other anti-angiogenic agents are known teratogens and retard growth.

Contraindications

- Not recommended for children or teenagers still experiencing growth due to the theoretical risk of growth retardation from the anti-angiogenic effect.
- Avoid in individuals with seafood allergy.

Interactions

Reliable information is not available.

Common dosage ranges[16]

The method of preparation and purification is not standardised, and it has been proposed that some processes may denature the anti-angiogenic proteins, reducing the active constituents.

Oral:

Tablets/capsules: *shark cartilage extract*—80–100 g daily (depending on preparation) in two to four doses for cancer.

Liquid extract: *derivative AE-941 (Neovastat)*—30–240 mL daily has been used in trials for cancer.

Topical:

Topical cream: 5–30% has been recommended for psoriasis.

skullcap, American/scutellaria

Scutellaria lateriflora (leaf)

There are over 200 members of the genus *Scutellaria*. Different species have different flavonoid profiles and are not considered interchangeable.

Common use

Anxiety

Evidence: A very small 2003 study reported a reduction in general anxiety levels[183], although further research is needed before skullcap could be considered effective for this indication.

Other reported uses: Ischaemic stroke, insomnia and epilepsy.

Notes

- Very little is known about the safety of American skullcap, although high doses may cause giddiness, stupor, confusion, limb twitching and seizures.
- Fatal hepatotoxicity has been reported, possibly related to contamination with germander from *Teucrium* species, a contaminant often found in skullcap preparations.[18]

Pregnancy and breastfeeding

Due to insufficient reliable data and the risk of contamination, use should be avoided.[20]

Interactions

Reliable information is not available.

Common dosage ranges[20]

Dried herb: A common recommendation is 1–2 g infused in 150 mL of boiling water for five to 10 minutes, strained and taken three times daily. Some references suggest up to 6 g daily may be used.[184]

Liquid extract (1:1, 25% ethanol): 2–4 mL three times daily.

skullcap, Chinese/baical skullcap

Scutellaria baicalensis (root)

There are over 200 members of the genus *Scutellaria*. Different species have different flavonoid profiles and are not considered interchangeable. Baical skullcap differs substantially from American skullcap (*S. lateriflora*) and is one of eight ingredients of a herbal combination that is widely promoted and sold over the internet for the treatment of prostate cancer, marketed under the trade names *PC-SPES, PC PLUS* and *ProstaSol*.

Common use

Prostate cancer

Evidence: Early uncontrolled studies of *PC-SPES* found positive reductions in prostate-specific antigen (PSA) levels, although a 2002 Food and Drug Administration investigation discovered ongoing contamination with indomethacin, diethylstilboestrol and warfarin. No rigorous research has been carried out on the combination since the withdrawal of the proprietary product involved.[16] In view of the possibility of contamination and lack of supporting pharmacological data, its use by patients undergoing treatment for cancer cannot be recommended.[20]

Other reported uses: Allergic rhinitis, bronchiolitis, and psoriasis.

Notes

- Generally well tolerated, but there has been one case report of hepatitis.
- Theoretically, an additive sedative effect may occur when taken with other sedating medicines.

Pregnancy and breastfeeding

Due to insufficient reliable data and the risk of contamination, use should be avoided.[20]

Interactions[3]

None documented, although very preliminary data suggest possible inhibition of cytochrome P450 CYP1A2.

Common dosage ranges[3,18]

The studies of baical skullcap have generally focused on the flavonoid constituents baicalin, wogonin and baicalein, rather than the whole herb. Baical skullcap, like most traditional Chinese medicines, is often used in combination with other CAMs and in personalised doses.

Dried herb: 6–15 g daily.

Standardised extract (baicalin): 500 mg three times daily has been used for viral hepatitis. two to three tablets containing 50 mg in combination with 100 mg of shung hua taken four to six times daily has been recommended for upper respiratory tract infection.

Liquid extract (1:2): 4.5–8.5 mL daily in divided doses.

slippery elm

Ulmus rubra (inner bark)

Common uses

Traditionally, slippery elm has been recommended for dyspepsia, gastritis, reflux, irritable bowel syndrome and Crohn's disease and as an antitussive agent and skin emollient. There is insufficient reliable clinical evidence to support any of the reported uses.

Notes

- The inner bark is the part used therapeutically, but some poor-quality products may contain elements of whole bark, which is toxic and should be avoided.
- Topical use may cause contact dermatitis and the pollen is allergenic: avoid in patients with hypersensitivity to slippery elm or its components.
- Theoretically, the high mucilage content may reduce or slow the absorption of orally administered drugs although no interactions have been reported.[16,18] Separate doses from other medicines by two to three hours where possible.

Pregnancy

When used orally in amounts normally found in food, the inner bark is likely to be safe. Some poor-quality products may contain elements of whole bark, a known abortifacient. Avoid use.[16,18]

Breastfeeding

Due to insufficient reliable data and the risk of contamination with whole bark, use should be avoided.[18]

Interactions

None documented.[20]

Common dosage ranges

There are no universally adopted dosing regimens for slippery elm, and references vary. The optimal safe and efficacious dose has not been established.

Oral:

Tablets/capsules: 400–500 mg three or four times daily. 200 mg two or three times daily has been recommended for bronchitis.

Powdered inner bark: 0.5–1 g in 200 mL water three to four times daily.

Liquid extract (1:1 in 60% alcohol): 5 mL three times daily.

Topical:

Paste: The coarse powdered inner bark is mixed with boiling water in varying concentrations.

soy

Glycine max (soya bean, soy flour, soy protein, soy isoflavone extracts)

Soy isoflavones are believed to have oestrogen-like activity and are often referred to as phytoestrogens, although it is unclear if the isoflavones stimulate or block the effect of oestrogen or act as a mixed receptor agonist/antagonist.[16] While soy has a similar isoflavone profile to red clover, it contains much higher amounts of daidzein and genistein.

Common uses

A variety of dietary soy and isoflavone extract products have been investigated for a wide range of conditions. A large proportion of the studies suffer from poor reporting or study design, hence limiting their value. Some trials have found an inconsistent relationship between dose and effect for soy protein and isoflavones products. Variations in processing techniques may be responsible for differing effectiveness of isoflavones in products.

Menopausal symptoms

Evidence: Clinical trials studying soy as an alternative to conventional hormone replacement therapy for menopausal symptoms are inconclusive. A 2004 systematic review of 10 RCTs using soy products or isoflavone extracts (34–134 mg daily) found positive results in four trials but no statistically significant difference in menopausal symptom scores and hot flushes in the remaining six.[185] Overall, the review found dietary soy protein may modestly reduce the frequency and severity of menopausal hot flushes, although better quality studies are needed to identify the reasons different populations respond differently.

Bone Density

Evidence: A 2005 systematic review identified 31 studies evaluating markers of bone health. A wide variety of soy interventions had been used (various sources of soy protein and isoflavones) but most were of limited duration and design, making it difficult to draw an overall conclusion. Among the five studies of at least one year duration, no consistent effect on bone mineral density was seen.[186] Until better research is available, no firm conclusion can be drawn.

Hyperlipidaemia

Evidence: A 2005 systematic review identified a total of 68 RCTs reporting data on lipid levels. The total dose of isoflavones used was 0–185 mg daily (median 80 mg) and soy protein was 14–113 g daily (median 36 g, which is equivalent to approximately 500 g tofu). Meta-analysis of the relevant trials found the 52 studies reporting on LDL levels had a net reduction of approximately 3%; 54 studies reporting triglyceride levels had a net reduction of approximately 6%; and 56 studies reporting on HDL found a slight but not statistically significant net increase.

Positive results were seen with soy protein products but not soy isoflavone extracts. A larger effect was seen in those with elevated baseline levels of LDL but not triglycerides or HDL.[186] Dietary intake of soy protein may

provide potential benefit on levels of total cholesterol, HDL and LDL, and triglycerides.

Hot flushes in breast cancer patients

Evidence: A number of trials using 70–150 mg soy isoflavone daily for four to 12 weeks found no evidence that soy was better than control to reduce symptoms.[186] With the lack of supporting evidence, plus a potential interaction with tamoxifen, supplements providing levels of isoflavones exceeding normal dietary levels should be avoided.

Prostate cancer

Evidence: It has been suggested that the weak oestrogen-like properties of phytoestrogens may assist in the prevention and treatment of prostate cancer, although trial results have been inconclusive. Soy protein containing 83 mg isoflavones taken daily for one year did not affect PSA levels in otherwise healthy men aged 50–80 years.[186,187] Large studies of men consuming an Asian diet (containing 10 times the soy content of the average western diet) have found isoflavone intake was associated with a decreased risk of localised prostate cancer.[188] It is unclear if soy protein in the diets of Asian populations is protective or if factors such as genetic or environmental influences such as the type of fat consumed are responsible.

Notes

- Patients undergoing chemotherapy and anti-oestrogenic treatments for cancer should discuss intended use of soy isoflavone with their medical practitioner(s). Consideration should be given to potential harms and benefits before these medicines are co-administered.
- As the oestrogenic properties of soy and its isoflavones have not been fully elucidated, use with caution in oestrogen-sensitive cancers or conditions associated with oestrogen excess.
- Soy products are generally well tolerated. Adverse effects include constipation, diarrhoea, bloating, nausea and mastalgia. Some individuals find soy foods and beverages unpalatable, and compliance may be difficult.
- Soy protein products may decrease the absorption of zinc, iron or calcium supplements. Separate doses by two hours.[3,15]
- Soy can act as an allergen, and individuals severely allergic to cow's milk are frequently sensitive to soy as well. Use with caution or avoid.

Pregnancy and breastfeeding

Likely to be safe when used orally in amounts commonly found in foods. Theoretically, the mild estrogen-like activity with therapeutic doses could adversely affect foetal development. Avoid use pending long-term safety studies.[3]

Interactions

Cytochrome P450 substrates: A study has reported inhibition of CYP1A2 isoenzyme in 20 patients receiving 100 mg theophylline and 200 mg daidzein, a soy isoflavone.[189] Until more is known, patients taking drugs metabolised by P450 enzymes should be monitored for drug efficacy and adverse effects. See Table D.1, Section D.

Tamoxifen: Preliminary evidence from *in vitro* and animal studies suggests soy isoflavones may compete with tamoxifen for oestrogen receptors, reducing tamoxifen's efficacy.[3,16] The clinical relevance in humans has not been clarified but, because of the potentially serious consequences of this interaction, individuals taking tamoxifen should discuss the intended use of a soy isoflavone supplementation with their medical practitioner(s). Consideration should be given to potential harms and benefits before the medicines are co-administered.

Thyroid hormones: A 2002 case report proposed that soy isoflavone supplements could decrease the absorption of levothyroxine.[186] Individuals on thyroid medication should be monitored for thyroid hormone levels and for adverse effects.

Warfarin: There have been several case reports of soy milk decreasing INR.[186] Patients on warfarin should advise their medical practitioner, monitor INR closely and watch for possible signs of bleeding (e.g. bruising).

Common dosage ranges

A dose of 36 g soy protein is equivalent to approximately 500 g tofu; 250 mL soy milk contains 4–10 g soy protein.

Isoflavones: Clinical trials have often used doses of 34–160 mg daily. 50–75 mg daily has been used for menopausal symptoms.

Soy protein: 30–50 g daily has been used for hyperlipidemia. 20–60 g daily of soy protein for menopausal symptoms.

St John's wort

Hypericum perforatum (herb)

Some St John's wort products may be standardised to a specific active constituent (e.g. hyperforin or hypericin), although research suggests several other components are involved, and the exact mechanism for modulation of serotonin, dopamine and norepinephrine is unclear.

Common uses

Hypericum extracts used in clinical trials are generally high-quality, well-standardised products, and results obtained cannot necessarily be extrapolated directly to all products.

Mild to moderate depression

Evidence: A 2005 Cochrane review of 37 RCTs (total of 4925 participants) over six to 12 weeks included 26 trials with placebo comparison and 14 using standard antidepressants. A variety of standardised preparations of St John's wort were used, with doses of 240–1,800 mg hypericum extract daily. The meta-analysis reported treatment was more effective than placebo and as effective as standard antidepressant treatments when used for mild to moderate depressive symptoms. The benefit in treating patients with major depression appeared to be minimal. The authors concluded the evidence was inconsistent and complex due to the diversity of products tested, methodologies and reporting.[190]

Menopausal mood symptoms

Evidence: Several studies of St John's wort (generally combined with black cohosh extract) for the treatment of menopausal symptoms with depressed mood have reported a response superior to placebo. A 2006 double-blind RCT in 301 women compared placebo with 70 mg hypericin herb extract combined with 3.75 mg *Cimicifugae rhizoma* extract siccus. After eight weeks the Menopause Rating Scale scores were reduced by 34.8% (placebo reduction 21.7%) and Hamilton Depression Rating Scale scores were reduced by 30% (13.7% in placebo group).[191]

Other reported uses: Seasonal affective disorder and atopic dermatitis and as an antiviral agent.

Notes

- Generally well tolerated but may cause gastrointestinal symptoms, anxiety, hypomania, allergic hypersensitivity, dizziness, dry mouth, restlessness and sleep disturbances.
- High doses may cause photosensitisation in fair-skinned people. An average threshold daily dose for increased risk appears to be approximately 2–4 g St John's wort extract, or 5–10 mg hypericin. Recommend protection from direct sunlight and avoidance of sun lamps for fair-skinned people when using either topical or oral St John's wort.[18,20]
- St John's wort is associated with many interactions (see below). Individuals considering taking it should be asked about the medicines they are currently taking. Those at risk of toxicity or undertreatment when taking it and either conventional medicines or other CAMs should discuss the potential harms and benefits with their medical practitioner(s).
- Tannins in St John's wort may reduce absorption of iron supplements.[16]

Pregnancy

There are insufficient reliable data, although there is some evidence that constituents may be teratogenic and increase uterine tone and risk of contractions. Recommend that a safe approach would be to discontinue the medication one month before attempting to get pregnant.[192]

Breastfeeding

Infants of nursing mothers using oral St John's wort may experience colic, drowsiness and lethargy. Until more is known about the safety of breastfeeding, avoid use.[18]

Contraindications

- St John's wort is known to interact with many drugs and CAMs. Individuals taking drugs with a narrow therapeutic safety index, poor bioavailability, or whose blood levels should remain stable for maximal therapeutic efficacy should be carefully advised about the risk of adverse outcomes with concomitant use of St John's wort. Pharmacists should advise patients on these types of drugs or who are elderly or very ill, to avoid St John's wort, or discuss intended use with their medical practitioner.
- Avoid in individuals with a history of allergy to St John's wort or its components or who are prone to photosensitivity.
- Cease use at least 10 days prior to surgery due to potential enzyme induction and anaesthetic failure.
- St John's wort can induce hypomania or mania in patients with bipolar disorder or depressed patients with occult bipolar disorder. Avoid use.[18]

Interactions

St John's wort is the most commonly reported CAM involved in drug interactions.

Clinical importance

Clinically significant pharmacokinetic interactions have been reported with, for example, warfarin, cyclosporin, HIV protease inhibitors, digoxin, oral contraceptives, and anticonvulsants. Clinically significant pharmacodynamic interactions have also been identified with the SSRI antidepressants and the triptans. The absence of standardisation of active constituents in CAMs generally makes it difficult to quantify the clinical importance of specific drug interactions. The clinical relevance of many of the following interactions is currently uncertain: until further information becomes available caution should be

used when individuals taking these agents start or cease using St John's wort.

St John's wort has a half-life of 26.5 hours, and trials investigating drug interactions with it often require a 14-day study period to allow for maximal induction of enzymes and drug transporters.

Note that the following list of interactions is not exhaustive, and that medicines not included may also interact with St John's wort. Products using St John's wort extracts with low hyperforin content are reported to have lower potential for interactions and may be safer in some individuals.[3]

Anaesthetics/pre-operative medicines (e.g. midazolam, fentanyl, propofol, sevoflurane): St John's wort may cause reduced blood levels and a risk of therapeutic failure. Due to the long elimination half-lives of hypericin and hyperforin, use of St John's wort should be discontinued at least 10 days prior to elective surgery.[193]

Antiarrhythmics (e.g. digoxin, ivabradine, amiodarone, disopyramide): Many of these drugs are substrates of cytochrome P450, and there is a potential for reduced blood levels with risk of therapeutic failure.[194] Use with caution and monitor for reduced effect.

Anticonvulsants (e.g. phenobarbitone, phenytoin): St John's wort may cause reduced blood levels with a risk of seizures. Cease any use of St John's wort. Monitor anticonvulsant blood levels as they may increase on ceasing St John's wort, requiring adjustment of dose.[195] The effect on carbamazepine is unclear.[16,196,197] Levetiracetam, lamotrigine and clobazam have also been associated with increased frequency and severity of seizures with St John's wort use, possibly via a mechanism unrelated to the cytochrome P450 pathway. In 2007 the UK Medicines and Healthcare Products Regulatory Agency recommended avoiding the concomitant use of St John's wort with all antiepileptic medicines.[197]

Antidepressants (e.g. paroxetine, sertraline, other SSRIs, TCAs), and other serotonergic drugs (e.g. tramadol, carbamazepine, triptans): St John's wort may cause an additive serotonergic effect and an increased risk of adverse reactions when used in combination with SSRI and TCA antidepressants. Advise individuals to discuss intended use of St John's wort with their medical practitioner, and weigh the benefits of use due to the increased risk of adverse effects.[195]

Benzodiazepines (e.g. alprazolam): St John's wort increases the clearance of alprazolam[198], and the CYP3A4 induction may also apply to other benzodiazepines. Monitor for lack of efficacy and adverse effects.

Calcium channel blockers (e.g. verapamil, nifedipine): St John's wort can cause significant reductions in blood levels of verapamil and nifedipine as a result of increased first-pass metabolism.[199,200] It is thought other calcium channel blockers (also CYP3A4 substrates) are likely to be similarly affected. Monitor for reduced efficacy.

Clopidogrel: Clopidogrel is a pro-drug requiring metabolism by CYP3A4 to form an active metabolite. Use of St John's wort with it will increase activity and, theoretically, the risk of adverse events such as bleeding. Some researchers have proposed that individuals not responding to clopidogrel use St John's wort to induce metabolism and increase antiplatelet activity.[201]

Cyclosporin, tacrolimus: There are numerous reports of significant reductions in drug levels and risk of transplant rejection, possibly due to CYP3A4 induction. Avoid combination with St John's wort. Monitor plasma drug concentrations of the immunosuppressant.[195]

Cytochrome P450 substrates (see also individual drugs): St John's wort is a highly potent inducer of CYP3A4, CYP2E1, CYP1A2, CYP2C9, CYP2D6 and CYP2C19.[16]

When St John's wort is ceased, blood levels of concomitant interacting medicines may rise, possibly leading to toxicity. Until more is known, patients taking drugs metabolised by P450 enzymes should be monitored for drug efficacy and adverse effects. See Table D.1, Section D.

Daunorubicin: Efficacy may be reduced due to induction of P-glycoprotein and decreased oral bioavailability.[202,203] Avoid combination with St John's wort due to the risk of serious adverse outcome.

Digoxin: Induction of P-glycoprotein by St John's wort can cause reduced blood levels and loss of control of heart rhythm or heart failure. Cease any use of St John's wort. Monitor digoxin blood levels as they may increase on ceasing St John's wort, requiring adjustment of dose.[195]

Fexofenadine: There is some evidence that St John's wort induces P-glycoprotein transport, although results of studies are conflicting. One trial reported a single dose of St John's wort caused significant inhibition of intestinal P-glycoprotein, increasing the maximum fexofenadine concentration by 45% and decreasing the oral clearance by 20%, without a change in half-life or renal clearance. Conversely, long-term treatment caused a 35% decrease in fexofenadine maximum concentration and a 47% increase in oral clearance.[204] The clinical significance of this interaction has not been clarified. Monitor for potential lack of efficacy and adverse effects.

HIV protease inhibitors and HIV non-nucleoside reverse transcription inhibitors (e.g. indinavir, nelfinavir, nevirapine, delaviridine): Increased oral clearance with use of St John's wort may cause reduced blood levels and possible loss of HIV suppression. Cease any use of St John's wort. Measure HIV RNA viral load.[195]

HMG-CoA reductase inhibitors: A 12-week RCT in patients stabilised on atorvastatin found therapy with St John's wort increased LDL from 2.34 mmol/L to 2.66 mmol/L.[205] St John's wort has also caused reduced blood levels of simvastatin,[206] although it does not appear to affect the plasma levels of pravastatin or fluvastatin, neither of which are substrates of CYP3A4 or P-glycoprotein. Avoid use of St John's wort with simvastatin or atorvastatin.

Imatinib: St John's wort can cause a significant reduction in plasma concentrations of imatinib due to induction of metabolism by CYP3A4 and the P-glycoprotein efflux transporter.[207] Avoid combination. Monitor for lack of efficacy and plasma drug levels if co-administered.

Irinotecan: A small study found St John's wort caused reduced plasma levels of the active metabolite of irinotecan (SN-38), decreasing efficacy.[208] Cease any use of St John's wort. Monitor blood counts and irinotecan plasma levels.

Lithium: Potentially causes reduced blood levels and risk of therapeutic failure may occur.

Methadone: Four patients using St John's wort were found to have a median decrease in methadone concentration-to-dose ratios of 47%. Two patients reported symptoms suggesting a withdrawal syndrome.[209] Monitor for withdrawal symptoms.

Omeprazole: St John's wort has been found to induce both CYP3A4 catalysed sulfoxidation and CYP2C19 dependent hydroxylation of omeprazole, significantly decreasing plasma concentrations.[210] Monitor for lack of efficacy and adverse effects.

Oral contraceptives: St John's wort can decrease norethisterone and ethinyloestradiol levels by 13–15%, resulting in breakthrough bleeding, irregular menstrual bleeding or unplanned pregnancy.[211] Women taking St John's wort and oral contraceptives concurrently should weigh the benefits of continuing use of St John's wort against possible reduced contraceptive efficacy or use an additional or alternative form of birth control.[195]

P-glycoprotein substrates (e.g. digoxin, daunorubicin, ketoconazole, amiodarone): Induction of P-glycoprotein impedes the absorption of some medicines and entry into the central nervous system. St John's wort is thought to have the same level of induction as grapefruit juice on P-glycoprotein. See 'Clinically important drug interactions', Section D, for further information.

Theophylline: It remains unclear if serum levels of theophylline or its metabolites are affected by St John's wort: results of clinical studies are conflicting.[16] It is proposed that reduced blood levels and loss of bronchodilator effect may occur. Cease any use of St John's wort. Monitor theophylline blood levels as they may increase on ceasing St John's wort, requiring adjustment of dose.[195]

Tramadol: Theoretically, concurrent use may cause an additive serotonergic effect, increasing the risk of serotonin syndrome.[18]

Warfarin: Reduced INR has been reported with a risk of lowered anticoagulant effect. Cease any use of St John's wort. Monitor INR levels closely as they may increase on ceasing St John's wort, requiring adjustment of warfarin dose.[195]

Common dosage ranges

The levels of bioactive constituents in different hypericum products vary according to the plant material, the extraction process and solvents used.

It has been recommended to avoid products that do not provide adequate identifying information about the content, such as the amount of total extract (e.g. 900 mg), the extraction fluid (e.g. methanol 80% or ethanol 60%), and the ratio of raw material to extract (e.g. 3–6:1).[190] Analysis of German products found inter-batch variability.

Standardised hydroalcoholic extract: 300 mg of standardised 0.3% hypericin extract (products may be standardised to 2–5% hyperforin as well) three times daily initially, with a maintenance dose of 300–600 mg for depression. Clinical trials for depression have used a range of doses and forms, such as 0.17–2.7 mg hypericin and 240–1800 mg of extract daily.[16,20]

Dried herb: 2–4 g as an infusion daily.

tea tree

Melaleuca alternifolia (oil from leaf and branch)

Common uses

Dandruff

Evidence: A placebo-controlled trial in 126 participants with mild-to-moderate dandruff using 5% tea tree oil in a shampoo daily for four weeks found a significant reduction in self-reported itchiness and greasiness.[212]

Tinea pedis

Evidence: A systematic review of four RCTs found 10% tea tree oil as effective as placebo. Concentrations of 25% and 50% tea tree oil were, however, more effective than placebo but not as effective as clotrimazole or terbinafine.[213]

Onychomycosis

Evidence: An RCT on 117 patients with subungual onychomycosis found comparable resolution of symptoms using topical tea tree oil 100% or clotrimazole 1% topical solution over six months, with similar rates of conversion to negative cultures and improvement in symptoms (approx 60% in both groups).[214]

Acne

Evidence: An RCT of 124 participants with mild to moderate acne compared 5% tea tree oil gel with 5% benzoyl peroxide lotion over three months. Tea tree oil was as effective in reducing symptoms but with a slower onset of action than benzoyl peroxide gel and was associated with significantly fewer adverse effects. The absence of a placebo control group limits the value of the study, however.[215]

Notes

- Oral consumption has resulted in serious adverse events, including coma. Although used in mouthwashes and toothpaste, avoid oral ingestion.[15]
- Use cautiously in patients with allergy to components of tea tree oil.
- May cause local irritation and allergic contact dermatitis in some individuals.
- Tea tree oil may worsen the drying effect of skin treatments such as tretinoin, benzoyl peroxide and salicylic acid.
- Not to be confused with Chinese or New Zealand tea tree oils (which are different species of *melaleuca*).

Pregnancy

Not intended for oral consumption due to toxicity. Insufficient reliable data. Avoid topical use during childbirth: animal studies suggest it may cause a decrease in the force of spontaneous contractions.[16]

Breastfeeding

Not intended for oral consumption due to toxicity. Women nursing infants should not apply tea tree oil to the nipple or breast as it may be absorbed by the infant.[16]

Interactions

None reported.

Common dosage ranges

'Standardised tea tree oil' describes 14 of the nearly 100 constituents of tea tree oil (ISO 4730 Oil of *Melaleuca*). 100% oil is often diluted with inert excipients. Preparations for external use containing 5–100% concentration of tea tree oil are used, depending on condition.

tribulus

Tribulus terrestris (leaf)

Tribulus is a plant steroid also known in Australia as tribestan and triboxin. Its status for use by athletes liable to drug testing is currently undetermined (see 'Drugs in sport', Section F).

Common use

Athletic ability

Evidence: A 2007 RCT found that 450 mg tribulus extract daily did not produce any gain in strength or lean muscle mass after five weeks. It did not alter the urinary testosterone–epitestosterone (T–E) ratio or increase the risk of testing positive based on the World Anti-Doping Agency's urinary T–E ratio limit of 4:1.[216]

Other reported uses: Infertility, angina, impotence and improving libido.

Notes

The saponin content may cause some gastrointestinal irritation.[3]

Contraindications

Theoretically, tribulus may aggravate androgen-sensitive tumours or hormone-dependent conditions. Avoid use.[3]

Pregnancy

There are insufficient reliable data, although animal studies suggest a possible adverse effect on fetal development.[18]

Breastfeeding

Insufficient reliable data. Possibly unsafe due to theoretical risk of hormonal effects on the infant.[18]

Interactions

Anabolic steroid drugs: Concurrent use with anabolic steroids could theoretically cause additive androgenic effects.

Common dosage ranges

Some tribulus products are standardised to 40% furostanol saponins.

Standardised extract: 250–450 mg daily has been used for athletic performance. Manufacturers' recommended doses for a range of indications range from 750 to 1,500 mg daily.

valerian

Valeriana officinalis (root and rhizome)

Common uses

Insomnia

Evidence: A 2006 systematic review and meta-analysis identified 16 eligible studies within a total of 1,093 participants. Most studies were considered to be methodologically weak, and there was considerable variation between doses, preparations and length of treatment, making analysis difficult. Six of the studies found a statistically significant benefit (relative risk of improved sleep of 1.8) but there was also some evidence of publication bias. The review concluded that valerian might improve sleep quality without producing side effects, but it recommended studies were needed to assess standardised preparations and use standard measures of sleep quality and safety.[217]

Research from the 1980s found valerian reduces the time to sleep onset (sleep latency) and improved subjective sleep quality, with greatest benefit seen in patients using 400–900 mg of valerian extract up to two hours before bedtime.[18]

Anxiety

Evidence: A 2006 Cochrane review identified only one RCT, of 36 patients (which found no significant difference between valerian and placebo), and concluded there is insufficient evidence to draw any conclusions about the efficacy or safety of valerian compared with placebo or diazepam for anxiety disorders.[218]

Notes

- Adverse effects are generally mild, transient and rare. May cause stomach upset, headaches, palpitations and insomnia.
- Overdose has caused symptoms including hypotension, hypocalcaemia, hypokalaemia, light-headedness, fatigue and gastrointestinal complaints.[16]
- Some studies have suggested that maximum effect is found with continuous nightly use over several days to four weeks, although others have suggested one-time or short-term use.[15]
- Long-term use of high doses may lead to withdrawal symptoms if ceased abruptly. Delirium and cardiac complications during withdrawal have been reported.[219]
- Use with caution in patients with hepatic impairment: there is a risk of hepatotoxicity.
- Avoid use with alcohol.

Pregnancy and breastfeeding

Insufficient reliable data.

Contraindications

Avoid in patients with a history of valerian allergy.

Interactions

Benzodiazepines: Valerian can alter binding at benzodiazepine receptors. Theoretically, additive central nervous system depression may occur through enhanced GABA release and uptake inhibition.[16] Monitor for additive effects.

Cytochrome P450 substrates: Studies to date have generally found minimal or no effect on CYP3A4, CYP2D6, CYP1A2 or CYP2E 1 isoenzymes.[20]

Common dosage ranges[16]

Extracts are often standardised to 0.3% valerenic (valeric) acid, although other constituents may be responsible for the pharmacologic activity. Products often combine valerian with other CAMs.

Tablets/capsules: 400–900 mg dried extract (aqueous or aqueous-alcoholic) 30–60 minutes before bedtime for insomnia. 100 mg of the extract has been used prior to a stressful activity.

Dried root: 1.5–3 g in 150 mL hot water as a decoction prior to bedtime.

willow

Salix spp. (bark)

Willow contains salicin, a pro-drug of acetylsalicylic acid. The pharmacological actions and adverse effects of salicylates also apply to willow.

Common uses

Lower back pain

Evidence: A 2006 Cochrane review of herbal medicines used for low back pain included two RCTs with *Salix alba* (white willow bark) and found moderate evidence that daily doses standardised to 120 mg or 240 mg salicin were better than placebo for short-term improvements in pain and the need for rescue medication.[220]

Osteoarthritis and rheumatoid arthritis

Evidence: Results from studies using willow bark extract for osteoarthritis are conflicting. An RCT in 78 participants with osteoarthritis taking the equivalent of 240 mg salicin daily for two weeks found analgesic efficacy just reached statistical significance (p=0.047).[221] Two other RCTs using the same dose for six weeks, however, found no effect on pain scores in 127 osteoarthritis patients and 26 rheumatoid arthritis patients compared with placebo.[222]

Other reported uses: Inflammatory musculoskeletal conditions, fever and headache.

Notes

- Theoretically, salicin, like salicylates, could raise serum creatinine without affecting glomerular filtration rate or renal function. This is thought to be due to changes in plasma protein binding or competitive inhibition of tubular secretion of creatinine.[223]
- Nausea, gastrointestinal discomfort, dizziness, fatigue and allergic reactions have been reported in clinical trials.

Pregnancy

Insufficient reliable data, although there are some sources with conflicting reports on safety.[20]

Breastfeeding

Salicylates are excreted in breast milk and may cause hypersensitivity, macular rashes and other adverse effects in the infant. Avoid use.[20]

Contraindications

- Avoid in known cases of salicylate sensitivity or aspirin-sensitive asthma.
- Avoid use in children. Both salicylic acid and aspirin are contraindicated in children with viral infections and, although Reye's syndrome has not been reported, the salicin constituent in willow bark is similar to aspirin and might pose the same risk.[18]
- Salicylates can inhibit prostaglandins and reduce renal blood flow. Salicin can cause renal papillary necrosis and the risk of toxicity is greater with chronic or high acute doses.[18] Use with caution in renal impairment.

Interactions

Given the similarity to aspirin, willow would be expected to interact with drugs such as methotrexate, sulphonamides, metoclopramide, phenytoin, probenecid, spironolactone and valproate.[15,20]

Anticoagulants (e.g. warfarin), antiplatelet drugs (e.g. aspirin, clopidogrel) and NSAIDs (e.g. ibuprofen): There is a theoretical risk that concurrent use with drugs that increase clotting time or inhibit platelet function may increase the risk of bleeding, particularly in the elderly.[20] However, a study of 35 patients found 240 mg salicin daily affected platelet aggregation to a far lesser extent than acetylsalicylate.[224] Until further data becomes available, monitor for bruising and overt bleeding. Monitor INR if using warfarin: dose may require adjustment.

Common dosage ranges

Standard doses of willow bark are the equivalent of approximately 100 mg of aspirin. There is considerable variation in salicin content of different *Salix* species.[20]

Standardised extract (hydroalcoholic, tincture or aqueous): 120–240 mg of total salicin daily.[15]

Dried bark: 1–3 g as a decoction three times daily (equivalent to 60–120 mg total salicin daily).[20]

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Section D

Clinical and therapeutic information

Medication review

It has been estimated that medication-related problems represent 2–3% of hospital admissions in Australia each year (up to 50% of which are potentially avoidable), and that older people are particularly at risk.[1,2]

The general principles outlined here apply to medication management reviews irrespective of where they are conducted, be it in an aged care home[a] (a Residential Medication Management Review, or RMMR) or in the domiciliary setting (a Home Medicines Review, or HMR—also known as a Domiciliary Medication Management Review, or DMMR).

Pharmacists who are accredited to conduct medication management reviews are entitled to conduct reviews in both of these settings and to be remunerated for their reviews. Different obligations and business rules apply to HMRs, and RMMRs, which may be initiated by a pharmacist or a general practitioner (i.e. collaborative review). Further information is available in a number of sources including the Pharmaceutical Society of Australia's 'Policy' page (www.psa.org.au/policy), the Australian Association of Consultant Pharmacy website (www.aacp.com.au) and The Society of Hospital Pharmacists of Australia website (www.shpa.org.au).

MMR facilitators in Divisions of the Australian General Practice Network provide support to community pharmacies and pharmacists accredited to provide medication management reviews on all aspects of the medication review process. Contact details for local facilitators can be found on The Pharmacy Guild of Australia website at www.guild.org.au/mmr/content.asp?id=435.

General principles of medication review

A comprehensive medication review focuses on the drug therapy of each patient as an individual, with the aim of maximising the potential benefits whilst minimising the potential risks of therapy.

The aim of a comprehensive medication review is to identify, resolve or prevent actual or potential medication-related problems or concerns.

A medication-related problem can be defined as any undesirable event experienced by the patient that is thought to involve drug therapy and that actually or potentially interferes with a desired patient outcome.[3]

The first step in a medication review is to gather relevant information about the patient and his or her medicines and medical issues. Information for RMMRs can be obtained from medication charts, case notes, care plans, comprehensive medical assessments, general practitioner referrals (in some cases), aged care home staff, and the resident. Information for HMRs can be obtained from the general practitioner referral, the dispensing history and, most importantly, the patient during the home visit and interview. Relevant and important information, which can be acquired by careful listening to the patient (and/or their carer), includes:

- understanding of their therapy, including knowledge of the medicines they are taking and of their condition
- problems with current therapy, both real and perceived
- expectations of their therapy—what they believe the medication will do to alleviate, control or eliminate their medical problem and whether it is actually doing it
- fears and concerns about their therapy—is it safe to take? Will there be adverse effects? Is it the most appropriate medication for their condition?
- willingness to participate in the therapeutic process—to take the medication and observe all the prescribed conditions (dose, timing, route, formulation).

The pharmacist's responsibilities are to:

- help ensure the patient's therapy is appropriate for the condition, the most effective available, the safest possible and can be taken as intended
- identify, resolve or prevent any medication-related problems and to bring potential or actual problems to the attention of the general practitioner
- assist in ensuring the goals of therapy are met and optimal outcomes are realised
- provide the referring general practitioner with a complete and current medication list.

Identification of medication-related issues

A medication review conducted in a home enviroment can provide valuable information such as the use of another person's medicines, or foods/beverages that are contraindicated; and inappropriate storage of medicines.

a. May also be referred to as a Residential Aged Care Facility, RACF.

Group medicines by indication and consider whether each is necessary and its regimen optimal. Consider also whether additional medication or patient education is required. Bear in mind that 'medicines' includes prescription medicines, over-the-counter medicines, vitamins, herbal medicines and any other form of complementary medicine or supplement.

Sections in this handbook that may be useful when considering potential problems include: 'Clinical monographs', Section B, 'Clinically important drug interactions', Section D, 'Normal physiological values', Section D, 'Medicines and older people', Section D and 'Complementary medicines monographs', Section C.

For each medication, consider the following possible causes of medication-related issues.[4]

Additional therapy required

- untreated indication
- synergistic or potentiating therapy
- preventative or prophylactic therapy.

Unwarranted therapy

- no medical indication
- non-drug therapy indicated
- use of multiple medications where a single agent would be effective
- treating avoidable adverse reaction of another medication
- duplication of therapy
- different brands of the same medicine.

Medicine issues

- inappropriate dosage form
- more effective medication available
- contraindication present
- not cost effective
- safety issues
- condition refractory to therapy
- not indicated for the condition being treated.

Dosage issues

- greater or less than recommended dosage
- escalating use of medicines that cause dependence
- inappropriate over- or under-use
- inappropriate frequency
- inappropriate duration
- medical condition significantly influencing pharmacokinetics
- inappropriate route or administration time
- poor administration technique.

Adverse drug reaction

- undesirable or excessive effect
- allergic reaction
- contraindications
- drug–drug interaction
- drug–disease interaction
- dosage change too rapid
- inadequate monitoring
- effect of concomitant food, alcohol or other drinks—e.g. grapefruit juice.

Adherence issues

- inadequate instructions
- medication administration error
- cost
- directions not clearly understood
- lack of understanding due to issues including language and cultural differences
- physical or mental disability
- health beliefs and perceptions
- lack of motivation
- concern about potential adverse effects
- patient prefers not to take.

General guidance to help prevent medication-related problems

- Remember to assess the patient thoroughly considering all factors that influence the patient's health.
- Aim to have medical conditions managed without medicines whenever possible.
- Know the pharmacology of the prescribed drug and how it might interact with other drugs.
- Consider how the clinical status of the patient could influence the pharmacology and effectiveness of the drug(s).
- Be sensitive to potential barriers to adherence (e.g. impaired cognitive function, diminished vision or hearing, cultural beliefs).
- For medications or their active metabolites that are renally eliminated, consider appropriate age-related adjustments in dosages.
- If there is a question about drug dosage, start low and increase gradually.
- Where appropriate, suggest the use of serum drug concentrations to monitor potentially toxic drugs (particularly those used frequently in older people).

- Monitor older patients frequently for adherence, drug effects and toxicity—i.e. not just at the time a medication review is conducted.

Conducting a medication review

- Undertake the review in a timely manner.
- Listen to what the patient has to say; be responsive to their concerns.
- Consider whether the patient's signs or symptoms could be medication-related adverse effects.
- Offer to dispose of out-of-date medications: this may help alleviate confusion for the patient.
- Aim to make the medication regimen simple and relevant to the patient's needs, taking into account their health beliefs and lifestyle to achieve desirable health outcomes.
- Check that therapeutic devices are functioning properly (may need replacement or service) and get the patient to demonstrate their technique when using devices.
- Often the patient may need information, instruction on technique, or reassurance.
- Consider the possible contribution of the patient's lifestyle and physical constraints to medication issues.
  - Falls may be due to poor gait, balance or eyesight.
  - Poor compliance could be a result of:
    - hearing impairment (unable to hear instructions)
    - poor memory (unable to remember when the last dose was taken)
    - diminished eyesight (unable to read label)
    - physical disabilities (unable to open containers)
    - difficulty swallowing (e.g. due to a cerebrovascular accident or another condition such as Parkinson's disease).
- Document each problem, provide concise management options for the patient and/or general practitioner to consider (supported by appropriate references) and a proposed time line for implementation and monitoring of outcomes.

Communication with the general practitioner

Communication about a medication review usually involves the preparation of a written report. However it may be beneficial to supplement or precede the report with verbal communications. Reports may not be read for some time after a medication review; therefore urgent matters should be discussed with the GP by phone or in person. Written communications are also more likely to be misconstrued or misinterpreted than verbal communications. Other benefits of verbal communication include being able to convey more information in a short of time and building relationships with other health professionals.

The introduction to the written report should include a statement of acknowledgment of the referral with a list of the reasons originally presented by the referring doctor. This helps to reaffirm or better define the context in which the medication review was initiated.

The main part of the report (i.e. the written recommendations to the general practitioner) can then be presented using the following structure:

- start with a statement of fact (i.e. patient's concerns or symptoms)
- link to medication(s)
- make suggestions or recommendations to resolve the problem.

In the report include:

- a comprehensive list of what the patient is actually taking (including complementary and over-the-counter medicines)
- an overview of the patient's medication management; this may include the patient's understanding of their medicines, compliance and ability to manage their medicines (e.g. difficulties with swallowing or with opening containers, inhaler techniques, any identified storage or hoarding problems)
- patient concerns and beliefs
- education or advice provided to the patient (carer) or aged care staff
- recommendations to address the reason/s for referral
- actual or potential problems
- prioritised recommendations, supported where appropriate by references.

Follow-up

As well as answering questions and providing verbal or written education at the time of interview, consider what ongoing support can be offered to the patient or aged care home.

Incorporate review findings into ongoing care (e.g. document important points in dispensing software). Store reports securely.

References

1. Roughead E, Semple S. Literature review: medication safety in acute care in Australia. Canberra: Australian Commission on Safety and Quality in Health Care, 2008. At: www.safetyandquality.gov.au/internet/safety/publishing.nsf/Content/D0DABD9912D44A14CA257516000FDABB/$File/16566-LitRev-MedSafetyAcuteCare.pdf.
2. Roughead EE, Gilbert AL, Primrose JG, Sansom LN. Drug-related admissions: a review of Australian studies published 1988–1996. MJA. 1998;168:405–8.
3. Cipole RJ, Strand LM, Morley PC. Pharmaceutical care practice. New York: McGraw Hill, 1998.
4. Strand LM, Morley PC, Cipolle RJ, Ramsey R, Lamsam GD. Drug-related problems: their structure and function. DICP, Ann Pharmacother 1990;24:1093–7.

Further information

1. Disease state management
   - Therapeutic information is available from the National Prescribing Service, *Australian Prescriber*, Adverse Drug Reactions Advisory Committee bulletins and the *Medical Journal of Australia* (free online). Other texts that may be purchased are:
     - Bochner F, ed. Australian medicines handbook drug choice companion: aged care. 2nd edn. Adelaide: Australian Medicines Handbook Pty Ltd, 2006.
     - Nissen L, Rigby DA. Home medicines review disease state management guide, 3rd edn. Brisbane: Pharmacy Guild of Australia, 2005.
     - the therapeutic guidelines series.
2. Medication review process
   - The *Australian Pharmacist*, the *Australian Journal of Pharmacy*, *Pharmacy News* and the *Accredited Pharmacist* have regular articles about medication review. Professional standards and guidelines provide process information—see 'Standards and guidlines', Section H. The SHPA Standards of Practice for Clinical Pharmacy may be found on the SHPA website at www.shpa.org.au or in J Pharm Pract Res. 2005;35(2):122–46.
   - The Australian Association of Consultant Pharmacy website at www.aacp.com.au.
   - The Pharmacy Guild of Australia website at www.guild.org.au.
   - Hughes J, Tenni P. The *Australian Pharmacist* medication review companion. Canberra: Pharmaceutical Society of Australia; 2004.
   - Hughes J, Tenni P, Peterson G, Jackson S, Naunton M. The Australian Pharmacist aged care primer. Canberra: Pharmaceutical Society of Australia, 2007.
   - Hughes J, Tenni P, Soulsby N, James A. Case studies in clinical practice. Use of laboratory test data: process guide and reference for pharmacists. Canberra: Pharmaceutical Society of Australia, 2004.

Clinically important drug interactions

Medication interaction and medication-food interaction can have a significant negative impact on the quality use of medicines.

There is a clear need for pharmacists to keep up to date with their knowledge of interactions. Pharmacists should also be able to make informed recommendations on how to proceed when a patient has been prescribed two or more medicines that are known to interact.

The importance of interactions in terms of incidence, clinical significance and cost to society is difficult to assess. What is known is that in the majority of cases where an interaction leads to hospitalisation, generally the interaction could have easily been avoided with appropriate management and early intervention. Pharmacists must therefore be capable of identifying which interactions are likely to be clinically important in a particular setting. In recent years there has been an exponential growth in the number of published 'potential' interactions, and there is a danger that the relatively small number of well-established and clinically significant interactions can become buried within exhaustive interaction tables.

There is significant inter-patient variability in response to drug interactions. An interaction might manifest clinically with adverse outcomes in one patient and have no consequences in another. In general, the elderly will be more susceptible to the effects of drug interactions, as their homeostatic reflexes are less able to respond to additive pharmacological effects and they have reduced renal function.

This section provides background information that should enable pharmacists to place published information about interactions in a clinical context. It is not intended to provide an exhaustive list of possible interactions. Furthermore, the section does not specifically cover herb–drug interactions (see 'Complementary medicines monographs', Section C).

Just as interactions can lead to an increased pharmacological effect, and therefore risk of toxicity, they can also result in a reduction in pharmacological effect, leading to a possible sub-therapeutic outcome. In both cases the interaction may never come to the attention of the health care team if no medication review is conducted. Thus, an assessment of the concomitant use of interacting medicines is a vital component of the medication review, as are the ensuing recommendations on how the interaction can be avoided (e.g. change in medication) or on how the potential clinical impact of the interaction can be minimised (e.g. dose change, change in timing of doses).

It is important to note that drug interactions can also be clinically beneficial and intended (e.g. combining antihypertensive drugs, the use of diltiazem in combination with cyclosporin to reduce the dosage and cost of the latter, and the treatment of benzodiazepine overdoses with flumazenil).

What follows is a discussion of the mechanisms of potential medicine interactions. Understanding the mechanism of an interaction provides an insight into the interaction management and potential clinical significance. Interactions are generally classified as being pharmacodynamic or pharmacokinetic.

Pharmacodynamic interactions

Pharmacodynamic interactions are those in which the clinical effects of one medicine, given a particular effector-site concentration, are modified by co-administration of another. Undesirable pharmacodynamic interactions, which can often be predicted if the pharmacological properties and mechanisms of action of the individual medicines are understood, include the following.

Additive or synergistic interactions. If the observed effect is **equal** to the sum of the two medicines' individual effects the interaction is **additive**; if the combined effect is **greater** than the sum of the individual effects it is **synergistic**. Synergistic interactions have the potential to be more harmful than additive interactions. Examples of interactions leading to additive or synergistic toxicity are[1-3]:

- Alcohol with central nervous system depressants—increased central nervous system depression.
- Verapamil with beta-blockers—additive cardiodepressant effects.
- Anticholinergics with tricyclic antidepressants or some antipsychotics—increased anticholinergic effects.
- Nonsteroidal anti-inflammatory drugs with angiotensin-converting enzyme inhibitors—increased risk of renal impairment and hyperkalaemia.
- NSAIDs with anticoagulants—increased risk of bleeding.
- Methotrexate with co-trimoxazole—additive antifolate activity and increased toxicity.
- Tramadol with selective serotonin reuptake inhibitors—increased risk of serotonin syndrome.

Antagonistic or opposing interactions. One medicine may counteract or oppose the desirable actions of another. Examples are[1–3]:

- Vitamin K opposes the anticoagulant activity of warfarin.
- Oral hypoglycaemics and glucocorticoids have opposing effects on blood glucose levels.
- Caffeine antagonises the sedative effects of benzodizepines.
- Beta-blockers with beta-receptor agonists.
- Metoclopramide with dopaminergic agents in Parkinson's disease.

Interactions due to disturbances in fluid and electrolyte balance. Examples are[1–3] :

- Diuretics causing potassium loss sensitise the myocardium to the effects of digoxin.
- ACE inhibitors plus potassium supplements or potassium-sparing diuretics (e.g. spironolactone) may lead to hyperkalaemia.
- NSAID-induced fluid retention may oppose the desirable actions of antihypertensive, diuretic or heart failure drugs.
- Lithium carbonate with thiazide diuretics may increase serum lithium levels and increase the risk of lithium toxicity.

Drug or neurotransmitter uptake interactions. Some drugs that act on adrenergic neurons can be prevented from reaching the sites of action by the presence of other drugs. Examples are[1,3]:

- Non-selective beta-blockers (e.g. propranolol) may antagonise the effects of beta-agonist bronchodilators (e.g. salbutamol).
- Drugs with alpha2-adrenergic receptor blocking properties (e.g. phentolamine) may abolish the alpha2-adrenergic receptor mediated effects of clonidine.

Pharmacokinetic interactions

Pharmacokinetic interactions occur when one drug alters the absorption, distribution, metabolism or excretion of another, thus modifying the concentration of the drug at the effector-site. In assessing the potential importance of a pharmacokinetic interaction, several factors need to be considered:

- Only a small percentage of theoretical pharmacokinetic interactions actually lead to adverse outcomes.
- Clinically important interactions are more likely to be encountered when the affected medicine has a narrow therapeutic index or a steep dose–response curve.
- Only a relatively small number of medicines consistently inhibit or induce hepatic metabolism to a significant extent.
- Any medicine that has the potential to adversely affect kidney function may influence the pharmacokinetics of other medicines that are renally excreted.
- Adverse outcomes from interactions are more likely in older patients, in those with liver or kidney dysfunction and in those who are taking a large number of medicines.

Although thousands of pharmacokinetic interactions have been reported in the literature, most are of doubtful clinical importance. Moreover, those that are important tend to involve a relatively small number of medicines.

By considering the mechanisms by which one medicine may influence the pharmacokinetics of another, rational thinking can be applied to such issues as the likelihood of a pharmacokinetic interaction, the potential significance of such an interaction and how a potential interaction can be avoided.

Absorption

One medicine may alter the absorption of another via a number of mechanisms:

- *Modification of gastric pH.* Gastric pH is increased by antacids and antisecretory agents (PPIs, H2-receptor blockers). This may lead to an increase in the solubility (in gastric contents) of a poorly soluble weak acid, a decrease in the solubility of a weak base, an increase in the stability of an acid-labile drug, and an enhanced release of drug from enteric-coated formulations. Each of these effects can modify the onset, rate and/or extent of absorption. However, the absorptive surface area of the small intestine is sufficiently large that most drugs will be well absorbed even if gastric pH conditions are not ideal. Ketoconazole is an example of a medicine that is less soluble in alkaline conditions and for which the rate and extent of absorption are decreased substantially when gastric pH is elevated.
- *Complexation and adsorption*. Compounds that can form poorly soluble complexes with medicines include metal ions (such as those present in antacids, ferrous sulfate, sucralfate and dairy products), ion exchange resins (cholestyramine) and non-digested substances (such as kaolin, pectin and dietary fibre). Medicines that are susceptible to these interactions include tetracyclines, fluoroquinolones, some anticonvulsants, thyroxine, warfarin and digoxin. Complexation and adsorption interactions can normally be avoided by careful planning of dosage

regimens. The aim of such planning is to ensure that the medicine that is susceptible to complexation has moved from the stomach into the intestine well before the complexing agent is administered. This may involve taking the medicine 30 to 60 minutes before the complexing agent. Once the complexing agent has been taken, it is advisable to wait at least two to three hours before taking medicines that are susceptible to complexation or adsorption (see Label 4 in 'Counselling and cautionary advisory labels for medicines', Section A).

- *Effects on gastrointestinal motility*. Since most drugs are largely absorbed in the upper part of the small intestine[1], any medicine that can modify gastric emptying and gastrointestinal motility can theoretically alter the rate of absorption. Opioid analgesics and anticholinergic agents can slow gastric emptying and can therefore reduce the rate of absorption of other medicines. Conversely, metoclopramide increases the gastric emptying rate and can increase the rate of absorption of other medicines, including paracetamol and diazepam. The clinical significance of this observation is often unclear.
- *Pathological changes to the gastrointestinal tract*. A number of medicines, including antibiotics, colchicine and antineoplastic agents, can cause reversible pathological changes to the gastrointestinal tract. Such changes can reduce the absorption of other medicines.
- *Effects on bacterial flora*. In rare instances, the gastrointestinal bacterial flora are involved in the metabolism of medicines. This metabolism might be altered if the flora are modified through the use of antibiotics. However, the clinical importance of this effect probably does not extend beyond the well-documented interaction between oral contraceptives and antibiotics. It is thought that antibiotics may reduce the efficacy of oral contraceptives by inhibiting the bacterial hydrolysis of oestrogen conjugates secreted into bile. Under normal circumstances, the regenerated oestrogen is absorbed back into the bloodstream and contributes to the medicine's efficacy. However, if the hydrolysis is impaired (due to reduced intestinal bacteria), the blood levels of the oestrogen can decrease. Elevated digoxin plasma levels in some individuals treated with antibiotics, particularly macrolides, were thought to be due to a reduction in pre-systemic metabolism by gut flora. However, more recent evidence suggests that inhibition of P-glycoprotein in the intestinal wall may be responsible.[4]
- *Effects on metabolising enzymes and transporters in the intestinal wall*. Within the intestinal wall, enzymes and drug transporters, particularly CYP3A4 and P-glycoprotein respectively, work together to reduce drug absorption. Where one or both of these are induced or inhibited by co-administered drugs, herbs or food there is the potential for altered bioavailability of a range of therapeutic drugs. In the case of inhibition, the consequences are more likely to be clinically relevant where the drug has a low bioavailability. For example, down-regulation of intestinal CYP3A4 by grapefruit juice causes felodipine bioavailability to significantly increase (from 14% to 25%) in healthy volunteers[5], whereas changes in amlodipine bioavailability are relatively minor (81% to 88%).[6] Induction of intestinal P-glycoprotein by rifampicin and other agents such as St John's wort can lead to significant reduction in the bioavailability of drugs such as digoxin.[7] (See St John's wort in 'Complementary medicines monographs', Section C.)

When assessing the likely impact of a medicine interaction that is mediated via an alteration in absorption, it is important to review the literature to determine whether the interaction will lead to a change in the rate or extent of absorption (or both) of the affected medicine. Alterations in the rate of absorption will primarily be important for medicines that are administered for immediate, short-term effects (analgesics, anti-emetics) since the onset of these effects may be delayed if the absorption rate is decreased. The most common cause of a reduction in the rate of absorption is delayed gastric emptying (a delay in the time taken for an orally administered medicine to move from the stomach into the intestine). Medicines that can delay gastric emptying include aluminium-containing antacids, opioids and medicines with anticholinergic effects.

A reduction in the rate of absorption will not usually lead to a reduction in the extent of absorption (the amount absorbed). A general principle is that the average concentration of a medicine in plasma is affected by alterations in the extent of its absorption but not by changes in the rate of absorption. Therefore, if a medicine is being taken chronically, it is most important to focus on interactions that lead to changes in the extent of absorption. Another general principle is that the plasma levels of medicines that already have a low to medium bioavailability are most likely to be affected significantly by interactions that lead to changes in the extent of absorption. In contrast, medicines for which oral bioavailability is close to 100% under normal circumstances tend to be less susceptible to changes in the extent of absorption.

Distribution

Most medicines are reversibly bound to plasma proteins, and competition between medicines for plasma protein binding sites is common. In some instances this competition can result in one medicine being displaced from the plasma protein binding sites, leading to an increase in the fraction unbound in plasma. Although one might expect an increase in 'unbound fraction' to lead to an increase in the unbound concentration in plasma, this rarely occurs and if it does it is usually transient (a few hours). This is because, for most medicines, an increase in unbound fraction will also mean that it distributes more extensively throughout the body and is eliminated more readily by the body. This explains why there are very few documented examples of clinically significant displacement interactions. This is often misunderstood by pharmacists and health care practitioners. Only when there is displacement from plasma proteins occurring alongside a change in the intrinsic clearance of unbound drug would clinically significant changes be expected. Such an interaction occurs between phenytoin and valproate, where valproate displaces phenytoin from plasma proteins and also inhibits its metabolism.[8] In such cases any change in drug therapy should be guided by unbound drug concentration rather than total (bound plus unbound) plasma concentration.

The potential exists for altered distribution of drugs into the brain if the drug is a substrate for transporters on the blood–brain barrier and is co-administered with an inhibitor or an inducer of these transporters.[9] The best evidence for this is limited to animal studies[10]—i.e. where the concentration of drug in the brain can be easily measured—and so may not reflect the human situation. However, where patients develop unexplained central nervous system side effects or toxicity this is a mechanism that should be considered.

Metabolism

A wide range of enzymes mediate the metabolism of medicines. Details of specific enzyme systems, the medicines they metabolise (i.e. substrates) and the medicines that cause inhibition and induction are provided in Table D.1.

Inhibition of metabolism is probably the most common cause of clinically important pharmacokinetic interactions because it can lead to a dramatic increase in the plasma concentrations of the affected medicines. Fortunately, there are relatively few medicines that are capable of significantly inhibiting metabolism (see Table D.1). Caution should be exercised whenever one of these 'enzyme inhibitors' is added to or withdrawn from a patient's dosage regimen if the patient is also taking other medicines that are primarily eliminated by metabolism. Interactions due to inhibition or induction of metabolism cannot generally be avoided by changing the timing of administration of one medicine relative to the other. Individual variations in enzyme activity is covered in greater detail in 'Individualised medicine', Section D.

Where a pro-drug or drug with active metabolites is affected by induction or inhibition of metabolism, this will affect the pharmacological response in a way different from what would be expected if an active drug were administered. When the metabolism of a pro-drug is inhibited, less of the active moiety is produced and so the pharmacological effect may be reduced (and vice versa).

Induction of metabolism arises when one medicine induces the synthesis of enzymes involved in the metabolism of another. It may take a week or more for enzyme induction to occur and several weeks for enzyme levels to return to normal once the inducer medication is ceased. This may lead to a decrease in the plasma concentration of the affected medicine. Enzyme induction is therefore most likely to lead to a reduced pharmacological effect. Conversely, when an inducing agent is withdrawn from the regimen of a patient receiving multiple-medicine therapy, there is a possibility that the plasma levels of other medicines may increase. Caution is therefore needed whenever these medicines are added to or removed from a patient's regimen.

Inhibition, unlike induction, can occur within two to three days, resulting in rapid development of toxicity.[1] The time taken for the affected medicine to reach a new steady-state plasma level after commencing therapy with an enzyme inhibitor is essentially dictated by the half-life of the affected medicine (as a general rule, it would take about three to four half-lives for the full impact of an inhibition interaction to emerge). The clinical significance of many enzyme inhibition interactions depends on the extent to which the serum levels of the drug rise. If the serum levels remain within the therapeutic range the interaction may be advantageous.[1]

Saturation of metabolism may occur when two or more medicines that are the substrates for the same enzyme are administered. This may lead to an increased pharmacological effect.

Renal excretion

Interactions involving renal excretion mechanisms (secretion, filtration and reabsorption) will generally be important only in the case of narrow therapeutic index medicines that are primarily excreted unchanged in urine (fe >0.7; see 'fe' in 'Pharmacokinetic data', Section D). Such medicines include aminoglycosides, vancomycin, methotrexate, digoxin and lithium.

Some medicines are excreted from blood into urine by active transport systems located within the renal

tubules. There are separate systems for weak acids and weak bases. Competition between two weak acids (e.g. probenecid and penicillin, NSAIDs and high-dose methotrexate) can lead to an increase in the plasma concentration of the affected medicine (penicillin and methotrexate, respectively).

Medicines that are relatively non-polar may undergo passive tubular reabsorption, whereby the medicine passes from tubular urine back into blood. Thus, for a given rate of administration, the plasma concentration will increase if reabsorption is enhanced, and vice versa. The reabsorption of relatively non-polar weak acids and bases (e.g. salicylates and amphetamines) can be altered by changes in urinary pH. For example, an increase in urinary pH tends to favour tubular reabsorption of amphetamine, nicotine and morphine derivatives (because a greater proportion of the drug will be in the un-ionised, and therefore diffusible, form), which can lead to an increase in the plasma concentrations. The clinical significance of this mechanism is small because although many drugs are weak acids or bases almost all are largely metabolised in the liver to inactive compounds and few are excreted unchanged in the urine. In cases of overdose, urinary alkalinisation has been used to increase the excretion of drugs such as phenobarbitone and salicylates.[1]

Drugs that influence renal haemodynamics can also affect the excretion of renally cleared medicines by decreasing filtration rate. See 'Acute renal failure associated with commonly used medicines' in 'Dosing in renal impairment', Section D.

Factors determining the clinical importance of a pharmacokinetic interaction

In making a judgment about whether a reported pharmacokinetic interaction is likely to be important in a particular setting, several factors need to be taken into consideration.

Therapeutic index and steepness of the dose–response curve

Subtle changes in the plasma concentration of a medicine will normally be of little consequence if the affected medicine has a wide therapeutic index (e.g. most oral antibiotics, diuretics, beta-blockers, NSAIDs). However, an interaction will be more important if a relatively small change in the plasma concentration is associated with a substantial change in therapeutic or toxic response—that is, if the medicine has a narrow therapeutic index or a steep dose–response curve (e.g. digoxin, lithium, warfarin, theophylline, phenytoin, aminoglycosides). As a general rule, a narrow therapeutic index medicine is one for which some form of patient monitoring is used to guide therapy. This may include therapeutic drug monitoring (see 'Optimal medicine concentration ranges', Section D). Pharmacists should be alert whenever another medicine is added to (or removed from) the regimen of patients taking a narrow therapeutic index medicine.

As noted, interactions are also important if the affected medicine has a steep dose–response curve. In practical terms, these are medicines that do not elicit a graded response: either they elicit the desired effect or they do not. For example, combination oral contraceptives work in part by blocking ovulation. If they do not achieve this effect then the therapeutic objective has not been met. The critical issue for such a medicine is that a reduction in blood levels due to an interaction may render it completely ineffective.

The magnitude of the change in plasma concentration

If the magnitude of the change in the plasma concentration of medicine is small relative to the changes normally observed within an individual, the consequences of the interaction will probably be negligible. For example, a 20% reduction in the rate of absorption will not in itself be of significance if there is normally a twofold variation in the absorption rate. Similarly, if there is normally a twofold to threefold variation in the plasma concentrations among different individuals, anything leading to a 20% reduction in clearance would not normally be expected to be clinically important. In contrast, for a narrow therapeutic index agent, such as digoxin, for which dosages are normally individualised, any interaction leading to a 20% reduction in clearance may be enough to precipitate toxicity.

Temporal considerations

The consequences of a pharmacokinetic interaction between two medicines may depend on the sequence in which they are commenced and/or ceased. For example, if an enzyme inhibitor is commenced in a patient stabilised on phenytoin for epilepsy, the plasma concentration of phenytoin is likely to increase and this may lead to phenytoin toxicity. However, if a medicine that inhibits the metabolism of phenytoin is withdrawn from the dosage regimen of a patient already stabilised on phenytoin, the outcome may be a reduction in plasma phenytoin levels and an associated loss of seizure control. Therefore, the impact of an interaction should be considered not only when a new medicine is started but whenever a patient's regimen is altered.

Other factors

Interactions tend to be much more prevalent in older people (who may receive multiple medications for multiple diseases) and in those with liver and/or kidney disease. Genetic factors and/or frailty may explain why some individuals are more susceptible to the adverse consequences of a particular combination of medicines. At this time it is not possible to predict which patients are more susceptible to pharmacokinetic interactions. However, if there is evidence that the dosage in a particular person may already be too high (e.g. from therapeutic monitoring data or signs of adverse events) or too low (e.g. from breakthrough bleeding in a woman taking the contraceptive pill) special care would obviously need to be taken.

Examples of clinically important drug interactions

The following examples illustrate the diverse mechanisms by which medicines can interact. Also included is a discussion of the possible strategies that might be employed by a pharmacist when faced with such an interaction.

Example 1: medicines that inhibit warfarin metabolism

This is an example of a clinically significant interaction arising from inhibition of metabolism. Warfarin has a narrow therapeutic index and relies almost exclusively on metabolism for its elimination from the body. Moreover, the metabolism of warfarin is susceptible to inhibition. A number of agents (including ketoconazole, metronidazole, amiodarone, oral miconazole[1–3] and cimetidine), have been found to inhibit the metabolism of warfarin and lead to the risk of excessive bleeding.

When faced with a prescription for one of these medicines in a patient stabilised on warfarin, the first course of action would be to consider the use of a similar medicine that does not interact (e.g. use ranitidine instead of cimetidine). Another option would be to decrease the dose of warfarin and closely monitor the patient's clotting status (INR). Either way, the prescriber should be consulted so that appropriate action can be discussed in an informed manner. Whether or not a dose reduction is implemented, the patient should be counselled to be especially aware of the signs of abnormal bleeding and what action to take if this occurs. Warfarin has a half-life of about one day so a new steady-state plasma level should be achieved within a few days. The effect on INR is dependent on the half-lives of the clotting factors and lags behind the effect on warfarin plasma levels.

Example 2: medicines that reduce the effectiveness of oral contraceptives

Oral contraceptives are relatively safe, but the consequences of even a transient reduction in efficacy (i.e. a pregnancy) are significant. This is in contrast with many other medicines, where a reduction in efficacy is usually short-lived and easily remedied. Pharmacists need to be particularly diligent in providing appropriate counselling when dispensing a medicine that can alter the pharmacokinetics of oral contraceptives.

Anti-epileptic agents, St John's wort and rifampicin induce metabolism of oestrogens, reducing their effectiveness as oral contraceptives. In patients taking 'enzyme inducers', a high-dose contraceptive pill or an alternative form of contraception could be considered. Broad-spectrum antibiotics are believed to interfere with the enterohepatic recycling of oestrogens and may decrease their effectiveness in a small percentage of women. The timing and duration of the course of antibiotics is important. Often it is not possible to identify women at risk of oral contraceptive ineffectiveness. However, women who have in the past experienced signs of contraceptive ineffectiveness may be especially vulnerable to the effects of oral antibiotics.

Example 3: theophylline, caffeine and smoking

This is an example of how ceasing a substance that is a drug-metabolising enzyme inducer can lead to potential toxicity. Smoking tobacco is known to accelerate the metabolism of caffeine and related medicines such as theophylline. Studies have found that cessation of smoking can be associated with a threefold increase in the plasma concentration of caffeine despite no change in caffeine consumption. It has been suggested that these increased caffeine levels may contribute to the perceived symptoms of tobacco withdrawal syndrome, including headache and agitation. When counselling a patient who plans to stop smoking, it is good advice to suggest that they also reduce their caffeine intake.

Example 4: NSAIDs, COX-2 inhibitors, ACE-inhibitors, angiotensin II receptor antagonists

These classes of medicines can influence renal haemodynamics via different mechanisms. Post-marketing surveillance has linked the combinations to serious deterioration in renal function. The interaction is more likely in patients with under-perfused kidneys (e.g. congestive cardiac failure) or with pre-existing renal disease (including age-related renal decline). Therefore, renal function should be checked before a NSAID or a COX-2 inhibitor is started in patients taking

ACE-inhibitors or angiotensin II receptor antagonists. The risk is further increased if the patient is also taking a diuretic.[2] This combination can result in what is commonly referred to as the 'Triple Whammy' effect. For further information, see 'Acute renal failure associated with commonly used medicines' in 'Dosing in renal impairment', Section D. NSAIDs and COX-2 inhibitors can also reduce the antihypertensive effects of ACE-inhibitors, angiotensin II receptor antagonists and other antihypertensives and the effects of drugs in treating heart failure.

Example 5: NSAIDs—inhibition of renal clearance

There are several case reports of morbidity and mortality resulting from the use of NSAIDs in patients taking methotrexate. The signs and symptoms of methotrexate toxicity generally occur one to two weeks after the start of co-administration. The interaction has been reported most commonly with high-dose methotrexate (>20 mg weekly) and the incidence is higher in patients with renal impairment. Although the exact mechanism of this interaction is unclear, one possibility is that NSAIDs inhibit the renal clearance of methotrexate via competition for renal secretion. Alternatively, NSAIDs may have a direct effect on renal blood flow (via inhibition of prostaglandin synthesis)[1] which reduces renal clearance. Monitoring of renal function and full blood counts are recommended in patients receiving this combination. NSAIDs can also decrease the renal clearance of lithium, and monitoring of lithium levels is essential during initiation of NSAID therapy.

Cytochrome P450 interactions

Many medicines are metabolised by the cytochrome P450 super-family of enzymes. While humans may possess as many as 50 individual P450 enzymes, only a small number are responsible for the metabolism of most medicines. The term 'cytochrome P450' is a generic term for the entire family of enzymes. Individual enzymes are named according to a nomenclature system developed in 1987. Under this system, the P450 enzymes are divided into families and subfamilies. P450s are named with the root symbol CYP followed by an Arabic numeral designating the P450 family, a letter denoting the subfamily, and a further Arabic numeral designating the individual enzymes. Thus, CYP1A1 represents the first enzyme in family 1 and subfamily A.

The activity of metabolising enzymes such as the cytochrome P450s may be influenced by a variety of factors, including genetic differences between people, enzyme inhibition and induction, diet, health status, gender and age. A large number of clinically important interactions arise from inhibition or induction of cytochrome P450-mediated metabolism. Table D.1 provides information on the P450s involved in the metabolism of medicines. Substrates are those medicines that are significantly metabolised by the given enzyme, while inhibitors are compounds that are generally capable of inhibiting the metabolism of the various substrates (as a result, administration of the inhibitor may lead to an increased plasma concentration of the listed substrate). Inducers of the specified P450 have the capacity to increase the activity of the designated enzyme and therefore reduce the plasma concentrations of the listed substrates. The information in Table D.1 is subject to the following caveats:

- The table is not comprehensive. Information concerning the metabolic fate of many medicines is still lacking.
- Many medicines are metabolised by multiple P450 enzymes and are thus listed under more than one enzyme.
- The listing of two medicines under the same P450 does not indicate a definite interaction of clinical significance.
- Information about substrates, inhibitors and inducers of cytochrome P450 is being updated all the time. For a recent update or to look for new medicines, visit www.medicine.iupui.edu/flockhart. This site also contains information about other CYP isoenzymes.

Note that antiretroviral agents used for the treatment of HIV infection are known to be involved in a large number of interactions. A website has been created to provide interaction information for these agents in a user-friendly format. The address is www.hiv-druginteractions.org.

Table D.1 Medicines that are substrates for, or inhibitors or inducers of, the cytochrome P450 super-family of enzymes[1–3]

Cytochrome P450	Substrates	Inhibitors	Inducers
CYP1A2	amitriptyline, caffeine, clomipramine, clozapine, diazepam, flutamide, fluvoxamine, haloperidol, imipramine, mexiletine, mirtazapine, naproxen, oestradiol, olanzapine, ondansetron, paracetamol, phenobarbitone, propranolol, ropinirole, tacrine, tamoxifen, theophylline, terbinafine, verapamil, *R*-warfarin, zolmitriptan	amiodarone, anastrozole, cimetidine, ciprofloxacin, clarithromycin, erythromycin, fluvoxamine, grapefruit juice, isoniazid, methoxsalen, mexiletine, paroxetine, propranolol, quinolone antibiotics (ciprofloxacin, norfloxacin), tacrine, ticlopidine	carbamazepine, cruciferous vegetables (e.g. broccoli, brussel sprouts), lansoprazole, omeprazole, phenobarbitone, phenytoin, polycyclic aromatic hydrocarbons (e.g. meat cooked over charcoal, tobacco smoking), primidone, rifampicin, ritonavir, St John's wort
CYP2C9	amitriptyline, carvedilol, celecoxib, desogestrel, diclofenac, fluoxetine, fluvastatin, glibenclamide, glimepiride, glipizide, ibuprofen, imipramine, indomethacin, irbesartan, losartan, meloxicam, montelukast, naproxen, phenytoin, piroxicam, rosiglitazone, rosuvastatin, tamoxifen, terbinafine, tetrahydrocannabinol, tolbutamide, voriconazole, *S*-warfarin, zafirlukast	amiodarone, chloramphenicol, cimetidine, clopidogrel, diclofenac, fenofibrate, fluconazole, fluorouracil, fluoxetine, imatinib, isoniazid, omeprazole, sertraline, sitaxentan, sulfamethoxazole, trimethoprim, voriconazole, zafirlukast	aprepitant, bosentan, carbamazepine, phenobarbitone, phenytoin, rifampicin, St John's wort
CYP2C19	amitriptyline, citalopram, clomipramine, cyclophosphamide, diazepam, escitalopram, esomeprazole, imipramine, indomethacin, lansoprazole, moclobemide, nelfinavir, nilutamide, omeprazole, pantoprazole, pentamidine, phenobarbitone, phenytoin, primidone, propranolol, rabeprazole, terbinafine, topiramate, *R*-warfarin	cimetidine, fluoxetine, fluvoxamine, indomethacin, isoniazid, ketoconazole, letrozole, modafinil, omeprazole, oxcarbazepine, probenecid, sertraline, ticlopidine, topiramate, tranylcypromine, voriconazole	carbamazepine, phenobarbitone, phenytoin, prednisone, rifampicin
CYP2D6	amitriptyline, aripiprazole, atomoxetine, carvedilol, chlorpromazine, citalopram, clomipramine, clozapine, codeine, dextromethorphan, dolasetron, donepezil, doxepin, escitalopram, flecainide, fluoxetine, fluphenazine, galantamine, haloperidol, hydrocodone, imipramine, labetalol, methadone, metoclopramide, metoprolol, mexiletine, mianserin, mirtazapine, morphine, nortriptyline, olanzapine, ondansetron, oxprenolol, oxycodone, paroxetine, perhexiline, pethidine, procainamide, promethazine, propranolol, quetiapine, risperidone, tamoxifen, thioridazine, timolol, tramadol, trimipramine, venlafaxine	amiodarone, bupropion, celecoxib, chloroquine, cimetidine, clomipramine, diphenhydramine, escitalopram, haloperidol, methadone, metoclopramide, moclobemide, quinidine, ritonavir, selective serotonin reuptake inhibitors (all SSRIs inhibit 2D6, with fluoxetine and paroxetine the most potent), terbinafine, thioridazine, yohimbine	carbamazepine, dexamethasone, phenobarbitone, phenytoin, rifampicin, ritonavir
CYP2E1	dapsone, enflurane, ethanol, halothane, isoflurane, methoxyflurane, paracetamol, sevoflurane, theophylline	cimetidine, disulfiram	ethanol, isoniazid
CYP3A4	alfentanil, alprazolam, amiodarone, amitriptyline, amlodipine, aprepitant, aripiprazole, atazanavir, atorvastatin, bosentan, bromocriptine, budesonide, buprenorphine, busulfan, carbamazepine, citalopram, clarithromycin, clindamycin, clomipramine, clonazepam, cocaine, cyclophosphamide, cyclosporin, dapsone, dexamethasone, dextromethorphan, diazepam, diltiazem, donepezil, doxorubicin, eplerenone, ergot alkaloids, escitalopram, everolimus, erythromycin, esomeprazole, ethinyloestradiol, ethosuximide, etoposide, felodipine, fentanyl, fexofenadine, finasteride, flutamide, galantamine, haloperidol, hydrocortisone, ifosfamide, imatinib, imipramine, indinavir, irinotecan, itraconazole, ivabradine, ketoconazole, lansoprazole, lapatinib, lercanidipine, lignocaine, lopinavir, loratadine, losartan, methadone, miconazole, midazolam, mirtazapine, montelukast, nelfinavir, nevirapine, nifedipine, nimodipine, oestradiol, omeprazole, ondansetron, paclitaxel, pioglitazone, quetiapine, quinidine, reboxetine, repaglinide, ritonavir, saquinavir, sertraline, sibutramine, sildenafil, simvastatin, sirolimus, sodium valproate, sunitinib, tacrolimus, tadalafil, tamoxifen, teniposide, tetrahydrocannabinol, theophylline, tiagabine, tolterodine, tramadol, trazodone, triazolam, vardenafil, venlafaxine, verapamil, vinblastine, vincristine, voriconazole, *R*-warfarin, zolpidem	amiodarone, aprepitant, cannabinoids, cimetidine, ciprofloxacin, clarithromycin, delavirdine, diltiazem, efavirenz, erythromycin, fluconazole, fluoxetine (due to norfluoxetine metabolite), fluvoxamine, grapefruit juice, imatinib, indinavir, itraconazole, ketoconazole, metronidazole, miconazole, protease inhibitors (all inhibit 3A4, with ritonavir the most potent), verapamil	aprepitant, bosentan, carbamazepine, dexamethasone, ethosuximide, efavirenz, glucocorticoids, griseofulvin, modafinil, nevirapine, phenobarbitone, phenytoin, primidone, rifabutin, rifampicin, St John's wort

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Further Information

Rx List: www.rxlist.com/script/main/art.asp?articlekey=64467.

Epocrates online: www.epocrates.com/index.html.

Pharmacologic management of acute and chronic pain. South Med J, 2001;94(8):756–812. At: www.medscape.com/viewarticle/410825_4.

Normal physiological values

The results of diagnostic tests on body fluids, such as blood and urine, are commonly used in the screening, diagnosis and clinical management of patients.

'Reference ranges', or 'reference intervals', are a statistical calculation of the range of results expected to be found in 95% of 'healthy individuals' unless otherwise specified.[1] They are method and laboratory specific, so, although most laboratory methods are standardised, inter-laboratory differences may occur due to differences in specimen collection and analysis method. Reference ranges may be influenced by patient characteristics such as age and gender and factors such as time of collection, exercise, and the presence of food or some drugs.

Unless otherwise referenced, reference ranges and terminology in this section of the handbook are standardised to those found at the time of publishing in the manual published by the Royal College of Pathologists of Australasia (RCPA).[1]

Units of measurement

Reference ranges are generally expressed in SI (Système Internationale) units. The litre is the standard unit of 'volume', and 'mole' is preferred to 'gram' whenever possible for describing values of concentration. Readers may note some North American textbooks use conventional units (e.g. g/100 mL) when discussing laboratory results. Conversion tables are available in most medical dictionaries. Values of concentration may be expressed in gram units rather than moles when the:

- analyte being measured is a heterogenous group of compounds with differing molecular weights; and
- the molecular weight of the analyte being measured is not precisely known.

The accepted SI unit where functional activity rather than molecular mass is measured (e.g. enzymatic activity) is the International Unit (IU), defined as that quantity of enzyme that will catalyse the reaction of one micromole of substrate per minute.

Interpretation of laboratory test data

Individual results should ideally be interpreted using the reference intervals of the pathology laboratory performing the test and the clinical status of the patient.

The sensitivity and specificity of individual laboratory tests influence the clinical significance of test results.

Pharmacists should adopt a holistic approach when interpreting laboratory test results and, where possible, consider the combined results of several analytes, as well as the health status and medication profile of the patient.

Blood studies[1,2]

Electrolytes

Aluminium

..... <0.30 micromol/L

Toxic level..... >7.4 micromol/L

Because of the ubiquity of aluminium compounds, natural human exposure is unavoidable, and moderate amounts of the element enter the body constantly through inhalation of atmospheric dusts and ingestion of food and drink. Despite an oral intake ranging from 5–10 mg daily, little aluminium is absorbed, and serum levels are usually <0.30 micromol/L. Tissue aluminium levels are very low. No biological function for the metal has been found. Aluminium is readily excreted in the urine in normal renal function. In patients with chronic renal failure undergoing long-term haemodialysis, however, aluminium may accumulate, resulting in dialysis dementia and osteodystrophy. In dialysis patients, serum aluminium >7.4 micromol/L generally leads to clinical symptoms of aluminium toxicity. Levels >3.7 micromol/L are of clinical concern and close surveillance is required, while levels >2.2 micromol/L need attention.

Anion gap

..... 8–16 mmol/L

if potassium not included..... 4–13 mmol/L

The calculated anion gap (AG) is the difference between the cations and anions in the extracellular space. It is equal to $(Na + K) - (Cl + HCO_3)$, although some laboratories do not include K in the equation. AG is used to investigate the cause of metabolic acidosis.

Increased AG occurs in lactic acidosis, diabetic ketoacidosis, renal failure and alcohol intoxication. Lithium toxicity reduces the anion gap.[1,2]

Bicarbonate

..... 22–32 mmol/L

When used with the other electrolytes, bicarbonate levels are an indicator of acidosis and alkalosis. However, the acid-base status can only be accurately assessed by measuring serum pH, as part of arterial blood gases. A low serum bicarbonate is generally associated with an elevated serum potassium, whereas an elevated bicarbonate is usually associated with a low serum potassium. These changes in potassium levels occur as a result of potassium movement in and out of cells in response to extracellular hydrogen ion concentrations.

Calcium

Total calcium ..... 2.10–2.60 mmol/L
Corrected calcium..... 2.15–2.60 mmol/L
Ionised calcium..... 1.16–1.30 mmol/L

Calcium is the most abundant mineral in the body and is involved in bone metabolism, protein absorption, fat transfer, muscular contraction, transmission of nerve impulses, blood clotting and cardiac function.

Calcium occurs in plasma in ionised, complexed and protein bound forms. It can be expressed as total calcium, ionised calcium or corrected calcium (in which total calcium is corrected, usually in relation to the patient's albumin level).[1]

Corrected calcium (mmol/L)
= total calcium (mmol/L)
+ [(40 – serum albumin (g/L)) × 0.02]

Calcium levels are influenced by magnesium, iron and phosphorus and by hormonal activity, vitamin D levels, alkalinity and acidity, and many drugs.

Hypocalcaemia—symptoms when corrected calcium <2.15 mmol/L:

- neurological features—tingling, tetany and mental changes
- cardiovascular system—abnormal ECG and reduced cardiac output
- cataracts.

Hypercalcaemia—symptoms when corrected calcium >2.85 mmol/L:

- neuropsychiatric—lethargy, confusion, irritability, depression
- gastrointestinal—anorexia, abdominal pain, nausea, vomiting and constipation
- renal—thirst, polyuria and renal calculi
- cardiac arrhythmias.

Corrected calcium levels >3.50 mmol/L are considered life-threatening.

Chloride

..... 95–110 mmol/L

Chloride is the most abundant extracellular anion, but intracellular concentrations are low. It is involved in maintaining cellular integrity through its influence on osmotic pressure. Serum chloride values may be used to assess fluid balance and acid–base abnormalities. As is the case with sodium, a change in serum chloride does not necessarily indicate a change in total body chloride; rather, it indicates alterations in fluid status and/or acid–base balance. Elevated chloride levels are seen in both metabolic and respiratory acidosis and in cases of dehydration. In metabolic alkalosis, renal excretion of chloride is increased and hence serum chloride decreases. Hypochloraemia is seen in patients who are overhydrated.

Copper

.....13–22 micromol/L

Copper is essential to many functions in the biological system. Copper deficiency in infants may arise due to chronic diarrhoea, a malabsorption syndrome or a high-milk diet. In adults, it occurs in patients on long-term hyperalimentation low in copper or with certain malabsorption syndromes (coeliac disease and ulcerative colitis), protein-losing enteropathies and nephrotic syndrome. Copper excess is usually iatrogenic. Wilson's disease causes excessive accumulation of copper, leading to chronic hepatitis, neurological disorders and renal failure.

Lead

Desirable goal .....<0.48 micromol/L[5]

Lead poisoning may arise through abnormal ingestion (especially lead-containing paint, sniffing lead petrol), occupational exposure (metal smelters, miners, welders, printing workers, oil refinery workers, paint manufacturers) and retained bullets.[3] Blood lead levels >0.72 micromol/L require intervention.[4,5]

Children are more susceptible to lead poisoning than adults and may show neurological symptoms with blood lead levels >2.17 micromol/L.

Chronic lead poisoning is usually associated with moderate anaemia with basophilic stippling. Acute lead poisoning is rare and is associated with abdominal pain and constipation.

Magnesium

..... 0.8–1.0 mmol/L

Magnesium is essential for a wide range of neuromuscular functions and enzyme systems.

Levels of magnesium and other electrolytes are closely linked, with hypomagnesaemia often being associated with hypocalcaemia, hypokalaemia, hyponatraemia and hypophosphataemia.[6]

Hypermagnesaemia may also cause hypocalcaemia, possibly by inhibiting the release of parathyroid hormone. Hypercalcaemia can block the renal reabsorption of magnesium, resulting in hypomagnesaemia.[6]

Hypomagnesaemia is more common than hypermagnesaemia and may occur as a result of renal or gastrointestinal loss of magnesium. Patients with hypomagnesaemia may have a low plasma calcium that remains refractory to calcium supplementation until the magnesium deficiency is corrected. Serum magnesium levels <0.7 mmol/L are usually associated with neuromuscular symptoms such as weakness, muscle fasciculations with tremor, tetany and hyper-reflexia. Hypomagnesaemia is also associated with central nervous system effects such as personality changes, disorientation, psychosis, convulsions, stupor and coma. However, the most important effects of magnesium are on the heart. Low magnesium levels are associated with prolongation of the QT interval (as measured by ECG) and associated risk of ventricular arrhythmias.

Hypermagnesaemia is commonly caused by an excess magnesium intake in patients with renal failure. Mild hypermagnesaemia is associated with bradycardia, flushing, sweating, sensation of warmth, nausea and vomiting. As levels increase, respiratory distress and asystole may occur.

Phosphate (inorganic)

Adult ..... 0.8–1.5 mmol/L

Child 2–10 years..... 1.0–2.0 mmol/L

Infant 0–1 years..... 1.4–2.4 mmol/L

Phosphorus is an abundant element found in most tissues and cells. It is needed for its buffering action, calcium transport and osmotic pressure. It has a close inverse relationship with calcium. When calcium is increased, phosphate tends to decrease and vice versa. Elevated phosphate levels are commonly seen in patients with chronic renal failure.

To ensure that calcium phosphate is not precipitated out into bone and tissues, it is important to maintain the calcium–phosphate product (serum calcium × serum phosphate) <4.2 mmol/L.[2]

Potassium

Plasma ..... 3.4–4.5 mmol/L

Serum ..... 3.8–4.9 mmol/L

Potassium is the major intracellular cation in the blood. Along with sodium, it helps to maintain osmotic balance and is also involved in acid–base balance. It is needed for proper nerve and muscle action. The main clinical feature of hypokalaemia is muscle weakness, which may be preceded by paraesthesia, hyporeflexia and cardiac arrhythmias. Correction of hypokalaemia is recommended for all patients with a potassium level <3.0 mmol/L, but in patients with cardiac disease, serum potassium should be maintained >3.5 mmol/L.

The need for treatment of hyperkalaemia is indicated by both the serum potassium and electrocardiograph changes (tall or peaked T-waves). Significant signs and symptoms of hyperkalaemia are not usually seen at levels <6.0 mmol/L, but at levels >7.0 mmol/L there is an increased risk of cardiac arrest.

Sodium

..... 135–145 mmol/L

Sodium is the most abundant cation in the extracellular fluid. Its main functions in the body are to regulate osmolality and maintain fluid and acid–base balance. It is also involved in the transmission of nerve impulses. Symptoms of hyponatraemia (lethargy, apathy, confusion, agitation, disorientation, muscle twitching and cramps, irritability, convulsions and coma) are not generally seen until serum sodium falls below 125 mmol/L. The symptoms of hypernatraemia (thirst, confusion, altered mental state, muscle twitching, convulsions and coma) usually occur at levels >160 mmol/L. Plasma and urinary osmolality are often used to differentiate the cause of hyponatraemia.

Zinc

..... 12–20 micromol/L

Zinc is an essential element in over 200 metalloproteins and has a wide range of functions. Zinc deficiency may arise from inadequate dietary intake. Zinc levels also fall during the acute–phase response to infection or injury. Zinc deficiency may manifest as poor wound healing, rash and hair loss. Zinc toxicity, usually iatrogenic, causes fever, vomiting, stomach cramps and diarrhoea.

Erythrocytes (red blood cells)

Erythrocyte count (red cell count–RCC)

Female ..... $3.8–5.8 \times 10^{12}$/L

Male ..... $4.5–6.5 \times 10^{12}$/L

The main function of erythrocytes (red blood cells, or RBCs) is to carry oxygen to the tissues and to transfer carbon dioxide to the lungs. A high red cell count (RCC) may indicate low oxygen tension in the

blood from congenital heart disease, cor pulmonale, pulmonary fibrosis, polycythaemia rubra vera or dehydration. A low RCC may indicate blood loss from anaemia, haemorrhage, bone marrow failure, renal disease, haemolysis, leukaemia, multiple myeloma or malnutrition. Low levels may also arise from nutritional deficiencies of iron, folate, vitamin B_{12} and vitamin B_6. Overhydration will also cause a reduced RCC.

Erythrocyte sedimentation rate

(Westergren method)

Female ..... 17–50 years: ..... 3–19 mm/hr
..... 51–70 years: .....<20 mm/hr
.....>70 years: .....<35 mm/hr
Male ..... 17–50 years: ..... 1–10 mm/hr
..... 51–70 years: .....<14 mm/hr
.....>70 years: .....<30 mm/hr
Child..... 2–15 mm/hr

The erythrocyte sedimentation rate (ESR) is a measurement of the rate that RBCs settle in saline solution or plasma over a specified time period. An elevated ESR is indicative of organic pathology, but a normal ESR does not exclude the presence of disease. The ESR is a non-specific indicator of inflammation and malignancy. Elevated values occur with kidney disease, pregnancy, rheumatic fever, rheumatoid arthritis, severe anaemia, syphilis, systemic lupus erythematosus, thyroid disease and tuberculosis. Markedly elevated values occur with giant cell (temporal, cranial) arteritis, multiple myeloma, macroglobulinaemia—primary, hyperfibrinogenaemia, necrotising vasculitis and polymyalgia rheumatica. Lower than normal levels occur with congestive heart failure, hyperviscosity, hypofibrinogenaemia, low plasma proteins, polycythaemia and sickle cell anaemia.

Haematocrit (packed cell volume)

Female 0.37–0.47 (35–47%)
Male 0.40–0.54 (40–52%)

Haematocrit is the measure of the fraction or percentage of red blood cells in whole blood. It is an important determinant of anaemia (decreased), polycythaemia (elevated), dehydration (elevated), increased red blood cell breakdown in the spleen (decreased) or possible overhydration (decreased).

Haemoglobin

Female .....115–165 g/L
Male .....130–180 g/L
Infant-term (cord blood).....135–195 g/L
Child 1 year.....105–135 g/L
Child 2–12 years.....105–145 g/L

Haemoglobin is the main transporter of oxygen and carbon dioxide in the blood. It consists of globin (a protein) and haem, which contains iron atoms and the red pigment porphyrin.

When used in conjunction with the haematocrit, haemoglobin level is an important indicator of anaemia (decreased haemoglobin), dehydration (increased haemoglobin), polycythaemia (increased haemoglobin), poor diet or nutrition, or possible malabsorption.

Mean cell haemoglobin concentration

.....300–350 g/L

The mean cell haemoglobin concentration (MCHC) is a measure of the average concentration (or percentage) of haemoglobin in a single RBC, derived by dividing the total haemoglobin concentration by the haematocrit.[2]

A low MCHC is described as hypochromic, a normal MCHC as normochromic, and an elevated MCHC as hyperchromic.

Mean cell volume

..... 80–100 fL

Mean cell volume (MCV) is a measure of the average volume, or size, of a single RBC and is used in classifying anaemias.

A low MCV (<80 fL) is described as microcytic, a normal MCV is a normocytic and an elevated MCV (>100 fL) as macrocytic.

Anaemias are classified according to the size of the RBC and then the MCHC:

- normocytic and normochromic—acute blood loss, aplastic anaemia, prosthetic heart valves, sepsis and tumours
- microcytic and normochromic—erythropoietin deficiency secondary to renal disease
- microcytic and hypochromic—iron deficiency, lead poisoning, thalassaemia
- macrocytic and normochromic—vitamin B_{12} and folate deficiencies and chemotherapy.

Red cell distribution width

For an indication of reference range, consult the individual laboratory in question: results may vary according to the instrument used for testing, although a common result may be 11–15%.

The red cell distribution width (RDW) is an indication of the variation in RBC size. It is therefore helpful in further

classifying the types of anaemia. The RDW may become abnormal before the MCV changes.

Normal RDW:

- increased MCV—aplastic anaemia, pre-leukaemia
- normal MCV—anaemia chronic disease, acute blood loss, haemolysis, chronic lymphocytic leukaemia, chronic myelogenous leukaemia, haemoglobinopathy, normal variant
- decreased MCV—anaemia of chonic disease, thalassaemia (heterozygous).

Increased RDW:

- increased MCV—vitamin B_{12} deficiency, folate deficiency, immune haemolytic anaemia, liver disease
- normal MCV—early stage of vitamin B_{12}, folate and iron deficiency anaemias, anaemic globinopathy
- decreased MCV—iron deficiency anaemia, RBC fragmentation, HbH disease.

Reticulocyte count

Using microscopy..... 10–100 × 10^9/L (0.2–2% of total number of RBCs)

The reticulocyte count gives an indication of the ability of the bone marrow to respond to anaemia and produce RBCs. The count will be reduced in untreated anaemia arising from iron, folate or vitamin B_{12} deficiency and elevated in acute bleeding and haemolysis.

Enzymes

Alpha$_1$-antitrypsin

Serum (method dependent) .....0.9–1.7 g/L

Alpha$_1$-antitrypsin deficiency is seen in approximately 1% of patients with emphysema. However, it is more common in younger patients. Neonatal jaundice and hepatic cirrhosis in children are often associated with alpha$_1$-antitrypsin deficiency.

Amylase

.....(method dependent) 70–300 U/L

Amylase is present in large amounts in the pancreas and salivary glands; with smaller amounts found in other tissues. Plasma amylase is elevated in the following conditions: acute pancreatitis (usually >5 × normal), other acute abdominal conditions (perforated peptic ulcer, acute biliary obstruction and small bowel obstruction), salivary gland disease (e.g. mumps), renal disease, opioid-induced spasm of the sphincter of Oddi (2–10 × normal) and macroamylasaemia. Serum amylase does not correlate with the severity of disease, nor does it help in distinguishing acute pancreatitis from other diseases masquerading as pancreatitis.

Creatine kinase

Adult female ..... 30–180 U/L

Adult male ..... 60–220 U/L

Neonate ..... 70–380 U/L

CK-MB .....<4 micrograms/L (<10 U/L)

Creatine kinase (CK) is an enzyme that exists as three isoenzymes[7]:

- CK-MM from skeletal muscle, which accounts for >94% of total CK
- CK-MB from cardiac muscle but with a small contribution from skeletal muscle
- CK-BB from brain tissue which is found in low concentration and is clinically unimportant except occasionally in tumours.

Elevation of creatine kinase may be used as a marker of muscle damage due to trauma or exercise or from medicines that can cause muscle damage (e.g. statins, fibrates) or acute myocardial infarction. An elevated CK, where the MB isoenzyme (CK-MB) is >4 micrograms/L and >2.0% of the total CK, indicates acute myocardial damage. CK testing has largely been superseded by use of troponin levels, although due to CK's short half-life compared with cardiac troponins it may be used to detect re-infarction.

Lactate dehydrogenase

.....(method and age dependent) 110–230 U/L

Lactate dehydrogenase (LDH) is an intracellular enzyme found in the kidney, heart, skeletal muscle, brain, liver and lungs. Increases are usually found in cellular death and/or leakage from the cells. It has traditionally been used to test for myocardial infarcion, but with the advent of more specific cardiac markers such as troponin, the use of LDH has fallen out of favour.[8]

Decreased levels of the enzyme may be seen in cases of malnutrition, hypoglycaemia, adrenal exhaustion and low tissue or organ activity.

Iron homeostasis

Ferritin

Female (pre-menopausal) .....15–200 microgram/L

Female (post-menopausal) and male.....30–300 microgram/L

Ferritin is the main iron storage protein present in the reticulo-endothelial cells of the liver, bone marrow and spleen. It is used as a measure of total body iron stores and may be low before serum iron has substantially

declined.[3] Levels are markedly reduced (<10 microgram/L) in patients with iron deficiency anaemia. Ferritin levels are increased with increased iron stores and iron overload (e.g. primary haemochromatosis 500–5,000 microgram/L).

Iron

.....10–30 micromol/L

Iron is needed to make some proteins, haemoglobin, myoglobin and cytochrome. It is necessary for oxygen transport, cellular respiration and peroxide deactivation. Low levels are seen in many anaemias, copper deficiencies, low vitamin C intake, liver disease, chronic infections, high calcium intake and women with heavy menstrual flows. High levels are seen in haemochromatosis, liver damage, pernicious anaemia and haemolytic anaemia.

Total iron-binding capacity

.....45–80 micromol/L

Total iron-binding capacity (TIBC) measures the iron-binding capacity of transferrin. In iron deficiency the levels of transferrin are increased, so TIBC is increased. However, as serum iron is low, the percentage transferrin saturation is decreased. Infections, malignant tumours and uraemia may reduce TIBC and serum iron.

Transferrin

.....1.7–3.0 g/L

Transferrin is the iron transport protein. Estimation of transferrin levels has largely replaced TIBC. Transferrin levels are elevated in iron deficiency anaemia. They are reduced secondary to inflammation and chronic liver disease.

Leucocytes

White blood cell count

Total white blood cell (adults)..... 4–11 × 10^9/L

Differential count:

Neutrophils ..... 2.0–7.5 × 10^9/L

Basophils.....<0.1 × 10^9/L

Eosinophils..... 0.04–0.4 × 10^9/L

Lymphocytes ..... 1.5–4.0 × 10^9/L

Monocytes ..... 0.2–0.8 × 10^9/L

An increased total white blood cell (WBC) count usually indicates the presence of infection, inflammation, tissue necrosis, or leukaemic neoplasma. Trauma or stress may also increase WBC count. Serial total WBC and differential counts may be diagnostic and prognostic.[2]

Neutrophils, also known as granulocytes, or segmented neutrophils, are the main defender of the body against infection and antigens. High levels may indicate an active infection; a low count may indicate a compromised immune system or depressed bone marrow (low neutrophil production). Neutrophilia (neutrophil count >7.5 × 10^9/L) may be caused by acute bacterial infection, trauma, myocardial infarction, chronic bacterial infection, leukaemia and certain drugs, notably corticosteroids, lithium and colony-stimulating factors.[8] Neutropenia (neutrophil count <1.5 × 10^9/L) and agranulocytosis (neutrophil count <0.25 × 10^9/L) place the patient at increased risk of infection. Depression of the neutrophil count may occur due to drugs (e.g. cytotoxic agents, ticlopidine, antithyroid agents, ganciclovir, clozapine), overwhelming bacterial infection, vitamin B_{12} and folate deficiency, salmonellosis and pertussis.

Lymphocytes are involved in protection of the body from viral infections such as measles, influenza, rubella and chickenpox or infectious mononucleosis. Lymphocytosis, and an elevation of the lymphocyte count (>4 × 10^9/L), may be encountered in pertussis, tuberculosis, lymphoma and syphilis. Lymphopenia, a reduction in the lymphocyte count (<1 × 10^9/L), may occur in patients with HIV/AIDS, Hodgkin's lymphoma and aplastic anaemia and following radiation exposure.

Monocytes are helpful in fighting severe infection and are considered the body's second line of defence against infection. They are the largest cells in the blood stream. Elevated levels (>0.8 × 10^9/L) occur in the recovery phase of acute bacterial infection, leukaemia (monocytic), disseminated tuberculosis, endocarditis, and protozoal or rickettsial infection.

Eosinophilia is usually associated with allergic disorders (e.g. asthma, drug reactions) and parasitic infections. A low eosinophil count (eosinopenia, <0.04 × 10^9/L) may be seen in acute infections.

Basophilic activity is not fully understood, but these cells are known to carry histamine, heparin and serotonin. Basophils are probably involved in immediate as well as delayed hypersensitivity reactions. High levels are found in chronic inflammation and certain leukaemias.

Lipid profile

In patients with an increased risk of cardiovascular events more stringent target levels than shown here may apply.

High-density lipoprotein

Female .....1.0–2.2 mmol/L

Male .....0.9–2.0 mmol/L

Target goal with increased CV risk..... >1.0 mmol/L

High-density lipoprotein (HDL) is the cholesterol carried by the alpha lipoproteins. A high level of HDL is an indication of a healthy metabolic system if there is no sign of liver disease or intoxication. HDL offers protection against chronic heart disease because it:

- inhibits cellular uptake of LDL
- serves as a carrier to remove cholesterol from the peripheral tissues and transport it back to the liver for catabolism and excretion.

Very high triglyceride levels can falsely elevate the measured HDL level.[9]

Low-density lipoprotein

.....2.0–3.4 mmol/L

Target goal with increased CV risk.....< 2 mmol/L

Low-density lipoprotein (LDL) is the cholesterol-rich remnant of the lipid transport vehicle, VLDL (very low density lipoprotein). There have been many studies to correlate the association between high levels of LDL and arterial atherosclerosis.

LDL is calculated using the Friedewald formula:

$$\text{LDL} = \text{total cholesterol} - \text{HDL} - \frac{\text{triglyceride}}{2.2}$$

Ratio: total cholesterol/HDL cholesterol

The ratio of total cholesterol to HDL is used as a marker of cardiovascular risk (e.g. NZ Cardiovascular Risk Calculator).[10]

Total cholesterol

Desirable goal .....<5.5 mmol/L

At increased CV risk.....<4 mmol/L

Cholesterol is a structural component of cell membrane and plasma lipoproteins and is important in the synthesis of steroid hormones, glucocorticoids and bile acids. Most cholesterol is synthesised in the liver, but some is absorbed through the diet, especially one high in saturated fats. HDL is cardioprotective. LDL and VLDL are involved in the pathogenesis of atherosclerotic plaques. Elevated cholesterol levels are associated with polygenic hypercholesterolaemia, familial hyperlipoproteinaemia, a high-fat diet, diabetes mellitus, hypothyroidism, nephrotic syndrome and the use of various drugs (e.g. cyclosporin, isotretinoin).

Low cholesterol levels may be seen in depression, malnutrition, liver insufficiency, malignancies, anaemia and infection.

Total triglycerides

Fasting .....<1.7 mmol/L

Target goal with increased CV risk.....<1.5 mmol/L

Triglycerides, stored in adipose tissue as glycerol, fatty acids and monoglycerides, are reconverted to triglycerides by the liver. 90% of the dietary intake and 95% of the fat stored in tissues consists of triglycerides.

Accurate triglyceride levels depend on prolonged fasting and are sensitive to weight change and many medications (e.g. diuretics and oral contraceptives).[3] Increased levels may be present in metabolic syndrome, uncontrolled diabetes, alcohol excess, atherosclerosis, hypothyroidism, liver disease, pancreatitis, myocardial infarction, metabolic disorders, toxaemia, and nephrotic syndrome. Decreased levels may be present in chronic obstructive pulmonary disease, brain infarction, hyperthyroidism, malnutrition and malabsorption.

Liver function tests

Liver function tests (LFTs) are used to detect liver damage or disease.[6] The term 'liver function tests' can be misleading as only bilirubin and albumin levels reflect liver function; bilirubin levels are indicative of the excretory function and albumin the synthetic function. Only gamma glutamyltransferase is specific for the liver. Aspartate aminotransferase is also found in muscle; lactate dehydrogenase has many sources, including red blood cells and cardiac and skeletal muscle; and alkaline phosphatase is found in bone and intestine as well as liver.

Because of this, although elevated LFT results are associated with liver inflammation, chronic liver disease is frequently associated with only mild to moderate enzyme elevations.

Alkaline phosphatase

Adult (non-pregnant)..... 25–100 U/L

Growing child..... 70–350 U/L

The highest concentrations of alkaline phosphatase (ALP) are found in the bone, liver, placenta and biliary tract epithelium. Elevations seen in liver disease are primarily due to hepatobiliary obstruction but also occur in many other types of liver disease. Another source of raised ALP is bone (e.g. in Paget's Disease). Growing children normally have higher levels of this enzyme, as do pregnant females and people aged over 50.

A simultaneous elevation of 5-nucleotidase establishes liver disease as the cause of an elevated ALP.

ALP levels may be low in vitamin D excess, milk–alkali syndrome, scurvy, hypophosphatasaemia and hypothyroidism.

Aminotransferases

Alanine aminotransferase (ALT) .....<35 U/L
(formerly called serum glutamic-pyruvic transaminase, or SGPT)

Aspartate aminotransferase (AST).....<40 U/L
(formerly called serum glutamic-oxaloacetic transaminase, or SGOT)

The aminotransferases are very sensitive indicators of hepatic inflammation and necrosis. Damage to the hepatocyte results in release of the enzymes into the circulation.

Markedly elevated levels (>1,000 U/L) usually indicate viral hepatitis, severe drug or toxic reactions or hepatic ischaemia. However, the level of elevation is not a reliable marker of hepatic dysfunction or damage.

ALT is found primarily in the liver and so is a more specific marker of hepatocellular damage. It is, however, found in other tissues and may be elevated in muscular damage, acute myocardial infarction and renal infarction. Haemolysis is associated with falsely elevated levels.
AST is an enzyme found primarily in the liver, heart, kidney, pancreas and muscles. Elevated levels are seen in cases of hepatocellular damage, acute myocardial infarction (in this case all other liver function tests remain normal), musculoskeletal diseases (e.g. polymyositis, muscular dystrophy, muscle crush injury), intestinal injury, haemolysis, hypothyroidism, pulmonary embolism and necrotic tumours. Vitamin B_6 deficiency and pregnancy are two instances where the enzyme may be decreased.

Bilirubin

Total ..... <20 micromol/L

Direct..... <7 micromol/L

Bilirubin is a breakdown product of haemoglobin that is conjugated and eliminated by the liver. Total bilirubin comprises unconjugated, conjugated and delta bilirubin, whereas direct bilirubin comprises conjugated and delta bilirubin.

Jaundice is usually not detectable until bilirubin is >50 micromol/L. The three main reasons for the elevation of plasma bilirubin are:

- intravascular haemolysis
- failure of conjugation mechanisms within the hepatocytes
- obstruction in the biliary system.

The different causes of jaundice are associated with different patterns of biochemical abnormalities, as shown in Table D.2 below.

Gamma glutamyltransferase (GGT)

Female .....<30 U/L

Male .....<50 U/L

Gamma glutamyltransferase (glutamyltranspeptidase) is a microsomal enzyme believed to be involved in the transport of amino acids and peptides into cells and in glutathione metabolism. It is mainly found in liver cells. Its main clinical applications are as a sensitive indicator of early liver disease or alcoholism. Increased levels occur following microsomal induction, particularly by alcohol, herbal remedies and drugs such as some anticonvulsants.[9]

Metabolic function tests

Ammonium

Adult, plasma ..... <50 micromol/L

Infant.....64–107 micromol/L

Serum ammonia may be elevated in patients with acute or chronic liver disease, resulting in hepatocellular damage. In patients with cirrhosis, portal shunting of blood results in ammonia from the gut bypassing the liver, resulting in hyperammonaemia and hepatic encephalopathy.[11]

Serum ammonia may also be elevated as a result of genetic defects in urea formation. In the most severe

Table D.2 Biochemical abnormalities associated with different types of jaundice

Jaundice type	Causes	Bilirubin	Alkaline phosphatase	AST, ALT
Pre-hepatic	• Haemolysis • Hereditary uptake disorders	↑ (unconjugated)	Normal	Normal
Intra-hepatic damage	• Hepatitis • Drugs	↑ (mostly conjugated)	Normal—↑	↑↑
Intra-hepatic cholestasis	• Viral hepatitis • Biliary cirrhosis • Drugs • Metastases • Cysts	↑ (mostly conjugated)	↑	Normal—↑
Post-hepatic	• Gallstones in common bile duct • Compression of common bile duct	Normal—↑ (conjugated)	↑↑	Normal—↑

Note: AST = aspartate aminotransferase; ALT = alanine aminotransferase.

cases there is an absence of enzyme activity, and neonates present within the first week of life with hyperammonaemic coma; in milder cases, where patients have some enzyme activity, they present later in life (infancy or adulthood) with recurrent episodes of hyperammonaemia. High ammonia levels lead to brain oedema. Neonates may present with symptoms of vomiting, lethargy and confusion at levels of 100 to 200 micromol/L, with higher levels associated with coma.[12]

Beta-hydroxybutyrate

.....<1.2 mmol/L

Beta-hydroxybutyrate is a metabolite of fatty acids, and its levels are elevated in patients with diabetic ketoacidosis.

Blood gases (arterial)

pH 7.36–7.44

pCO_2 ..... 35–45 mmHg (4.6–6.0 kPa)

pO_2.....80–100 mmHg (11.0–13.5 kPa)

Bicarbonate..... 22–28 mmol/L

Base excess .....–3 to +3 mmol/L

O_2 ..... saturation>95%

The pH provides information on the patient's acid–base status. A reduced pH indicates acidosis and an elevated pH indicates alkalosis.

The partial pressure of carbon dioxide (pCO_2 or $PaCO_2$) is used to assess the ability of the lungs to excrete carbon dioxide. Hypercapnia (pCO_2 >45 mmHg or 6 kPa) is usually due to either hypoventilation or ventilation perfusion mismatch.

The partial pressure of oxygen (pO_2 or PaO_2) provides information on the level of oxygenation of arterial blood. In cases of effective circulation and a normal pO_2, oxygen supply to the tissues is usually adequate. Where pO_2 falls in conjunction with an elevated pCO_2, the fall in pO_2 will stimulate the respiratory centre, correcting the hypercapnia but not the hypoxia. If a patient breathing room air at rest has a pO_2 <8 kPa they are in respiratory failure. Classically, hypoxia with carbon dioxide retention is classified as type 2 respiratory failure, whereas hypoxia without carbon dioxide retention is type 1. The pO_2 is critical to oxygen saturation. Oxygen saturation will remain above 90% as long as the pO_2 remains above 8 kPa. If, however, pO_2 falls below 8 kPa, rapid oxygen desaturation can occur, resulting in severe tissue hypoxia.

Cortisol

Morning peak level.....200–650 nanomol/L

Trough (approx 8 pm) ..... <50% of the morning peak

Elevated serum cortisol levels are seen in patients with Cushing's syndrome. The diagnosis is confirmed using a 24-hour urinary cortisol excretion test or a dexamethasone suppression test. A low serum cortisol may indicate primary (Addison's disease) or secondary adrenal dysfunction. In primary adrenal insufficiency, adrenocorticotropic hormone (ACTH) will not induce any increase in serum cortisol, but in secondary adrenal insufficiency, due to hypothalamus pituitary axis (HPA) depression, the administration of ACTH will elicit a rise in serum cortisol.

Glucose

Fasting ..... 3.0–5.4 mmol/L

Glucose, which is formed by the digestion of carbohydrates and the conversion of glycogen by the liver, is the primary source of energy for most cells. Insulin, glucagon, thyroid hormone, liver enzymes and adrenal hormones regulate the glucose level. Elevated levels occur in diabetes mellitus, liver disease (cirrhosis), obesity and pancreatitis. Serum glucose may also be elevated by glucocorticosteroids, stress and diet. Low levels may be indicative of extensive liver disease, overproduction of insulin, hypothyroidism or alcoholism. Diabetes mellitus should be suspected in any person with a fasting blood glucose ≥7.0 mmol/L or a random blood glucose >11.1 mmol/L. Symptoms of hypoglycaemia are not usually seen until blood glucose falls below 2.2 mmol/L.

Glucose tolerance test (2 hours after 75 g glucose load)

Normal.....<7.8 mmol/L

Impaired glucose tolerance ..... 7.8–11.0 mmol/L

Diabetes mellitus .....≥11.1 mmol/L

The glucose tolerance (GTT) test is used in patients with equivocal fasting glucose test results.

Glycosylated haemoglobin (HbA_{1C})

..... <7%

Haemoglobin A combines with glucose to form glycosylated haemoglobin. The proportion of haemoglobin (HbA_{1C}) in the glycated form gives an indication of the blood glucose concentration over the preceding three months (the life of a red blood cell). The test provides an accurate long-term indicator of the patient's average blood glucose level.

Osmolality

Adult ..... 280–300 mOsmol/kg H_2O (280-300 mmol/kg – SI units)

Osmolality is an indicator of hydration status, being elevated in patients who are volume depleted (dehydrated) and lowered in those patients who are over hydrated. It may, however, be elevated in the presence of hyperglycaemia. In the presence of an elevated serum osmolality the urine osmolality should increase as the body attempts to retain fluid. The opposite should occur in cases of reduced serum osmolality, where the normal body response would be to produce large volumes of dilute urine. Patients are said to exhibit the syndrome of inappropriate antidiuretic hormone (SIADH) when their serum osmolality is low (<280 mOsmol/kg) yet the urine is inappropriately concentrated (>300 mOsmol/kg).

Thyroid function tests

Free thyroxine (T_4) .....10–25 picomol/L

Free liothyronine (T_3) .....4.0–8.0 picomol/L

Thyroid stimulating hormone (TSH).....0.4–5.0 mIU/L

TSH is used as a screening test to evaluate thyroid function. T_3 test is used primarily to diagnose hyperthyroidism and amiodarone-induced thyrotoxicosis.[2,3] In patients with primary hyperthyroidism (e.g. Graves' disease) TSH levels are suppressed, whereas in those with primary hypothyroidism the TSH levels are elevated. In patients with secondary (pituitary dysfunction) and tertiary (hypothalamic dysfunction) hypothyroidism both T_4 and TSH levels are reduced.

Increased levels of thyroxine are found in hyperthyroidism, acute thyroiditis and hepatitis. Low levels of thyroxine can be found in cretinism, hypothyroidism, cirrhosis, malnutrition and chronic thyroiditis. T_4 and TSH are used when monitoring therapy. Values of T_4 up to 35 picomol/L may be acceptable for patients receiving full replacement therapy with thyroxine. Low TSH levels may represent over-replacement with thyroxine. In patients with acute non-thyroid illness thyroid function test may be difficult to interpret. Up to 70% of such patients admitted to hospital develop 'euthyroid sick syndrome' with low thyroxine levels and elevated TSH. This usually resolves without the need for treatment.

Urea

..... 3.0–8.0 mmol/L

Urea is the end product of protein metabolism. Therefore serum urea concentrations are influenced by both the rate of protein breakdown and the protein's renal excretion. Increases can be caused by excessive protein intake, kidney damage, certain drugs, dehydration, gastrointestinal bleeding, excessive sweating during exercise and heart failure. Decreased levels may be associated with malnutrition, malabsorption, liver damage and low nitrogen intake. A high serum urea to serum creatinine ratio may indicate prerenal failure (secondary to volume depletion or decreased cardiac output) or gastrointestinal haemorrhage. Alternatively, a low urea to creatinine ratio may indicate liver dysfunction or excessive muscle breakdown (rhabdomyolysis) (see Table D.3).

Uric acid (urate)

Female ..... 0.15–0.40 mmol/L

Male ..... 0.20–0.45 mmol/L

Catabolism of purines results in the formation of uric acid, which is normally excreted in the urine. Elevated uric acid levels (hyperuricaemia) are noted in gout, infections, kidney disease, alcoholism, high-protein diets, in association with tumour lysis syndrome and with toxaemia in pregnancy. Low levels may be indicative of Fanconi's syndrome, pregnancy, Wilson's disease, drug effects, malabsorption, poor diet or liver damage.

Plasma proteins

Albumin

.....32–45 g/L (varies with age)

Albumin, the main constituent of serum protein (usually over 50%), is synthesised in the liver. Hypoalbuminaemia may result from:

- increased albumin loss (nephrotic syndrome, burns, Crohn's disease)
- increased catabolism (infection, trauma, thyrotoxicosis)
- decreased synthesis (chronic hepatitis, severe acute hepatitis, malnutrition).

Clinical effects become particularly apparent when the serum albumin falls below 30 g/L; such effects include peripheral oedema, ascites and pulmonary oedema.[13] Protein binding of drugs such as phenytoin and warfarin is reduced.

Hyperalbuminaemia is seen rarely in liver disease, shock, dehydration or multiple myeloma.

C-reactive protein

..... <5 mg/L

C-reactive protein (CRP) is an acute-phase reactant produced by the liver in response to cytokine release during inflammation. Levels rise and fall more quickly than ESR (erythrocyte sedimentation rate). CRP has been used in clinical practice to follow systemic inflammation (especially bacterial infection, systemic lupus erythematosus, and rheumatoid arthritis). Basal levels of CRP, in the absence of apparent inflammatory disease, may be useful for predicting myocardial or

cerebrovascular events, although biological and analytical variability currently limit routine clinical use.[8,9]

Globulins

Alpha$_1$-globulin .....2–4 g/L

Alpha$_2$-globulin .....4–9 g/L

Beta-globulin.....6–12 g/L

Gamma-globulin.....6.5–16 g/L

Globulin, a larger protein than albumin, is important for its immunologic responses, especially its gamma portion (IgA, IgG, IgM and IgE).[2] Globulins have diverse functions, such as transporting some hormones, lipids, metals and antibodies. When chronic infections (liver disease, rheumatoid arthritis, myeloma, and systemic lupus erythematosus) are present, elevated levels are seen. Lower levels may be associated with immunocompromised patients, poor dietary habits, malabsorption, and liver or kidney disease.

Rheumatoid factor

.....<30 IU/L

Rheumatoid factor (RF) consists of auto-antibodies of the IgM class. Approximately 80% of patients with rheumatoid arthritis have positive RF levels, and a negative result does not exclude a diagnosis of rhemumatoid arthritis.

Total protein

.....62–80 g/L

Proteins are the most abundant compounds in serum. They are constituents of enzymes, hormones and antibodies and contribute to osmotic pressure balance, maintaining acid–base balance, and act as a reserve source of nutrition for muscle and other body tissues. The main serum proteins measured are albumin and globulins (alpha$_1$, alpha$_2$, beta and gamma). In reviewing total protein, it is important to consider the individual's albumin, globulin and albumin–globulin ratio. A reduction in the albumin–globulin ratio may indicate the presence of multiple myeloma.

Troponin

Cardiac troponin I .....<2.0 micrograms/L

Cardiac troponin T.....<0.1 microgram/L

Troponins are proteins in skeletal and cardiac muscle that regulate contraction of striated muscle. Structurally unique forms of troponin T and troponin I are found in cardiac tissue.[2,7,9]

These proteins are normally undetectable in plasma but are reliably elevated after acute myocardial infarction. In myocardial injury troponins become elevated sooner and remain elevated longer than creatine kinase–MB (a specific isoenzyme of creatine kinase).[2] Concentrations rise within four to 12 hours of commencement of cardiac pain and remain elevated for seven days in the case of troponin I or 10 days for troponin T.

They may be used to differentiate between cardiac and skeletal muscle injury, detect minor myocardial cell damage in coronary insufficiency syndromes, detect peri-operative myocardial infarction, estimate infarct size and assess the therapeutic success of reperfusion therapy. In 'unstable angina' even a minor increase in troponin T should be regarded as defining the episode as a myocardial infarction.[1]

Elevated troponin levels are also seen in patients with chronic renal failure, including those on dialysis. These troponins are likely to be cardiac in origin, arising from uraemic myocarditis or coronary artery disease.

Renal function tests

Diseases that affect the blood vessels, such as diabetes, hypertension and atherosclerosis, impair the kidneys' ability to filter blood and regulate fluids. Renal impairment may be symptom free until late in its course and can lead to end-stage kidney failure. For this reason management of some conditions requires routine use of tests such as serum creatinine, serum urea and urinary albumin.

Creatinine[1,9]

Adult female .....50–100 micromol/L

Adult male .....50–120 micromol/L

Creatinine is the metabolic product of muscle metabolism. Its level is a reflection of both muscle mass and kidney function, since it is principally eliminated by glomerular filtration through the kidney. Low levels may indicate protein starvation, liver disease or pregnancy. Elevated levels are seen in kidney failure and muscle degeneration and as a result of some drugs blocking its renal secretion (e.g. cimetidine, trimethoprim).

Alterations in the urea–creatinine ratio can have modest diagnostic implications, as shown in Table D.3. When serum urea (reference range 3.0–8.0 mmol/L) is expressed as mmol/L and creatinine as micromol/L, the urea–creatinine ratio is approximately 1:20.[14] As urine flow falls, tubular reabsorption of urea is enhanced and is reflected by a change in the urea–creatinine ratio.[15] This effect is seen in prerenal and postrenal failure. If there is an increase in protein intake or catabolism, a similar pattern is seen. In cases where there is an increase in muscle breakdown, and hence creatinine production, the opposite is seen. The same is true where there is a reduction in urea production (e.g. severe liver disease, low-protein diet) or an increase in urea elimination disproportionate to creatinine (e.g. renal dialysis).[9]

Table D.3 Urea–creatinine ratio

Where both urea and creatinine are raised proportionately, the urea–creatinine ratio may remain normal (↑ urea with ↑ creatinine)
Renal failure
Increased urea–creatinine ratio (↑↑↑ urea with ↑ creatinine)
Prerenal failure due to an absolute or relative hypoperfusion of the kidney
Postrenal failure due to obstruction of urine flow (e.g. urethral stricture)
Dehydration
Heart failure
Haemorrhage
Gastrointestinal tract bleeding
Excessive diuresis
Increased protein breakdown (e.g. trauma, corticosteroids)
Decreased urea–creatinine ratio (↑ urea with ↑↑↑ creatinine)
Rhabdomyolysis
Impaired tubular secretion (e.g. cimetidine, trimethoprim)
Post-dialysis state
Decreased urea–creatinine ratio (↓ urea with ↑ or N creatinine)
Advanced liver failure
Pregnancy
Low-protein diet
High fluid intake

Diagnosis is made on the basis of the history, clinical examination and further investigations. Comparison of serum creatinine levels with levels obtained previously can be used to differentiate acute and chronic changes in renal function, while the urea–creatinine ratio can be used as a guide to the possible cause of a patient's renal dysfunction. In the management of renal failure it is important to differentiate between acute and chronic renal failure and prerenal, intrarenal and postrenal causes in order to ensure the most appropriate treatment.

Creatinine clearance

Creatinine clearance (Cl_{cr}) is an estimate of the glomerular filtration rate (GFR), which is a direct measure of renal function. The value can be calculated by dividing the urine creatinine (derived from a 24-hour urine collection) by the serum creatinine. With each decade of age the Cl_{cr} falls 6.5 L/min because of a decrease in GFR.[2]

Inaccuracies arising from incomplete urine collection may be overcome by the use of a calculated creatinine clearance using serum creatinine levels (e.g. Cockcroft–Gault equation or Modified Diet of Renal Disease formula).

eGFR

Female ..... 85–160 mL/min/1.73 m^2 surface area

Male ..... 75–190 mL/min/1.73 m^2 surface area

The abbreviated Modified Diet of Renal Disease (MDRD) formula is used to estimate GFR and assists the early detection of renal disease. This formula uses only the patient's serum creatinine (micromol/L), age and sex. If eGFR is >60 and <90 mL/min/1.73 m^2, further investigation may be indicated in those at increased risk (e.g. diabetes). Further investigation is routinely required if the eGFR <60 mL/min/1.73 m^2.[16] An eGFR between 30–59 mL/min/1.73 m^2 indicates moderate kidney disease, 15–29 mL/min/1.73 m^2 severe kidney disease, and <15 mL/min/1.73 m^2 end-stage renal disease. An eGFR calculator is available at the Kidney Health Australia website—www.kidney.org.au/healthprofessionals/egfrclinicaltools/tabid/632/language/en-gb/default.aspx.

For futher information see 'Dosing and renal impairment', Section D.

Cockcroft–Gault equation

The Cockcroft–Gault equation should be used to estimate GFRs for drug dosage adjustments.

$$\text{Creatinine clearance } (Cl_{cr}) \text{ in mL/min} = \frac{(140 - \text{Age (years)}) \times \text{ideal body weight (kg)}}{0.815 \times \text{serum creatinine (micromol/L)}}$$

For females, multiply by 0.85 to account for the reduced muscle to ideal body weight ratio in comparison with males.

Ideal body weight for males =
50 kg + 0.9 kg/for each cm above 152 cm

Ideal body weight for females =
45.5 kg + 0.9 kg/for each cm above 152 cm

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

The *Australian Medicines Handbook* defines the following categories of renal impairment for dosage adjustments:

- mild impairment ..... 25–50 mL/min
- moderate impairment..... 10–25 mL/min
- severe impairment.....< 10 mL/min

Tests relating to blood clotting

Activated partial thromboplastin time

Normal (baseline) range ..... 25–35 seconds

Anticoagulation therapeutic range ..... 1.5–2.5 times normal (baseline) range

This test is used to monitor the efficacy of unfractionated heparin.

Anti-Factor Xa

Continuous IV infusion ..... 0.5–1.0 anti-Xa units/mL

Subcutaneous injection
..... > 0.3 anti-Xa units/mL (trough)
..... < 1.0 anti-Xa units/mL (peak)

The recommended test for monitoring low molecular weight heparin (LMWH) is an anti-factor Xa (anti-Xa) assay. LMWH, unlike unfractionated heparin, does not affect the activated partial thromboplastin time (APTT). Patients with renal failure, extremes of body weight, or in situations where there is an increased risk of bleeding may have their dose of LMWH adjusted for a given anti-Factor Xa result.

International normalised ratio

Normal (baseline) range 0.9–1.3

The international normalised ratio (INR) is also a marker of the activity of the extrinsic coagulation pathway[2], and is elevated by the same conditions as those affecting prothrombin time. INR is used as the standard monitoring parameter for patients on oral anticoagulants.

Target range for oral anticoagulation
for all indications 2.0–3.0

except:

- thrombosis associated with antiphospholipid antibodies 3.0–4.0
- mechanical prosthetic heart valves 2.5–3.5

Platelet count

Normal range ..... 150–400 × 10^9/L

Certain diseases affect platelet number. Stress and infection are associated with thrombocythaemia, as may be splenectomy, trauma, asphyxiation, rheumatoid arthritis, iron deficiency anaemia, haemorrhage, cirrhosis, chronic pancreatitis, tuberculosis and recovery following bone marrow transplantation. In these cases the values rarely exceed 500–800 × 10^9/L. Platelet counts >800 × 10^9/L occur in primary thrombocythaemia, polycythaemia rubra vera, chronic myelogenous leukaemia and myelosclerosis.

Thrombocytopenia is defined as a platelet count <150 × 10^9/L. Platelet counts <50 × 10^9/L may be associated with increased risk of bleeding with trauma, whereas platelet counts <20 × 10^9/L are associated with an increased risk of spontaneous bleeding. Thrombocytopenia may occur in idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation and haemolytic–uraemic syndrome. Numerous drugs may also decrease platelet levels, especially heparin, quinine and antineoplastic agents.

Prothrombin time

Normal (baseline) range ..... 11–15 seconds

Anticoagulation therapeutic range ..... >1.5–2 times normal (baseline) range

Prothrombin time (PT) is an indicator of the activity of the extrinsic coagulation pathway[2] and may be used as an indicator of the effectiveness of oral anticoagulants. It may be elevated in patients with poor dietary intake of vitamin K, malabsorption of fat-soluble vitamins and chronic liver disease.

Vitamins

Folic acid

Serum folate ....7–45 nmol/L

Red cell folate ..... 360–1400 nmol/L

Serum folate levels are of minimal diagnostic value since levels may be reduced with a short-term decrease in dietary intake and in systemic illness.[1] Red cell folate is a direct measure of tissue folate stores and falls after about four months of negative folate balance.[9]

Low folate levels may arise due to poor dietary intake, increased folate requirements (e.g. pregnancy, renal dialysis), malabsorption (e.g. coeliac disease, tropic sprue, giardiasis) and certain drugs (e.g. methotrexate, anticonvulsants, proton pump inhibitors). Low folate levels may result in macrocytic anaemia, neural tube defects (in newborns), cardiovascular disease (as a result of elevated homocysteine levels) and cognitive impairment.

High levels usually are a result of vitamin supplementation or the ingestion of a folate-rich meal.

Vitamin B_{12}

Normal..... 120–680 picomol/L

Deficiency of vitamin B_{12} can be associated with a range of non-haematological signs and symptoms. In co-existing vitamin B_{12} and folate deficiency, the haematological signs (low haemoglobin) may

correct with folate replacement, but the neurological symptoms may continue to progress without vitamin B_{12} replacement.

Signs and symptoms of vitamin B_{12} deficiency are classified as:

- haematological (megaloblastic anaemia, pancytopenia)
- neurological (paraesthesia, peripheral)
- neuropathy and combined systems disease)
- psychiatric (irritability, personality change)
- dementia (depression, psychosis)
- cardiovascular (possible increased risk of myocardial infarction and stroke).

Vitamin B_{12} deficiency may also be associated with pallor, slight jaundice, anorexia, mild weight loss, diarrhoea, dyspnoea, palpitations, weakness, vertigo, tinnitus, mild fever, urination difficulty and atrophic glossitis.

Where the vitamin B_{12} level is only mildly reduced but there are symptoms suggestive of vitamin B_{12} deficiency, methylmalonic acid (for which vitamin B_{12} acts as a cofactor during amino acid metabolism) and homocysteine levels may also be useful.[5] Methylmalonic acid levels are elevated when vitamin B_{12} levels are low, whereas elevations in homocysteine levels may reflect vitamin B_{12} or folate deficiency among other things.

Urine studies[1,2,17,18]

Calcium

..... 2.5–7.5 mmol/24 hours

Increased urinary excretion occurs with high dietary calcium intake, increased mobilisation of calcium from bone, and most conditions associated with hypercalcaemia. Hypercalciuria is a risk factor for renal calculi.[1]

Catecholamines

Adrenaline ..... <80 nanomol/24 hours

Noradrenaline..... <780 nanomol/24 hours

Dopamine ..... <3,500 nanomol/24 hours

Urinary catecholamine levels are raised in patients with phaeochromocytoma and are used in the diagnosis of that condition. Urinary catecholamines may also be increased due to physiological stress (e.g. acute myocardial infarction), drugs, strenuous exercise and food (e.g. bananas).

Chloride

..... 100–250 mmol/24 hours (dependent on intake)

Changes in spot urinary chloride concentration usually mirror those of sodium and may be used in a similar manner. Urinary chloride is also useful for differentiating between hypovolaemic states associated with renal loss of a poorly reabsorbed anion (e.g. bicarbonate, sulfate). In the case of hypovolaemia associated with metabolic alkalosis or proximal renal tubular acidosis, the urinary chloride is low (<10 mmol/L) while the urinary sodium is high (>20 mmol/L).

Copper

.....<1.2 micromol/24 hours

High urinary copper is found in Wilson's disease and in other diseases affecting copper excretion (e.g. primary biliary cirrhosis).

Cortisol (free)

.....100–300 nanomol/24 hours

An abnormally high 24-hour level of free cortisol confirms the diagnosis of Cushing's syndrome. Levels may be elevated in obesity, stress, depression and alcoholism.

Creatinine

Female ..... 5–16 mmol/24 hours

Male ..... 9–18 mmol/24 hours

The level of urinary creatinine depends on age, gender, muscle mass, and amount of meat in diet. It is of no diagnostic value in its own right but can be used with urinary urea levels to assess the concentrating ability of the kidney.

The urine to plasma ratio of either urea or creatinine may be used to differentiate between prerenal uraemia and acute tubular necrosis.

Prerenal uraemia .....≥14:1 (usually >20:1)

Acute tubular necrosis .....≤14:1

Magnesium

.....2.5–8.0 mmol/24 hours (related to daily intake)

Renal wasting of magnesium may occur in patients with renal tubular acidosis.

Oxalate

..... <0.3 mmol/24 hours (method dependent)

Very high oxalate levels occur in patients with ethylene glycol poisoning. Urine oxalate levels of two to three times normal are seen in patients with primary hyperoxaluria. Such patients are at risk of recurrent urinary stones and hypercalcinosis.

pH

..... 4.5–8.0

Any pH near the reference range can be interpreted as normal as long as it reflects the kidney's attempts at regulating blood pH. The urine pH is alkaline in cases of metabolic alkalosis, some urinary tract infections, renal tubular acidosis and ingestion of alkalinising agents. Vegetarians do not produce fixed acid residues, so they have alkaline urine. The urine is acidic following ingestion of certain drugs (e.g. ascorbic acid, ammonium chloride) and foods (e.g. cranberries, plums).

Phosphate

..... 10–40 mmol/24 hours

Phosphate's renal transport is active, saturable, and pH and sodium ion dependent. Low serum and urinary phosphate may be associated with diminished phosphate intake or excessive use of phosphate binding antacids (e.g. Ca^{2+}, Al^{3+}). An increase in urinary phosphate suggests hyperparathyroidism or renal tubular dysfunction. Primary hyperparathyroidism and excessive intake of vitamin D are characterised by hypercalcaemia and increased urinary phosphate levels.

Porphyrins

Porphyrins (total) ..... <250 nanomol/L

Uroporphyrin ..... <40 nanomol/L

Used in the diagnosis of porphyria, although only reliable if the patient is symptomatic when the specimen is collected.[1]

Potassium

..... 40–100 mmol/24 hours (varies with intake)

Twenty-four-hour urinary potassium measurements are of little value if potassium intake is not known. Mineralocorticoid excess, some renal tubular disorders, metabolic alkalosis, some diuretics and Bartter's syndrome cause renal potassium loss.

Spot urine potassium concentration may be used to differentiate between renal (>20 mmol/L) and extrarenal loss (<20 mmol/L).

Protein (total)

.....<150 mg/24 hours

Pregnancy .....<250 mg/24 hours

Excreted proteins consists of albumin, globulins and Tamm-Horsfall protein.[8] The presence of abnormal amounts of total protein (proteinuria) represents the single most important indicator of renal disease. Proteinuria may, however, arise from extrarenal disease (e.g. multiple myeloma, macroglobulinaemia). This is a useful test for assessing the efficacy of drug treatment for renal disease (e.g. ACE inhibitors) and for the detection of specific drug toxicity (e.g. gold, captopril).

Protein (albumin)

Albumin is a small protein molecule that seeps into urinary filtrate when there is increased glomerular permeability and levels are generally below 20 mg/L. Because urine levels of albumin may be affected by hydration status, the albumin/creatinine ratio (ACR) is generally referred to in clinical practice.[2] Microalbuminuria refers to urinary albumin concentrations up to 300 mg/L, which is the minimum sensitivity point for testing with conventional urine dipsticks. Microalbuminuria is used as a marker in diabetics for early nephropathy (where it is reversible with good control of hypertension and hyperglycaemia). It is a powerful risk marker for vascular disease in Type 2 diabetes. Concentrations greater than 300 mg/L are referred to as macroalbuminuria, persistent proteinuria or clinical proteinuria and indicate irreversible nephropathy.

Table D.4 Urinary albumin testing[19]

	Spot urinary albumin–creatinine ratio *morning void* mg/mmol	Albumin excretion rate *timed overnight* microgram/min	24-hour albumin excretion mg/24 hours
Normal	<3.5 (female) <2.5 (male)	<20	<30
Microalbuminuria	3.6–35 (female) 2.6–25 (male)	20–200	30–300
Macroalbuminuria	>35 (female) >25 (male)	>200	>300
Test use	*Initial screening*	*Confirm microalbuminuria*	*Monitor macroalbuminuria*

Sodium

.....75–300 mmol/24 hours

The 24-hour urinary sodium output is dependent on dietary intake, so its estimation is of little value unless sodium intake is known. Spot urinary sodium, in conjunction with serum sodium, may be useful in evaluating patients with volume depletion, oliguria or hyponatraemia. In volume depletion where sodium is being lost through the kidney (e.g. nephritis, hypoaldosteronism, diuretic therapy), the spot urine sodium will be high (>20 mmol/L). Where sodium loss is extrarenal (e.g. diarrhoea), the kidney will attempt to conserve sodium, leading to low urinary sodium (<10 mmol/L). Oliguria secondary to prerenal failure is associated with a low urinary sodium (<10 mmol/L), whereas oliguria due to acute tubular necrosis, in which sodium escapes reabsorption, is associated with high urinary sodium (>20 mmol/L). Where hyponatraemia is secondary to extrarenal loss, the urinary sodium will be low (<10 mmol/L). Hyponatraemia associated with a high urinary sodium (>20 mmol/L) may be caused by renal salt wasting, syndrome of inappropriate antidiuretic hormone release, diuretic use and urinary loss of complex anions.

Specific gravity

..... 1.01–1.022

Specific gravity (SG) reflects the total solids concentration (principally sodium chloride and urea) present in the urine. It varies with urine volume and solids excreted. Loss of diluting (high SG) or concentrating (low SG) capacity is an indication of renal dysfunction. Urine specific gravity may also reflect the degree of hydration (low SG) or dehydration (high SG) of the patient.

Urate (uric acid)

Adult female (normal diet) ..... 1.6–5.6 mmol/24 hours

Adult male (normal diet)..... 2.2–6.6 mmol/24 hours

Purine-free diet .....<3.6 mmol/24 hours

Patients with high uric acid excretion have an increased risk of forming uric acid renal calculi.[1]

Urea

.....420–720 mmol/day

See 'Creatinine' in this 'Urine studies' section for information about use of urine to plasma ratios. Urine urea concentration may be increased in hypercatabolic states, chronic renal failure, post-obstructive nephropathy and post-acute tubular necrosis.

Urine volume

..... 0.6–2.5 L/24 hours

Urine volume is an indicator of both hydration status and kidney function. Patients who are dehydrated will produce small volumes of concentrated urine. Patients who are overhydrated will produce larger volumes of dilute urine. In renal failure there may be reduced (anuria <100 mL/day or oliguria 100–500 mL/day), increased (polyuria >3 L/day) or normal urine output. In patients receiving diuretic therapy for cardiac failure, urine output should increase; however, it should not exceed 1 L per day in order to avoid intravascular dehydration and potential prerenal failure. Drugs (such as lithium) that are toxic to the renal tubule may produce polyuria.

Cerebrospinal fluid studies

CSF volume (adult) ..... 100–160 mL

CSF pressure..... 50–100 mm H_2O

Glucose..... 2.7–4.2 mmol/L

Lactate ..... 1–2 mmol/L

The glucose concentration in the cerebrospinal fluid (CSF) is usually less than plasma glucose, often by up to 1 mmol/L, so it is important to measure the plasma glucose to allow interpretation of the CSF level. The CSF glucose concentration may fall as a result of hypoglycaemia or central nervous system infection. A reduction in the CSF glucose associated with an elevation in CSF white cell count (particularly neutrophils) and an elevated protein level is suggestive of bacterial meningitis. A normal CSF glucose in the presence of an elevated CSF lymphocyte count and normal or moderately elevated protein suggests viral meningitis.

Leucocytes

Total ..... <4 per mL

Differential—Lymphocytes.....60–70%

In patients with bacterial meningitis the leucocyte count is usually elevated above 1,000 per mL, with greater than 60% neutrophils. In the case of viral meningitis the leucocyte count is elevated, but is less than 1,000 per mL and with a predominance of lymphocytes. In fungal meningitis the leucocyte count is usually less than 500 per mL, with an elevated number of lymphocytes.

Protein

.....0.15–0.45 g/L

The CSF protein falls during first year of life from <1.94 g/L for neonates to <0.36 g/L for children 1–10 years old. It may be elevated in central nervous system infections (refer to CSF glucose), chronic inflammatory conditions of the central nervous system (e.g. tuberculosis, syphilis), multiple sclerosis, chronic alcoholism, Guillain–Barré syndrome, blood contamination and Froin's syndrome.

Stool tests

Faecal fat

Total lipid ..... <20 mmol/24 hours

Faecal fat estimations are used to identify steatorrhoea and vary according to the amount of fat in the diet. Higher levels may be associated with malabsorption states secondary to hepatobiliary disease, cystic fibrosis[2], small bowel disease (e.g. coeliac disease), pancreatic disease or lower ileal disease.

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Medicines and older people

There is no widely accepted definition of an 'older person'. The terminology used to describe older people is also variable (e.g. aged, elderly, frail elderly). Although chronological age on its own may not be an appropriate way to categorise people, in general those over 65 (over 50 for Aboriginal and Torres Strait Islander people) are often described as aged, older or elderly.

People over 65 years comprise approximately 12% of the Australian population, but consume a disproportionate number of prescription and other medicines. Older people are more likely to have multiple medical problems and to be taking multiple medications. As a result of this and their advancing age, they experience unique problems with the use of medications. They also experience more adverse events involving medicines than younger people.

Pharmacists can play a role in improving the quality use of medicines in older patients.

Factors complicating medicine use in older people

Changes in pharmacokinetics

A number of physiological changes occur with ageing, and these may modify the absorption, distribution, hepatic metabolism and renal excretion of medicines. Many medicines are cleared more slowly in older people.

In particular, the age-related decline in kidney function may lead to a decrease in the renal clearance of medicines and their metabolites. Decreases in both the glomerular filtration rate and renal clearance of drugs of up to 50% occur between the ages of 25 and 85 years, with a mean decrease of about 1% per year after age 40 years. Common medical conditions in the elderly, such as hypertension and diabetes, can also adversely affect renal function.[1] This is important for those medicines that are predominantly renally cleared (e.g. digoxin, lithium) or that have a renally cleared active metabolite (e.g. allopurinol, morphine). Special care is required in using these medicines, particularly if there is only a small margin between the plasma concentrations that produce the desired clinical effect and those that cause toxicity (i.e. drugs with a narrow therapeutic index). In general, elderly patients require smaller drug doses. It must be recognised, however, that physiological variability increases with age and therefore the dosage regimens must be individualised and reassessed over time.

Alterations in receptor sensitivity and homeostatic mechanisms

Older patients may differ from younger people in their pharmacodynamic sensitivity to medicines: generally, they are more sensitive to the effects of medicines. This may be partly explained by changes in the neuro-endocrine system that occur with ageing. The following examples illustrate this point.

Orthostatic hypotension

The homeostatic mechanism that protects against orthostatic hypotension may be impaired in older people. As a result, they are at increased risk of this adverse effect with any medicine that causes blockade of α-adrenergic receptors as a primary effect (e.g. prazosin) or secondary effect (e.g. tricyclic antidepressants, phenothiazines). In addition, several other vasodilators (e.g. glyceryl trinitrate, isosorbide dinitrate), diuretics, ACE inhibitors and anti-Parkinsonian drugs (e.g. levodopa, bromocriptine, pergolide) are more likely to cause orthostatic hypotension in older people.

Orthostatic hypotension may decrease quality of life by decreasing the person's confidence in their ability to move around and may lead to falls and fractures, which can cause significant morbidity in the elderly.[2]

Central nervous system effects

Hypnotics, anxiolytics and other central nervous system depressant medicines may cause confusion, incontinence and unsteady gait, which may result in falls and fractures. People receiving dopamine agonists (e.g. pergolide, ropinirole) may experience episodes of uncontrollable somnolence that have the potential to compromise safety and quality of life. Benzodiazepine hypnotics are useful drugs but are on occasion over-used, especially in the elderly. These agents lose their effectiveness as hypnotics after about 10 to 14 days' continuous use because of the development of tolerance. Unfortunately, they may continue to exert the effects previously mentioned and therefore lead to significant morbidity in older patients.

Confusion is common in the elderly. Causes include infection (e.g. urinary tract infection), metabolic abnormalities (e.g. acute renal failure), hypothyroidism and electrolyte disturbances, and medicines (e.g. drugs with anticholinergic properties).

Anticholinergic effects

Medicines with anticholinergic effects (e.g. tricyclic antidepressants, some anti-Parkinsonian drugs,

and oxybutynin, as well as some non-prescription medications) may cause the well-known range of adverse effects, including constipation, blurred vision, confusion, dry mouth and urinary retention. Urinary retention is of special concern in older males who may have prostate problems. Patients experiencing urinary frequency may, however, find some benefit from the anticholinergic effect of these drugs. Agents with antihistaminic properties (e.g. doxepin) can also be useful in patients with irritant skin conditions and where insomnia is troublesome.

Hyponatraemia

Hyponatraemia can present insidiously and if undetected can lead to serious morbidity (e.g. lethargy, apathy, confusion, agitation, disorientation, muscle twitching and cramps, irritability, convulsions, coma and death). The signs are not generally seen until the serum sodium concentration falls below 125 mmol/L (see 'Sodium' in 'Normal physiological values', Section D). Rapid decline in the serum sodium concentration and an age of over 70 years are factors that increase the likelihood and severity of symptoms. There are a number of causes of hyponatraemia, including excess fluid intake, medical conditions such as congestive heart failure, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and gastrointestinal loss of sodium as a result of vomiting. Medicines should be considered as a possible cause of hyponatraemia in older people. Overzealous use of diuretics may precipitate hyponatraemia, as may use of medicines that have been associated with SIADH (e.g. selective seratonin reuptake inhibitors, carbamazepine).

Other effects

Medicines causing blockade of α-adrenergic receptors (e.g. prazosin) may affect bladder control (especially in older women) and lead to urinary incontinence.

Nonsteroidal anti-inflammatory drugs (NSAIDs), including selective COX-2 inhibitors, should be used with great care in older patients since there is an increased risk of gastrointestinal, renal and cardiovascular adverse effects. In addition, these agents may cause central nervous system effects such as dizziness, confusion and psychosis.

Some common presentations of adverse drug reactions in the elderly are summarised under individual medicines in 'Clinical monographs', Section B. It is important to note that some medicines are best avoided or should be used with extreme care in older people. In those cases where an alternative is not available and the risk—benefit analysis supports the use of the medicine, monitor closely for effectiveness and adverse effects.

Multiple diseases and multiple medicines

Many older people have several chronic diseases, and this has a number of potential consequences:

- The diseases may further modify the pharmacokinetic handling of the medicine and the pharmacodynamic response to the medicine.
- More than one medicine may be needed for each condition and as more medicines are added to the medication regimen, the risk of poor adherence increases.
- It may not always be appropriate to treat a condition which may be a manifestation of normal ageing (e.g. inability to sleep right through the night) or an adverse effect of a medicine already being taken by the patient (e.g. mental confusion, incontinence).
- The potential for interactions and adverse drug reactions increases substantially as the number of medicines taken increases. Older people receiving multiple medications need careful monitoring.

Under-use of medicines

It is becoming increasingly recognised that undertreatment poses at least as much risk for elderly patients as the use of multiple medicines.[3] Many instances of under-use of appropriate drug therapy have been documented. These include the treatment of chronic atrial fibrillation, hypertension, hyperlipidaemia, congestive heart failure, asthma, depression, pain and osteoporosis. Possible factors contributing to undertreatment include insufficient evidence of clinical benefit due to under-representation of older patients in clinical trials, doctors' nonspecific fear of 'polypharmacy' and often a lack of effective coordination between hospitals and aged care facilities when patients move from one to the other. There is also a need for systems of care that improve drug safety and enhance adherence in elderly people on complex medication regimens. Efforts should focus on avoiding errors of omission in prescribing indicated medications, appropriate monitoring, patient education, and follow-up.

Factors affecting medication adherence

There are many factors that may compromise the ability of older people to use their medicines as intended. Not taking medicines as directed may lead to a sub-optimal clinical outcome and/or increase the risk of adverse drug reactions.

The complexity of the therapeutic regimen is an obvious factor that affects adherence. This is an important, but not the only, reason to minimise complex regimens involving multiple medicines.

Older people may have cognitive impairment, memory loss and confusion (which may be medicine-induced) that may seriously affect their ability to understand the doctor's and pharmacist's counselling about the correct use of medicines. They may be unable to fully comprehend the advice of health care providers because their hearing is impaired and, if their vision is poor, they may find it difficult to read labels or written information about medicines (such as Consumer Medicine Information leaflets).

Older people may also find it hard to open some medicine containers or to operate certain devices (e.g. metered-dose aerosols) as a result of muscle weakness, joint deformity (especially in people with arthritis) or poor coordination.

People can unintentionally consume different brands of the same medicine at the same time. Medication duplication is particularly a risk when patients return to their community health care providers after a stay in hospital or a residential aged care facility or are given multiple generic brands. The pharmacist has a primary role to ensure that patients, carers and nursing staff are aware of different brands of medicines; the decision to switch brands should be made in consultation with the relevant people.

An additional complication may arise for older people who live alone and so do not have access to immediate assistance with their medication.

Improving the quality use of medicines

Pharmacists and other health care providers can make a contribution to the promotion of quality use of medicines in older people who live in the general community as well as those in hospitals and residential aged care facilities.

The following checklist relates to the use of prescribed and over-the-counter medications. If the guidelines embodied in this checklist are followed, there may be an improvement in therapeutic outcomes and quality of life and a decrease in the risk of adverse drug reactions.

Is medication necessary?

Before a new medicine (prescription or over-the-counter) is started, the health care provider should pose some fundamental questions:

- Is the medicine really necessary?
- Are you confident that the condition for which treatment is being contemplated is not an untreatable manifestation of normal ageing or an adverse reaction to another medicine?
- Where appropriate, have non-drug options for treatment been considered or tried?
- Do the possible benefits of drug treatment outweigh the risk of harm?

Which medicine and formulation?

If medication is considered necessary, give careful thought to the choice of medicine and formulation. Older people are very sensitive to many medicines and, as discussed, some medicines pose a special risk of adverse reactions.

Some older people may have difficulty swallowing oral formulations. The cause of the problem should be investigated, since this knowledge will assist in deciding the most appropriate strategy. For example, following a stroke many people are at risk of aspirating liquids when trying to swallow them. Where there is difficulty swallowing a solid dose form, an alternative formulation may be used (e.g. an oral liquid or transdermal patch). (Pharmaceutical Benefits Scheme availability may also influence the formulation selection). An alternative solution may be to crush a tablet or open a capsule and disperse the powdered material in a small amount of soft food or another suitable medium. This approach is not appropriate for some drugs or formulations (see 'Modification of oral formulations', Section A and, for individual medicines, see 'Clinical monographs', Section B).

Keep the medication regimen as simple as possible. As noted, there are potential problems associated with the use of multiple medicines.

What dose to use?

For some medicines that may be required on a long-term basis (e.g. allopurinol) the starting dose should be low and be increased slowly to reduce the risk of adverse events. A useful dictum for many drugs is 'start low and go slow'.

Does the patient have adequate instructions?

Care is required to ensure that the patient and/or their carer receives adequate written and verbal instructions for the correct and safe use of the medicine.

The practices of 'mdu' (use as directed) prescribing and 'take as directed' labelling are rarely acceptable.

Many older people cannot read the small type used on standard dispensing labels, and in these cases it may be necessary for the pharmacist to consider a different option.

The patient and/or the carer will require information on what each medicine is for, how to use it, and precautions

to take when using it. The use of written information suitable for older patients is encouraged. Good-quality written information tailored to an individual's needs and cognitive capacity is in valuable.

Is an adherence aid needed?

Adherence is likely to be increased (and the risk of adverse effects decreased) if the smallest possible number of medicines is used within a simple overall medication regimen. Even then, the patient may benefit from the use of a compartmentalised medication organiser and a daily medication planner, both of which can be arranged by the pharmacist.

For individuals who have difficulty opening containers with child-resistant closures, consider the use of an alternative container. If this is done though, it is important to stress the general warnings about safe storage of medicines to minimise the risk to children.

The use of certain other pharmaceutical products may present problems for older patients. For example, some patients may find it hard to activate a metered-dose aerosol or they may have problems coordinating the steps necessary for optimal use of such inhalation devices. These patients may benefit from the use of an inhaler aid that facilitates aerosol activation or a large volume spacer, or the prescriber may consider substituting a dry powder inhalation device or nebuliser. Suppositories, eye drops and nasal sprays may also require special attention.

Does the patient have a medication profile?

Encourage each patient to keep an up-to-date medication profile which contains important details relating to their prescribed and over-the-counter medicines, including complementary medicines. This will be useful not only for the patient but also for the health care providers involved in reviewing the patient's medication.

Has the medication regimen been reviewed recently?

Factors to be considered in the review include:

- the need for each medicine
- appropriate duration of therapy
- medicine–disease interactions (contraindications, precautions)
- clinically relevant drug interactions
- the suitability of doses and dosage intervals
- the suitability of formulations (e.g. the ability of the person to swallow)
- the complexity of the medication regimen, and the ability of the patient to adhere to the regimen
- the adequacy of instructions
- patient adherence, and the need for medication organisers and other adherence aids
- duplication of different brands of the same medicine or different medicines from the same pharmacological or therapeutic class
- adverse reactions
- changes in the clinical status of the patient
- biochemical parameters (e.g. serum electrolyte levels or indicators of renal or hepatic function) that should be monitored, either to determine drug dosage needs or to monitor for adverse drug effects.[4]

Research continues to highlight that good communication among all the members of the multidisciplinary health care team is essential to achieve quality use of medicines in older people. A formal medication management review (available through the Medicare Benefits Schedule) can be a useful initiative in promoting such communications and thereby optimising medication use.

For more detailed information, see 'Medication review', Section D.

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4. Peterson GM. Laboratory monitoring of drug therapy in the elderly: often inadequate. Aust Pharmacist 2006;25:690–3.

Further information

The Pharmaceutical Society of Australia's *Pharmacy Self Care* fact cards: many of those available may be of particular relevance to older people, e.g. 'Dry mouth' and 'Preventing falls'.

The Australian Pharmacist Aged Care Primer. Canberra: Pharmaceutical Society of Australia, 2007.

Beers MH, ed. Merck manual of geriatrics. 3rd ed. Online version. www.merck.com/mkgr/mmg/home.jsp.

A specific resource that may assist with the use of medications in older people is the AMH *Drug Choice Companion: aged care*.

Dosing in renal impairment

Renal excretion is the major route of elimination for many medicines and/or their metabolites. A reduction in renal function occurs with increasing age and certain disease states. Severe impairment of renal function may also affect the absorption, distribution and metabolism of some drugs.

Estimation of renal function from serum creatinine

Measurement of serum creatinine concentration is a readily available laboratory test that can be used to monitor renal function or estimate glomerular filtration rate (GFR). Correct interpretation of the relationship between a patient's serum creatinine concentration and their GFR requires an understanding of the theory of why creatinine is used to estimate GFR. See also 'Creatinine' in 'Normal physiological values', Section D.

To be an ideal endogenous marker of GFR, a substance must be produced at a constant rate, not be bound to plasma proteins and be exclusively cleared by glomerular filtration. Its laboratory measurement must also be accurate and reproducible. Creatinine fulfils some, but definitely not all, of these requirements.

Creatinine is a source of energy produced by the liver and used by muscles. It is an end product of muscle metabolism, with production being constant and proportional to muscle mass, resulting in a stable serum creatinine concentration in an individual.

Creatinine excretion can be used to estimate GFR because creatinine is not bound to plasma proteins and is freely filtered at the glomerulus and not reabsorbed. Some tubular secretion of creatinine does occur, although it is not clinically significant in normal renal function. Thus its clearance is relatively proportional to GFR.

Since creatinine production is usually constant, an increase in serum creatinine concentration almost always reflects a decrease in GFR for an individual. However, a serum creatinine concentration within the normal reference range does not necessarily indicate normal renal function. An instance where this assumption is inappropriate is in older people. Reduced muscle mass results in reduced creatinine production and therefore lower steady-state concentrations of creatinine for a given renal function. Because of this, an estimation of creatinine clearance (the volume of plasma that is cleared of creatinine by the kidney per unit of time) gives a better estimation of renal function than serum creatinine concentration alone.

Age, sex and muscle mass (as indicated by ideal or lean body weight) are therefore important factors to consider when using serum creatinine concentration to estimate creatinine clearance.

There are a number of methods for estimating renal function in adults, including the Cockcroft–Gault and the Modification of Diet in Renal Disease equations.

Cockcroft–Gault equation

$$\text{Creatinine clearance } (Cl_{cr}) \text{ in mL/min} = \frac{(140 - \text{age (years)}) \times \text{ideal body weight (kg)}}{0.815 \times \text{serum creatinine (micromol/L)}}$$

For females, multiply by 0.85 to account for the reduced muscle to ideal body weight ratio in comparison to males.

Ideal body weight for males =
50 kg + 0.9 kg/for each cm above 152 cm

Ideal body weight for females =
45.5 kg + 0.9 kg/for each cm above 152 cm

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

- *Creatinine serum concentration <60 micromol/L.* If the measured creatinine is less than the minimum value reported by the laboratory reference range (<60 micromol/L), this may be a reflection of decreased production as opposed to enhanced clearance of creatinine. To prevent overestimation of GFR, use the minimum value of the reference range (60 micromol/L) rather than the actual creatinine concentration.
- *Renal replacement therapy.* (e.g. haemodialysis) Do not use this equation if renal replacement therapy is being used; instead assume that GFR is <10 mL/min.

Modification of Diet in Renal Disease equation

The Modification of Diet in Renal Disease equation is a recently developed method of estimating GFR. It originated from data relating to patients with mild to severe renal impairment who participated in the Modification of Diet in Renal Disease Study.

Australasian pathology laboratories now automatically report an estimated glomerular filtration rate (eGFR) based on the Modification of Diet in Renal Disease formula with results of serum creatinine tests in adults.

The revised MDRD formula (the '175' formula) is:

$$eGFR\ (mL/min/1.73m^2) = 175 \times (\text{serum creatinine (micromol/L)} \times 0.0113)^{-1.154} \times (age)^{-0.203} \times (0.742\ [\text{if female}])$$

Studies have validated the MDRD formula in the general population, although no data currently exist for Aboriginal and Torres Strait Islander peoples, Maori, Pacific Island peoples and other ethnic groups.

Children

Formulae are also available for estimating GFR from serum creatinine concentration in children. Expert advice should always be sought.

Summary

In summary, it should be stressed that all the methods listed *estimate* rather than directly measure GFR. Under- or over-estimation of renal function is possible. Dose adjustments based on these formulas should always consider a patient's individual treatment requirements.

The Australasian Creatinine Consensus Working Group recommended in 2007 that, in most out-of-hospital settings where an eGFR (MDRD) result is available and no other measure of GFR is known or readily accessible, it may be appropriate to use the eGFR (with caution) to assist drug dosing decision making in patients with chronic kidney disease. However, when amending the dosing of critical-dose drugs, particularly in the hospital setting, it is important to adhere to published recommendations, which usually involve the use of the Cockcroft–Gault formula to estimate eGFR, or to measure creatinine clearance, which provides a more accurate measure of GFR.

Adjustment of dosing in renal impairment

The most important consideration in dosage adjustment for renal impairment is patient outcome. Fundamental questions that should be asked include:

- Is the drug having the desired effect?
- Are side effects evident?
- Is the outcome optimal?

Clearance of some medicines and/or metabolites is significantly affected by a reduction in renal function. In these instances consideration must be given to maintenance dosage reduction, particularly when the medicine or metabolites have a narrow therapeutic index.

It is not uncommon to find conflicting dosage adjustment recommendations in different sources. Clinical judgment should be used in consideration of the drug and patient characteristics. The *Australian Medicines Handbook* defines the following categories of renal impairment for dosage adjustments:

- Mild impairment.....25–50 mL/min
- Moderate impairment.....10–25 mL/min
- Severe impairment .....<10 mL/min

Pharmacists selecting drug therapy or managing dosage adjustment in patients with reduced renal function, should consider the potential for changes to the drug's pharmacodynamics; and altered absorption, distribution, metabolism, or elimination. For example, changes in distribution (and free drug fraction) may occur due to changes in the hydration state, protein binding or tissue binding stop.

Consider the extent of renal impairment because, with a few important exceptions, most drugs in clinical use do not routinely require dosage adjustment until Cl_{cr} falls to below 50–60 mL/min. Generally, if more than half the drug is excreted unchanged, consider a dose reduction.

Renally eliminated drugs with narrow therapeutic indexes (e.g. aminoglycosides, digoxin, flucytosine, vancomycin) may require dose adjustment at lesser impairment:

- If a medicine or metabolite is nephrotoxic and estimated Cl_{cr} is <30 mL/min, use an alternative medicine where possible.
- If a medicine or metabolite is not nephrotoxic or estimated Cl_{cr} is >30 mL/min, the 24-hour dose in renal impairment (Df) is calculated from the following relationship:

  $Df = Dn\ (1 - fe\ (1 - \text{est. } Cl_{cr}\ [mL/min]/100))$, where Dn represents the normal dose in 24 hours, fe is the fraction excreted unchanged in the urine. Assumes normal estimated Cl_{cr} of 100 mL/min.

This equation can be used as a guide, but it does not take into account the impact of renal impairment on the accumulation of medicine metabolites. When an active or toxic metabolite occurs, clearance of the metabolite may also need to be considered. If metabolites are pharmacologically active or toxic, further dosage adjustment will be necessary (e.g. norpethidine is a toxic metabolite of pethidine and will accumulate in patients with impaired renal function).

Where a loading dose is recommended as part of a dosage regimen it is usually the same in patients with renal impairment. In a few cases of renal impairment it may be necessary to adjust the loading dose if there is a significant change in the volume of distribution due to changes in protein and/or tissue binding. For example,

the volume of distribution for digoxin in renal failure changes from 500 L to 300 L, resulting in a reduced loading dose.

Renal impairment may necessitate a dose adjustment of highly protein bound drugs such as phenytoin. The hypoalbuminaemia caused by renal impairment increases the unbound (active) fraction of the drug. In such cases, dosing is preferably based on unbound phenytoin levels, rather than total drug concentration. Where dosing is based on total drug concentration, however, the therapeutic range should be reduced (e.g. therapeutic range in normal renal function is 10–20 mg/L and in renal failure is 5–10 mg/L).

See also 'Optimal medicine concentration ranges' and 'Pharmacokinetic Data', Section D.

Acute renal failure associated with commonly used medicines

NSAIDs (including selective COX-2 inhibitors), ACE inhibitors and angiotensin II receptor antagonists can all cause an acute decline in renal function if used in patients with actual or relative renal hypoperfusion or pre-existing renal impairment.

Renal hypoperfusion occurs in patients suffering from dehydration, cardiac failure, excess diuretic effect, hypotension or shock. In these situations, glomerular filtration pressure is locally regulated by the vasodilating effect of prostaglandins on afferent glomerular arterioles (blood flow to the glomerulus) and the vasoconstricting effect of angiotensin II on efferent glomerular arterioles (blood flow from the glomerulus).

When a patient's kidneys become hypoperfused or there is pre-existing renal impairment, angiotensin II is produced. This constricts the efferent arteriole, which causes back pressure on the glomerulus thus maintaining glomerular filtration. This back pressure maintenance of filtration is complemented by vasodilation of the afferent arteriole (blood supply to the glomerulus) under the action of prostaglandins.

Patients receiving NSAIDs, ACE inhibitors or angiotensin II receptor antagonists however, will not be able to instigate these two normal compensations to hypoperfusion. Patients on any of these medications should be well hydrated prior to surgery and be warned of situations where dehydration may occur (e.g. when vomiting or diarrhoea occurs or in hot weather). Patients on a combination of NSAIDs and an ACE inhibitor or angiotensin II receptor antagonist are at particular risk. This risk is even further increased if loop diuretics are also administered.

Maintenance of residual renal function

In patients with declining renal function, preservation of the remaining renal function is paramount. This is the case even when renal replacement therapy (e.g. dialysis) has commenced. Avoidance of nephrotoxic agents along with the maintenance of optimal blood pressure, fluid balance and blood glucose (if diabetic) are all important. Other risk factors such as hypercholesterolaemia should also be addressed.

Renal replacement therapies

Renal replacement therapies are based on passive diffusion (from a region of high concentration to lower concentration) or convection (movement as a solute in water being sucked across a membrane) of waste products across a semipermeable membrane. This membrane may be manufactured (as used in haemodialysis) or be the patient's own peritoneal lining (peritoneal dialysis).

The waste products contained in the blood side of the membrane are bathed against a dialysis fluid on the other side of the membrane. The ability to dialyse a medicine and its metabolites can be predicted by molecular size, protein binding and volume of distribution (refer Gwlit and Perrier 1978).

Molecular size

The larger the molecule, the slower it moves and the less likely it is to be removed by passive diffusion. However, many centres now use high-flux (large membrane pore size) dialysis in conjunction with high blood flow rates, minimising the impact of molecular size on clearance.

Protein binding

Binding to proteins essentially makes medicine molecules too large to be dialysed; only unbound drug is dialysed.

Volume of distribution

The larger the volume of distribution of a medicine with respect to plasma, the less medicine is available to be dialysed at any time.

Control of oedema with renal disease and cardiac failure

Renal impairment in association with cardiac failure may result in excessive fluid retention leading to overt heart failure and/or pulmonary oedema manifesting as

shortness of breath. With such a massive accumulation of fluid, the gastrointestinal tract becomes oedematous and loop diuretic absorption is diminished. This situation necessitates the use of intravenous frusemide and diuresis at a rate of approximately 1 kg per day. A more rapid rate of diuresis results in intravascular hypovolaemia as diuresis exceeds the rate at which the water redistributes from the interstitial space into the vascular space. This extreme situation may be avoided by titration of salt and fluid intake and daily weighing in conjunction with a diuretic dosing plan.

For example, when a patient is deemed to be at their ideal weight (at which they are not overhydrated) they should weigh themselves on a set of reliable scales that are accessible at about the same time each day. If a patient's weight increases by 1 kg, an increased diuretic dose should be taken by the patient on that day. If the weight is less than ideal, the diuretic dose may be reduced for that day or withheld altogether. Consistent charting that shows a patient's weight is less than ideal should raise the question of the patient losing actual body weight, and a reassessment of fluid status may need to be made.

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Medicines and urinary incontinence

Many patients with urological symptoms are older and may be taking multiple medications, which may affect urinary symptoms. Table D.5 lists some of these.

'Urinary incontinence' is defined as the 'complaint of any involuntary leakage of urine'. Risk factors for urological symptoms include female gender, old age, bladder outflow obstruction, neurogenic bladder dysfunction, urinary tract infection, acute pain, an unfamiliar environment, constipation, recumbency and gait disturbance.

Many patients may also be taking a range of complementary medicines that may, through the claimed mechanism of action, contribute to urinary incontinence (e.g. those that have a diuretic effect, sedative properties or antidepressant actions).

A number of agents may exert a cytotoxic effect on the bladder wall, leading to cystitis, which may manifest as urinary incontinence (e.g. cyclophosphamide, vincristine and cisplatin). Some of the NSAIDs have also been associated with this effect (e.g. tiaprofenic acid).

Types of incontinence

The following types of incontinence may occur independently; in the clinical situation, however, it may not be so clearcut as combinations of these basic types often occur (mixed incontinence).

Stress incontinence

Stress incontinence is involuntary loss of urine from the urethra in association with raised intra-abdominal pressure (e.g. through coughing, exercise or bending). Storage failure is due to impaired urethral support and/or poor urethral closure. It most commonly occurs in women.

Urge incontinence

Urge incontinence is involuntary loss of urine associated with a strong desire to void, which is usually caused by detrusor overactivity voiding of urine before the toilet can be reached or storage failure due to uninhibited contraction of the detrusor muscle.

Overflow incontinence

Overflow incontinence is involuntary loss of urine associated with an over-distended bladder. Continuous or intermittent leakage may occur. The post-voiding residual volume is elevated. Emptying failure may be caused by outlet obstruction (e.g. by prostatic hypertrophy or constipation) or inability to contract the detrusor muscle (e.g. neurogenic bladder), resulting in bladder distension.

Functional incontinence

Functional incontinence occurs in otherwise continent individuals who are unable or unwilling to get to the toilet in time. It can be a result of impaired mobility (e.g. due to arthritis or muscle weakness) or medications that affect balance, cognition or mental alertness. Other causes include severe cognitive impairment.

Further information

PSA *Pharmacy Self Care* fact card 'Bladder and urine control'.

Continence Foundation of Australia, National Continence Helpline, Tel: 1800 33 00 66

Table D.5 Medications that can cause or aggravate urinary incontinence

Medicines	Mechanism	Type of incontinence
Analgesics		
Opioids, e.g. morphine, tramadol	Inhibit voiding reflex, reduce detrusor activity, urinary retention, constipation, confusion	Overflow, functional
Anticholinergic agents[1]		
E.g. oxybutynin, propantheline, tolterodine, solfenacin	Reduce detrusor activity, voiding difficulty, urinary retention, constipation	Overflow
Antihypertensives		
Antihypertensives (all)	Postural hypotension (unsteadiness)	Functional
ACE inhibitors	Cough-induced sphincter weakness	Stress
Diuretics	Polyuria, constipation, frequency	Urge
Verapamil	Reduces detrusor activity, constipation	Overflow
Cholinergic agents		
Bethanechol[2]	Enhance detrusor activity (instability), urgency	Urge
Psychotropics		
Amisulpride, clozapine, olanzapine, quetiapine, risperidone	Constipation, confusion, sedation, parkinsonism	Overflow, functional, stress
Benzodiazepines	Sedation, impaired mobility	Functional
Chlorpromazine, haloperidol, pericyazine, thioridazine, trifluoperazine	Anticholinergic, sedation, confusion, parkinsonism, impaired mobility	Overflow, functional
Lithium	Polydipsia, nocturia, frequency	Functional
SSRIs (paroxetine has some anticholinergic effects), moclobemide, venlafaxine	Enhance detrusor activity (instability), sedation, impaired mobility	Urge, functional
TCAs[1], mianserin, mirtazapine, reboxetine	Anticholinergic, sedation, impaired mobility	Overflow, functional
Selective alpha blockers[3]		
Prazosin, tamsulosin, terazosin	Sphincter relaxation, unconscious dribbling of urine	Stress
Other		
Donepezil, galantamine, rivastigmine	Cholinergic effect, detrusor instability, frequency, urgency	Urge, overflow
Pseudoephedrine	Enhance sphincter activity, retention, voiding difficulty	Overflow
Tiaprofenic acid	Enhance detrusor activity, frequency, urgency	Urge, cystitis-like symptoms

1. Relax the bladder and increase its capacity; used for urge incontinence. Older people are more sensitive to their adverse effects.
2. Bethanechol increases bladder contraction; used to treat urinary retention and overflow incontinence; has limited efficacy and is not recommended.
3. Block receptors in bladder neck and urethra; may help to reduce outflow obstruction in males; may exacerbate or precipitate incontinence in women.

Prevention and treatment of opioid-induced constipation

Prevalence

Constipation is the most troublesome adverse effect of opioid analgesia, reported to occur in up to 57% of patients taking opioid therapy for non-cancer pain.[1,2]

Constipation unrelated to opioids is common in patients with advanced cancer, with a reported prevalence of 52%.[3] This is due to the presence of other risk factors such as hypercalcaemia, reduced mobility, reduced fluid and food intake, dehydration, anal fissures, mechanical obstruction, and other medications (e.g. $5HT_3$ antagonists, anticholinergics, iron). In patients with advanced malignancy who are taking opioids, the prevalence of constipation rises to 87%.[3]

Pathophysiology

The constipating effect of opioids is mediated through mu opioid receptors in the gastrointestinal tract. Propulsive peristalsis is reduced, pancreatic and biliary secretions are reduced, and intestinal fluid absorption is increased.[3] Intrathecal opioids can also decrease gastric emptying and prolong transit time through a central descending opioid-mediated effect.[3]

The constipating effect appears to be dose related and tolerance rarely develops.[4]

Comparative opioid information

The prevalence of constipation is not the same with all opioids. Opioids that are more lipid soluble (e.g. fentanyl, buprenorphine) are less likely to cause constipation than those that are water soluble (e.g. morphine, oxycodone), possibly due to the reduced time in systemic circulation.[3]

Prevention and treatment

Unlike other opioid-induced side effects (e.g. respiratory depression, nausea and sedation), constipation is unlikely to improve over time and should be anticipated, monitored and addressed for the duration of opioid treatment. Counselling on the benefit of non-pharmacological treatments (i.e. diet, fluid intake, etc.) should be provided. Generally, laxatives should be used for the shortest duration possible; however, chronic laxative use may be unavoidable with long-term opioid therapy.[5]

See Table D.6 for details of prevention and treatment of opioid-induced constipation.

Table D.6 Prevention and treatment of opioid-induced constipation

Condition	Suggested laxative	Comments
Prevention		
Commence regular laxative protocol on initiation of opioid analgesia.		
	• Administer (regularly) docusate with senna—two tablets once or twice daily. • Encourage mobilisation, adequate hydration and optimal (not high) dietary fibre intake.	As opioid-induced constipation is largely due to reduced peristalsis and hardened faeces, the most useful laxatives are those that increase peristalsis and soften the stool. Fibre and bulk laxatives should not be used in patients taking opioids because increasing faecal bulk may cause obstruction, particularly if the patient is dehydrated.[6]
Treatment		
The treatment selected for established constipation is dependent on whether the faeces are soft or hard and whether faecal impaction is suspected. Assessment generally requires a physical examination.		
If faeces are soft[6]	• Add oral bisacodyl 10 mg at night to regular laxative protocol, increasing to 10 mg twice daily if necessary. • If this is unsuccessful, a bisacodyl 10 mg suppository can be used.	
If faeces are hard[6]	• Use oral osmotic laxatives to draw water into the bowel lumen and increase the moisture content of the stool (e.g. macrogol 3350, one to three sachets daily or sodium phosphate solution, 2–5 mL twice daily). • Avoid lactulose if fluid intake is poor. • If this is unsuccessful, a combination of a faecal softener and a stimulant suppository can be used (e.g. a glycerol suppository with a bisacodyl suppository). Lactulose solution contains galactose and lactose, so should be used with caution in people with diabetes since blood glucose levels may be elevated (particularly with prolonged use).	
If faecal impaction is suspected[6]	• Use a faecal softener or rectal lubricant (e.g. glycerol suppository or oil retention enema) to soften the stool, lubricate and irritate the bowel, thus increasing peristaltic activity and stool movement. • If softening is effective but peristaltic stimulation is ineffective, use a daily enema, alternating between sorbitol with sodium citrate and sodium lauryl sulfoacetate (*Microlax*) and oil enemas. • Macrogol 3350 (*Movicol*), eight sachets taken over two to four hours, can be used; it can take two to four days to have an effect.	Manual removal of impacted rectal faeces may be necessary before laxatives can be effective.

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Medicines causing discolouration of urine and faeces

Some medicines, including complementary medicines and vitamins, can cause discolouration of urine, faeces or bodily secretions. To avoid unnecessary concern for patients prescribed these medicines, pharmacists should advise them of this possibility.

Some foods, such as blackberries and rhubarb, and dyes used in confectionery or diagnostic testing may also cause discolouration. Changes in the colour of urine and faeces may also be a result of underlying medical conditions. Changes that are not diet or drug related, particularly if they are associated with symptoms such as urinary urgency, dysuria or abdominal colic or have persisted for several days, should be reported to a medical practitioner.[1,2]

Variations in urine colour

Urine appearance and colour are studied during routine urinalysis. The range of colours for normal urine extends from pale yellow to dark amber, depending on concentration. The yellow colouration is caused by the pigment urochrome, a product of bilirubin metabolism.

- Dark yellow or orange colouration may be a result of low fluid intake, dehydration or excessive carotene intake.
- Dark red urine may indicate bleeding from the kidney, while bleeding from the lower urinary tract generally causes bright red urine.
- Dark-coloured urine may be a sign of cholestasis or acute viral hepatitis.
- Cloudy, murky or turbid urine may be caused by the presence of necrotic white blood cells, red blood cells or bacteria (e.g. in a urinary tract infection) or the ingestion of large amounts of fat, urates or phosphates.
- Green, odorous urine may indicate *Pseudomonas* infection.

Drugs that produce abnormal urine colours can affect the accuracy of urinalysis reagent strips.

Variations in faeces colour

The normal brown colour of faeces is due to the presence of bile salts; diseases affecting the pancreas, gall bladder or liver can produce light-coloured faeces.

- Black or 'tarry' faeces may be a result of ingested iron supplements or bleeding from an ulcer in the oesophagus or stomach (the blood remains in the intestines sufficiently long to be broken down by digestive enzymes).
- Pink, red or maroon faeces are due to the presence of undigested blood, either from low down in the digestive tract or from a more profusely bleeding site in the upper digestive tract.
- Silver, white, grey or yellow faeces may be associated with cholestasis or acute viral hepatitis.
- Yellowing of faeces may occur in giardiasis.
- Greenish faeces with an altered consistency in infants digesting solid food for the first time may be due to the presence of cells discarded during the development of the digestive tract.

Tables D.7 and D.8 list some medicines that can cause discolouration of urine and faeces. The list is not exhaustive. This detail is also provided in 'Clinical monographs', Section B.

Table D.7 Medicines that can cause discolouration of urine[1–4]

Medicine	Colour of urine
Amitriptyline	Blue–green
Bismuth	Red–brown
Cascara	Red (in alkaline urine), yellow–brown (in acid urine)
Chloroquine	Rust yellow, brown
Clofazimine	Discolouration[a]
Dantrolene	Orange, red
Daunorubicin	Red
Deferiprone	Red–brown
Desferrioxamine	Red
Doxorubicin	Red
Entacapone	Brownish orange
Epirubicin	Red
Ferrous salts	Black
Fluorescein (IV)	Yellow, orange
Flutamide	Amber, yellow–green
Indomethacin	Green
Iron dextran	Black on standing
Levodopa	Red on voiding, darkens on standing[b]
Loratadine	Discolouration[a]
Mesalazine	Red[b]
Methyldopa	Darkens on standing[b]
Methylene blue	Blue–green
Metronidazole	Dark brown
Mitozantrone	Blue–green
Nitrates	Brown–black

Table D.7 Medicines that can cause discolouration of urine[1-4] (continued)

Medicine	Colour of urine
Nitrofurantoin	Rust yellow, brown
Olsalazine	Red[b]
Paracetamol	Dark brown (in overdosage)
Phenolphthalein	Pink, red, red–brown (in alkaline urine)
Phenothiazines	Pink, red, red–brown
Phenytoin	Pink, red, red–brown
Primaquine	Rust yellow, brown
Propofol	Green
Quinine	Brown, black
Rhubarb	Rust
Riboflavin	Yellow
Rifabutin	Red–orange
Rifampicin	Red–orange
Salicylates	Pink
Senna	Yellow, red, red–brown
Sulfasalazine	Orange, yellow (in alkaline urine)
Thalidomide	Green
Triamterene	Blue
Trimethoprim with sulfamethoxazole	Rust yellow, brown
Warfarin	Orange/yellow

a. The approved Product Information notes that an unspecified discolouration may occur.
b. On contact with hypochlorite toilet bleach.

Table D.8 Medicines that can cause discolouration of faeces[2–4]

Medicine	Colour of faeces
Acetazolamide	Black
Aluminium hydroxide	White speckling
Aminophylline	Black
Amphotericin B	Black
Aripiprazole	Discolouration[a]
Aspirin	Pink, red, black[b]
Barium (oral)	White speckling
Bismuth	Green, black
Cascara	Yellow–green
Charcoal	Black
Chloramphenicol	Blue, black
Clindamycin	Black
Clofazimine	Red, brown–black
Clopidogrel	Pink, red, black[b]
Colchicine	Grey
Corticosteroids	Pink, red, black[b]
Ergot alkaloids	Pink, red, black[b]

Table D.8 Medicines which can cause discolouration of faeces[2-4] (continued)

Medicine	Colour of faeces
Ethacrynic acid	Black
Ferrous salts	Black
Fluorouracil	Black
Gold	Yellow, green
Heparin	Pink, red, black[b]
Hydralazine	Black
Indomethacin	Pink, red, black[b], green
Iodine preparations	Black
Levodopa	Black
Medroxyprogesterone	Green
Mesalazine	Black
Methotrexate	Black
Nitrates	Black
NSAIDs (COX-1 and COX-2)	Pink, red, black[b]
Olsalazine	Black
Omeprazole	Discolouration[a]
Orlistat	Discolouration[a]
Pantoprazole	Discolouration[a]
Phenindione	Pink, red, black[b]
Phenolphthalein	Black, red
Rhubarb	Yellow, green
Rifabutin	Red–orange
Rifampicin	Red–orange
Risperidone	Discolouration[a]
Salicylates	Pink, red, black[b]
Saquinavir	Discolouration[a]
Senna	Yellow, green
Tetracyclines	Black
Theophylline	Black
Triamterene	Black
Trimethoprim with sulfamethoxazole	Black
Warfarin	Pink, red, black[b]

a. The approved Product Information notes that an unspecified discolouration may occur.
b. The colour may indicate medicine-induced gastrointestinal bleeding.

References

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2. Mason P. Tests on specimens of urine or stools. Pharmaceutical Journal 1 May 2004;272. At: www.pharmj.com/pdf/cpd/pj_20040501_clinicaltesting04.pdf.
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Pharmacokinetic data

This section contains information on the basic pharmacokinetic properties of individual medicines. Pharmacokinetics describes the relationship between the dose and the unbound drug concentration at the site of action (drug receptor) and the time course of drug concentration in the body.[1] This brief overview of pharmacokinetic principles and the table of pharmacokinetic data complement information from sources such as the approved Product Information. The pharmacokinetic properties of individual drugs influence pharmacists' decisions on issues such as dosage adjustment in certain disease states and assessment of the clinical significance of a possible drug interaction.

Half-life

The half-life ($t_{1/2}$) of a medicine is defined as the time required for half of the medicine in the body to be eliminated. It is governed by the volume of distribution and clearance of the drug, in accordance with the following equation.

$$\text{Half-life} = \frac{0.693 \times \text{volume of distribution}}{\text{clearance}}$$

Volume of distribution is a measure of the extent to which the medicine distributes out of the bloodstream and into the tissues of the body (i.e. the site of the drug receptors). Since it takes longer for organs eliminating drugs to access molecules that are distributed extensively throughout the body, half-life tends to increase as volume of distribution increases. Clearance is a measure of how efficiently a medicine is removed from the bloodstream by an organ of elimination (generally the liver and kidneys). For any given medicine, a reduction in clearance (e.g. due to impaired liver or kidney function) will result in an increase in half-life.

The half-life of a medicine is clinically important because it dictates[1]:

1. Frequency of dosing

It may be necessary, for example, to administer a medicine with a short half-life (e.g. morphine in non-sustained release formulations has a half-life of two to three hours) up to four times a day to achieve a constant therapeutic effect and avoid undesirably large fluctuations in plasma levels. Sustained-release formulations may be necessary to allow the dosage interval to be extended to once or twice daily, especially if the medicine has a narrow safety margin. In contrast, once-daily dosing is usually adequate for medicines with a half-life period of days (e.g. digoxin).

2. Time taken to reach steady state with constant dosing

The half-life of a medicine dictates how long the medicine must be administered before the plasma concentrations reach a steady state. As a general rule, this takes about four to five half-lives. This has important implications for drugs with long half-lives. Similarly, once a person stops taking a medicine, it will take about four to five half-lives before achieving very low or negligible drug concentrations.

3. Duration of action after a single dose of a medicine

For a single dose of a medicine, generally the longer the half-life the longer the plasma concentration will remain in the effective range. The decrease in duration is logarithmic rather than linear, however, and increasing the dose by a certain percentage, does not result in an identical increase in duration of action.

In some instances the onset and offset of the clinical effects of a medicine will not be related to that medicine's half-life. This usually occurs in the following circumstances:

- The drug acts via an irreversible mechanism (e.g. aspirin's effect on platelets).
- The drug acts via an indirect mechanism (e.g. the effect of warfarin on the synthesis of blood coagulation factors).
- The medicine is a pro-drug (in which case it is the half-life of the active species that is important).
- The medicine is converted to an active metabolite possessing a long half-life. For example, allopurinol ($t_{1/2}$ 0.5–2 hours) has a primary metabolite (oxypurinol) with the same pharmacological effects but a half-life of 18–30 hours. Allopurinol is therefore suitable for once-a-day dosing despite its short half-life.

A pharmacist may use a medicine's half-life to guide recommendations on issues such as:

- the timing of administration
- the likely impact of missing a dose
- assessing when a person starting a new medicine (or changing dosage) might be expected to reach a steady-state plasma level

- the optimal timing to obtain blood samples for therapeutic drug monitoring
- interpreting the likely onset and offset of a potential medicine interaction.

In Table D.9, p. 323, the stated half-life should be considered as a population average. Within the population there may be a twofold to fourfold variation (or more in some cases) in half-life, and in most cases it is not possible to predict what the half-life of a medicine will be in an individual.

Clearance

The clearance (Cl) of a medicine is a measure of how efficiently the body irreversibly eliminates the medicine from the systemic circulation. The higher the clearance the more efficiently the medicine is removed. The term refers to excretion of the unchanged drug from the body via the urine and gastrointestinal contents, expelled in exhaled air and in sweat, and metabolic conversion to a different chemical entity, most usually by the liver. The total body clearance is the sum of the individual organ clearances contributing to the clearance of the drug:

$$\text{Total clearance} = Cl_{(\text{metabolic})} + Cl_{(\text{renal})} + Cl_{(\text{other})}$$

Clearance can be defined as the volume of plasma from which the drug is completely removed per unit of time (e.g. mL per minute, or L per hour).

Clearance may also be normalised for body size; it is then expressed as mL/minute/kg.[2] Table D.9 includes clearance values that have been normalised in this way.

Along with volume of distribution, clearance is an important determinant of a medicine's half-life.

The clinical importance of clearance stems from the pharmacokinetic relationship described by the following equation.

$$\text{plasma concentration} = \frac{\text{rate of drug input into body}}{\text{clearance}}$$

Therefore, for a given dosage rate the plasma concentration of a medicine will double if the clearance of the medicine is halved.

For an individual, the clearance value will be influenced by genetic, physiological and pathological factors. In disease states such as renal or hepatic failure, clearance and volume of distribution can sometimes change in the same direction, exerting opposing effects on half-life (which remains unchanged), while clearance is decreased. Environmental factors (e.g. diet and other medicines) can also alter an individual's clearance value. Indeed, many clinically important interactions occur because one medicine alters the clearance of the other. In summary, clearance is an important parameter in determining the maintenance dose required to achieve a particular target average concentration such that:

$$\text{maintenance dose rate} = C_{ss} \times \frac{CL}{F}$$

where C_{ss} is the average steady state concentration associated with optimal drug effects and F is the bioavailability.

Fraction excreted unchanged

Elimination of unchanged drug via the kidneys is the net result of three processes—glomerular filtration, tubular secretion and tubular reabsorption.

The fraction of a dose excreted unchanged in urine (fe) indicates how a medicine is eliminated from the body. As the relative importance of the kidney as an elimination organ increases the fe value approaches 1, whereas when other (non-renal) mechanisms become dominant fe approaches zero. For a drug that is predominantly metabolised, a low fe value is to be expected. For a drug that is filtered and not resorbed or secreted, renal clearance is determined only by the plasma protein binding (see below) and the glomerular filtration rate.

A drug's fe value indicates whether a reduced dose is likely to be necessary to maintain a safe and effective plasma concentration in renal impairment. Dosage adjustment in patients with impaired renal function is discussed in greater detail in 'Dosing in renal impairment', Section D.

Fraction unbound in plasma

Drugs tend to bind reversibly to plasma proteins such as albumin; the fraction unbound in plasma fu represents the fraction of drug in plasma that exists in the unbound (free) form. Extensively bound medicines include the non-steroidal anti-inflammatory agents, while paracetamol and L-dopa are examples of poorly bound medicines.

For a highly bound drug (fu less than 0.2) the fu value can increase in disease states that are associated with a reduction in plasma proteins (e.g. liver or kidney disease). Similarly, co-administration of two medicines that compete for common plasma-binding sites can also lead to an increase in fu of one or both drugs. As discussed in 'Clinically important drug interactions', Section D, these changes in fu are rarely of clinical importance.

Therapeutic drug monitoring

An understanding of binding is, however, important in the interpretation of plasma concentrations of extensively bound medicines in the field of therapeutic drug monitoring (TDM). There is a demonstrated benefit in monitoring drug concentrations for some medicines: these are identified with the abbreviation 'TDM' in Table D.9. Readers should refer to 'Optimal medicine concentration ranges', Section D, and the relevant clinical monograph for more comprehensive information about a specific medicine.

Oral bioavailability

The oral bioavailability (F) of a medicine is the fraction of a dose that reaches the bloodstream intact. The fraction that is not bioavailable may have remained unabsorbed within the intestinal lumen or may have been metabolised by the liver (and occasionally the intestinal tract) during the initial passage through that organ (during the 'first pass'). With medicines that have low oral bioavailability (e.g. morphine), the dose used orally is much greater than for intravenous administration. Generally, a medicine with low bioavailability due to high hepatic extraction (e.g. diltiazem, verapamil, propranolol, morphine) will also have a more variable bioavailability (referred to as 'highly variable medicines'), and the dosage requirements may vary more significantly among individuals. Similarly, for those medicines with low bioavailability due to poor absorption (e.g. griseofulvin), the extent of absorption is more likely to be affected by the ingestion of foods and the timing of dosage. Such medicines are also more likely to be involved in interactions at the level of absorption (see 'Clinically important drug interactions', Section D).

References

1. Birkett DJ. Pharmacokinetics made easy. Sydney: McGraw Hill, 2002.
2. Helms RA, Quan DJ, eds. Textbook of therapeutics: drug and disease management. 8th edn. Philadelphia: Lippincott Williams & Wilkins, 2006.

Table D.9 Pharmacokinetic data

Medicine	Half-life (hours)	Clearance (Cl)[a] (mL/min/kg)	Fraction excreted unchanged (f_e)	Fraction unbound (f_u)	Oral bioavailability (F)	Comments
Abatacept	360	0.004		<0.01		
Acetazolamide	4	0.5	>0.9	0.1		
Acetylcysteine	6			0.3		
Aciclovir	3	4.5	0.5	0.8	0.2	
Aclarubicin	3			0.5		
Adalimumab	10–18 days	0.003				
Adefovir	7.5	0.6		0.95	0.59	
Adrenaline	1–2 min		<0.01	0.5		
Alcuronium	3	1.3	0.8	0.6		
Aldesleukin	1	3.8	<0.1			
Alefacept	270	0.004				IM bioavailability 0.63
Alendronate	*	3	0.33	0.22	<0.01	* Alendronate is irreversibly incorporated in bone
Allopurinol	1*	10	0.2	>0.9	0.9	* Active metabolite (oxypurinol) has a half-life of about 24 hours
Amantadine	16	4.8	0.95	0.3	0.9	
Amikacin	2	1.3	0.95	>0.9		
Amiloride	8	7.4	0.5	0.6	0.5	
Aminoglutethimide	15.5	9.5	0.47	0.75	0.96	
Amiodarone	25 days	2	<0.05	0.01	0.5	TDM
Amisulpride	12	5.6	0.5	0.84	0.48	
Amitriptyline	24	10	<0.02	0.05	0.5	Active metabolite (nortriptyline); TDM
Amlodipine	35	10	<0.1	0.03	0.6	
Amoxycillin	2	2.6	0.9	0.8	0.9	
Amphotericin B	18	1	<0.05	0.05	<0.1	
Ampicillin	1	1.7	0.9	0.8	0.6	
Amprenavir	7–10	7.7	0.03	0.1	*	* Bioavailability varies between oral formulations
Amsacrine	4.5	5	<0.01	0.05	Poor	
Anagrelide	1.3		0.01		0.7	
Anastrozole	45		<0.1	0.6		Active metabolites with half-lives of up to 37 hours
Apomorphine	1	65				
Aprepitant	9–13	1		0.05	0.6	Weakly active metabolites
Aprotinin	8	0.6	0.05	0.2		
Aripiprazole	75	0.7	<0.01	0.02	0.87	Dehydroaripiprazole is an active metabolite
Artemether	2 (artemether and dihydro-artemisinin)			0.02		Dihydroartemisinin is an active metabolite
Asparaginase	10		<0.05	<0.05		
Aspirin	0.25	10	<0.02	0.66	0.70	Undergoes rapid hydrolysis to salicylic acid
Atazanavir	6.4	4		0.14		
Atenolol	7.5	2.7	0.4	0.95	0.5	
Atomoxetine	3.6	6	0.03	0.01	0.63	7% of Caucasians are poor metabolisers; see Product Information for further information
Atorvastatin	14		<0.02	0.02	0.1	
Atovaquone	2–3 days		0.9	0.1		
Atracurium besylate		0.3	5	<0.01	0.2	
Atropine	3	14	0.6	0.8	0.5	
Auranofin	40 days	0.1	0.15			
Azatadine	9		0.2			
Azathioprine	10 min	57	<0.1	>0.7	>0.8	Rapidly converted to mercaptopurine

a. For some values in this table clearance has been calculated using the half-life

Table D.9 Pharmacokinetic data (continued)

Medicine	Half-life (hours)	Clearance (Cl)[a] (mL/min/kg)	Fraction excreted unchanged (f_e)	Fraction unbound (f_u)	Oral bioavailability (F)	Comments
Azelastine	22 azelastine,56 desmethyl-azelastine	7.6	0.13	0.12 azelastine, 0.03 desmethyl-azelastine	0.2	Desmethylazelastine is an active metabolite
Azithromycin	70	9	0.06			
Azlocillin	1.5	3	0.6	0.7		
Aztreonam	2	0.6	0.6	0.3		
Baclofen	3		0.8	0.7	0.7	
Balsalazide			<0.01	0.01	0.01	
Beclomethasone dipropionate		15		<0.01	0.1	
Bendrofluazide	4	4	0.3	0.05	0.9	
Benzhexol	9		<0.05	0.05		
Benzylpenicillin	0.5	10	0.75	0.4		
Betamethasone	6	3	0.05	0.3	0.7	
Bimatoprost	0.75	25	0.67	0.1	very low	
Bisoprolol	10–12	3.7	0.5	0.65	0.85–0.90	No active metabolites
Bleomycin	3	1	0.4	0.99		
Bosentan	6	1	<0.03	0.02	0.4	Clearance is non-linear and auto-inducible
Brinzolamide	111 days		>0.9	0.4		N-desethyl brinzolamide is an active metabolite
Bromazepam	20	0.5	0.02	0.3		
Bromhexine	6		<0.01			
Bromocriptine	7		<0.05	0.05	<0.1	
Budesonide	2	15	<0.01	0.1		Nasal bioavailability is 0.2
Bumetanide	1.5	3	0.5	0.05	0.8	
Bupivacaine	3	6	2	0.05		
Buprenorphine	4	18	<0.1	0.04		
Bupropion	20	50	<0.01	0.16		
Buspirone	5	30	<0.01	0.05		
Busulfan	2.5	4.5	<0.01			
Cabergoline	60–110		0.02	0.6		
Calcitonin	1	2	<0.05			
Calcitriol	4.5					Pharmacological half-life of 4 days
Candesartan cilexetil	9*	0.37*	0.5*	0.4*		* Pro-drug of candesartan; parameters are for candesartan formed from the pro-drug
Capreomycin	3		0.5			
Captopril	1.5	13	0.4	0.7	0.7	
Carbamazepine	15	1.3	<0.05	0.25	>0.7	Induces its own metabolism—values are for chronic therapy. Value for oral bioavailability is for conventional formulation (TDM)
Carbimazole	0.85		0.1	>0.9		Rapidly hydrolysed to methimazole, which has a half-life of 3–5 hours
Carboplatin	1.5	1.5	0.7			
Carmustine	0.3	60	<0.01	0.2		
Cefaclor	0.75	6	0.5	0.75		
Cefepime	2	1.7	0.9	0.8		
Cefotaxime	1.3	4	0.5	0.7		
Cefotetan	3.5	0.4	0.6	0.1		
Cefoxitin	0.7	4	0.8	0.3		
Cefpodoxime	2	3	0.8	0.6		
Ceftazidime	1.6	2	0.8	0.8		
Ceftriaxone	7.3	0.3	0.5	0.2		
Celecoxib	11	7	0.03	0.03		
Cephalexin	1	4.3	0.9	0.85	0.9	

a. For some values in this table clearance has been calculated using the half-life

Table D.9 Pharmacokinetic data (continued)

Medicine	Half-life (hours)	Clearance (Cl)[a] (mL/min/kg)	Fraction excreted unchanged (f_e)	Fraction unbound (f_u)	Oral bioavailability (F)	Comments
Cephalothin	0.6	7	0.5	0.8		
Cephamandole	0.8	2.8	0.95	0.3		
Cephazolin	1.8	1	0.8	0.1		
Cerivastatin	2.5		<0.01	0.01	0.6	Active metabolites
Chlorambucil	1.3	2.6	<0.01	0.01	>0.7	
Chloramphenicol	4.5	2.5	0.25	0.5	0.9	TDM
Clorazepate	40			0.05		Rapidly metabolised to nordiazepam (kinetic data cited for this metabolite)
Chlormethiazole	6	15	0.01	0.4		
Chloroquine phosphate	45 days	1.8	0.7	0.5	0.75	
Chlorothiazide	1	4.5	0.8	0.05	<0.3	
Chlorpheniramine maleate	30	1.7	0.2	0.3		
Chlorpromazine	30	9	0.01	0.05		
Chlorthalidone	50	1.4	0.5	0.25	0.6	
Cholecalciferol	18 days		<0.01			
Ciclesonide	0.94	250		0.01	<0.01	
Cimetidine	2	7	0.6	0.8	>0.8	
Cinacalcet	35	5	<0.05	0.03	0.25	
Ciprofloxacin	4.0	6	0.6	0.6	0.6	
Cisplatin	0.5	6.3	0.2	<0.1		
Citalopram	36	5	0.12–0.23	0.2	0.8	Active metabolites, demethylcitalopram, didemethylcitalopram, citalopram-N-oxide
Cladribine	7	15	<0.1	0.8	0.5	
Clarithromycin	4.0		0.3			
Clavulanic acid	1	3.6	0.3	0.6		
Clindamycin	3	4.7	0.1	0.05	0.9	
Clobazam	25	0.6		0.2		
Clodronate	2	1.7	0.70		0.01	
Clofibrate	12*			0.05*	0.9	* Active metabolite, clofibric acid
Clonazepam	25	1.2	<0.01		>0.95	TDM
Clonidine	15	3	0.4	0.7	0.95	
Clopidogrel			0.5	0.02	>0.5	
Cloxacillin	0.6	2.2	0.75	0.05	0.4	
Clozapine	14		<0.01	0.05	0.5	Active metabolites
Codeine	3	12	<0.1	0.9		Converted to active metabolite, morphine
Colchicine	0.3	9	0.1	0.5		
Colistin	4		0.8	0.5		
Cromoglycate	0.1		<0.05	>0.9	<0.05	
Cyclophosphamide	9	1.3	<0.2	0.80	>0.75	
Cyclosporin	20	5	<0.01	0.05	0.4	TDM
Cytarabine	3	13	<0.1	0.9	0.2	
Dacarbazine	5		0.5	0.9		
Dactinomycin	36		0.2			
Dantrolene	9		<0.01	0.1		
Darunavir	15 (in presence of ritonavir)	8 1.5 (in presence of ritonavir)	0.07	0.05	0.4 0.8 (in presence of ritonavir)	
Dasatinib	6		0.001			
Daunorubicin	45	3	0.25			Liposomal daunorubicin has a terminal half-life of 5 hours
Deferiprone	2–3	10	0.05	0.9		
Delavirdine	5		0.05	0.02		
Demeclocycline	14	0.5	0.4			
Desloratadine	27			0.15		
Desmopressin	2–3	1.3	0.45		0.0008	Values for oral tablets
Desvenlafaxine	11	4	0.45	0.7	0.8	

a. For some values in this table clearance has been calculated using the half-life

Table D.9 Pharmacokinetic data (continued)

Medicine	Half-life (hours)	Clearance (Cl)[a] (mL/min/kg)	Fraction excreted unchanged (f_e)	Fraction unbound (f_u)	Oral bioavailability (F)	Comments
Dexamethasone	4	3.7	<0.05	0.3	0.9	
Diazepam	40	0.4	<0.01	0.01	>0.95	
Diazoxide	30	0.05	0.4	0.1		
Diclofenac	1.5	4	<0.01	0.01		
Dicloxacillin	0.7		0.5	0.02	0.6	
Didanosine	1.5	16	0.5	>0.9	<0.5	
Digoxin	40	1	0.7	0.8	0.7	TDM
Dihydrocodeine	3	4	0.2		0.3	
Dihydroergotamine				<0.1	0.1	
Diltiazem	4	15	<0.05	0.1	0.4	
Diphenoxylate	7*		0.1*			* Active metabolite, diphenoxylic acid
Dipyridamole	10	2.5	<0.1	0.05		
Disopyramide	7	1	0.5	0.5	0.75	
Dobutamine	2 min	60	<0.1			
Docetaxel	12	8	0.05	0.05		
Dolasetron	6	50	<0.05		0.9	
Domperidone	10	8	<0.05	0.1	0.15	
Donepezil	70		0.17	0.04		Active metabolites
Dopamine	2 min	60	<0.01			
Dothiepin	20	25	0.01	0.1		
Doxapram	3.5	5		0.05	0.6	
Doxazosin	20	1.5	<0.01	0.01		
Doxepin	20	15	<0.01	0.15	0.3	
Doxorubicin	30	17	<0.07	0.2	0.05	
Doxycycline	16	0.5	0.4	0.1	0.9	
Duloxetine	12	25	<0.01	0.1		
Eculizumab	270	0.005				
Emtricitabine	10	5	0.7	0.95		adjust dose in renal impairment
Enalapril	30*		0.5*	0.5*	0.6	* Active metabolite, enalaprilat
Enfuvirtide	3.8	0.4		0.08	0.85	
Enoxacin	4		0.4	0.7		
Ephedrine	8		0.6			
Epirubicin	36	19	0.1			
Eplerenone	3.5–6.0	2	0.05	0.5	0.7	
Epoetin	5	0.1	0.05			
Eprosartan	5–9	2.2	0.4	0.02		
Ergotamine	2	10	<0.1			
Erlotinib	36	1	<0.05	0.05	0.6	
Erythromycin	1.5	9	0.12	0.2	0.4	
Esomeprazole	1.5	2.2	<0.01	0.03	0.5–0.9	
Ethacrynic acid	1		0.2			
Ethambutol	4	9	0.8	>0.9	0.8	
Ethinyloestradiol	10	5	<0.05	0.05	0.5	
Ethosuximide	60	0.2	0.2	>0.9		
Etidocaine	2.5		0.01	0.05		
Etidronate	6*	2.4	0.5		0.05	* Binds irreversibly to bone
Etomidate	5			0.24		
Etoposide	6	0.5	>0.3	0.05	0.5	
Etoricoxib	22	0.8	0.01	0.08	1	
Everolimus	25	8.8	0	0.25		TDM
Exemestane	24		<0.01	0.1		
Exenatide	2–3	2	1			
Famciclovir	2*		<0.01	0.8*	0.8*	Rapidly converted to active metabolite penciclovir. Parameters marked * are for peniciclovir
Famotidine	3	6	0.7	0.8	0.5	
Felodipine	14	15	<0.01	0.01	0.15	
Fentanyl	3	12	0.06	0.08		

a. For some values in this table clearance has been calculated using the half-life

Table D.9 Pharmacokinetic data (continued)

Medicine	Half-life (hours)	Clearance (Cl)[a] (mL/min/kg)	Fraction excreted unchanged (f_e)	Fraction unbound (f_u)	Oral bioavailability (F)	Comments
Fexofenadine	15		0.6	0.35	0.3	
Finasteride	6	2.5		0.07	0.8	
Flecainide	15	10	0.3	0.5	0.9	
Flucloxacillin	1		0.5	0.08		
Fluconazole	27	0.3	0.75	0.9	0.9	
Flucytosine	5	3.5	0.9	0.95	0.8	TDM
Fludarabine	20	2	0.5		0.6	
Flunitrazepam	25	1.5	0.01	0.2	0.9	
Fluorouracil	10 min	16	<0.1	0.9	0.3	
Fluoxetine	2–3 days	2.5	0.025	0.05		Active metabolite (norfluoxetine) has a half-life >7 days
Fluphenazine	14			0.01		
Flutamide	8		<0.06	0.05		Hydroxyflutamide is an active metabolite with a half-life of 10 hours
Fluticasone	3	14	<0.05	0.1		
Fluvastatin	2	25	<0.01	0.02	0.2	
Fluvoxamine	20	12	0.04	0.3		
Formestane	5 days		<0.01	0.15		
Fosamprenavir	7.7	9	0.03	0.1		Pro-drug; values are for amprenavir
Foscarnet	3		0.9	0.8		
Fosinopril	4 (12*)	0.5*	0.75*	0.05*		* Active metabolite, fosinoprilat
Fotemustine	80		<0.1	0.7		
Frusemide	1	2	0.7	0.03	0.6	
Fusidic acid	9		<0.01	0.05		
Gabapentin	6	2	0.95	>0.9	0.7	
Galantamine	8	4	0.2	0.8		
Ganciclovir	3	4	0.9	0.3		
Gemfibrozil	2	2	<0.05	0.01	>0.9	
Gentamicin	2.5	1.3	0.9	>0.9		TDM
Glibenclamide	2	0.5	<0.01	<0.01	>0.8	
Gliclazide	11		0.05	0.10		
Glimepiride	6.5	0.7	<0.01	<0.01	1	Half-life may increase at higher doses
Glipizide	3		0.04	0.05	>0.9	
Glucagon	0.1	20				
Glyceryl trinitrate	2 min	300	<0.01	0.4		Bioavailability depends on route of administration
Glycopyrrolate	0.5	20				
Granisetron	9	4	0.12	0.35	0.6	
Griseofulvin	17		0.01			Bioavailability influenced by fat content of meals
Haloperidol	20	12	0.01	0.1	0.7	
Hydralazine	2.5	50	<0.1	0.1	0.2	
Hydrochlorothiazide	10	5	0.7	0.4	0.7	
Hydrocortisone	1.5	5	<0.01	0.2		
Hydromorphone	2.5	25	<0.1		0.25	Active 3-glucuronide accumulates in renal failure
Hydroxyurea	3.5		0.8			
Hyoscine	3	1	<0.1		0.2	
Hyoscyamine	2.5		<0.05			
Ibandronate	10–60	1–2	0.5	0.15	0.01	
Ibuprofen	2	0.75	<0.01	0.01	>0.9	
Idarubicin	20	25	0.03	0.03	0.3	The elimination half-life of active metabolite (idarubicinol) is >45 hours.
Iloprost	5–25 min	20		0.4		
Imatinib	13–18	2.5	0.05	0.05	0.98	
Imipenem	1	2.9	0.7	0.8		
Imipramine	12	16	0.02	0.1	0.5	TDM
Indapamide	15	0.3	0.05	0.2	>0.9	

a. For some values in this table clearance has been calculated using the half-life

Table D.9 Pharmacokinetic data (continued)

Medicine	Half-life (hours)	Clearance (Cl)[a] (mL/min/kg)	Fraction excreted unchanged (f_e)	Fraction unbound (f_u)	Oral bioavailability (F)	Comments
Indinavir	2		0.01	0.4		
Indomethacin	6	1.5	0.05	0.05	1	
Ipratropium	4		0.03	0.8		Fraction of inhaled dose absorbed ~0.05
Irbesartan	14	2.2	0.02		0.7	
Irinotecan	6	12.5	0.2	0.35		Active metabolite SN-38 half life 6–30 hours
Isoniazid	2	5	0.2	0.5		
Isosorbide dinitrate	1	34	<0.01	0.5	0.25	
Isosorbide mononitrate	4	10	0.02	0.95	0.9	
Isotretinoin	20		<0.1	0.01		
Itraconazole	5			0.01		
Ivabradine	2	6	0.15	0.3	0.4	
Ketamine	3		<0.02	0.6	<0.2	
Ketoconazole	8	8	<0.01	0.01		
Ketoprofen	2	1.5	<0.01	<0.01	0.9	
Labetalol	4	20	<0.05	0.5	0.3	
Lamivudine	6	5	>0.7		0.8	
Lamotrigine	27	0.6	<0.2	0.5	>0.95	
Lansoprazole	1	7	<0.05	0.02	>0.8	
Lanthanum	26 weeks		<0.01	<0.01	<0.01	
Lapatinib	24		<0.01	0.01		
Lenalidomide	9	3 (CL/F)	0.65	0.7		
Letrozole	48	0.5	0.06	0.4	1.0	
Leucovorin	0.5	4	0.1	0.6		Parameters are for the active (–) isomer
Levodopa	1.5	9	<0.05		0.8	Value for oral bioavailability is for conventional oral formulation
Lignocaine	2	10	<0.1	0.4	0.4	
Lincomycin	5		0.2	0.35		
Linezolid	6	2	0.35	0.7	1.0	
Lisinopril	13	0.7	>0.9	>0.9	0.4	
Lithium carbonate	24	0.4	>0.95	1	1	TDM
Loperamide	10		<0.05		0.4	
Loratadine	12			0.02		
Lorazepam	15	1	<0.05	0.1	0.95	
Losartan	2	10	<0.05	0.02	0.4	Converted to active metabolite (E3174), which has a half-life of 8 hours
Lumefantrine	5 days			0.001		N-demethyl lumefantrine is active
Lumiracoxib	3–6	2	0.05		0.75	
Maraviroc			0.08	0.25	0.23	
Mefenamic acid	3.5		<0.05			
Melphalan	1.5	5	0.1	0.2		
Mepivacaine	2.5			0.2		
Mercaptopurine	1	11	>0.1	0.3	0.15	
Mesna	0.3	20	0.4			
Metformin	4	6.5	0.8	>0.9	0.5	
Methadone	20	1.4	0.25	0.1	0.9	
Methohexital	4	11	<0.01			
Methohexitone	4.5			0.3		
Methotrexate	7	2	>0.7	0.4	>0.75	
Methyldopa	2	6	0.5	0.9	0.4	
Methylprednisolone	2	6.5	0.05	0.2	>0.7	
Metoclopramide	7	6	0.3	0.6	0.8	
Metocurine	5	1.3	0.5	0.6		
Metoprolol	4	16	<0.05	0.9	0.5	
Metronidazole	8	1.3	0.1	1	1	
Mexiletine	10	8	0.15	0.3	0.9	TDM
Mianserin	12	10		0.1	0.3	

a. For some values in this table clearance has been calculated using the half-life

Table D.9 Pharmacokinetic data (continued)

Medicine	Half-life (hours)	Clearance (Cl)[a] (mL/min/kg)	Fraction excreted unchanged (f_e)	Fraction unbound (f_u)	Oral bioavailability (F)	Comments
Miconazole	24			0.1		Systemic absorption can occur after buccal or vaginal delivery
Midazolam	2	8	<0.01	0.05		
Milrinone	1	4	0.8	0.3		
Minocycline	16	1	0.1	0.3	1	
Minoxidil	4	10	0.1	>0.9		
Misoprostol	1*			0.2*	>0.8*	Rapidly converted to the active metabolite* misoprostol acid
Mitomycin C	50 min	20	0.1			
Mitozantrone	12 days		0.05	0.2		
Moclobemide	1.5	8	0.01	0.5		
Monoxidine	2–3	12.5	0.5	0.9	0.88	
Montelukast	3–6	0.5	<0.01	0.01		
Morphine	2	20	<0.1	0.7	0.3	Active metabolite, morphine-6-glucuronide
Mycophenolate	18	2.5	<0.01	0.03		Data are for mycophenolic acid
Nalidixic acid	5	0.1		0.08		
Naloxone	1	22	<0.01		0.02	
Naltrexone	3	22	<0.01	0.8	0.2	
Naproxen	14	0.1	<0.01	0.01		
Natalizumab	250	0.004				
Nedocromil	2		0.7	0.15		Fraction of inhaled dose absorbed ~0.05
Nefazodone	3	3	0.01	0.01		
Nevirapine			0.03	0.4	0.4	
Neomycin	2.5		0.01			
Neostigmine	1	8	0.7			
Nicorandil	1		0.01	0.75	0.35	
Nicotinic acid	0.5		0.4			
Nifedipine	3	9	<0.01	0.04	0.5	
Nilotinib	17		<0.1	0.02	0.3	Blood/serum = 0.68
Nimodipine	1	15	<0.01	0.02	0.1	
Nitrazepam	26	1	<0.01	0.15	0.8	
Nitrofurantoin	1		0.5	0.5		
Nizatidine	1.6	10	0.6	0.7	>0.9	
Norfloxacin	5	7	0.3		0.45	
Nortriptyline	30	10	0.02	0.1	0.6	TDM
Octreotide	1.5	3	0.1	0.35	<0.02	Intranasal bioavailability = 0.2
Ofloxacin			1			
Olanzapine	30	5	<0.1	0.07		
Olmesartan	13		0.5	0.01	0.26	
Omeprazole	1	7.5	<0.05	0.05	0.5	
Ondansetron	4	7.5	<0.05	0.25	0.6	
Orlistat						Minimal absorption
Orphenadrine	14					
Oseltamivir	7.5	5	>0.9	>0.9		Data presented for active metabolite
Oxaliplatin	270*	2*	0.34			* Ultrafiltrable platinum
Oxazepam	8	1	<0.05	0.1		
Oxcarbazepine	2	0.85*	0.01	0.6*		* Active monohydroxy-metabolite, which has half-life of 9 hours. This metabolite is cleared hepatically and renally.
Oxpentifylline	1		<0.05	>0.9		
Oxprenolol	2.5	3	<0.05	0.1	0.5	
Oxybutynin	2			<0.001	0.06 (oral)	N-desethyl active metabolite
Oxycodone	5	10	<0.1	0.50	<0.5	
Paclitaxel	3	6	0.05	0.02	Low	
Paliperidone	24		0.6	0.25	0.28	
Pamidronate	1	2	0.4		<0.01	Extensive uptake into bone
Pantoprazole	1	2	<0.01	0.03	0.8	
Paracetamol	2	5	0.05	0.8	0.65	TDM. F = 0.35 after rectal administration

a. For some values in this table clearance has been calculated using the half-life

Table D.9 Pharmacokinetic data (continued)

Medicine	Half-life (hours)	Clearance (Cl)[a] (mL/min/kg)	Fraction excreted unchanged (f_e)	Fraction unbound (f_u)	Oral bioavailability (F)	Comments
Paricalcitol	4–7	1.5	<0.1	0.002	0.8	
Paroxetine	24		0.02	0.05		
Penicillamine	90		0.1	0.7		
Pentazocine	2	17	0.3	0.5		
Perhexiline	*	0.7 (poor metaboliser), 7.2 (extensive metaboliser), 17.2 9 ultra-extensive metaboliser)		0.1		* Half-life highly variable (48–144 hours). Metabolised by CYP2D6—poor metabolisers require reduced dose. TDM.
Perindopril	2 (28*)	10*	0.7*	>0.8*		* Active metabolite, perindoprilat
Pethidine	3	15	0.1		0.6	
Phenobarbitone	96	0.05	0.3	0.5	0.8	TDM
Phenoxybenzamine		24		<0.01		
Phenoxymethylpenicillin		0.5		0.5	0.15	
Phenytoin	20	0.3	<0.05	0.1	0.9	TDM
Pimozide	29		<0.1			
Pindolol	3.5	8	0.4	0.5	0.9	
Pioglitazone	6		0.01	0.02	0.85	
Piperacillin	1	2.6	0.7	0.8		
Piroxicam	40	0.04	0.05	0.01		
Posaconazole	35	8	<0.01	0.02		Bioavailability increases significantly when administered with food
Pramipexole	10	8	0.9	0.85	0.9	Erythrocyte/plasma ratio = 2
Pravastatin	2			0.5	0.2	
Prazosin	3	3	0.05	<0.1	0.6	
Prednisolone	2		<0.2	0.1		
Prednisone	4		0.03	0.25		
Pregabalin	6	1	0.95	1	0.9	Dose adjustment may be required in renal impairment
Primidone	10	0.8	0.4	0.8	0.7	TDM. Metabolised to phenobarbitone
Probenecid	8		0.075	0.1		
Prochlorperazine	24		0.01		0.2	
Promethazine	8	4	0.02	0.05	0.25	
Propantheline	2	20	0.05			
Propofol	5	20		<0.05		
Propranolol	4	15	<0.01	0.05	0.35	
Propylthiouracil	1.5	5	<0.05	<0.2	>0.8	
Pseudoephedrine	10	0.1	0.7			
Pyrazinamide	0.5	8.5	0.9			
Pyridostigmine	1	8	0.9		0.15	
Quetiapine	7		0.05	0.17		
Quinapril	25*	2*	>0.9*	0.03	>0.6	* Active metabolite, quinaprilat
Quinidine	8	4	0.3	0.2	0.75	TDM
Quinine	11	2	0.1	0.05	0.8	
Rabeprazole	1	4	<0.01	0.03	0.5	
Raloxifene	28		<0.05	0.01	0.02	
Raltegravir			0.1	0.17	>0.3	
Raltitrexed	170	0.7	>0.95	0.07		
Ramipril	12*	1*	<0.02 (>0.9*)	0.5*	0.3	* Active metabolite, ramaprilat
Ranitidine	2.5	10	0.7	0.85	0.5	
Repaglinide	1		0.08	0.02	0.63	
Ribavirin	28	5.0	0.3	1	>0.4	
Rifabutin	40		0.05	0.15		
Rifampicin	3.5	3.5	0.07	0.1		

a. For some values in this table clearance has been calculated using the half-life

Table D.9 Pharmacokinetic data (continued)

Medicine	Half-life (hours)	Clearance (Cl)[a] (mL/min/kg)	Fraction excreted unchanged (f_e)	Fraction unbound (f_u)	Oral bioavailability (F)	Comments
Risedronate	1.5 (initial) 480 (terminal)	1.7	0.85	0.75	<0.01	
Risperidone	3 (extensive metaboliser) 19 (slow metaboliser)	4 (extensive metaboliser) 0.5 (slow metaboliser)	0.2	0.1		Active metabolite 9-OH-risperidone half-life = 24 hours
Rivastigmine	1.5		<0.01	0.6	0.4	
Ropinirole	6	15	small	0.75	0.45	
Rosiglitazone	3–4	0.71	<0.01	<0.01	0.99	
Rosuvastatin	19	12	0.05	0.1	0.2	
Rotigotine	6	1400	<0.02	0.08	0.37	
Roxithromycin	12		0.07	0.05	0.5	
Salbutamol	4	12.8	0.25	>0.9	0.44	
Salcatonin	1–2		<0.02	0.65	0.7 (SC and IM)	Biological half-life is several hours
Selegiline	2			0.05	<0.2	
Sertraline	26		0.1	0.02		Active metabolite, N-desmethyl-sertraline
Sibutramine	1	420 (Cl/F)		0.03		
Simvastatin	2		<0.01	0.05	0.05	Extensively converted to active metabolites after oral dosing
Sitagliptin	12	6	0.8	0.6	0.87	
Sitaxentan	8		<0.01	0.01		High-fat meal reduces bioavailability
Sorafenib	24–48		<0.01	0.01	0.45 (tablets relative to oral solution)	High-fat meal reduces bioavailability
Sotalol	12	2.5	0.7	>0.9	1	
Spectinomycin	2		0.85	>0.9		
Spironolactone	1.5		Low	0.1	>0.9	Active metabolites with half-lives of up to 24 hours
Stavudine	1.5		0.4		0.9	
Streptomycin	3	1	0.6	0.5		
Sufentanil	3	13	0.05	0.06		
Sulfamethoxazole	12	0.3	0.3	0.4		
Sulfasalazine	6		0.05	<0.1		Metabolised in colon to sulfapyridine and 5-amino salicylic acid
Sulindac	7		<0.20	0.05		Metabolised to active sulfide which has long half-life (16 hours)
Sumatriptan	2	16	0.2	0.8	<0.2	
Sunitinib	40–60 (80–110*)	2 (Cl/F)	<0.1	0.05		* Active metabolite
Tacrine	3		<0.01	0.45	0.2	
Tacrolimus	43 (whole blood) in healthy subjects 11–15 in transplant patients	0.5 in healthy subjects 1–2 in transplant patients	<0.01	0.01	0.2	TDM
Tamoxifen	8 days	1.4	<0.01	<0.02		
Tamsulosin	16	0.3	0.05	0.01	0.55	
Teicoplanin	100		0.8	0.05		
Telbivudine	40		>0.9	0.95		
Temazepam	13	0.9	<0.01	0.02	0.9	
Teniposide	20	0.4	0.1	<0.01		
Tenoxicam	70	0.04	<0.01	<0.01		
Terazosin	12		0.1	0.1		
Terbutaline	15	3	0.5	0.8	0.15	
Testosterone	1.0	25	0.05		<0.05	
Tetracycline	10	1.7	0.6	0.4		

a. For some values in this table clearance has been calculated using the half-life

Table D.9 Pharmacokinetic data (continued)

Medicine	Half-life (hours)	Clearance (Cl)[a] (mL/min/kg)	Fraction excreted unchanged (f_e)	Fraction unbound (f_u)	Oral bioavailability (F)	Comments
Thalidomide	9	2.5	<0.01			
Theophylline	9	0.6	0.1	0.4	>0.9	TDM
Thiopental	9	4	<0.01	0.15		
Thioridazine	12	5	<0.01	0.01		
Thiotepa	2	5	0.9	>0.6		
Thyroxine	6 days	0.01	0	<0.01		
Tiaprofenic acid	2.5	0.1	0.6	0.02	1	
Tibolone	Very short			0.04		Effect due to active metabolites with half-lives of 7 hours
Ticarcillin	1.3	2	0.9	0.5		
Timolol	4	8	0.2	0.7	0.6	
Tobramycin	4	1	>0.9	>0.9		TDM
Tolbutamide	6	0.25	<0.05	<0.1	>0.9	
Topiramate	20	0.5	0.6	>0.8		
Topotecan	2	15	0.4			
Toremifene	12 days		<0.1	0.01		
Trandolapril	1 (22*)		0.8 (0.95*)	0.2 (0.05*)	0.5*	* Active metabolite, trandolaprilat
Triamterene	3	20	0.05	0.4	0.5	
Triazolam	3	2	0.02	0.1		
Trimethoprim	11	2	0.45	0.40	1	
Trimipramine	15	15		0.05	0.4	
Tropisetron	7	1.0	<0.1	0.4	0.6	
Tubocurarine	2	2	0.63	0.4		
Valaciclovir	3		<0.01	0.75		
Valproate	14	0.12	<0.05	0.1	>0.95	TDM
Vancomycin	6	1.5	0.85	0.45		TDM
Varenicline	24	3	0.9	0.8	>0.9	
Venlafaxine	5	15		0.7		Active metabolite (o-desmethyl-venlafaxine) has a half-life of 11 hours
Verapamil	4	15	0.05	0.1	0.2	
Verteporfin	5	2	<0.01			
Vigabatrin	6	1	0.7	>0.8		
Vinblastine	24			0.2		
Vincristine	50		0.05	0.25		
Vindesine	24	4	0.15			
Warfarin	40	0.05	<0.05	0.01	1.0	
Zafirlukast	10		<0.01	0.01		
Zalcitabine	2	4	>0.5	>0.95	0.7	
Zaleplon	1		<0.1	0.4		
Zidovudine	1.5		0.15	0.6	0.6	
Zoledronic acid	170	1	1	0.8		
Zolpidem	2.4		Low	0.1	0.7	
Zonisamide	60	0.2	0.2	0.5	1.0	

a. For some values in this table clearance has been calculated using the half-life

Individualised medicine

Pharmacogenetics is the study of the effect of genetic factors on the response of individuals or population subgroups to certain drugs. Completion of the mapping of the human genome in 2003 and the introduction of new technologies have made it possible to analyse multiple genes simultaneously, giving rise to the science of pharmacogenomics.

The term 'pharmacogenetics' usually describes a single-gene approach, whereas 'pharmacogenomics' emphasises a larger genome approach that considers not only single-gene effects but also multi-gene interactions and pathways.[1] This permits the broader application of genomic technologies to new drug development and prediction of patient responses to existing drugs. The aim of pharmacogenomics is to enable the prescribing of drug therapy to be genetically guided, thereby optimising its effectiveness and reducing adverse side effects.

The genomes of individuals are 99.9% identical. However, the small 0.1% difference can predict as many as 3 million polymorphisms, the most common being single nucleotide polymorphisms (SNPs)—inter-individual variations in the genetic code at the level of one nucleotide.[2] SNPs are scattered throughout the human genome and are major determinants of many clinically relevant variations in drug response and other human traits, including appearance and disease susceptibility.

Identifying genes involved in drug response

Following a clinical observation of variation in drug response, identification of the genes involved may be achieved in several ways:

- The traditional approach involves delineation of drug pathways to identify any gene that may influence a particular drug—e.g. genes encoding proteins likely to modify pharmacokinetics, such as drug-metabolising enzymes and drug transporters, or genes involved in the pathogenesis of the condition being treated. This approach has been used for many drugs, including perhexiline, 5-fluorouracil and irinotecan.
- The previous approach is limited by our understanding of a drug's pharmacological, pharmacokinetic and toxicological pathways. A newer approach involves studying the entire genome to identify genetic differences in a population that explain certain observed responses to a drug or susceptibility to a health problem. The value of this approach is demonstrated through the identification of HLA-B57 as a determinant of allergy to the antiretroviral drug abacavir.[3] This potentially powerful approach has been limited by factors such as cost and the significant numbers of patients required.
- A third approach involves gene expression profiling, which provides a snapshot of gene activity in a specific tissue at a specific time. By comparing gene expression profiles of patients with different responses to a drug, it is possible to identify genes whose regulation may be linked to differential drug outcomes. This approach is particularly useful in the oncology setting and has been used in breast cancer patients to identify a group of 70 genes (the gene signature) that can be used to predict likely prognosis.[4]

Once candidate genes have been selected for pharmacogenomic analysis, they are assessed for variability across ethnically diverse population groups. A number of technologies have emerged for rapid detection of multiple SNPs, including gene chip technology. Chips for certain cytochrome P450 genes have been introduced into clinical practice in the United States and are among commercially available pharmacogenomic tests that can be used to optimise the use of certain medications. Significant projects are under way in most large pharmaceutical companies and major research institutes to prioritise those SNPs predictive of drug and health outcomes. Currently the major challenges to be overcome include assessment of the likely clinical relevance of the large number of emerging SNPs and the provision of cost-effective SNP detection by diagnostic laboratories.

Genetic variation in drug response

Metabolic pathways

Until recently most examples of variation in drug response involved genes encoding drug-metabolising enzymes (DMEs). Numerous differences in the genes encoding many DMEs have been identified, some producing marked variations in enzyme activity. These differences (polymorphisms) may be:

- structural—a polymorphism in the region of a DME gene which stipulates the structure of the encoded protein has the potential to alter enzyme activity,

- regulatory—variability in regulatory regions of DME genes is also an important determinant of individual drug metabolising capacity.

As more variability in DME genes is identified it is becoming increasingly apparent that each individual possesses a distinct genetically determined complement of DMEs. This diversity might be described as a 'metabolic fingerprint'.

Variations in the cytochrome P450 2D6 gene

The cytochrome P450 2D6 (CYP2D6) gene is responsible for the metabolism of nearly 25% of all drugs, including antiarrhythmics, antidepressants and major tranquillisers, many of them drugs with a low therapeutic index. Genetic variations in the level of expression or function of CYP2D6 may have significant effects on the efficacy and toxicity of these drugs.

Individuals are broadly classified as poor or extensive metabolisers of CYP2D6 substrates. The proportion of slow metabolisers varies with ethnicity but ranges between 5–10% in Caucasian populations. These patients are considered to be at increased risk of adverse reactions; e.g. nortriptyline is dosed in most patients at a range of 75–150 mg, but in poor CYP2D6 metabolisers the effective tolerable dose is 10–20 mg.[2] However, they may also experience therapeutic failure; e.g. poor metabolisers do not achieve adequate analgesia when treated with codeine, which requires metabolic activation to morphine via CYP2D6.

A small number of individuals (1–2% in Caucasians) are classified as having ultrarapid drug metabolism mediated by CYP2D6. In ultrarapid metabolisers a genetic variation results in the inheritance of as many as 13 copies of the gene. These patients are generally considered to be at risk of therapeutic failure; e.g. they metabolise nortriptyline so quickly they may require a dose of more than 500 mg to achieve therapeutic effect.[2] However, when treated with pro-drugs such as codeine they may experience an exaggerated response. The impact of this may not be immediately obvious; e.g. a nursing mother who is an ultrarapid metaboliser may not be aware of experiencing an exaggerated response to codeine but there may be profound consequences, including respiratory depression, in the infant.

Drug targets (receptors)

Genes determine how many receptors are produced on or within cells, and genetic variation causes some people to produce a greater number of receptor sites.[5]

For example, the monoclonal antibody drug trastuzumab is approved for use in breast cancer patients who test strongly positive for receptors HER2 on the cell surface. The gene encoding HER2 is amplified in some tumour cells, and this correlates with overproduction of the receptor, a rapid proliferation rate and a poor prognosis. Testing positive for HER2 overproduction does not, however, guarantee a response to the drug. Trastuzumab is not approved for use in women who test negatively for HER2 gene amplification as they are unlikely to respond to treatment.

Receptor polymorphisms with a direct effect on drug response also occur in the gene for the $beta_2$-adrenoreceptor, affecting the response to $beta_2$-agonists, and angiotensin-converting enzyme (ACE), affecting the renoprotective actions of ACE inhibitors.[2,6]

Pharmacogenomics and pharmacy practice

Currently there is limited availability of genetic testing for drug response. However, pharmacogenomics has a number of applications relevant to pharmacy practice. For example, a subset of patients with a genetic variation of the $beta_2$ adrenergic receptor experience a worsening of their asthma if treated excessively with salbutamol.[7] In addition, the use of long-acting $beta_2$ agonists (LABAs) in these patients, without the use of inhaled corticosteroids (ICS), results in a further exacerbation of symptoms (but not when used in combination with ICS).[8,9] Pharmacists should promote appropriate asthma management for each patient, regardless of the $beta_2$ receptor genotype. It is important to ensure that patients are not excessively reliant on salbutamol solely and are compliant with ICS if being treated with LABAs. Pharmacists also have an important role in ensuring that patients understand that taking medications incorrectly may actually exacerbate symptoms.

Pharmacogenomics in the future

In drug development, pharmacogenomics has the potential to limit the size of patient markets for new medicines, but this is counterbalanced by dramatic cost savings from streamlined clinical trials and a decreased drug failure rate. Genetically informed clinical trials are likely to be significantly smaller because populations are chosen specifically on the basis of a greater likelihood of response or a reduced risk of toxicity. For example, the availability of a pharmacogenomic test has enabled an estimated 90% reduction in the size of clinical trials studying the efficacy of trastuzumab, resulting in a significant cost reduction. Drugs that have previously failed during the drug development process may now

be reconsidered using pharmacogenomics, again with considerable potential economic benefits to the industry.

The clinical impact of pharmacogenomics is likely to be considerable; e.g. it may guide the choice of how aggressively to treat patients with chemotherapy. Tumour profiling using a variety of genomic strategies will be used to identify the molecular characteristics of those tumours most likely to metastasise and result in a poorer prognosis. Individuals at high risk could then be managed with more aggressive therapy, while strategies aimed at minimising toxicity could be chosen for low-risk patients.

Genetically informed treatment strategies for colorectal cancer are gradually evolving from genomic studies which have identified multiple genes involved in drug disposition, those encoding drug targets, and those involved in disease pathogenesis. In the future, clinicians may be able to choose therapy with a view to maximising efficacy and/or limiting toxicity.

Pharmacogenomics may also guide drug dosage, as illustrated by the widely prescribed anticoagulant warfarin. Warfarin's narrow therapeutic index and greater than 10-fold inter-individual therapeutic dose variability cause problems with dosing regimens and significant risk of bleeding. Many factors influence the dose–response relationship of warfarin, including age, gender, vitamin K intake, other medications and comorbidities. In addition, genomic factors have been identified which account for much of the inter-patient variability seen with warfarin.

It is well established that polymorphisms exist in the CYP2C9 enzyme, which is responsible for the metabolism of S-warfarin. Individuals with CYP2C9 variant alleles are at greater risk of bleeding and require a significantly lower mean warfarin dose to obtain therapeutic anticoagulation.[10] The recently identified vitamin K epoxide reductase complex 1 (VKORC1) gene has also been found to affect warfarin dose requirements. Low dose–requiring and high dose–requiring polymorphisms of the VKORC1 gene have been identified. By using a combination of CYP2C9 and VKORC1 genotypes, individuals can be assigned to low-, medium- and high-maintenance dose groups.[11]

Favourable pharmaco-economic analyses of pharmacogenomic interventions have begun to appear in the literature, and the US Food and Drug Administration is creating a regulatory framework to incorporate pharmacogenomics. This includes documentation and guidance for industry pharmacogenomic data submissions and the development of an Office of Combination Products to consider combined medicine–pharmacogenomic test submissions. A number of drugs are under active review with respect to their labelling in the light of recent pharmacogenomic data.

As the population continues to age, the health care budget will come under increasing pressure. In order to maintain the viability of medication subsidy measures such as the Pharmaceutical Benefits Scheme, the cost-effectiveness of medication use must be maximised. Pharmacogenomics will increasingly provide a mechanism by which this can occur. The narrowing of the criteria for subsidy of the anti-cancer agent gefitinib indicates the willingness of the Pharmaceutical Benefits Advisory Committee to embrace this philosophy.

Barriers to progress

Pharmacogenomics is a technically challenging discipline, but perhaps an even greater challenge is the successful translation of pharmacogenomic research into mainstream clinical practice.

Barriers to the incorporation of pharmacogenomics in clinical practice include not only prevailing attitudes and prescribing practices but also a variety of technical, economic, ethical, regulatory and educational issues. Perhaps the greatest challenges lie in changing prescribing behaviour. This can only be achieved through education. The majority of health care professionals, including most pharmacists, are not well versed in the basic genetic methodologies underpinning pharmacogenomics. Increasing consumer awareness, as a result of innovations such as a pharmacogenomically restricted drug subsidy, will drive the need for health care professionals to improve their understanding and knowledge of pharmacogenomics.

Summary

Pharmacogenomics has been advocated as a new therapeutic paradigm, moving us from a population-based approach to individualised medicine. The role of pharmacogenomics in aiding clinical decision making is likely to become steadily greater. While uptake is currently limited, it is incumbent on pharmacists to be aware of pharmacogenomics, its potential impact on therapeutics, and the various practical issues related to its implementation.

Table D.10 Examples of pharmacogenomic associations

Drug	Gene	Protein	Clinical significance
Abacavir	HLA	Human leucocyte antigen (HLA) system (also called the major histocompatibility complex, MHC)	Patients with HLA-B*5701, HLA-DR7 and HLA-DQ3 haplotype likely to experience a potentially life threatening hypersensitivity reaction
ACE inhibitors	Bradykinin $beta_2$ receptor	Bradykinin $beta_2$ receptor	Polymorphism in promoter region: 58 thymine(T)/cytosine(C). Patients homozygous for TT genotype are more susceptible to ACE Inhibitor–induced cough than those homozygous for CC genotype
Azathioprine, 6-mercaptopurine	TPMT	TPMT	Patients with low or undetectable TPMT activity are at risk of severe toxicity
β-blockers and Calcium antagonists	Gly460Tr		Variant is sensitive to salt and reacts with high blood pressure when given salt. In those patients beta blocker and calcium antagonists will never result in risk reduction, and thiazides are the drugs of choice
Codeine	CYP2D6	CYP2D6	Patients with two inactive alleles do not achieve analgesia
Diuretics: frusemide and hydrochlorothiazide	α-adducin	α-adducin	Patients with Gly460Trp mutation have significantly increased blood pressure reduction. Blood pressure also more susceptible to changes in salt balance
Fluorouracil (5-FU)	DPYD	Dihydropyrimidine dehydrogenase	Deficiency leads to 5-FU toxicity (neutropenia, thrombocytopenia, neurological damage)
Irinotecan	UGT1A1	UGT1A1	Patients homozygous for 7 TA repeats in the promoter sequence are greater than 9 times more likely to experience severe irinotecan-induced neutropenia than other patients
Isoniazid	NAT2	Arylamine N-acetyltransferase type 2 (NAT2)	Rapid acetylators metabolise isoniazid faster, so require a higher dose for same effect
Salbutamol	ADRβ_2	Beta$_2$ adrenergic receptor	Patients homozygous for Gly17Arg mutation experience a decline in respiratory function with regular use of salbutamol
Sibutramine	GNB3 CC		Carriers respond much better to obesity treatment with sibutramine than non-carriers
Trastuzumab	HER2	Human epidermal growth factor receptor type II (HER2)	Tumours not over-expressing HER2 will not respond to trastuzumab. Tumour regression with trastuzumab therapy in up to 35% of patients with tumours that strongly over-express HER2
Warfarin	CYP2C9	CYP2C9	Patients with defective alleles require significantly lower maintenance doses, have longer times to dose stabilisation, and are at higher risk for serious and life-threatening bleeding than are patients without these variants
Warfarin	VKORC	Vitamin K epoxide reductase complex 1	Variants stratify patients into low-, intermediate- and high-sensitivity groups

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Optimal medicine concentration ranges

This section describes the optimal concentration ranges of selected medicines to help guide effective dose selection and prevent toxicity. Monitoring the therapeutic effect of all medications involves determination of the efficacy and adverse effects. Most medicines can be evaluated using a range of clinical signs and symptoms, however, some medicines may require direct measurement of drug levels to obtain useful information. Therapeutic drug monitoring is most useful where the following apply:

- The therapeutic or toxic effect is difficult to measure directly (e.g. the early toxic effects of paracetamol are clinically difficult to ascertain).
- A relationship has been established between the concentration of the medicine and its therapeutic or toxic effects, or both.
- The drug has a low toxic: therapeutic ratio.
- The medicine does not have active metabolites (unless the active metabolites are included in the assay).
- There is a variation in response among individuals (e.g. the variation of response between slow and fast metabolisers of perhexiline).
- A reliable assay exists for the medicine and any relevant active metabolites.

It is emphasised that the listed target concentration ranges are those under which the patient is expected to have the highest probability of receiving therapeutic benefits and lowest probability of experiencing adverse effects. There is, however, a potential for lack of efficacy or side effects even within the target range.

Interpretation of concentration data

Target concentration ranges should be used as a tool to optimise patient treatment. The signs and symptoms of a patient's disease or toxicity should be the main indicators of the appropriateness of a dose. The ranges described here serve as a guide for optimising the treatment in a 'typical' patient and are based on available evidence in the literature and centres of best practice in Australia. Patient age and size, the extent and rate of drug absorption or excretion, and metabolic rate can all affect drug levels. The following information is required to accurately interpret concentration data:

- accurate dose history—including dose (with an assessment of compliance) and duration of therapy (to assess if steady-state conditions have been achieved)
- time and date of dose administration and of blood sampling
- biological fluid assayed—e.g. whole blood, plasma or serum
- medication history—including medicines, complementary products and over-the-counter products that may potentially interact with the medicine of interest.

This information should be evaluated along with patient clinical status and/or reason for request and characteristics such as organ function, age, height and weight before making dosing recommendations.

Concentration ranges

Table D.11 shows the concentration ranges for selected medicines. The following should be noted:

- Concentrations are expressed as total (bound plus unbound) concentration ranges unless specifically denoted 'unbound'.
- Concentrations are expressed in SI units and may differ from the units used in some international publications.
- For some medicines, optimal concentrations may vary between laboratories, depending on assay methods (e.g. cyclosporin and tacrolimus) or local interpretation of the literature.
- Blood samples used for monitoring can be taken at the drug's peak level or at the lowest level (trough). Both peak and trough levels should fall in the therapeutic range, particularly for anti-infectives. Trough levels may be requested if there is concern about inadequate dose. Samples for trough levels are generally taken at or near the end of the dosing interval and before the next dose during multiple dosing at steady state; it takes about four to five half-lives after the start of dosing (or the change of a regimen) before a patient can be considered to be at steady state (see 'Half-life' in 'Pharmacokinetic data', Section D). Some drugs with a long half-life require loading doses to more quickly obtain therapeutic levels and clinical benefit.
- Recommended concentrations may not be appropriate for the very young or very old patient, who may be more sensitive to the effects of specific medications.

Advice

- An assessment of the appropriateness of the timing of the blood sample is necessary before making any dosage adjustments.
- An assessment of compliance is essential before changing a dose regimen based on observation of a lower than expected concentration.
- Always assess the clinical status of the patient before increasing or decreasing the dose.
- After a change in dose, take another sample once the patient has achieved a new steady state (which may be up to five half-lives for the drug) or earlier if toxicity is suspected.
- For medicines with long half-lives, concentrations may be measured before reaching a new steady state in order to detect potentially toxic accumulation earlier (e.g. amiodarone, perhexiline and sirolimus).
- Medicines other than those included in Table D.11 may be monitored by selected laboratories, although clinical benefit is yet to be established. These include clozapine, isoniazid, lamotrigine, methotrexate, sotalol, teicoplanin, warfarin (to confirm resistance), mycophenolate mofetil, rifampicin, oxypurinol, procainamide, HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine).

Table D.11 Optimal concentration ranges for selected medicines

Medicine	Therapeutic range		Toxic concentration	Time to steady state	Comments
	Gravimetric units	Molar units (SI)			
Analgesics					
Paracetamol	10–30 microgram/mL	66–199 micromol/L	>195 microgram/mL 4 hours after ingestion. 100 microgram/L 4 hours after ingestion for those with alcohol-induced liver impairment on enzyme inducers or with HIV/AIDS	10–20 hours	Paracetamol levels are only indicated in cases of overdose. The time of ingestion must be obtained in order to assess whether the level is toxic or non-toxic
Salicylate	150–300 mg/L (anti-inflammatory) 300–400 mg/L (rheumatic fever)	1.0–2.5 micromol/L	>3.6 micromol/L (>500 mg/L)	5–7 days	Dose and urinary pH–dependent half-life
Anticonvulsants					**To monitor seizure control and sedation**
Carbamazepine	6–12 mg/L	20–40 micromol/L	>15 mg/L	7–10 days	Induces its own metabolism. Pre-dose testing not as critical with slow-release formulations
Phenobarbitone	10–40 mg/L (adult) 10–30 mg/L (child)	45–180 micromol/L (adult) 45–135 micromol/L (child)	>40 microgram/mL	14–20 days	
Phenytoin	Trough Total: 10–20 mg/L Unbound: 1–2 mg/L	Trough total: 40–80 micromol/L	>20 mg/L	5–7 days	Non-linear pharmacokinetics. Monitor adverse effects
Valproate	50–100 mg/L (up to 150 mg/L in some patients)	350–700 micromol/L	in some patients from >100 mg/L	3–5 days	Poor correlation between concentration and effect. Monitoring useful to confirm toxicity or assess compliance

Table D.11 Optimal concentration ranges for selected medicines (continued)

Medicine	Therapeutic range		Toxic concentration	Time to steady state	Comments
	Gravimetric units	Molar units (SI)			
Anti-infectives					
Chloramphenicol	Trough <10 mg/L Peak <25 mg/L	Trough <31 micromol/L Peak <78 micromol/L	>25 microgram/mL	7.5–20.5 hours	
Flucytosine	Trough >25 mg/L	>190 micromol/L	>100 mg/L	13–30 hours	
Gentamicin	5–10 microgram/mL (6–14 hours post dose if once per day dosing)		Multiple daily dosing: Peak >10 microgram/mL Trough >2 microgram/mL	5–15 hours (adult); 3–12 hours (child); 15–25 hours (infant); 20–40 hours (neonate); 8–30 hours (elderly)	Use of nomogram recommended. Area under the curve (AUC) monitoring recommended for some situations (e.g. pulmonary infections in cystic fibrosis patients)
Tobramycin	5–10 microgram/mL		Multiple daily dosing: Peak >10 microgram/mL Trough >2 microgram/mL	5–15 hours (adult); 3–12 hours (child); 15–25 hours (infant); 20–40 hours (neonate); 8–30 hours (elderly)	
Vancomycin	5–10 mg/L (non-MRSA) 10–20 mg/L (MRSA infection) (trough level during once or twice daily dosing)		Peak >40 microgram/mL Trough >10 microgram/mL	28–43 hours (adult); 18–39 hours (child/infant); 7–54 hours (premature neonate)	Peak levels do not correlate with efficacy or toxicity
Antineoplastics and immuno-suppressives					
Cyclosporin	**Following transplant: C_0(trough) concentrations:** First 3 months / Maintenance Kidney: 150–300 microgram/L / 100–200 microgram/L Liver: 150–300 microgram/L / 100–200 microgram/L Heart: 250–350 microgram/L / 150–250 microgram/L Bone marrow: 100–300 microgram/L / 100–300 microgram/L **C_2 (2 hour) target concentrations** Heart: 0–3 months: 600–800 microgram/L 3–6 months: 500–700 microgram/L >6 months: 300–600 microgram/L Renal: 2 months: 1,500 microgram/L 3 months: 1,300 microgram/L 4–6 months: 1,100 microgram/L 7–12 months: 900 microgram/L >12 months: 800 microgram/L Liver: 0–6 months: 1,000 microgram/L 7–12 months: 800 microgram/L >12 months: 600 microgram/L			30 hours Time to steady state may be longer soon after transplant or if patient has hepatic impairment	EDTA—whole blood is used and trough concentration ranges reported Multiple interactions—caution needed. Monitoring concentration at 2 hour post dose is preferred method
Everolimus	Trough 3–8 microgram/L			4–5 days	
Sirolimus	With calcineurin inhibitor 6–15 microgram/L, without inhibitor up to 20 microgram/L			14 days	Minimise calcineurin inhibitor 2–4 months post transplant due to risk of synergistic nephrotoxicity
Tacrolimus	Transplant of: Kidney: 10–20 microgram/L (0–3 months); 5–15 microgram/L (4–12 months) Liver: 2–15 microgram/L Heart: 10–15 microgram/L		>15 microgram/L	2–2.5 days	EDTA—whole blood is monitored. May depend on assay. Trough concentrations monitored

Table D.11 Optimal concentration ranges for selected medicines (continued)

Medicine	Therapeutic range		Toxic concentration	Time to steady state	Comments
	Gravimetric units	Molar units (SI)			
Bronchodilators and respiratory stimulants					
Theophylline	Adult: 10–20 mg/L (2–4 hours post dose)	55–110 micromol/L Neonates: 38–85 micromol/L	>20 mg/L	1–7 days	Pharmacokinetics influenced by smoking, heart failure, liver disease and some medicines—e.g. carbamazepine, cimetidine, ciprofloxacin, erythromycin
Cardiovascular drugs					
Amiodarone	1.0–2.5 mg/L (>8 hours after last dose)	1.5–4.0 micromol/L	from >2 mg/L	5 months	
Digoxin	0.5–1.0 microgram/L (atrial fibrillation and heart failure)	0.6–1.3 nmol/L (atrial fibrillation and heart failure)	>2.4 microgram/L	6–20 days depending on renal function	The incidence of anorexia increases at concentrations higher than 1.2 nmol/L. Assess visual disturbances, monitor potassium as hypokalaemia may lead to toxicity with levels in target range
Mexiletine	0.5–2.5 mg/L	2.8–14 micromol/L	>2 mg/L	2 days	
Perhexiline	0.15–0.60 mg/L 0.60–1.2 mg/L for non-responders	0.5–2.5 micromol/L	>0.6 mg/L	30 hours for extensive metabolisers, longer in poor metabolisers	Poor metabolisers have longer half-lives and greater risk of toxicity. Non-linear pharmacokinetics
Quinidine	2–6 mg/L	6–15 micromol/L	>6 mg/L	1–2 days	
Psychopharmacological					
Amitriptyline/ Nortriptyline	60–250 microgram/L (amitriptyline) 50–170 microgram/L (nortriptyline)	150–900 nmol/L (amitriptyline) 200–650 nmol/L (nortriptyline)	>500 microgram/L	7–10 days	Both the parent drug and the active metabolite (nortriptyline) are effective and levels should be interpreted by considering the combined level
Clonazepam	15–50 microgram/L	0.05–0.16 micromol/L	>80 microgram/L	5–7 days	Relationship between serum concentration and seizure control is not well established
Imipramine/ desipramine	100–300 microgram/L (imipramine) 90–250 microgram/L (desipramine)	350–1000 nmol/L (imipramine) 150–550 nmol/L (desipramine)	>500 microgram/L	7–10 days	Both the parent drug and the active metabolite (desipramine) are effective and levels should be interpreted by considering the combined level

Table D.11 Optimal concentration ranges for selected medicines (continued)

Medicine	Therapeutic range		Toxic concentration	Time to steady state	Comments
	Gravimetric units	Molar units (SI)			
Lithium		0.8–1.2 micromol/L (Acute mania) 0.4–1.0 micromol/L (prophylaxis)	>1.9 micromol/L (adult; although toxicity may occur at 1.0–1.5 micromol/L) >1.2 micromol/L (elderly)	5–7 days	Assess renal function. Therapeutic levels influenced by indication

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Medicines and breastfeeding

The advantages of breastfeeding to a mother and her infant are widely recognised, and the practice is encouraged. Although most medications cross into breast milk, most do so in clinically insignificant amounts. For many drugs, there are published data on transfer into breast milk, levels in plasma of exposed infants and adverse effects or lack thereof in exposed infants. An individual risk–benefit analysis of the safety of breastfeeding while taking medication should be undertaken with the mother, her partner and her medical practitioner. In most cases the benefit to the mother–baby pair of breastfeeding outweighs the possible adverse effects on the infant of the drug ingested via milk. However, mothers should be advised to observe their infants carefully after any exposure to medication via breast milk and to discuss any unusual or adverse reactions with their doctor or pharmacist.

Factors determining infant exposure to medicines in breast milk

The following parameters may be used to determine infant exposure to a drug via breast milk:

- *Absolute infant dose.* This is the total amount of drug ingested via breast milk over 24 hours. It may be compared directly with known safe doses of a drug in infants or neonates.
- *Relative infant dose (RID).*

$$\text{RID} = \frac{\text{Absolute infant dose (mg/kg/day)}}{\text{Maternal dose (mg/kg/day)}} \times 100$$

  Values <10% are generally considered safe if the drug is without serious side effects and is taken within the usual dose range. The 10% notional level of concern is less in preterm infants with reduced clearance capacities.
- *Drug concentration in infant plasma.* Expressed as a percentage of known therapeutic concentrations of a particular drug, this figure may give an estimation of likely drug effects in the infant.
- *Reported adverse effects after breast milk ingestion.* A literature search can be undertaken to determine if adverse effects to a drug have been reported after an infant has ingested a drug via breast milk.
- *Milk to plasma ratio.* This is the ratio of the concentration of a drug in milk to that in the maternal plasma. It has little value in assessing safety of a drug in breastfeeding, although it can be used to calculate milk drug concentration when maternal plasma concentration is known.

Factors determining drug transfer into breast milk and infant exposure

Drugs mostly transfer to breast milk by passive diffusion. As the drug is metabolised by the mother and her plasma drug concentration falls, the drug may then diffuse back from the breast milk into the mother's plasma.

Factors affecting drug transfer

- *Maternal plasma concentration of drug.* This is determined by the dose administered to the mother and maternal pharmacokinetics.
- *The pKa of drug and the pH of milk.* Only unionised drug can diffuse into milk. Ion trapping of basic drugs may occur as milk is 0.2 pH units less than plasma.
- *Lipid solubility and fat content of milk.* Fat enhances transfer of highly lipid soluble drugs and often results in higher drug concentrations in hind-milk compared with fore-milk.
- *Molecular mass.* Large polypeptides and proteins generally do not transfer into milk.
- *Plasma protein binding.* Highly protein bound drugs have restricted transfer to breast milk.

Factors affecting infant exposure

- *Volume of milk ingested by infant each day.* An estimate of this volume in a fully breast fed baby is 150 mL/kg/day. Exclusivity of breastfeeding is an important consideration in assessment of exposure.
- *Gestational and postnatal age of baby.* The ability of infants to metabolise and excrete drugs increases from about 33% at birth to 100% at 7–8 months of age.
- *Oral bioavailability of drug in the infant.*

Minimising transfer of medicine to an infant

- Consider alternative routes of medicine administration and alternative products—e.g. nasal drops in preference to an oral decongestant; a topical non-steroidal anti-inflammatory instead of oral; or a poorly absorbed laxative such as a bulk-forming agent instead of a stimulant cathartic.

- Use the lowest appropriate dose to treat the mother.
- Only medicines essential for the treatment of a maternal condition should be prescribed.
- Administer maternal medicine immediately after a feed. This could be a useful strategy for drugs with short half-lives or those given once daily. It is of limited value for drugs with long half-lives, particularly in the neonatal period, when infants feed frequently.
- Breastfeeding may be withheld temporarily where a drug is administered in a single dose or intermittently (e.g. some radio-isotopes or chemotherapeutic drugs). Milk should be expressed and discarded during the period breastfeeding is withheld. However, advice to discontinue breastfeeding or to express and discard milk should not be given without consideration since this may cause difficulties for both mother and infant and deprive them of the benefits of breast milk.
- Within a drug class, choose a drug that has a lower relative infant dose if it is clinically suitable for the mother (e.g. sertraline rather than fluoxetine, ibuprofen rather than naproxen).

Specific medicines

Breastfeeding is contraindicated if a drug has a direct adverse effect on the infant or if the drug decreases milk supply (e.g. pseudoephedrine, oestrogens). For information on medicines that are contraindicated or require caution when breastfeeding, see monographs in 'Clinical monographs', Section B). Some of the recommendations are theoretical and are usually based on the relatively high level of toxicity of the agents concerned. While there have been instances of adverse effects with complementary medicines, each substance should be considered on its own merits (see 'Complementary medicines monographs', in Section C). Social (also known as recreational) drugs may also affect the infant. Alcohol, amphetamines, cannabis and nicotine all transfer readily to breast milk. Nicotine ingested by the mother in nicotine replacement therapies such as patches or gums is preferable to nicotine ingested from smoking.

Specialist medicines information centres

Medicines information centres attached to the major women's hospitals can provide additional specialised information on the use of medicines in breastfeeding and during pregnancy. See below for contact details.

ACT

The Canberra Hospital
Tel: (02) 6244 3333

NT

Royal Darwin Hospital
Tel: (08) 8922 8424

SA

Women's and Children's Hospital
Tel: (08) 8161 7222

VIC

Royal Women's Hospital
Tel: (03) 8345 3190
Email: drug.information@rwh.org.au

NSW

Mother Safe
Tel: (02) 9382 6539
Toll free (NSW): 1800 647 848

QLD

Queensland Drug Information Centre
Tel: (07) 3636 7098 or (07) 3636 7599

TAS

Royal Hobart Hospital
Tel: (03) 6222 8737

WA

Women and Newborn Health Service
Tel: (08) 9340 2723

Further information

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Gastroenteritis in children

Dehydration and gastroenteritis account for almost 7% of avoidable hospitalisations in Australia—the second greatest contribution to avoidable hospitalisations for acute conditions (after dental conditions).[1] Viral pathogens account for about 70% of episodes of acute gastroenteritis in children under 5 years, with 50% of all admissions for severe diarrhoea attributable to rotavirus infection.[2,3] Bacterial causes are responsible for about 15% of cases of gastroenteritis, commonly in Australian children who have travelled overseas.[3]

Immunisation against rotavirus is available for eligible children and should be encouraged.[4] Extensive immunisation uptake will have a significant impact on the incidence of severe rotavirus infection in young children.

Symptoms of acute gastroenteritis

The clinical features of acute gastroenteritis are generally non-specific in children.

In viral gastroenteritis, children usually present in autumn or winter with watery diarrhoea without blood, with or without vomiting, low-grade fever and anorexia.

In bacterial gastroenteritis, children are more likely to have a high fever and blood and mucus in the stool.[3] Stool cultures are not always necessary but may guide treatment in very young immunocompromised children or particularly unwell children with a high fever, in children with bloody diarrhoea or a recent history of travel overseas, or in children who are part of an outbreak of diarrhoea in a childcare, school or hospital setting.[3]

Symptoms of diarrhoea and vomiting may also be caused by other conditions, such as urinary tract infections, meningitis, appendicitis, intussusception (prolapse of one segment of bowel into the lumen of another segment, a common cause of bowel obstruction in young children with the majority of patients being less than 1 year old) or systemic illness.[5]

Children and infants can become rapidly dehydrated during an episode of gastroenteritis. Replacement of fluid and electrolyte losses is therefore crucial.

Management of dehydration

Appropriate treatment of gastroenteritis depends on the presence and severity of dehydration. Table D.12 describes the clinical features of dehydration and the appropriate management strategies. Oral rehydration solution is the preferred treatment of fluid and electrolyte losses caused by diarrhoea in children with mild to moderate dehydration.

Routine use of antibiotics to treat gastroenteritis is not recommended; they should be reserved for children with invasive bacterial infections (giardiasis, shigella and cholera).[3]

Anti-emetics have no proven benefit in acute gastroenteritis and may result in adverse effects in children (e.g. acute dystonic reactions). Antimotility agents may reduce the duration of diarrhoea but are not recommended in children aged less than 12 years, and there are concerns about adverse effects (e.g. lethargy, ileus, respiratory depression, coma, death).[3]

Transient lactose intolerance

Lactose-free or lactose-reduced diets are usually unnecessary in children with acute gastroenteritis. Although there is some evidence that a lactose-free diet may reduce the duration of diarrhoea, there is enough variability in the results of published randomised controlled trials to make a general recommendation difficult.[3]

However, transient lactose intolerance may occur following acute gastroenteritis due to causative pathogens damaging the small intestine mucosal surface. In children with prolonged watery diarrhoea (more than seven days) with perianal excoriation, carbohydrate malabsorption should be excluded by testing the stool for reducing substances.[3] If transient lactose intolerance is confirmed, a temporary change for two to four weeks to lactose-free feeds could be suggested.[5]

Referral

Referral is required in the following circumstances[3,6]:

- child is less than 6 months old
- bile- or blood-stained vomit or stools

- child appearing severely dehydrated and/or unsure about dehydration status (see Table D.12)
- high fever
- severe abdominal pain
- abdominal distension or a mass present
- minimal oral intake (e.g. due to persistent vomiting)
- recent travel overseas
- pre-existing disease such as short bowel syndrome, chronic renal failure, diabetes or congenital heart disease
- worsening symptoms.

Table D.12 Dehydration in children

Degree of dehydration[6,7]	Clinical features[3,6,7]	Treatment[3,6,8]
No or minimal dehydration (<3% loss of body weight)	• No clinical signs • Pinch test: skin fold retracts immediately	• Increase frequency of usual drinks (there is no evidence for diluting these). Avoid soft drinks. Lactose-free or lactose-reduced formulas are usually unnecessary. • Continue an age-appropriate diet. Recommended foods include complex carbohydrates, meats, yogurt, fruit and vegetables. Foods high in simple sugars should be avoided (e.g. soft drinks, juice, gelatin). • Breast-fed infants should continue nursing on demand. • Formula-fed infants should continue their normal formula in amounts sufficient to satisfy energy and nutrient requirements. Supplement with oral rehydration therapy if necessary.
Mild to moderate (3–9% loss of body weight)	Two or more of: • restlessness or irritability • sunken eyes • thirsty and drinks eagerly • pinch test: skin fold visible <2 seconds.	• Rehydrate with oral rehydration solution (ORS) in frequent small volumes: – <10 kg body weight—60–120 mL for each diarrhoeal stool or vomiting episode – >10 kg body weight—120–240 mL for each diarrhoeal stool or vomiting episode. • ORS should be reconstituted with water according to the manufacturer's specifications. No other sweeteners or fluids should be added. • Most children who are mildly dehydrated can be treated at home. Children with mild to moderate dehydration should be observed in a paediatric facility for 4–6 hours to confirm oral intake is adequate and to determine the need for intravenous fluids and/or admission to hospital. • In children with concomitant vomiting, most can still be successfully rehydrated with ORS (5 mL volumes given every 5 minutes, gradually increasing the amount consumed). • Continue breast or bottle feeding and if necessary supplement with oral rehydration solution. • Gradually reintroduce an age-appropriate diet after 4–6 hours of rehydration. Solid feeds should be withdrawn for no more than 24 hours.
Severe (>9% loss of body weight)	Two or more of: • abnormally sleepy or lethargic • sunken eyes • drinking poorly or not at all • pinch test: skin fold visible >2 seconds. Additional signs may include: • circulatory collapse (e.g. weak, rapid pulse, cool or blue extremities, hypotension) • rapid breathing • sunken anterior fontanelle.	• Referral for hospital admission necessary for immediate intravenous rehydration.

Note: The percentage loss of body weight per degree of dehydration may vary between sources.

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Managing missed doses of oral contraceptives

The counselling recommendations provided in this section are in accordance with the recommendations of Family Planning NSW, the *Australian Medicines Handbook* and *Therapeutic Guidelines*. Recommendations from other sources may differ and may be more, or less, conservative. Pharmacists should use this information as a general guide only, and should treat each case on an individual basis, using their clinical knowledge and professional judgement to suggest the most appropriate course of action.

Combined oral contraceptive pill

Combined oral contraceptives (active pills) should be taken at approximately the same time each day. The sugar tablet or hormone-free phase of the contraceptive cycle should not exceed seven days.[1]

Contraceptive efficacy is affected if[2,3]:

- Two or more active pills are missed (i.e. the period between active pills is greater than 48 hours).
- Medications are taken that interfere with the pill's effectiveness.
- Severe vomiting and/or diarrhoea persist for more than 24 hours.

The risk of pregnancy depends not only on how many pills were missed, but also on when those pills were missed. The risk is greatest when active pills are missed at the beginning or at the end of the active pills (i.e. when the hormone-free interval is extended beyond seven days). The rationale for this is summarised in the 'seven-day rule'[1,4]:

- Seven consecutive days of active pills are necessary to reliably prevent ovulation.
- Seven active pills may be omitted without ovulation (as happens in the pill-free or inactive pill week).
- Missing more than seven consecutive active pills risks ovulation occurring.

See Table D.13.

Progestogen-only pill

The progestogen-only pill (POP; minipill) is taken continuously without a break. Its efficacy depends largely on its effect on thickening of cervical mucus. This is maximal between three and 21 hours after ingestion, therefore POPs should be taken at the same time each day, preferrably some hours prior to sexual intercourse.[5]

Counselling recommendations if the POP is more than **three hours** overdue; **or** vomiting occurs within two hour after taking a pill; **or** severe vomiting or diarrhoea persists for more than 24 hours[2,3]:

- Take one pill as soon as possible.
- Take the next pill at the usual time.
- Continue taking pills regularly at the same time each day.
- Use extra contraception or abstain from sexual intercourse for the next 48 hours.
- Consider using emergency contraception if sexual intercourse has occurred after the three-hour delay in taking a pill and before two consecutive pills have been taken to restore contraceptive effect.

Table D.13 Counselling recommendations for missed combined oral contraceptive pills[2,3,5]

Scenario	Advice
One active pill is missed (i.e. >24 hours but <48 hours between active pills), or vomiting occurs within 2 hours of taking an active pill.	• Take an active pill as soon as possible • Take the next pill at the usual time[a] • Continue taking active pills as usual • Contraception will not be affected
Pack is started more than **one** day late or 2 or more pills are missed or severe vomiting and/or diarrhoea for >24 hours in the **first week** of active pills	• Take an active pill as soon as possible, and continue taking pills as usual[a] • Use extra method of contraception or avoid sexual intercourse for the next 7 days • Consider using emergency contraception if sexual intercourse has occurred since the end of the preceding packet of pills
Two or more pills are missed or severe vomiting and/or diarrhoea for >24 hours in the **middle week** of active pills	• Take an active pill as soon as possible, and continue taking pills as usual[a] • Use extra method of contraception or avoid sexual intercourse for the next 7 days
Two or more pills are missed or severe vomiting and/or diarrhoea for >24 hours in the **last week** of active pills	• Take an active pill as soon as possible, and continue taking pills as usual[a] • Use extra method of contraception or avoid sexual intercourse for the next 7 days • On finishing the active pills in the present pack immediately start on the active pills in the new pack i.e. do not have a break from the active pills.
An inactive tablet is missed	Contraception will not be affected
Emergency contraception is used	Start taking active pills within twelve hours of emergency contraceptive dose and use an extra method of contraception until 7 active tablets have been taken.

a. Depending on when the missed pill is remembered, 2 pills may be taken on the same day (one at the moment of remembering, and the other at the regular time).[4]

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Weight management

Being overweight, and in particular obese, is known to be associated with numerous adverse health conditions. Excess weight increases the risk of developing Type 2 diabetes, cardiovascular disease, hypertension, certain cancers, sleep apnoea, osteoarthritis, psychological problems, and reproductive problems for women. It is also associated with a reduced life expectancy.[1]

Weight reduction, if appropriate, should be an integral component of the management of people with these conditions, as well as of all preventive health programs.

Assessing and measuring body weight

Weight should not be considered in isolation, but in conjunction with risk factors for associated health conditions. For example, for cardiovascular disease, factors such as blood pressure, lipids and smoking status should also be considered and addressed.

Abdominal (central) obesity

Abdominal or visceral fat deposition is associated with an increased risk of morbidity independent of total body fat. While it is the mass of the visceral fat that is important, waist circumference, measured at the narrowest part of the torso, is a more practical measure of increased disease risk due to overweight and obesity (see Table D.14).

Table D.14 Waist circumference and risk of disease[2]

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Risk of disease[a]	Waist circumference (cm)	
	Males	Females
Increased	≥94	≥80
Substantially increased	≥102	≥88

a. Risk of Type 2 diabetes, hypertension and cardiovascular disease

Waist circumference will not be an accurate measure of body fat in people who are pregnant or have medical conditions that distend the stomach. Further, the circumference ranges are based on Caucasian adults. Cut-offs for Asians and Indians at the same level of risk are thought to be lower, and cut-offs for Pacific Islanders and African-Americans are thought to be higher.[2]

The waist-to-hip ratio (WHR) may also be used as a measure of abdominal obesity. It is a better predictor of cardiovascular disease than waist circumference and body mass index. An Australian study has suggested that increasing cardiovascular death rates appear to occur when the WHR is >0.80 in women and >0.90 in men.[3] However, WHR may be less valuable as a relative measure after weight loss because of the loss of hip as well as waist dimensions in some individuals.[2]

Body mass index

Body mass index is defined as body weight (in kilograms) divided by the square of the height (in metres):

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)}^2}$$

Considering the population as a whole, the BMI is closely correlated with body fat, although the correlation can be misleading because it does not distinguish fat mass from muscle mass. Thus BMI may be physically underestimated in the elderly due to their reduced muscle mass and overestimated in muscular people.

The ranges of BMI shown in Table D.15 are used in Australia to classify adults according to weight.

Table D.15 Body mass index[2]

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Classification	BMI (kg/m^2)
Underweight	<18.5
Acceptable weight	18.5–24.9
Overweight	≥25
Pre-obese	25–29.9
Obese I	30–34.9
Obese II	35–39.9
Obese III	≥40

The 'acceptable weight' range is based on a number of prospective studies which indicate that BMIs in this range are associated with the lowest death rate. However there are some limitations in using these cut-offs[2]:

- The BMI does not reflect body fat distribution. A measure of fat distribution is important as abdominal fat is a potential risk factor for disease independent of total body fat.

- The BMI cut-off points are based on adults of European descent so may not indicate morbidities in specific ethnic groups or in children or adolescents.

A structured weight management service

Pharmacists can assist people in weight management and weight loss programs.

Setting goals

The following table shows realistic goals that should be set for weight loss.

Table D.16 Realistic goals for weight loss[2]

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Duration	Weight	Waist circumference
Short term	1–4 kg/month	1–4 cm/month
Medium term	10% of initial weight	5% after six weeks
Long term	10–20% of initial weight	≤88 cm (females) ≤102 cm (males)

The main goal of any weight loss should be an improvement in health. Such goals may include:

- *A reduction in blood pressure.* A 4–5 kg reduction in body weight can provide an 8–9 mmHg drop in systolic and diastolic blood pressure.[4]
- *Improved lipid levels.* A 10 kg reduction in body weight can produce ~10% reduction in total cholesterol, ~7% reduction in LDL, and ~20% reduction in fasting triglycerides.[5]
- *Improved glycaemic control.* A 7–10% reduction in body weight can reduce fasting plasma glucose values by >25%.[6]

Identifying contributing factors

Body weight is primarily a result of the balance between energy intake and energy expenditure. Sustainable weight loss therefore requires life long changes in diet and exercise which result in energy intake being less than the individual's expenditure.

Non-optimal body weight may also be drug or disease induced. Such contributing factors should be identified and addressed as part of a weight management service and may involve referral to a doctor or other health care professional.

Strategies for weight loss

Non-pharmacological strategies (e.g. healthy eating, physical activity, behaviour modification) should underpin all weight loss efforts. Pharmacological therapies or surgery may also be considered.

Because no predictors of responsiveness to pharmacological therapy in an individual or class of patients have been established, medication selection should involve consideration of the following[7]:

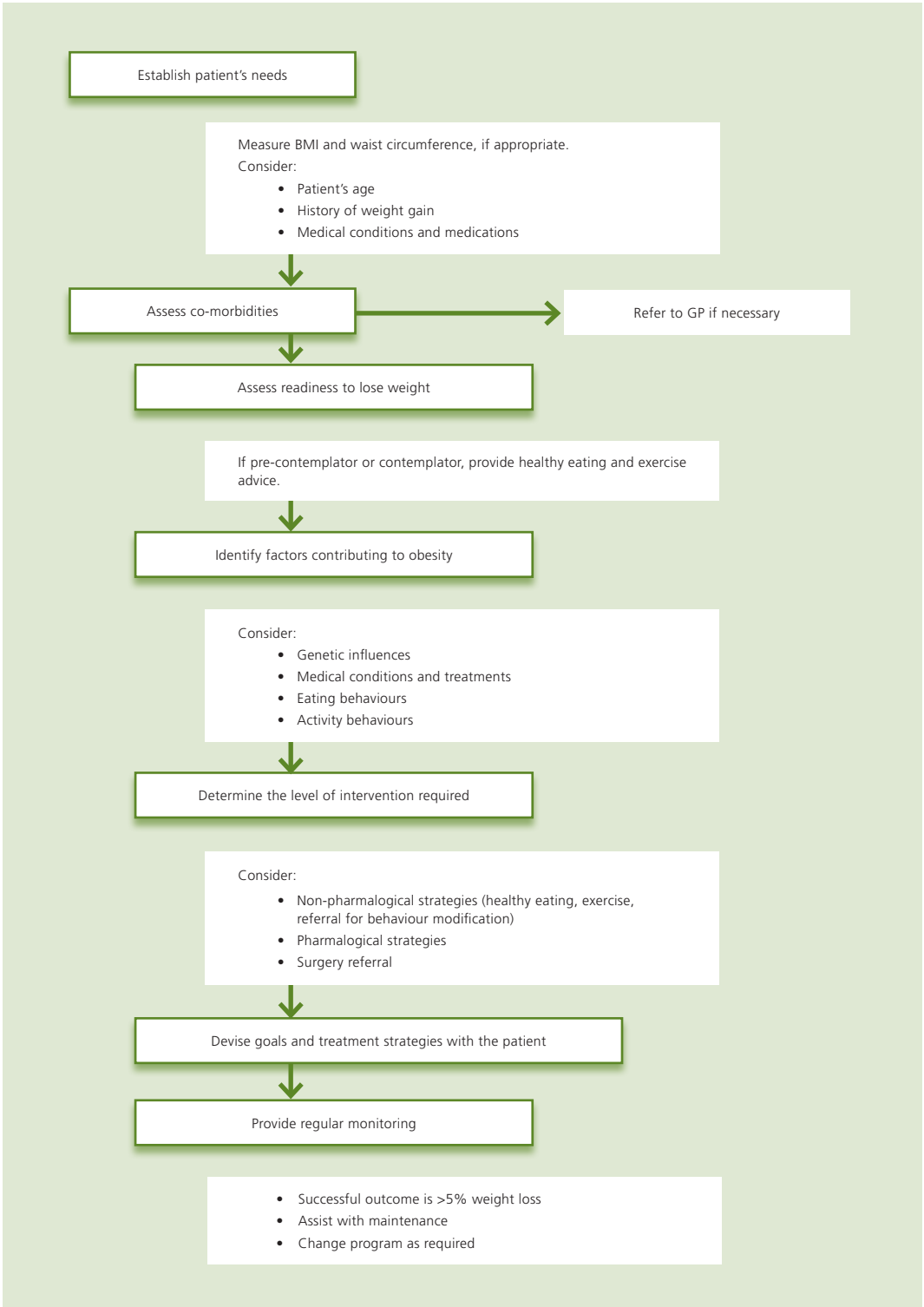
- BMI and waist circumference
- underlying medical conditions
- failure to lose weight with non-pharmacological strategies
- contraindications to particular drugs
- concurrent medications
- the need for monitoring
- approval for long-term use
- cost
- patient preference.

Providing information

Information and advice provided by pharmacists must be accurate, up to date and supported by a sound evidence base. Written information to support advice can be found in the Pharmaceutical Society of Australia Pharmacy Self Care fact cards—e.g. *Weight and Health, Fat and Cholesterol, High Blood Pressure,* and *Exercise and the Heart*.

Figure D.1 is intended for use in a pharmacy-based weight management service and is reproduced from the Society's *Essential CPE* publication on weight management (July 2006).[8] See this publication for further details.

Figure D.1 Flow chart for a pharmacy based weight management service[8]



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Comparing and mixing insulins

Insulin preparations

There are four groups of insulins available for clinical use:

- *Rapid-acting insulins.* These are human insulin analogues that have a more rapid onset of action than human insulin when administered subcutaneously. They can be used immediately (no more than 15 minutes) before or soon after meals.
- *Short-acting insulins.* These are clear solutions that may be used intravenously as well as subcutaneously. They should be used no more than 30 minutes before a meal.
- *Intermediate-acting insulins.* These are cloudy because they are suspensions. Many have an increased duration of action achieved by complexing the insulin with a protein such as protamine (NPH/isophane insulin).
- *Long-acting insulins.* These human insulin analogues are clear solutions. Insulin glargine has a low solubility at neutral pH. Insulin detemir is soluble at neutral pH but reversibly binds to albumin, thus delaying its action.

There are also various premixed combinations of intermediate and rapid- or short-acting insulins (see Table D.17).

Guidelines for mixing insulins

Use of commercially available premixed insulins is recommended if the insulin ratio is appropriate to the patient's insulin requirements.[1]

Patients who are well controlled on a particular regimen of more than one insulin should maintain their standard procedure for preparing insulin doses.[1] There may, however, be some circumstances where it is appropriate to mix insulins in a single syringe.

Be aware that on mixing, physicochemical changes in the insulin mixture may occur (either immediately or over time). As a result, the physiological response to the insulin mixture may differ from that of the injection of the insulins separately. No other medication or diluent should be mixed with any insulin product without on a specialist's advice.[1]

Table D.17 Activity characteristics of insulins

	Insulin type	Brand name	Onset of action (hrs)	Time to peak (hrs)	Duration of action (hrs)
Rapid acting	Insulin lispro	*Humalog*	0.25	1	3.5–4.5
	Insulin glulisine	*Apidra*	0.25	<1	4
	Insulin aspart	*NovoRapid*	0.20–0.30	1–3	3–5
Short acting	Neutral insulin	*Actrapid, Humulin R, Hypurin Neutral*	0.5–1	2–5	6–8
Intermediate acting (non-mixed)	Isophane (NPH) insulin	*Humulin NPH, Hypurin Isophane, Protaphane*	1–2	4–12	16–18
Intermediate acting (premixed biphasic)		*Humalog Mix 25* (lispro 25%/lispro protamine 75%)	0.25	1–2	16–18
		Humalog Mix 50 (lispro 50%/lispro protamine 50%)	0.5	2–4	22–24
		Mixtard (20/80, or 30/70 or 50/50 neutral/isophane)	0.5	2–12	24
		NovoMix 30 (aspart soluble 30%/aspart protamine 70%)	0.20–0.30	1–4	24
		Humulin (20/80, or 30/70 neutral/isophane)	0.5	1–12	16–19
Long acting	Insulin glargine[a]	*Lantus*	1–2	no peak	24+
	Insulin detemir	*Levemir*	3–4	3–14	12–23

a. Recommended not to be mixed with other insulins.

Rapid-acting insulin

When rapid-acting and NPH insulins are mixed, a slight decrease in the absorption rate, but not the total bioavailability, may occur. When rapid-acting insulin is mixed with intermediate-acting insulins, the mixture should be injected no later than 15 minutes before a meal.[1]

Insulin glulisine can be mixed only with *Humulin-NPH®* insulin. No data are available on whether it can be mixed with other insulins or diluents when using an infusion pump.[2]

Short-acting insulin

Short-acting neutral insulin formulations and NPH insulins may be mixed and preferably used immediately.[1,3]

Long-acting insulin

The manufacturer of insulin glargine recommends that it *not* be mixed with other insulins.[1] A clinical review of paediatric patients with Type 1 diabetes who mixed insulin glargine with rapid-acting preparations demonstrated that there was no change in diabetic control.[4] In patients on insulin glargine where multiple injections post a considerable compliance issue, mixing could be considered with close monitoring of diabetic control.

Insulin detemir has a neutral pH, but, it is *not* recommended that insulin detemir be mixed with a rapid-acting insulin.[5-7]

Insulin detemir and insulin glargine should not be administered intravenously or used in insulin infusion pumps, and intramuscular administration should be avoided.[5]

Preparing insulin mixtures

For all insulin suspensions (premixed insulins and non-mixed isophane insulin), the vial, pen or syringe should be gently rolled in the palms of the hands at two hours 20 times (not shaken) to resuspend the insulin before administration.[1]

When mixing rapid- or short-acting insulin with intermediate-acting insulin, the rapid- or short-acting insulin should be drawn into the syringe first.[1] If a cloudy insulin is drawn up first and the suspension is allowed to enter the regular insulin vial, the regular insulin may become cloudy. It would therefore be impossible to know if the short-acting insulin was cloudy from the introduction of the insulin suspension or if a problem had developed with the short-acting insulin.[8]

Storage of insulin syringes

If a health professional decides to use predrawn insulin syringes, cold storage for the shortest possible period is recommended. Predrawn syringes should be stored in a vertical position, with the needle pointing upward (protected by a plastic cap), so that suspended insulin particles do not clog the needle. Predrawn syringes containing suspensions should be rolled between the hands at least 20 times to resuspend the insulin before administration.[1]

Mixtures of insulin products

Manufacturers do not guarantee the stability of mixtures of insulins when stored in syringes and recommend the use of a premixed insulin with documented stability where appropriate.

Single insulin products

Syringes predrawn with a single insulin prepared under aseptic conditions are known to be stable for up to 30 days under adequate refrigeration.[1]

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Systemic and topical corticosteroids

Oral corticosteroids

Corticosteroids vary in their glucocorticoid and mineralocorticoid properties. Table D.18 provides information on relative potencies and equivalent doses of systemic corticosteroids.

Oral budesonide is not included in the table because it is used in inflammatory bowel disease for local gastrointestinal effects. Systemic absorption of budesonide is reduced by high first-pass metabolism, but some systemic effects can occur.

Tapering doses

Prolonged therapy with high-dose corticosteroids may cause adrenal suppression. Treatment with doses greater than prednis(ol)one 5 mg (or equivalent) for longer than two to three weeks may require tapering of the dose to avoid adrenal insufficiency and disease relapse. The rate of tapering is dependent on the dose, duration of treatment and underlying disease state. Studies have shown that acute treatment with courses of corticosteroids of up to 10 days' duration do not routinely require tapering.

Inhaled corticosteroids

Corticosteroids used for inhalation (beclomethasone, budesonide, ciclesonide and fluticasone) have high topical potency; any swallowed dose is subject to considerable hepatic first-pass metabolism. However, systemic effects can also occur. The following table shows dose equivalence.

Table D.19 Approximate dose equivalence of inhaled corticosteroids

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Inhaled corticosteroid	Dose (microgram)
Beclomethasone CFC-free	100
Fluticasone	100
Budesonide	200
Ciclesonide	80

Topical corticosteroids

General principles of use

Topical corticosteroids play an important role in the management of dermatological conditions, in particular inflammatory diseases. When used correctly, they are quite safe; prolonged therapy with mild or moderately potent preparations rarely leads to complications. Adverse effects may manifest locally (skin effects) as well as systemically, including adrenal suppression and Cushing's syndrome.

Table D.18 Systemic corticosteroids: potencies and equivalent doses

Compound	Anti-inflammatory potency (glucocorticoid activity)	Sodium-retaining potency (mineralo-corticoid activity)	Duration of action*	Approximate equivalent dose (mg)†
Hydrocortisone (cortisol)	1	1	S	20
Cortisone	0.8	0.8	S	25
Prednisone	3.5	0.8	I	5
Prednisolone	4	0.8	I	5
Methylprednisolone	5	0.5	I	4
Triamcinolone	5	0	I	4
Fludrocortisone	10	125	S	–
Betamethasone	25	0	L	0.6
Dexamethasone	30	0	L	0.75

* Duration of action: S – short or 8–12 hour biological half-life; I – intermediate or 12–36 hour biological half-life; L – long or 36–72 hour biological half-life

† These dose relationships apply only to oral or intravenous administration; relative glucocorticoid potencies may differ greatly when injected intramuscularly or into joint spaces. Fludrocortisone is not used for glucocorticoid effects.

Use an appropriately potent preparation for the shortest time required to control the skin disorder, then stop the corticosteroid.

The efficacy and potential for adverse effects of topical corticosteroids depend on the factors described below.

Corticosteroid potency and vehicle used

In general, acute inflammatory eruptions respond well to mild or moderate topical corticosteroids, the potent or very potent products being reserved for chronic, thickened dermatoses.

For a given strength of steroid, ointments are more potent than creams. This is because of the occlusive nature of ointment bases, which enhances penetration into the skin. Creams are suitable for moist and hair-bearing areas, while ointments are useful for their moisturising effect on dry and scaly areas. Other agents, such as propylene glycol, may also be added to vehicles to improve efficacy through increased penetration. The greater the corticosteroid potency, the greater the risk of adverse effects and the risk of rebound on cessation of treatment.

Information on the relative potencies of topical corticosteroids is contained in the following table.

Table D.20 Topical corticosteroids: potency of commonly used preparations

Corticosteroid	Strength
Mild	
Desonide	0.05%
Hydrocortisone	0.5–1.0%
Hydrocortisone acetate	0.5–1.0%
Moderate	
Betamethasone valerate	0.02–0.05%
Triamcinolone acetonide	0.02%
Potent	
Betamethasone dipropionate	0.05%
Betamethasone valerate	0.1%
Methylprednisolone aceponate	0.1%
Mometasone furoate	0.1%
Triamcinolone acetonide	0.1%
Very potent	
Betamethasone dipropionate	0.05% (optimised vehicle—OV)

Method of application

Initial treatment may often require a more potent corticosteroid and higher frequency of application, but as the condition improves both potency and frequency should be reduced. Once the condition has resolved, topical corticosteroids should be ceased; they are not used as preventive therapy. Prolonged use should be avoided wherever possible; intermittent therapy is preferred to continuous application for long-term use. Tapering doses following long-term therapy will reduce the chance of rebound flare and adrenal insufficiency.

According to the British Dermatology Working Group, current advice to patients to apply topical corticosteroid preparations 'sparingly' or 'thinly' contributes to 'steroid phobia', increasing the risk of poor clinical response and treatment failure. Most patients are prescribed topical corticosteroids of mild potency, for which the evidence suggests that the risk of harm is minimal. It is recommended that topical corticosteroids be applied according to the fingertip unit (FTU) rule. One FTU (the distance between the tip of the finger to the crease of the first joint) should cover the equivalent area of two palmar surfaces on the patient's body. One FTU in an adult is approx 0.5 g. More detailed information on FTU for topical corticosteroids can be found at www.patient.co.uk/showdoc/27000762.

Patients should also be advised that treatment should not exceed prescribed quantities.

Use under occlusive dressings (including gloves or plastic film) greatly increases corticosteroid absorption potentially increasing the risk of adverse effects. This approach is generally reserved for use on thickened skin areas such as the palms and soles of the feet.

Site of application

The thickness of the skin and local occlusive factors are important considerations in safe use of topical corticosteroids. Areas in decreasing order of penetration are mucous membranes > scrotum > axillae, perineal flexures > eyelids, face > chest, back > upper arms and legs > lower arms and legs > dorsum of hands and feet > palms, soles and nails.

Mild corticosteroids are preferred for the face and flexures, with short-term use of moderate agents if necessary. Potent or very potent agents are often required for management of disease on palms and soles.

Age of patient

An increased body-surface-to-weight ratio in infants, and the relatively thin skin in elderly patients, places these two groups at particular risk of adverse effects when topical corticosteroids are not used appropriately. The lower potency corticosteroids are preferred as first-line treatment. Particular care should be taken if application involves a large area or the nappy area.

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Australian medicines handbook July 2008 edition gives useful information of topical quantities per week for each limb.

Wound management

Trade names and the names of manufacturers of products are used in this section to assist in awareness of each type of product/dressing. The Pharmaceutical Society of Australia does not specifically endorse the products or manufacturers listed. The tables provide examples but may not be comprehensive.

Wound products are therapeutic devices that require appropriate product selection and counselling on effective use in order to improve healing and gain quality of life and economic outcomes. When these products are used inappropriately they can have negative consequences for a patient, including delayed healing, pain, other comfort issues, and increased financial burden.

The *British Pharmacopoeia* is the main reference source for surgical dressings and wound pharmaceuticals.

Ideally, a wound dressing should do the following:

- Remove excessive exudate from the wound while maintaining a moist environment and not allowing the wound to dry out.
- Allow gaseous exchange, so that oxygen, water vapour and carbon dioxide may pass into and out of the dressing.
- Provide insulation to maintain the wound at a core temperature of approximately 37 °C.
- Provide impermeability to micro-organisms, to minimise contamination of the wound.
- Prevent both particulate and toxic contamination of the wound.
- Be non-adherent to the wound to minimise trauma and damage to granulating tissue on removal .

Wound management principles

Skin repair is a complex process that begins the moment a wound or injury occurs, with the aim of closing the wound and re-establishing the skin's integrity. Each wound goes through a number of phases, including inflammation, destruction, proliferation and maturation.

It is important to understand that, even when the skin surface appears to have healed, the tissue below may still be recovering and it may take many months to regain tensile strength.

Many factors can affect wound healing. Systemic (patient) factors include:

- general state of health
- circulation
- disease states—e.g. diabetes
- age
- degree of deterioration of the skin
- body build—wounds in obese patients do not heal readily due to limited local blood supply
- nutritional status—a balanced diet of carbohydrates, fats, proteins, vitamins and minerals and an adequate fluid intake, will assist the healing process. The amino acid arginine has been shown to speed up wound healing. Vitamin A, ascorbic acid, iron and copper are essential for collagen synthesis. Zinc supplements may speed healing where there is zinc deficiency
- genetic factors—a tendency to form keloids often runs in families, suggesting a possible genetic basis.
- lifestyle—smoking and excessive consumption of alcohol
- drugs which can exert both a positive and a negative action by either stimulating or inhibiting wound healing.

Local (wound) factors include:

- mechanical stress—pressure, shearing forces and friction
- temperature—this may affect circulation and cell growth
- maceration or desiccation—both affect cells
- chemical stress—topically applied products may be cytotoxic and delay healing
- wound debris—either as necrotic tissue or particulate contamination
- infection—will delay healing
- blood supply—generally poorer to lower limbs in an elderly person
- venous congestion
- location of wound.

Moist wound management has a scientific basis. Maintenance of a moist environment at the wound interface has been shown to ensure cell growth and a more rapid re-epithelialisation of the wound. However, if a wound is wet rather than moist there is an increased risk of maceration.

Wound management rules

The treating health professional should consider the following:

- Establish the underlying cause of the wound.
- Treat both the wound and the cause, including infections, and consider specific local and extrinsic factors.
- If necessary, choose and apply an appropriate dressing.
- Plan appropriate follow-up.

Wound bed preparation

A new concept in wound healing is wound bed preparation. It was first presented by Professor Vince Falanga, who said that a wound must be in balance with respect to the healing cascade, bacterial balance, viable tissue and moisture management. A group of world leaders in the field developed the acronym TIME, which summarises the basic principles of wound bed preparation:

- **T—Tissue removal** of any non-viable slough or necrotic tissue is essential for healing.
- **I—Infection or Inflammation** in the tissue. If infected, treatment with the appropriate antibiotic is required; if inflamed anti-inflammatory medication (e.g. steroids) should be prescribed.
- **M—Moisture balance** involves maintaining the moist environment but removing excess exudate and protecting the peri-skin from damage caused by the high level of enzymes in the exudate.
- **E—Edge** of the wound must be healthy to allow for wound contraction.

Wound bed preparation is now accepted as the model by which wounds should be managed.

Classification of wound tissue

Assessment of a wound will depend on the colour, depth and the level of exudate present in the wound.

Colour

The colour of a wound will provide a guide to the status and stage of healing—see the following table.

Table D.21 Colour and status or stage of healing of wounds

Colour	Status or stage of healing
Pink	Epithelialising
Red, unbroken	Granulating
Black	Necrotic
Yellow	Sloughy
Green exudate	Infected

Depth

The wound may be superficial, moderate, deep or a cavity.

Exudate level

The wound may be dry or have slight, moderate or copious exudate.

Acute wound management

- Clean and decontaminate the wound of any dirt or foreign material, useing a surfactant solution diluted with water or 0.9% sodium chloride. Then apply a topical antiseptic, leave in place for three to four minutes, then wash off. Topical antiseptics will kill surface bacteria in approximately 90 seconds; washing off prevents any potential tissue damage.
- Stop bleeding by pressure and/or the application of a haemostat (e.g. alginate dressing).
- Close a laceration or deep cut with strips.
- Dress with a simple permeable dressing, either waterproof or not.
- If necessary, support with a retention bandage (e.g. lightweight cohesive).

Burns

Cool with cold running tap water for a minimum of 20 to 30 minutes. If the patient needs to be transferred to a doctor or hospital apply an amorphous hydrogel and cover with a non-adherent inert dressing. Burns are classified as superficial, partial thickness or full thickness.

Superficial

A superficial burn involves only the epidermis and the upper part of the dermal papillae. The burn may appear bright pink or red in colour. Blisters may or may not be present. The texture is normal or firm and the area is very painful and hypersensitive to touch. On application of pressure the burn area will blanch and capillary return will be rapid.

Partial thickness

A partial thickness burn results in the entire epidermal layer being destroyed, along with varying thickness of the dermis. It is characterised by a creamy coloured base that is mottled in appearance.

Full thickness

In a full thickness burn, injury occurs to the entire thickness of the epidermis, epithelial elements and dermal appendages. A full thickness burn is characterised by a whitish leathery appearance. It can

also be brown, cherry red or charred black. It is firm and leathery in texture. Few, if any, blisters are present. Those blisters that are present are thin walled and break easily. Areas will not blanch under pressure. Initially, nerve sensation is greatly diminished or lost completely; later, pain can be severe.

Treatment

Superficial or partial thickness burns should be referred for medical attention, if possible to a burns unit, if the area exceeds 15% body surface area in adults or 10% body surface area in children. If the wound is full thickness, even if small, or on the face, hands, feet or genital area, the patient should also be referred to a burns unit. Contact a burns unit for instructions on management whilst in transit.

For a simple superficial burn apply a hydrogel (either amorphous or sheet) for 48–72 hours then change to an adhesive fixation sheet (e.g. *Fixomull*® or *Hypafix*®) applied directly to the burn and left in place for seven days. Remove by soaking in oil to dissolve the adhesive. Clean the area and apply a new piece of tape.

Skin tears

Skin tears are a very common occurrence, especially in older people who have more fragile skin. Many protocols for the treatment of skin tears exist; a suggested protocol is as follows:

- Stop the bleeding by direct pressure or application of alginate dressing.
- Wash and decontaminate the area.
- Apply a *Steri-strip*® without tension to viable skin flaps (these should be left in place until they fall off naturally).
- Apply a small amount of amorphous hydrogel.
- Cover with a two- or three-layer foam dressing.
- Hold in place with a light cohesive bandage.
- Leave in place for seven days, then replace with a patch of non-preserved zinc paste bandage and leave on, covered with foam, for seven days. In most cases the wound will be healed; if not, repeat this step until healed.

In general, never apply any adhesive product to an elderly person's skin as removal may cause trauma to fragile skin.

Chronic wound management

With a chronic wound, it is important to identify the underlying aetiology because appropriate management of the wound will depend on the cause.

A high proportion of chronic leg ulcers are caused by chronic venous insufficiency and are treated with graduated compression.

The use of compression is, however, contraindicated in arterial disease. If in doubt, refer the patient for medical assessment.

It is essential to determine the efficiency of the arterial and venous circulations before full treatment can be undertaken. In addition, the presence of any underlying disease, such as diabetes, and any regular medication that may have an effect on healing; should be taken into consideration. Smoking, even in small amounts, will impact on wound healing by reducing the peripheral arterial circulation.

Venous leg ulcers

Venous leg ulcers are caused by venous hypertension and incompetent valves in the veins or a previous deep venous thrombosis. Observed signs include oedema, skin staining, irregular shape, shallow and moist ulceration. Management mainly involves the use of compression to aid venous return.

Arterial ulcers

Arterial ulcers are caused by reduced arterial blood flow to the area. Observed signs include deep ulceration with a cliff-like edge in association with pain and possible claudication (cramp-like pains in the calves). Management mainly involves surgical improvement of arterial circulation.

Diabetic ulcers

Diabetic ulcers usually occur on the feet, although can also appear on the leg and be confused with a venous ulcer. They are caused by reduced blood flow, neuropathies, pressure and secondary infection associated with lowered immune function. The risk of gangrene is a major concern with this ulcer type. The main aspects of management are prevention or treatment of infection, removal of non-viable tissue, removal of pressure, treatment of reversible arterial blockages, and stringent management of the patient's diabetes.

Pressure ulcers

Pressure ulcers are caused either by direct pressure over a bony prominence, friction or shear or by combinations of

the above. The ulcers may be minor or major in severity. Although a standard management approach is used, the first priority is removal of the source of pressure. An important aspect of pressure wounds is their prevention. Patients at risk should be nursed on pressure-reducing or pressure-relieving surfaces. Patients are assessed for risk by using one of a number of tools (e.g. Norton, Waterlow).

Vasculitic ulcers

Vasculitic ulcers are the result of damage to the lumen of the arterioles by antibodies, leading to a loss of red blood cells through the vessel wall and a lack of oxygenated blood in the microarterial circulation proximal to the wound. The ulcer looks similar to a venous ulcer. However, vasculitic ulcers are painful and have a bright red margin; there is a bluish haze in the skin around the wound. Management involves the use of systemic steroids and immunosuppressive drugs (e.g. cyclosporin). Application of an amorphous hydrogel covered with a foam dressing may help to alleviate pain.

Wound dressings and surgical dressing materials

Selection of an appropriate dressing depends on the nature of the wound, including wound colour, exudate and the depth of the wound.

Table D.23, on the following page, provides a guide to the management of wounds based on these characteristics.

Inert dressings

Inert dressings are simple absorbent fibres, including cotton wool, absorbent viscose (rayon) wool, absorbent lint and absorbent gauze.

Gauze

The most commonly used inert dressing is gauze, which consists of a cotton cloth of plain weave in different forms related to the thread count and weight in g/m^2 of the fabric. The main types of gauze products are gauze pads, folded swabs of multiple layers of gauze, and ribbon gauze. These are often provided as a sterile product.

Gauze products are used to aid in the cleaning of wounds, as primary dressings, as wet-to-dry dressings, and as wet dressings. Ribbon gauze is also used as nasal packing and in cavity wounds. Gauze is used as a pressure dressing to help achieve haemostasis. Gauze sponges are commonly used in surgery as absorbents.

The main problems associated with gauze dressings are that they allow the wound to dry out, shed fibres that contaminate the wound, adhere to the surface, thus causing trauma on removal, and are permeable to bacteria.

Non-woven alternatives to gauze for use as pads or for cleaning wounds include *Handy*® spun-bonded swabs and *Multisorb*® non-woven swabs.

Simple plastic strips

These wound dressings consist of an absorbent pad attached to a piece of plastic adhesive tape that is impermeable to water vapour. As a result, water vapour passing out of the skin can be trapped between the skin and the tape and the area may become macerated. There are now alternatives that are permeable to water vapour.

This type of dressing is commonly used for many simple superficial wounds.

Non-adherent dressings

These inert dressings are absorbent, non-adherent pads consisting of an outer layer of polyethylene-laminated rayon and an inner layer of absorbent rayon–polypropylene blend. They are used on lightly exudating wounds and on minor burns over a hydrogel.

Non-adherent wound contact dressings include knitted, viscose-type dressings and perforated film absorbent dressings that consist of a polymeric film perforated in a regular pattern plus an absorbent backing layer of non-woven material. These products are used on simple, low-exudating, superficial wounds or as protective dressings over lacerations and minor wounds.

Newer forms of non-adherent dressings have an anti-shear surface and a greater ability to absorb exudate.

Table D.22 Non-adherent dressings

Product®	Manufacturer
Newer types	
Mepore	Molnlycke
Exudry	Smith & Nephew
Zetuvit	Hartmann
Non-adherent island dressings (with an adhesive non-waterproof tape cover)	
Elastoplast conformable wound dressing	Beiersdorf
Microdon	3M
Primapore	Smith & Nephew
Cutiplast sterile, Hansapor sterile	Smith & Nephew
Telfa island	Tyco

Table D.23 Wound characteristics and management

Colour/exudate	Superficial wound	Deeper or cavity wound
Red/unbroken Aim: To prevent skin breakdown	Hydrocolloids or film dressings provide the best protection.	Not applicable
Pink/low exudate Aim: To maintain moist environment, protect and insulate	Foams, thin hydrocolloids, thin hydroactive dressings, film dressings and simple non-adherent dressings will provide the necessary cover.	
	Foam sheets Film dressings Hydrocolloids (thin) Hydroactive dressing (thin) Non-adherent Zinc paste bandage may also be used.	
Red/low exudate Aim: To maintain moist environment, promote granulation and epithelial regeneration	Hydrocolloids, foams, sheet hydrogels and film dressings will maintain the environment. It is possible to use a combination of amorphous hydrogel and foam cavity dressing for deeper wounds.	
	Hydrocolloids Foam sheet Sheet hydrogels Film dressing In addition, the use of zinc paste bandages in shallow granulating venous ulcers is appropriate.	Hydrocolloid wafer over hydrocolloid paste Amorphous hydrogels with foam cavity dressing Hydrocolloid/alginate cavity dressing
Red/high exudate Aim: To maintain moist environment, absorb exudate and promote granulation and epithelial regeneration	Foam dressings, alginates and hydroactive dressings help control exudate; hydrocolloids with paste or powder for deeper areas.	
	Foam sheets Alginates, hydrofibre Hydroactive dressing	Foam cavity dressings Alginates, hydrofibre Hydrocolloid/alginates Hydrocolloid over hydrocolloid paste or powder Hydroactive cavity dressing
Yellow/low exudate Aim: To remove slough, absorb exudate, maintain moist environment	Hydrogels in particular will rehydrate the slough; hydrocolloids, films and enzymes will aid autolysis.	
	Amorphous hydrogels Sheet hydrogels Hydrocolloids Film dressings Cadexomer iodine New topical silver dressings	Amorphous hydrogels Hydrocolloid wafer over hydrocolloid paste Enzymes Hydrocolloid/alginates Cadexomer iodine New topical silver dressings
Yellow/high exudate Aim: To remove slough, absorb exudate	Hydrocolloids with or without paste or powder for deeper wounds; hydrogels, alginates and enzymes will aid in removal of slough and absorb exudate.	
	Hydrocolloids Enzymes Hydrogels Hydroactive dressing Alginates, hydrofibre Cadexomer iodine New topical silver dressings	Hydrocolloid over hydrocolloid paste or powder Hydrogels Enzymes Alginates, hydrofibre Hydroactive cavity Hydrocolloid/alginate Foam cavity dressing Cadexomer iodine New topical silver dressings
Black/low exudate Aim: To rehydrate and loosen eschar	Surgical debridement is the most effective method of removing necrotic material; dressings can enhance autolytic debridement of eschar.	
	Amorphous hydrogels Hydrocolloid sheet Proteolytic enzymes	

Paraffin gauze dressings

Paraffin gauze (tulle) dressings consist of pieces of woven cotton or viscose, or a combination of the two, impregnated with yellow or white soft paraffin. This type of dressing is also available as a medicated tulle with either antibiotics (note that there is concern about the use of topical antibiotics) or antiseptics. However, some antiseptics may not be readily released from the hydrophobic paraffin.

Paraffin gauze may adhere to the wound and cause trauma on removal; it is also permeable to micro-organisms.

Newer tulle dressings are impregnated with polyethylene glycol, and these more readily release the antiseptic to the skin.

Table D.24 Paraffin gauze (tulle) dressings

Product®	Manufacturer
Paraffin/gauze type	
Jelonet	Smith & Nephew
Paranet	Smith & Nephew
Unitulle	Aventis Pharma
Non-paraffin synthetic pad type	
Adaptic	Johnson & Johnson
Atrauman	Hartmann
Cuticern	Smith & Nephew
Curity oil emulsion	Tyco
Mepitel (polyamide)	Molnlycke
Urgotul (lipocolloidal)	Urgo
Medicated tulle dressings	
Bactigras (chlorhexidine)	Smith & Nephew
Betadine pads (povidone iodine)	Mayne Consumer Products
Inadine (iodine tulle)	Johnson & Johnson
Xeroform (bismuth tribromophenate)	Tyco

Interactive dressings

Film dressings

Film dressings help create the optimum micro-environment for healing.

Semi-permeable adhesive film dressings consist of a thin polymeric membrane coated with a layer of acrylic adhesive. They are permeable to both gases and water vapour but are impermeable to micro-organisms. The permeability to water vapour varies from 800 g/m^2 to 10,000 g/m^2 and higher.

These dressings provide a moist environment and protect the wound and skin from chemicals, friction, shearing forces and microbes. They are used in the management of minor burns and simple injuries such as lacerations, abrasions and scalds. They are also used as post-operative dressings over sutures, as a protective layer around intravenous catheters, for the prevention and treatment of superficial pressure areas, and as a secondary dressing over gels, alginates and foams.

Care must be taken if applying film dressings to damaged or fragile skin because of the risk of further damage on removal. Film dressings are not recommended over deep cavity wounds, full thickness burns or wounds showing signs of clinical infection.

Film dressings are ideal for simple lacerations. They may be used as film only or as an island form containing an absorbent pad in the middle. The latter form is used when there is still some bleeding or exudate from the laceration.

Films are also used over suture lines once the sutures have been removed to protect the wound from breaking down as a result of sub-tissue tension. The film is placed over the suture line and kept in place for seven to 10 days. This procedure is repeated for up to five months until the tissue gains greater tensile strength.

When removing films, care must be taken to follow the instructions provided by the manufacturer to avoid causing further damage.

Table D.25 Film dressings

Product®	Manufacturer
Opsite	Smith & Nephew
Tegaderm	3M
Biofilm	Johnson & Johnson
Elastoplast Aqua Protect Film	Beiersdorf
Hydrofilm	Hartmann
Polyskin II	Tyco
Island film dressings	
Opsite Post Op	Smith & Nephew
Cutifilm Plus	Smith & Nephew
Tegaderm with Pad	3M
Elastoplast Aqua Protect Waterproof Dressing	Beiersdorf
Nexcare Tattoos	3M
Nexcare Clean Seals	3M
Hydrofilm Plus	Hartmann

Foam dressings

Foam dressings are produced from polyurethane as soft, open-cell sheets in single or multiple layers. They vary greatly in their ability to absorb exudate and in

their permeability. They provide a moist environment, are absorbent, conformable, protective and cushioning, non-residual, non-adherent, thermally insulating, and permeable to water vapour.

They are indicated for a wide range of minor and major wounds, including exudating wounds, leg and pressure ulcers, sutured wounds and skin grafts, donor sites and minor burns. They are also used as secondary dressings over amorphous hydrogels as they remove excess exudate from the wound, raise the core temperature, and assist in autolysis. Because they absorb fluid laterally across their surface, the dressings should be applied at least 3 cm beyond the wound edge. Foam dressings protect surrounding skin from maceration. They are of little value on dry wounds with a scab. The cavity form of these foams should be used in combination with an amorphous hydrogel in dry cavity wounds. Some foams may be cut to enable their use over a heel wound or cut in an L-shape and used on fingers or toes. Note, however, that dressings are sterile only until packaging is opened and that cutting may increase the risk of contamination if scissors are not clean.

Foams are now also available in a two-part liquid form of polydimethylsiloxane. When mixed together and poured into a wound cavity, the product becomes a solid foam stent. This product is removed from the wound, washed and cleansed in aqueous chlorhexidine, rinsed and returned to the wound. It is used in surgical wounds, e.g. broken-down surgical wounds, perineal wounds and pressure wounds.

A number of absorbent polymer dressings are also described as foams, but they are not interchangeable since their absorbent action involves binding the fluid into their structure and expanding in shape. In comparison, foams, like a seasponge, absorb by siphoning gently into the air spaces of the product.

Table D.26 Foam products

Product®	Manufacturer
Single-layer foams	
Curafoam	Tyco
Hydrasorb	Tyco
Cavity foams	
Cavicare	Smith & Nephew
Allevyn Cavity	Smith & Nephew
Dual-layer foams	
Lyofoam	Aaxis Pacific
Lyofoam Adhesive	Aaxis Pacific
PermaFoam	Hartmann

Table D.26 Foam products (continued)

Product®	Manufacturer
Trufoam	Unomedical
Triple-layer foams	
Allevyn Sheet	Smith & Nephew
Lyofoam Extra	Seton Scholl Ltd
Allevyn Adhesive	Smith & Nephew
Allevyn Island	Smith & Nephew

Hydrogels

Hydrogels are water-swollen, polymeric, three-dimensional, cross-linked structures formed from hydrophilic homopolymers or co-polymers. They may be either:

- amorphous, non-fixed, three-dimensional macro structures consisting of hydrophilic polymers or co-polymers. They donate moisture to the wound and can also absorb fluid but in doing so become less viscous and tend to leak out of any secondary dressing. They are free-flowing and will easily fill a cavity space
- fixed, three-dimensional macro structures, usually presented as thin, flexible sheets. They are moisture donors and will also absorb fluid.

All hydrogels contain a high proportion of water—up to 95% of their structure. These dressings provide a moist environment, aid in autolytic debridement, are conformable and are non-adherent.

They are indicated for dry and sloughy wounds because they rehydrate and enhance rapid debridement by autolysis. They are used on leg ulcers, pressure wounds, extravasation injuries and necrotic wounds. They facilitate granulation and epithelialisation by preventing drying out of the wound. They are used on simple and partial-thickness burns—the amorphous types on sunburn and simple scalds and the sheet types on necrotic, partial-thickness burns. In burns, they are used in the initial management to cool and remove non-viable tissue from the burn. The sheet types are also used on some shallow, sloughy pressure wounds, where they both aid removal of the slough and reduce shear and friction, the probable cause of the wound.

Amorphous hydrogels are also used as carriers for topically applied medications such as metronidazole and proteolytic enzymes. Hydrogels are useful in the management of chickenpox and shingles lesions as they reduce discomfort and minimise scab and scar formation. They should not be used on highly exudating wounds.

Sheet hydrogels are generally not indicated in clinically infected wounds.

Table D.27 Hydrogel products

Product®	Manufacturer
Amorphous hydrogels	
Duoderm Gel	ConvaTec
IntraSite Gel	Smith & Nephew
Solosite	Smith & Nephew
Solugel	Johnson & Johnson
Purilon Gel	Coloplast
Safgel	ConvaTec
Curafil	Tyco
NuGel	Johnson & Johnson
Aquaform Gel	Unomedical
Hydrosorb Gel	Hartmann
Sheet hydrogels	
Second Skin	Spenco
ClearSite	Hartmann
Curagel	Tyco

Bioactive dressings

Bioactive are dressings either initiate the healing cascade or contribute to the expression of specific growth factors. They also help control the micro-environment in a manner similar to the interactive dressings.

Hydrocolloid dressings

Hydrocolloid dressings occur as powders, pastes and sheets. They consist of various gel-forming compounds, including carboxymethylcellulose, bonded with adhesives onto either foam or film sheets. When applied to wounds, the dressings absorb fluid from the wounds and form a gel in the space between the dressing and the wound while at the same time remaining adhered to the intact skin. They are mostly occlusive dressings, as though some are semi-occlusive.

Hydrocolloids provide a moist environment, aid in autolytic debridement, are conformable, protect from microbial contamination, are waterproof, require no secondary dressing, and allow for easy removal of residue by irrigation. This residue, yellow and at times malodorous, is sometimes confused with pus. It is in fact the gel produced from the components of the hydrocolloid and exudate. This should be explained to the patient before applying the dressing.

Hydrocolloids are indicated in the management of superficial leg ulcers, burns and donor sites (once haemostasis has been established) and on pressure wounds. The powder and paste forms of these dressings may also be used on some small cavity wounds. Thin and transparent forms of this type of dressing are used after surgery to cover suture lines.

The use of hydrocolloids should be ceased once the wound has granulated sufficiently or if hypergranulation is present—this tends to occur if the level of exudate in the wound is high. Care should be exercised when applying these dressings to thin, fragile or damaged skin to minimise any further damage on removal. Hydrocolloids are not indicated in heavily exudating or clinically infected wounds or in diabetic wounds, but the presence of colonised bacteria does not contraindicate their use.

Table D.28 Hydrocolloid products

Product®	Manufacturer
Comfeel Ulcer Dressing	Coloplast
DuoDerm CGF	ConvaTec
Tegasorb	3M
Hydrocoll	Hartmann
Replicare	Smith & Nephew
Restore	Hollister
Comfeel Plus Transparent	Coloplast
Comfeel Plus Ulcer Dressing	Coloplast
Comfeel Plus Contour Dressing	Coloplast
Comfeel Plus Pressure Relieving Dressing	Coloplast
Curaderm	Tyco
Combiderm	ConvaTec
Cavity hydrocolloids	
Comfeel Paste	Coloplast
DuoDerm Paste	ConvaTec
Comfeel Powder	Coloplast

Hydroactive dressings

Hydroactive dressings differ from hydrocolloid dressings in that they are not gel-producing: in fact, they absorb large amounts of wound fluid into their structure and swell. They are multi-layered, polymeric products with an adhesive backing. They maintain a moist environment, are highly absorbent, waterproof and relatively elastic, aid in autolytic debridement, and are non-residual and semipermeable.

Hydroactive dressings are indicated for exudating wounds, including leg ulcers, pressure wounds, minor burns and exudating cavity wounds, and are of particular use over joints such as the elbow, knee, fingers, toes and ankles because of their ability to expand and contract without causing constriction. They should not be used on wounds with little or no exudate and are not considered suitable on clinically infected wounds. Care should be taken when using these products on patients with thin, friable or damaged skin to minimise further damage on removal.

Table D.29 Hydroactive products

Product®	Manufacturer
Surface hydroactive dressings	
Cutinova Hydro	Smith & Nephew
Allevyn Compression	Smith & Nephew
Allevyn Thin	Smith & Nephew
Tielle	Johnson & Johnson
Biatain	Coloplast
PolyMem	Ferris
Tender Wet (super absorbent polymer activated with Ringer's solution)	Hartmann
Cavity hydroactive dressings	
Allevyn Plus Cavity	Smith & Nephew

Alginate dressings

Alginate dressings are derived from alginic acids found naturally in brown seaweed. They are produced as the calcium and sodium salts. Alginates have a complex structure comprising two uronic acids: guluronic and mannuronic acids. The ratio of these components will result in variation in the physical characteristics of the gels produced from their alginates. Those rich in mannuronic acid tend to produce soft amorphous gels, while those rich in guluronic acid form a firmer gel that retains its basic structure.

When an alginate dressing is placed on an exudating wound, the calcium ions exchange with the sodium ions in the wound fluid and form a hydrophilic gel. They provide a moist environment, and are highly absorbent, conformable, protective, haemostatic and non-adherent. Alginates are used on exudating wounds such as leg ulcers, cavity wounds, pressure wounds, donor sites and other bleeding wounds. They are not indicated for wounds where the level of exudate is insufficient to form a gel. They should not be premoistened before application since the gelling process is part of their action. When applied to clinically infected wounds, alginates should be changed daily. These products are not indicated on dry wounds or those with a black eschar. Alginates are available as sheets, packing rope or ribbon.

Because of their haemostatic property, alginate dressings are also useful in the management of a bleeding nose and most types of lacerations and other wounds with minor bleeding to rapidly stop the bleeding.

Table D.30 Alginate products

Product®	Manufacturer
Sheet	
Soft	
Sorbsan	Uno Medical
Seasorb Soft	Coloplast
Firm	
Tegagen HI	3M
Algisite M	Smith & Nephew
Algoderm	Johnson & Johnson
Kaltostat	ConvaTec
Curasorb	Tyco
Melgisorb	Molnlycke
Restore CalciCare	Hollister
Sorbalgon	Hartmann
Extra-absorbent	
Sorbsan Plus	Unomedical
Rope	
Seasorb Filler	Coloplast
Sorbsan	Uno Medical
Algoderm	Johnson & Johnson
Kaltostat	ConvaTec
Curasorb	Tyco
Melgisorb	Molnlycke
Restore CalciCare	Hollister
Sorbalgon	Hartmann
Tegagen HI	3M

Hydrofibre dressings

An alternative to the alginate dressings is a fibre dressing based on the hydrocolloid technology called 'hydrofibres'. They are made of non-woven sodium carboxymethylcellulose spun into fibres and then into sheets and ribbon dressings. They mirror the action of the alginate dressings in absorbing exudate and forming gels. They are indicated for heavily exudating wounds such as leg ulcers, pressure wounds, cavity wounds, minor burns and donor sites. They do not have haemostatic properties but are useful to protect peri-wound skin as they are able to expand vertically.

Table D.31 Hydrofibre (alginate alternative)

Product®	Manufacturer
Aquacel	ConvaTec

Combination dressings

Hydrocolloids and alginates have been combined to form both a standard type of dressing sheet and a cavity dressing. The combination increases the ability of the dressing to absorb exudate and so increases the wear time of the dressing.

Hydrocolloids are also used in a combination, multi-layer absorbent pad combining a semipermeable hydrocolloid border with an absorbent padding containing hydrocolloid particles and a non-adherent cover against the wound. This product is highly absorbent and able to hold the exudate within the dressing, preventing maceration of the skin surrounding the wound. There are also dressings that combine polymers, foam and hydrocolloids in a single dressing.

Table D.32 Combination products

Product®	Manufacturer
Versiva Dressing	ConvaTec
Transorbent	Unomedical
Alione	Coloplast

Miscellaneous dressings

A number of other dressings do not fit into any of the general groups. These include:

- charcoal dressings
- hypertonic saline dressings for hypergranulation
- silicone-based dressings for use on keloid scars
- topical anti-infectives—topical silver dressings, cadexomer iodine.

Charcoal dressings

Malodour often occurs in chronic wounds. This may be due to the presence of anaerobic bacteria or tissue breakdown by other bacteria. It is important for the patient's quality of life to reduce the odour. There are several ways of achieving this, including the application of topical metronidazole gel or the use of dressings containing charcoal. These are available as charcoal odour-absorbent dressings or in combination with a cotton, foam or alginate/hydrofibre to absorb odour.

Table D.33 Combination charcoal dressings

Product®	Manufacturer
Carboflex (alginate/hydrofibre)	Convatec
Lyofoam C (charcoal)	Aaxis Pacific
Actisorb Plus	Johnson & Johnson
Carbonet	Smith & Nephew

Hypertonic saline dressings

Hypergranulation occurs when epithelium fails to cover the granulating tissue and the tissue continues to grow beyond the surface of the wound. Traditionally, this tissue has been reduced by the application of silver nitrate or copper sulfate solutions. However, these are toxic chemicals, and it is considered better to use dressings containing a less toxic substance, such as hypertonic sodium chloride, which achieves the same results. These dressings are applied daily until the tissue returns to normal surface depth. Hypertonic saline dressings are also used for infected or contaminated wounds or to assist in wound debridement.

Table D.34 Hypertonic saline dressings

Product®	Manufacturer
Curasalt (moist pads of sodium chloride 7%)	Tyco
Mesalt (dry pads of gauze)	Molnlycke

Silicone-based dressings for keloid scars

Silicone is a major component of dressings that are used to reduce hypertrophic and some keloid scars. These dressings should be applied as soon as sutures or clips are removed from the incision site. They should be removed after one to three days, the area washed and the dressing re-applied. The same piece of dressing may be used for about seven days, and then a fresh piece should be applied. Silicone is also used as the surface layer on a number of dressings from tulles to foams. In these, the silicone helps maintain adhesion of the dressing to the skin without sticking, thus allowing atraumatic and less painful removal. The dressing also reduces pain at the wound interface.

Silicone for scar reduction is also available as an oil and in combination with vitamins A and E.

Table D.35 Silicone dressings

Product®	Manufacturer
Scar reduction dressings	
Cica Care	Smith & Nephew
Spenco silicone gel sheet	Kimberly-Clark
Mepiform	Molnlycke
Foam dressings	
Mepilex	Molnlycke
Mepilex Transfer	Molnlycke
Mepilex Thin	Molnlycke
Combination	
Mepilex Border	Molnlycke

Table D.35 Silicone dressings (continued)

Product®	Manufacturer
Tulle	
Mepetil	Molnlycke
Silicone oils	
Dermatix Silicone gel	Valeant Pharmaceuticals International
Bio Oil	Union Swiss

Topical anti-infectives

The level of microbial contamination on the surface of a wound may retard healing. A dilemma arises when topical antiseptics are applied because they may have a negative effect on wound healing. In recent years new topical preparations have been developed based on silver and iodine, which do not impede healing

Silver

Silver has been used for many years and has proven antimicrobial activity. It is broad spectrum and can inactivate almost all known bacteria, including methicillin-resistant staphylococcus aureus and vancomycin-resistant enterococci. There is some concern over resistance to silver. However, most studies of the emergence of bacterial resistance to silver have not been related to the use of silver in dressings and further, more specific studies are required. In particular, silver has been used for the treatment of burns as silver sulfadiazine cream. This cream has also been applied to some wounds and, when applied to a wound, will encourage the development of a pseudo-eschar.

Contemporary silver dressings allow for continued release of silver for up to seven days. The silver content and the proportion of silver released into the wound vary greatly between dressings.

The choice of dressing will depend on the level of infection, the wound size and depth, and the amount of exudate.

Table D.36 Silver dressings

Product®	Manufacturer
Acticoat (nanocrystalline silver)	Smith & Nephew
Acticoat Absorbent (alginate base)	Smith & Nephew
Acticoat Moisture Control	Smith & Nephew
Avance (foam base)	Aaxis Pacific
Aquacel Ag (hydrofibre base)	ConvaTec
Contreet (hydroactive base)	Coloplast
Contreet H (hydrocolloid base)	Coloplast
Atrauman Ag	Hartmann

Iodine

Iodine in its various forms has been used as a topical antiseptic since 1840. Iodophores have been used since the 1950s. Most iodophores combine iodine in a complex with a polymer (e.g. povidone, cadexomer) that slowly releases the iodine. Iodine is active against bacteria, mycobacteria, fungi, protozoa and viruses. There is no evidence of resistance to iodine. Povidone iodine comes in many forms, including skin paints, throat gargle, scrub wash and ointments.

Cadexomer iodine is a form of iodophore in which iodine is cross-linked to cadexomer, a polysaccharide polymer. When applied to a moist wound the exudate is absorbed into the polysaccharide and the iodine is released over 72 hours. Inflammation and slough in the wound are reduced. There is evidence that this product stimulates inflammatory cytokines.

Table D.37 Cadexomer iodine products

Product®	Manufacturer
Iodosorb (paste)	Smith & Nephew
Iodosorb (powder)	Smith & Nephew
Iodosorb (dressing)	Smith & Nephew
Inadine (iodine tulle)	Johnson & Johnson

Secondary dressings

The choice of a secondary dressing will depend on the nature and position of the wound and the level of exudate. In general terms, foam dressings are useful over amorphous hydrogels and alginates. Film dressings may also be used but may cause some maceration. Film dressings may also be used to provide a waterproof cover over other dressings such as foam sheets.

The use of gauze as a secondary dressing, especially over hydrogels or alginates, is limited as the gauze will reduce the ability of the dressing to function at its optimal level.

The other consideration is the method of dressing retention. If the surrounding skin is good, the dressing may be held in place with quality adhesive tape. If the skin is fragile, thin or damaged, the use of a tubular bandage or a lightweight cohesive bandage is suitable.

Growth factors

Considerable research has identified a number of growth factors, or cytokines, present in wounds. The role of these cytokines is not fully understood, but they appear to play a vital role in the healing cascade. Some research has shown a benefit from topically applied growth factors; the first commercial form of platelet-derived growth factor (PDGF) has been released in the US for

the treatment of diabetic foot ulcers. The main growth factors identified in wounds include:

- platelet-derived growth factor
- fibroblast growth factor
- epidermal growth factor
- transforming growth factors
- insulin-like growth factor
- vascular endothelial growth factor (VEGF)
- whey-derived growth factors.

Research into the potential uses of growth factors is being undertaken in centres all over the world. This includes their use in scarless wound healing and the use of VEGF to enhance new blood-vessel formation.

Tissue-engineered products

Clinical trials of several skin substitutes developed by seeding neonatal cells onto a matrix in a controlled environment are under way. The matrix changes by the expression of a number of growth factors and cells into a dermis/epidermis and/or epidermis. Once mature, these skin substitutes are frozen and stored. They are thawed immediately before application to diabetic wounds and leg ulcers or as a temporary cover for burns. Many of these products are not yet available in Australia. One example of an available product is *Oasis*; others will be introduced into the Australian market over the next few years. There is excellent research in Australia developing future growth factor and tissue-engineered products.

Bandages and bandaging

There are three main types of bandages:

- retention bandages
- support bandages
- compression bandages.

Retention bandages

Retention bandages are used to hold a dressing in place. They are of particular use where a patient has very fine, friable skin that would be easily damaged by adhesive tape or other adhesive products. Cotton crepe bandages have been used for this purpose for many years but more effective and appropriate bandages are now available.

A lightweight conforming cohesive bandage is a crepe bandage coated with a thin latex. As a result of this coating the bandage sticks to itself but not to skin, hair or clothing, so pins or clips are not required. A very small length is sufficient to hold the dressing in place, compared with using a complete roll of a standard crepe bandage. This type of bandage comes in widths that are appropriate for fingers, toes and limbs, with a larger size for the head.

Another useful product is a lightweight non-elasticised tubular bandage that may be cut to the required size and placed over the dressing to hold it in place.

Table D.38 Retention bandages

Product®	Manufacturer
Handy Gauze Co-hesive	Beiersdorf/Smith & Nephew
Easyfix Co-hesive	Smith & Nephew
Peha-haft	Hartmann
Tubifast	Aaxis Pacific
Tubular Conforming	Sutherland Medical
Wool Bandages	
Artifex	Smith & Nephew
Soffban	Smith & Nephew
Velband	Johnson & Johnson
Webrill	Tyco
Rolta	Hartmann

Support bandages

Support bandages are made from both natural and synthetic fibres. They achieve their stretch by the use of high-twist yarns and heavier construction. Their main use is the support of joints in strains and in the management of muscular injuries. Strong support bandages can be used alone or in combination to restrict movement, help reduce oedema, and provide support following soft tissue injury.

Table D.39 Support bandages

Product®	Manufacturer
Elastocrepe	Smith & Nephew
Handycrepe	Smith & Nephew/Beiersdorf
Telfa Crepe	Tyco
Idealcrepe	Hartmann
CoPlus	Smith & Nephew
Co ban	3M
Handygrip	Smith & Nephew/ Beiersdorf
Flexwrap	Tyco
Tubigrip straight	Aaxis Pacific
Handyplast Tubular	Smith & Nephew/Beiersdorf
Tensogrip	Smith & Nephew

Compression bandages

Compression bandages are one of the main treatments for venous disease, especially when venous ulcers are

associated with varicose veins. They aid the healing of the ulcer and facilitate venous return to help prevent recurrence of the ulcer.

Effective therapeutic compression starts with a minimum sub-bandage pressure of 18 mm Hg at the ankle. Anything lower, whilst appropriate for support, is not considered appropriate for the treatment or prevention of venous leg ulcers. The primary aim of compression is to reduce the pressure in the superficial veins. This improves venous return to the heart by increasing flow velocity in the deep veins and limits oedema by reducing the pressure difference between the capillaries and the tissues. The most effective method is to apply graduated compression from the toe to the knee. The highest pressure should be exerted at the ankle, gradually falling to about 50% at the knee.

The aim of using compression bandages is to enclose the leg with pressure firm enough to compress the pathologically distended veins, thus enabling valves to function more efficiently, increasing the velocity of the venous blood stream, and normalising the return of blood flow to the heart. The accumulated fluid and waste products are removed from the affected tissue at an accelerated rate. Compression bandages are also used in the management of lymphoedema.

Compression bandages are available in several different types.

High-stretch compression bandages

These have an extensibility of 130–200%. They have high elasticity, high to medium resting pressure, and high to medium working pressure. They mainly exert their effect superficially by working in combination with the muscles and are indicated for the treatment of venous oedema and the management of venous ulcers.

Short-stretch bandages

These have an extensibility of 30–90%, low elasticity, and low to slight resting pressure but high to very high working pressure. They mainly exert their effect deep within the limb and are indicated for both venous oedema and lymphoedema.

Table D.40 Compression bandages

Product®	Manufacturer
Eloflex	Smith & Nephew
Setopress	Aaxis Pacific
Surepress	ConvaTec
Tensopress	Smith & Nephew
Comprilan	Smith & Nephew
Tensolan	Smith & Nephew
Tubigrip shaped	Aaxis Pacific
Tubular Bandage	Sutherland Medical

Multi-layer bandages

A development in bandaging has been the introduction of the Charing Cross four-layer system. This combines an orthopaedic wool, a crepe bandage, a lightweight compression bandage and a cohesive bandage in multiple layers. The combination achieves 40 mm Hg at the ankle, graduating to 17mm Hg at the knee. A number of published studies have shown good healing rates within 12 weeks with this system.

Another form of compression garment is the straight tubular bandage. When used for this purpose it is usually applied in multiple layers, with a full bandage from the toe to below the knee, a second bandage from toe to mid-calf and a third from toe to ankle. This type of product is also available in a shaped version that provides graduated compression. A single layer of shaped tubular bandage will produce a pressure of 12–15 mm Hg. They may also be applied in multiple layers.

Table D.41 Multiple layer compression bandages

Product®	Manufacturer
Profore	Smith & Nephew
Profore LIte	Smith & Nephew
Proguide	Smith & Nephew
Veno 4	Hartmann
Coban 2	3M

Contraindications for the use of compression bandages

Some compression stockings have been designed to prevent post-operative deep vein thrombosis and are *not* appropriate once the patient is ambulant (e.g. hosiery identified as anti-embolic stockings, such as TED stockings).

Great care must be taken before applying any pressure garment if there is an indication of arterial disease. It is important that, before compression bandages or similar are used, the patient's peripheral arterial circulation be checked to ensure that it will not be compromised by the application of compression bandages. Use of compression may lead to skin necrosis, direct trauma, ulceration and, ultimately, amputation. It is essential when applying a compression bandage to a leg, especially where there is unevenness of circumference, that the area around the ankle in particular is padded out with orthopaedic wool to ensure even distribution of the compression along the leg.

Table D.42 Levels of compression

Indication	Level of compression
Superficial/early Varices Prevention DVT	18–24 mm Hg
Medium Varices Mild Oedema **Ulcer prevention**	25–35 mm Hg
Gross varices Gross oedema **Ulcer treatment** Postthrombotic syndrome	35–45 mm Hg
Lymphoedema	35–50 mm Hg

Zinc and other medicated paste bandages

In general, plain non-preserved zinc paste bandages are suitable for use on a number of wound types, especially venous leg ulcers.

There are many paste bandages listed in pharmacopoeias either as the sole agent or with other medications such as castor oil, ichthammol and camphor. Examples of these include:

- zinc paste and coal tar used in the treatment of chronic eczema, dermatitis and infantile eczema but not suitable for open wounds
- zinc paste and ichthammol used in the treatment of chronic eczema (where coal tar cannot be tolerated) and in gravitational eczema. It is also not suitable for open wounds
- zinc paste and calamine used in the treatment of non-exudative stages of acute and subacute eczema, erythema and dermatitis after plaster removal. It is not suitable for open wounds.

Application methods

There are two structural types of zinc paste bandage: stretch or rigid-fibre bandage.

The stretch bandage is applied in a circumferential manner, with an overlap as the bandage is wound around the leg.

The rigid bandage is applied in a different manner. It is wound around the leg until it meets itself; the bandage is then reversed and wound in the opposite direction until it just covers itself again. This process continues as the bandage is wound up the leg. Note that at no stage does the bandage complete a full circle of the leg. The reason for this method of application is that the bandage, being rigid, will not expand as the leg enlarges due to oedema.

This system is left undisturbed for seven days, then removed, the leg washed with a simple surfactant (e.g. *Ego Wash*® or similar), and rebandaged.

Zinc paste also comes in the form of a stocking, a non-preserved expandable tubular bandage, which is applied in a similar way to conventional zinc paste bandages.

Table D.43 Zinc paste bandages

Product®	Manufacturer
Preserved zinc paste bandages	
Viscopaste	Smith & Nephew
Zincaband	Seton Scholl Ltd
Tenderwrap Unna Boot	Tyco
Non-preserved zinc paste bandages and tubular stockings	
Flexidress	ConvaTec
Gelocast	Smith & Nephew
Steripaste	Seton Scholl Ltd
Zipzoc Tubular	Smith & Nephew
Varolast	Hartmann

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Section E

OTC Counselling guides

OTC Counselling guides

Australian consumers are increasingly choosing to use over-the-counter medications to self-medicate for common ailments. Pharmacists are in a unique position to assist in the selection of these medicines by using their knowledge and the support of trained staff and creating an environment which facilitates and encourages quality use of medicines.[1]

The *Standards for the provision of* Pharmacy medicines *and* Pharmacist Only medicines *in community pharmacy*[1] outlines the actions to be taken by pharmacists and trained pharmacy staff in response to a direct product or symptom-based request. Information and advice should always be provided in a manner that is sensitive to the consumer's right to privacy and confidentiality.[2]

This section contains counselling guides for a number of symptoms and medicines, to assist pharmacists in the application of these standards. The guides summarise the clinical information to be considered by pharmacists when providing advice and/or supplying medicines for self-care.

Comprehensive advice on all treatment options is beyond the scope of the guides. Specific information, (e.g. on doses, precautions and adverse effects), can be found in publications such as *MIMS* and the *Australian Medicines Handbook*.

Pharmacists are advised to exercise professional judgment in adapting the guidance provided to individual circumstances.

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Constipation guide

Assess patient's needs

A. Patient characteristics

The age and pregnancy status of the patient should be determined because these will affect the advice provided.

B. Symptoms

A broad definition of constipation is the passage of hard stools less frequently than is normal. 'Normal' can be anything from passing stools two or three times a day to two or three times a week; it is the change that is significant. Symptoms commonly experienced include difficulty passing stools, abdominal discomfort and abdominal distension.[1]

If untreated, constipation can lead to faecal impaction and bowel obstruction, faecal and urinary incontinence, urinary tract infection, rectal bleeding and anal fissures.[1]

Straining to defecate can cause haemorrhoids, fainting and cardiac irregularities, worsen gastro-oesophageal reflux and mobilise a deep vein thrombosis.[1]

C. Prior treatment

Many misconceptions surround bowel habits and what is normal, leading to misdiagnoses and overuse of laxatives.[1]

D. Lifestyle factors

Many non-medical factors predispose to constipation, in particular[1,2]:

- inadequate fluid intake. The normal stool is about 70–85% water; dehydration results in a hard stool that can be difficult to pass
- inadequate dietary fibre
- reduced physical activity
- suppressing the urge to defecate.

Constipation is common in pregnancy and usually resolves shortly after delivery. Drugs can cause harm to a fetus at any time during pregnancy, so medicines advice should be consistent with Australian Drug Evaluation Committee pregnancy categories or be obtained from pregnancy drug information centres. The suitability of drug use during lactation may also need to be considered.

E. Medical history

Medical conditions predisposing to constipation include[1]:

- coeliac disease
- depression
- diabetes mellitus
- gastrointestinal obstruction—e.g. gastrointestinal carcinoma and ileus, ovarian or uterine tumours
- hypercalcaemia
- hypokalaemia
- hypothyroidism
- irritable bowel syndrome
- multiple sclerosis
- Parkinson's disease
- damage to pelvic floor muscles—e.g. post-childbirth.

Medications that can cause constipation include[1]:

- antacids containing aluminium or calcium
- some anticonvulsants (carbamazepine, phenytoin, pregabalin)
- antidepressants (tricyclic antidepressants, some monoamine oxidase inhibitors)
- antihistamines (predominantly sedating antihistamines)
- some antimuscarinic drugs used in parkinsonism (benztropine, orphenadrine, benzhexol), urinary incontinence, irritable bowel disease and diverticular disease
- many antipsychotics—e.g. clozapine, olanzapine, risperidone, quetiapine
- calcium supplements
- clonidine
- diuretics
- dopaminergic drugs used in parkinsonism
- 5-HT receptor antagonists
- iron
- opioid analgesics
- verapamil
- vinca alkaloids.

Select appropriate action

F. The need to refer

A person with constipation as a new symptom unattributable to changes in diet, lifestyle, medical condition or medications should be referred.

Referral for further investigation is also required when constipation is accompanied by the following symptoms[1]:

- constipation alternating with diarrhoea
- blood, mucus, or both, in the stools
- abdominal pain or vomiting
- unintentional weight loss
- tenesmus (a continuous feeling of the need to defecate).

Infants under the age of 3 months should be referred in order to exclude organic causes (e.g. Hirschsprung's disease).

Referral is also recommended when laxative misuse is suspected (e.g. in an individual with an eating disorder).

Recommend treatment

G. Goals of therapy

The aims of treatment are to[1]:

- restore normal frequency of defecation
- achieve regular, comfortable bowel movements using the least number of drugs for the shortest time
- avoid laxative dependence
- relieve discomfort.

H. Treatment options

All patients are likely to benefit from dietary and lifestyle changes:

- *Fibre*. The recommended daily fibre intake is 20–30 grams for adults and (age in years +5) grams for children.[2,3] Insoluble fibre (e.g. vegetables, legumes, fruits, nuts, wholegrain wheat and oats, rye meal, brown rice and seeds) and soluble fibre (e.g. oats, barley, ispaghula, rye, vegetables, pulses and fruits) are most effective in preventing or improving constipation.[3] Faecal impaction should be treated prior to initiating fibre supplementation.[2] The fibre content of food should be increased gradually to avoid adverse effects such as bloating or flatulence.[3] The benefits of a fibre-rich diet are generally seen in three to five days, but the full effect may not be seen for a month.[1]
- *Fluid*. 2 litres of fluid daily (unless contraindicated—e.g. in heart or renal failure) is recommended for adults.
- *Increased exercise and responding immediately to any urge to defecate*.[1–3]

Along with dietary and lifestyle changes, behavioural measures such as regular toileting and positive encouragement should be the first step in the management of constipation in children.[3]

Some people have recommended prune juice for infants. However, it contains a natural bowel irritant and is not recommended for infants less than 9 months of age, even when diluted.

Laxatives are used when dietary and lifestyle measures are not feasible, when such measures have failed, or while waiting for the measures to take effect.

There are four main groups of laxatives: bulk-forming, stimulant, osmotic and stool softening. Selection should be based on patient preference, desired onset of action (see Table E.1), consistency of the stool, possible side effects, and cost.[1] For children, progressive pharmacological treatment is recommended (see Table E.2).

Table E.1 Oral laxatives

Oral laxatives	Time to effect[1,3]	Comments[2,3]
Bulk-forming	Within 24 hours (2–3 days for full effect)	Faecal impaction should be treated before initiating fibre supplementation
Stimulant	Within 6–12 hours (oral); 15–60 minutes (suppository); 5–15 minutes (enema)	Not for long-term use unless for constipation in spinal damage, chronic neuromuscular disease and in people taking opioids. Stimulate intestinal motility and can cause abdominal cramps
Osmotic	Within 2–48 hours	Recommended when long-term use appears necessary
Stool softening	Within 12–72 hours	No evidence of efficacy as sole treatment for constipation in adults. Recommended in combination treatment and in children

A combination of laxatives may be more effective than a single agent. Suppositories or enemas may be useful for distal faecal impaction, but there is no evidence that they have a long-term effect on constipation or patterns of bowel emptying.[3]

Suppositories and enemas can be used when oral laxatives are ineffective. Choice of product depends on the site of impaction and whether the stools are hard or soft. Enemas are not intended for regular use but may need to be repeated several times to clear impacted faeces.[1]

Provide counselling supported by written information

I. How to use the medication

Once a medicine is selected the patient should be told how to use it, the correct dose, and any specific precautions[2,3]:

- *Bulk-forming agents.* Ensure adequate fluid intake; a gradual increase in fibre reduces adverse effects such as bloating or flatulence.
- *Stimulants.* Generally short-term use is preferred; usually taken at night to help produce a bowel motion the following morning; increased risk of faecal incontinence in the elderly.
- *Osmotic laxatives.* These should be taken with fluid to augment osmotic effect; more rapid effect when taken on an empty stomach.
- *Stool softeners.* Take with plenty of fluid; generally for use in combination with other agents; avoid dosing liquid paraffin at bedtime due to risk of aspiration.

J. Adverse effects

The patient needs to know the most common and important adverse effects of the therapy selected:

- *Bulk-forming.* Flatulence, bloating and abdominal discomfort are common.
- *Stimulants.* Diarrhoea, fluid and electrolyte imbalances (with prolonged use or excessive doses), abdominal discomfort, cramps and nausea occur infrequently.
- *Osmotic laxatives.* Fluid and electrolyte imbalances are more common with prolonged use or excessive doses; abdominal discomfort, cramps, nausea, diarrhoea and rectal irritation may occur.
- *Stool softeners.* Abdominal cramps, diarrhoea, nausea and rectal irritation may occur.

K. Follow-up advice

Where constipation is not a result of medication or chronic illness, laxatives should be used for a short time until dietary and lifestyle changes become effective.

Parents of children with constipation can be advised to maintain the most effective dose of laxative until defecation becomes too frequent and then to reduce the dose slowly over the following months.[4] Treatment may need to be continued for longer than six months in some cases.

Further investigation may be required if the recommended therapy has not relieved constipation within the expected time or if the patient experiences symptoms requiring referral (see 'The need to refer', previous page).

Provision of the *Constipation* Self Care Fact Card or other printed information for consumers is appropriate.

Table E.2 Progressive pharmacological treatment in children[3–5]

	Age	Dose	Notes
1. Aim is to produce a soft, easier-to-pass stool using regular doses of a stool softener, osmotic laxative or bulk- forming agent (e.g. ispaghula husk).			
Poloxamer (e.g. *Coloxyl* drops®)			
	<6 months	10 drops 3 times a day	• May be administered in feeding bottle or in fruit juice.
	6–18 months	15 drops 3 times a day	
	18–36 months	25 drops 3 times a day	
	>3 years	Consider tablets	
Docusate sodium (e.g. *Coloxyl* tablets®)			
	3–6 years	50 mg once daily	• If >3 years and cannot swallow tablets, do not break or crush the tablets. Use glycerin suppositories instead. See doses below. • Maximum faecal softening may not be observed until 2 to 3 days after commencing treatment.
	7–12 years	50–120 mg once daily	
Liquid paraffin (e.g. *Parachoc*®, *Agarol*®)			
	12 months – 6 years	15 mL once daily	• May affect absorption of fat soluble vitamins. • Avoid long-term use. • Do not give if lying down due to possibility of aspiration.
	7–12 years	20 mL once daily	
	>12 years	30 mL once daily	
Lactulose (e.g. *Actilax*®, *Duphalac*®, *Lac-Dol*®)			
	<1 year	5 mL daily	• May be more palatable if mixed with fruit juice, milk or water. May take 24–48 hours for defecation to occur.
	1–5 years	10 mL daily	
	6–12 years	15 mL daily	
	>12 years	20 mL daily	
Macrogol 3350 with electrolytes (e.g. *Movicol*®)			
	2–12 years	6.56 g daily (= 1 sachet *Movicol Half*®)	• Each sachet of *Movicol Half*® should be dissolved in approximately 60 mL of water.
	>12 years	6.56–13.125 g daily (= 1–2 sachets *Movicol Half*® or ½ –1 sachet *Movicol*®)	• Each sachet of *Movicol*® should be dissolved in 125 mL of water.
2. If the above is not working or if the child is withholding, try a stimulant laxative (e.g. senna or bisacodyl). This results in defecation becoming easier and the stool becoming smaller and softer, thus alleviating the child's fear of defecation.			
Sennosides (given orally, once daily at night—e.g. *Senokot*®)			
	2–6 years	0.5–1 tab/dose or a quarter to half a teaspoonful/dose	• Avoid prolonged use. • Granules can be mixed with milk, or water or eaten plain. • Effect within 8–12 hours.
	6–12 years	1–2 tabs/dose or half to one teaspoonful/dose	
Bisacodyl (e.g. *Dulcolax*®, *Bisalax*®)			
Oral	>3 years	5–10 mg at night	• Tablets are enteric-coated; do not crush or chew. • Tablets act within 6–12 hours.
Suppository	6 months – 3 years	5 mg at night	• Suppositories act within 20–60 minutes.
	>3 years	5–10 mg at night	
Enema	6 months – 3 years	Half an enema daily as required	• Enemas act within 15 minutes.
	>3 years	One enema daily as required	
Sodium picosulfate (e.g. *Dulcolax SP* drops®, *Picolax*®)			
Drops	4–10 years	5–10 drops daily	• Effect produced within 6–12 hours. • Can be added to water.
	>10 years	10–20 drops daily	
3. If individual agents fail, a combination of laxatives should be used (e.g. senna and lactulose)			
4. Glycerol suppository (e.g. *Glycerin* suppositories®)			
	<1 year	1 infant suppository (0.7 g) daily	• Allow to remain in rectum for 15–30 minutes. • Effect produced within 5–30 minutes. • Not for routine treatment of constipation.
	1–6 years	1 child suppository (1.4 g) daily	
	>6 years	1 adult suppository (2.7 g) daily	

Treatment may need to be continued for longer than 6 months in some cases. The doses of the various agents should be reduced slowly to prevent re-impaction. Parents can be advised to maintain the most effective dose of laxative until defecation becomes too frequent and then to reduce the dose slowly over the following months.

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Cough guide

Assess patient's needs

A. Patient characteristics

The age and pregnancy status of the patient should be determined because these will affect the advice provided.

B. Duration of cough

Cough may be[1]:

- acute—lasting less than three weeks
- subacute—lasting three to eight weeks
- chronic—persisting beyond eight weeks.

C. Symptoms

Acute cough

Viral. Sudden onset, accompanied by fever and cold symptoms; usually non-productive or produces a small amount of clear or white sputum. Symptoms often worse in the evening.[2,3]

Allergic. Often seasonal, non-productive, accompanied by sneezing, nasal discharge or blockage and itchy eyes and throat.[2]

Croup. Usually occurs in infants and young children; preceded by cold symptoms, has a harsh, barking quality and is often associated with difficulty in breathing and an inspiratory stridor.[2,4]

Pneumonia. A short, dry, painful cough; may be accompanied by fever, malaise, breathlessness, chills, headaches. Initially non-productive but rapidly becomes productive, with red-stained sputum.[2,5]

Subacute cough

Airway inflammation may follow a respiratory tract infection and result in a persistent, non-productive cough lasting for up to eight weeks. It usually resolves without treatment.[1,3]

Chronic cough

Chronic cough may be a result of a medical condition or medication being taken (see 'Medical and lifestyle history', this page).

D. Timing of cough

If the cough is worse in the morning and evening, consider bronchiectasis.[2]

If the cough is worse at night it could indicate pneumonia, asthma (especially in a child), postnasal drip, heart failure or gastro-oesophageal reflux disease.[5,6]

E. Medical and lifestyle history

Medical conditions that may contribute to chronic cough include:

- *Chronic bronchitis.* Usually due to cigarette smoking, the most common cause of chronic cough.[3,5,6]
- *Upper airway cough syndrome (postnasal drip syndrome).* May be due to allergic or vasomotor rhinitis, chronic sinusitis, post-infectious rhinitis, rhinitis medicamentosa or pregnancy-associated rhinitis. Characterised by frequent clearing of throat, cough when laughing or talking for prolonged periods and exacerbation of cough when lying down.[1,3,6]
- *Asthma.* Accompanied by wheeze, chest tightness and shortness of breath; exacerbated by cold or exercise; worsens at night.[1,3,6]
- *Gastro-oesophageal reflux disease.* Symptomatic heartburn occurs in only a minority of those affected.[1,3,6]

Other causes of chronic cough are drugs (ACE inhibitors, beta blockers, NSAIDs), pertussis, tuberculosis, bronchiectasis, heart failure, carcinoma of the lungs (associated symptoms may include dyspnoea, weigh loss, fatigue), interstitial lung disease, and psychogenic cough.[1-6]

Select appropriate action

F. The need to refer

Triggers for referral include[2,4]:

- duration longer than three weeks, although, postnasal drip and hay fever can last for more than three weeks and may not necessitate referral if successfully managed
- chest pain (possible cardiovascular cause)
- suspected whooping cough or croup
- wheeze and/or shortness of breath (possible asthma)

- sputum
  - thick, yellow or green (possible bronchiectasis or bronchitis)
  - blood stained (possible lung cancer or TB)
  - rust coloured (possible pneumonia)
  - frothy and pink–red (possible heart failure)
- recurrent nocturnal cough (possible asthma)
- pain on inspiration (possible pleurisy or pneumothorax)
- suspected adverse drug reaction
- cough that recurs on a regular basis.

Recommend treatment

G. Treatment options

Antitussives (cough suppressants)

Antitussives have a limited role in the treatment of acute non-productive cough. They should not be used in productive coughs and should be avoided in asthma and chronic obstructive pulmenary disease. They include dextromethorphan, and pholcodine (generally the antitussives of choice if a cough suppressant is deemed necessary), codeine and dihydrocodeine.[2,5,7,8]

Dextromethorphan may contribute to serotonin syndrome and should not be taken with serotonergic medications or with, or within 14 days of, a imonoamine oxidase inhibitor.[7–9]

Expectorants

Expectorants' efficacy is still unproven. They include guaifenesin, ammonium salts and senega. Ammonium salts are contraindicated in hepatic and renal impairment.

Use of cough mixtures containing both an antitussive and an expectorant is not recommended.[2,8]

Other Ingredients

Other ingredients in cough medicines include:

- *Bromhexine.* A mucolytic bromhexine may reduce frequency and duration of exacerbations in some patients with chronic bronchitis or chronic onstructive pulmonary disease.[8] It may disrupt the gastric mucosal barrier, so should be used with caution in patients with a history of peptic ulcer disease.[7–9]
- *Antihistamines*. non-sedating antihistamines are less effective because of their less pronounced anticholinergic actions. May be useful if cough is associated with postnasal drip or allergic rhinitis but avoid if cough is productive (risk of viscid mucus plugs).[8]
- *Decongestants*. These may be useful if patient has nasal congestion, but should otherwise be avoided.[8] Contraindicated in hypertension, hyperthyroidism, coronary heart disease, diabetes and with concurrent imonoamine oxidase inhibitors.[7–9]

H. Treating cough in children[2,4,5,8,10–12]

Recent information suggests that cough medication for children is no better than placebo. The function of the cough reflex is to clear secretions from the respiratory tract and retention of these secretions may lead to potentially harmful airway obstruction. Rarely, a child may become exhausted or have insomnia or repeated vomiting due to cough. In these circumstances the use of a cough suppressant may be helpful. The following guidelines should be followed:

- Medication should be supplied only once it has been established that there is no underlying condition requiring referral and/or specific therapy.
- Cough and cold medicines containing sedating antihistamines, cough suppressants, expectorants or decongestants should not be given to children under two years of age.
- Preparations containing camphor should be avoided in children: there is a risk of adverse effects on the central nervous system such as seizures or respiratory failure.
- Alcohol-containing syrups should not be used: alcohol may sedate the child and suppress the cough reflex.
- Some cough syrups may contain a high level of sugar; if given in excess, they can cause osmotic diarrhoea.
- Demulcents provide a safe alternative; paediatric simple linctus may provide a placebo effect in children (however, its high syrup content should be noted).
- Syrups should not be given to exclusively breastfed infants: the sugar they contain may suppress an infant's appetite for breast milk.

Provide counselling supported by written information

I. How to use the medication

Once a medicine is selected the patient should be told how to use it, the correct dose, and any specific precautions[8]:

- *Dextromethorphan.* Adult dose is 10–20 mg every four hours, to a maximum of 120 mg daily. Increases the likelihood of serotonin toxicity when used with other serotonergic drugs, so avoid or use with caution.
- *Codeine.* Adult dose is 15–30 mg three to four times a day.
- *Dihydrocodeine.* Adult dose is 10–20 mg three to four times a day.
- *Pholcodine.* Adult dose is 10–15 mg three to four times a day.
- *Bromhexine.* Adult dose is 8–16 mg three times a day.

J. Adverse effects[7–9]

- *Dextromethorphan.* Generally non-sedating and has few side effects.
- *Codeine, dihydrocodeine.* May cause constipation, induce drowsiness and enhance effects of central nervous system depressants.
- *Pholcodine.* Less likely than codeine or dihydrocodeine to cause constipation and respiratory depression; also less likely to produce dependence.
- *Guaifenesin.* Generally well tolerated; nausea and vomiting are the most common adverse effects.
- *Ammonium salts.* Large doses may cause nausea and vomiting; ammonium chloride produces a transient diuresis and acidosis.
- *Antihistamines (sedating).* Have anticholinergic drying action on mucous membranes; may result in formation of viscid mucus plugs.
- *Bromhexine.* Adverse effects include nausea, vomiting, diarrhoea and allergic reactions.
- *Decongestants.* May cause cardiovascular and central nervous system stimulation.

K. Non-pharmacological therapies

Demulcents—e.g. glycerol, simple linctus, lemon and honey—soothe and coat the pharynx. They are particularly suitable for children and pregnant women because of their lack of active ingredients (although their effectiveness may be largely due to a placebo effect).[2,4,7,8,10]

Steam inhalations can promote expectoration. There is no evidence that addition of substances such as menthol or eucalyptus to inhaled steam provides any additional benefit; however, they may provide a placebo effect. They should be used at a dilution of 5 mL to approximately 500 mL of hot (not boiling) water. Alternatively, steam may be inhaled during a hot shower.[4]

Oral intake of fluids is accepted as a safe and beneficial method of assisting expectoration.[10]

L. Additional information

Provision of the *Coughs* Self Care Fact Card or other printed information for consumers is appropriate.

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Diarrhoea guide

Assess patient's needs

A. Patient characteristics

The age and pregnancy status of the patient should be determined because these will affect the advice provided.

Management of dehydration associated with diarrhoea in children is described in 'Gastroenteritis in children', Section D.

B. Symptoms

'Diarrhoea' refers to an increase in faecal discharge, in terms of volume, fluid quantity and/or frequency.[1] The normal bowel habit can range between two motions a week and three motions a day, so deviations from an individual's usual pattern may be more important than the number of bowel motions a day.[2]

Faecal incontinence (the involuntary loss of anal sphincter control that leads to the release of faeces) may be described by patients as diarrhoea. This is most commonly caused by constipation and faecal impaction but may also result from a stroke, advanced dementia, or a number of other conditions.[3] It is important to differentiate this from diarrhoea in order to ensure appropriate assessment and management.

C. Symptom duration

Acute diarrhoea lasts less than 14 days and is often caused by infectious agents, drugs or food toxins.[4]

Diarrhoea is considered chronic if it lasts longer than 14 days or if there are repeated episodes of diarrhoea each lasting less than 14 days. Chronic diarrhoea is often indicative of an inflammatory process.[4]

D. Medical history

Diarrhoea is a non-specific symptom of a wide range of gastrointestinal disorders, including viral, bacterial and protozoal gastrointestinal infections, adverse drug reactions, lactose intolerance, irritable bowel syndrome, spurious diarrhoea (constipation with overflow), inflammatory bowel disease, gastrointestinal malignancy and a variety of malabsorption syndromes.[2]

Medications commonly implicated in causing diarrhoea include[1,2]:

- acarbose
- antibiotics—particularly amoxycillin plus clavulanate, erythromycin, clindamycin
- colchicine
- cytotoxic agents
- digoxin
- food and drug additives—sorbitol, mannitol, fructose, lactose
- laxatives
- magnesium-containing antacids
- metformin
- NSAIDs
- orlistat
- protease inhibitors, especially nelfinavir
- quinidine.

Excessive alcohol intake and abuse of laxatives can also be causes of diarrhoea. Discreet counselling should be used to direct the person to a doctor or other appropriate support.[1]

E. Lifestyle factors

Diarrhoeal pathogens are generally transmitted via the oral–faecal route. Diarrhoea due to viruses and bacteria usually develops within one to three days of contact with the infected person, food or surface. Diarrhoea due to parasites usually takes five to 15 days to develop. However, the source of infection often cannot be identified, even with these time frames as a guide.

Childcare centres are common sources of diarrhoeal pathogens. Recent travel, to developing countries in particular, may also be indicative of the source of infection.

Select appropriate action

F. The need to refer

Referral for further investigation is required when diarrhoea is chronic, or when it is accompanied by the following symptoms[2]:

- constipation alternating with diarrhoea
- blood, mucus, or both, in the stools
- high fever

- abdominal distension or signs of an abdominal mass
- marked abdominal pain
- unintentional weight loss
- moderate to severe dehydration.

Referral is also recommended:

- for all infants less than 6 months of age and elderly people (due to increased risk of dehydration)
- when the patient has recently returned from overseas travel
- when an infection outside the gastrointestinal tract is suspected
- when the patient has other chronic medical conditions that require management (e.g. diabetes)
- where laxative misuse is suspected (e.g. in an individual with an eating disorder).

Recommend treatment

G. Goals of therapy

The goals of therapy should be to:

- determine the specific aetiology and treat appropriately
- relieve the symptoms and re-establish normal stools
- avoid complications such as dehydration.

H. Treatment options

Treatment of the underlying disorder and fluid replacement to correct dehydration and electrolyte imbalance are the primary aims in the management of diarrhoea.

Oral rehydration solutions are the best method of treating dehydration in all but severe cases.[1]

Antimotility agents available include:

- *Diphenoxylate*. An opiate derivative with central nervous system effects similar to those of other opioids (e.g. dependence, sedation). It is combined with atropine to limit abuse potential: atropine has minimal therapeutic effect at this dose but in excess causes dry mouth and urinary retention.
- *Codeine*. Shares the properties of other opioids.
- *Loperamide*. An anticholinergic and opiate agonist but with limited central nervous system effects.

Symptomatic treatment with antimotility agents should be reserved for short periods of social necessity (e.g. for work or when travelling). Antimotility agents should not be used where severe diarrhoea may be caused by invasive organisms (e.g. *E. coli*, salmonella, pseudomembranous colitis). They delay clearance of organisms, increasing the risk of systemic invasion, and may also induce local complications such as toxic megacolon.[5] They should also be avoided in severe inflammatory bowel disease.

Provide counselling supported by written information

I. How to use the medication

Once a medicine is selected, the patient should be told how to use it, the correct dose, and any specific precautions[1]:

- *Oral rehydration solutions*. Dissolve powder or tablets in the volume of water directed on the packet; use only water as the diluent; sip slowly and frequently while symptoms persist.
- *Diphenoxylate*. Use for symptomatic treatment of acute diarrhoea; avoid alcohol and other sedating medications.
- *Codeine*. Use for symptomatic treatment of acute diarrhoea; avoid alcohol and other sedating medications.
- *Loperamide*. Use for symptomatic treatment of acute diarrhoea.

J. Adverse effects

The patient needs to know the most common and important adverse effects of the therapy selected:

- *Oral rehydration solutions*. Well tolerated.
- *Diphenoxylate*. Drowsiness, abdominal pain, bloating, nausea, vomiting and constipation are common.
- *Codeine*. Drowsiness, abdominal pain, bloating, nausea, vomiting and constipation are common. Long-term use may result in addiction.
- *Loperamide*. Abdominal pain, bloating, nausea, vomiting and constipation are common.

K. Prevention

To reduce the risk of transmitting diarrhoeal pathogens, encourage regular handwashing, particularly after defecation and handling of faeces (e.g. changing a nappy) and before preparing and eating food.

Food poisoning can be prevented by following the recommendations of the Food Safety Information Council (see www.foodsafety.asn.au). The website includes information on how to safely handle, store and cook food.

Children with diarrhoea should be excluded from childcare centres and preschools to prevent further transmission. See 'Exclusion periods for infectious conditions', Section F.

When travelling overseas, drink only boiled water or reputable commercially bottled beverages, hot coffee and tea (without milk), boiled milk, or alcohol. Choose fresh, well-cooked food that is served steaming hot. For further tips see 'Travel medicine', Section F.

L. Follow-up advice

Continue to monitor for signs of dehydration—in severe cases these can include dry mouth, thirst, sunken eyes, tiredness, deep breathing, rapid pulse and low blood pressure—and other symptoms that suggest the need for referral.

Further investigation may be required if symptoms persist for more than 48 hours in adults and 24 hours in children or the elderly, despite use of the recommended therapy.

Provision of the *Vomiting and diarrhoea* Self Care Fact Card or other printed information for consumers would be appropriate.

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Gastro-oesophageal reflux disease guide

Assess patient's needs

A. Patient characteristics

The age (in particular, whether >55 years or <18 years) and pregnancy status of the patient should be determined because these will affect the advice provided.

B. Symptoms

Symptoms typical of gastro-oesophageal reflux include[1]:

- heartburn—a burning feeling rising upwards from the stomach or lower chest, typically provoked by meals or bending, straining or lying down
- regurgitation—may be mistaken for vomiting
- waterbrash—sudden salivation as a result of oesophageal acidification.

Atypical symptoms include[1]:

- cardiac-type chest pain
- non-specific dyspepsia, nausea
- belching, bloating
- hoarseness
- sore throat
- cough.

Alarm symptoms include[1,2]:

- dysphagia—suggestive of severe or complicated oesophagitis)
- odynophagia (painful swallowing)
- nocturnal choking
- haematemesis (vomiting of bright red blood)
- unintentional weight loss
- chest pain radiating to chin or left shoulder.

C. Symptom frequency

Management of intermittent or occasional symptoms (once a week or less) may require only avoidance of precipitating factors. If drug treatment is required antacids, or H_2 antagonists when necessary, are generally recommended.[2]

For individuals who experience symptoms on two or more days a week, regular therapy may be indicated.[2]

D. Prior treatment

Where the goals of initial therapy are achieved, medication may be reduced or ceased and symptoms controlled with less intensive therapy. Individuals with more severe or frequently relapsing disease (e.g. occurring on most days) require continuous therapy and should be referred.[3]

E. Medical and lifestyle history

Reflux symptoms may be precipitated by[1,2,4,5]:

- dietary factors—e.g. chocolate, fats, spices, large meals or alcohol
- lying down—particularly within three hours of eating a meal
- medications that relax the lower oesophageal sphincter—e.g. anticholinergics, theophylline, dopaminergic agents, calcium channel blockers, nitrates, beta-adrenergic agonists, progesterone, benzodiazepines, tricyclic antidepressants, and sedating antihistamines. Oesophagitis may be exacerbated by aspirin, NSAIDs, bisphosphonates, iron salts, potassium chloride, quinidine, tetracycline, doxycycline and vitamin C.
- overweight and obesity
- smoking.

Heartburn is common in pregnancy and usually resolves after delivery. Because drugs can cause harm to a fetus at any time during pregnancy, medicines advice should be consistent with Australian Drug Evaluation Committee (ADEC) pregnancy categories or be obtained from pregnancy drug information centres. The suitability of drug use during lactation may also need to be considered.

Existing medical conditions and other medications being taken should also be considered.

Select appropriate action

F. The need to refer

Referral for further investigation is required in the following circumstances:

- Symptoms are non-specific or atypical of reflux disease or are mixed with gastroduodenal symptoms.

- Alarm symptoms are present.
- Symptoms occur daily.
- The patient has a family history of gastrointestinal cancer or is on long-term NSAID therapy.[3]
- Symptoms are inadequately controlled following a two-week trial of initial therapy.[2,3]

When the patient is aged over 55 years and is experiencing first-time or longstanding, frequent and troublesome symptoms, or the patient is aged less than 18 years, referral for further investigation may be required.

Recommend treatment

G. Treatment options

Patients who have mild typical reflux symptoms and no alarm symptoms may be given a trial of therapy without further investigation. Diagnosis can be confirmed through a clear symptom response to therapy.[1]

Initial therapy with a proton pump inhibitor (PPI) is appropriate for the majority of patients. If a standard daily dose results in symptom control within one week, the diagnosis will be confirmed.[1] In 80% of people, pantoprazole 20 mg daily will lead to complete relief of heartburn, acid regurgitation and pain on swallowing at two weeks. Symptom relief is not immediate, so adjuvant therapy with an antacid may be required initially.

Following a satisfactory response, intermittent, symptom-driven therapy with either an H_2 antagonist or PPI should be trialled.[1]

The traditional step-up approach from trialling antacids, then H_2 antagonists, then PPIs may take weeks to achieve symptom control. Oesophageal healing will be slow and diagnosis may still be uncertain.[1]

Provide counselling supported by written information

H. How to use the medication

Once a medicine is selected, the patient should be told how to use it, the correct dose, and any specific precautions[6]:

- *Pantoprazole.* Recommended dose for initial therapy is 20 mg daily for two weeks.
- *H_2 antagonists.* Due to risk of accumulation, consider dose reduction in severe renal impairment.
- *Antacids.* optimum effect if taken one to three hours after meals; separate administration with other medications by at least two hours because the antacids may affect their absorption.

I. Goals of therapy

The goals of treating reflux are to[1,6]:

- relieve symptoms and restore quality of life
- heal oesophagitis if present
- reduce the risk of complications.

A daily PPI at a standard dose will usually lead to symptom control in one week.

J. Adverse effects

The patient needs to know the most common and important adverse effects of the therapy selected[6]:

- *Pantoprazole.* Generally well tolerated; headache, nausea, vomiting, diarrhoea, abdominal pain, constipation, and flatulence most commonly reported.
- *H_2 antagonists.* Generally well tolerated; cimetidine has been associated with anti-androgenic effects (e.g. gynaecomastia, galactorrhoea, impotence, decreased libido) and more frequent central nervous system effects (e.g. dizziness, tiredness, confusion).
- *Antacids.* Aluminium-containing antacids commonly cause constipation; calcium-containing antacids commonly cause constipation, belching, flatulence and abdominal distension; magnesium-containing antacids commonly cause diarrhoea and belching.

K. Lifestyle modifications

Although lifestyle changes have not been comprehensively evaluated in clinical trials, some lifestyle modifications may be beneficial[1,4]:

- *Dietary modification.* Strict dietary control is unnecessary. Foods that are commonly associated with reflux (e.g. fatty and spicy foods, cola, excessive coffee, tomato and orange juice) should be avoided. Avoiding late, large meals, lying down shortly after meals and wearing tight fitting garments after meals may also help. Consuming excessive amounts of alcohol and low pH beverages (e.g. red wine) may exacerbate symptoms.
- *Bed-head elevation.* Patients with nocturnal or laryngeal symptoms may benefit from raising the bed-head or using a wedge pillow.

- *Medications.* Refer to E for medications that may exacerbate reflux and oesophagitis.
- *Obesity.* Improvement in reflux symptoms following weight loss is variable; however weight loss in obese patients should still be encouraged.
- *Smoking.* Smoking aggravates reflux; cessation should be encouraged.

L. Follow-up advice

Further investigation will be required if the individual exhibits any alarm symptoms or does not experience adequate symptom control after initial treatment.

Provision of the *Heartburn and Indigestion* Self Care Fact Card or other printed information for consumers is appropriate.

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Hay fever guide

Assess patient's needs

A. Patient characteristics

The age (in particular whether <12 years) and pregnancy status of the patient should be determined because these will affect the advice provided.

B. Symptoms

The classic symptoms of hay fever, or allergic rhinitis, are[1-4]:

- clear rhinorrhoea and nasal congestion
- sneezing
- watery, itchy eyes
- itchy nose, ears or throat.

Other possible symptoms include:

- sinus pressure
- headache
- dark circles under the eyes ('allergic shiner')
- postnasal drip
- fatigue and lethargy
- decreased sense of smell and taste.

C. Timing and severity of symptoms

Hay fever (both perennial and seasonal) is classified according to the timing and severity of the symptoms[2]:

Timing of symptoms

- *Intermittent.* Symptoms present for less than four days a week or less than four weeks at a time.
- *Persistent.* Symptoms present for more than four days a week and more than four weeks at a time.

Severity of symptoms and quality of life

- *Mild.* No impairment of sleep, daily activities, leisure or sport, school or work; no troublesome symptoms.
- *Moderate to severe.* One or more of the following present:
  - impairment of sleep
  - impairment of daily activities, including leisure, sport, school or work
  - troublesome symptoms.

D. Prior treatment

Prior use of, and the patient's response to, hay fever medications will help to determine either the need for referral or the type of medication recommended.

E. Medical and lifestyle history

The presence of one or more of the following risk factors will make a diagnosis of hay fever more likely[3,4]:

- Family history is the primary risk factor for developing allergic rhinitis. If both parents have allergic rhinitis, there is a 75% chance of their offspring developing it. If only one parent has it, the risk decreases to 50%.
- Allergies and conditions commonly associated with allergic rhinitis include eczema, asthma and food allergies.
- Exposure to cigarette smoke may increase sensitivity to allergens.
- Occupational or other exposure to the following allergens increases the risk of developing hay fever:
  - seed dust
  - chemicals
  - rubber latex
  - wood dust
  - animal dander
  - storage mites
  - textile dust
  - certain foods and spices.

Select appropriate action

F. The need to refer

Referral triggers include[2,4,5]:

- symptoms not responding to antihistamines and intranasal corticosteroids (INCS)
- patient's quality of life being seriously affected
- the nasal obstruction is unilateral or is present without rhinorrhea
- symptoms such as facial pain (may indicate sinusitis), anosmia (impaired sense of smell), recurrent nosebleeds, hearing loss or earache (may indicate otitis media)
- symptoms of infection—mucopurulent discharge, sore throat, myalgia, fever

- symptoms of asthma—wheezing, shortness of breath
- unacceptable side effects of treatment
- child under 12 if suspected first episode of allergic rhinitis
- pregnant or breastfeeding woman.

Recommend treatment

G. Treatment options

Table E.3 Allergic rhinitis treatment algorithm[5,6]

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Frequency of symptoms			
Intermittent		Persistent	
↓			
Severity of symptoms			
Mild	Moderate to severe	Mild	Moderate to severe
↓	↓	↓	↓
First-time treatment			
Antihistamine	INCS	INCS	INCS
↓	↓	↓	↓
If incomplete or poor response			
Add INCS	Add antihistamine	Add antihistamine	Immunotherapy

In all patients consider:

- intranasal saline—to counteract drying from using INCS; also has mucus-diluting properties
- anti-allergy eyedrops—if allergic conjunctivitis persists despite treatment
- ipratropium bromide—effective in cases of intractable rhinorrhoea.

Avoid the following:

- intranasal decongestants—except for short-term use
- oral decongestants where contraindicated—e.g. hypertension, coronary artery disease
- sedating antihistamines in patients with closed angle glaucoma, increased intra-ocular pressure, pyloroduodenal obstruction, bladder neck obstruction or hyperthyroidism.[6]

Provide counselling supported by written information

H. How to use the medication

Once a medicine is selected the patient should be told how to use it, the correct dose and any specific precautions[4,6]:

- INCS have a slow onset of action, and should be used continuously for maximum effect. A topical or oral decongestant may be used concomitantly to provide symptom relief during the first 24 to 48 hours.
- patients should be advised to shake the device and to clear the nasal passages before using an INCS (the use of a saline nasal spray may be helpful).
- for more detailed instructions on the use of nasal sprays, see 'Extemporaneous dispensing', Section A.
- to avoid rebound congestion, intranasal decongestants should not be used for longer than four days.

I. Adverse effects

The patient needs to know the most common and important adverse effects of the medicine[4–7]:

- First-generation antihistamines enter the central nervous system, causing sedation. They may also cause anticholinergic effects such as blurred vision, dry mouth and tachycardia.
- The newer, less-sedating antihistamines have fewer adverse effects than the older sedating antihistamines.
- Cetirizine is the most likely of the newer antihistamines to cause sedation.
- Side effects of INCS include nasal stinging, sore throat, dry mouth, cough and, occasionally, nasal bleeding.

J. Prevention

Suggest strategies to minimise exposure to allergens. For example[3,8]:

- Stay inside during the morning hours, when pollen counts are highest.
- Avoid outdoor activities when trees, flowers or moulds which trigger the allergy are blooming.
- Take a shower after outdoor exposure to remove pollen that is stuck to hair and skin.
- Keep the windows of the house and car closed to exclude pollen.

- Prevent mould and mildew growth by using an air conditioner to reduce indoor humidity during the warmer months; clean air conditioner filters regularly.
- Use vacuum cleaners and air conditioners with HEPA (high-efficiency particulate air) filters to trap allergens.
- Cover pillows and mattresses with impermeable covers to reduce exposure to house dust mites.
- Wash bedding weekly in hot water (>55 °C).
- Reduce dust-collecting furnishings such as curtains, bed skirts, carpeting and stuffed animals, especially in the bedroom.
- Vacuum frequently.
- Exposure to smoke, fumes and strong perfumes, rapid changes in temperature, and outdoor pollution can be non-specific triggers in patients with allergic rhinitis and should, if possible, be avoided if they seem to aggravate symptoms.

K. Additional information

Provision of the *Hay fever* and/or *Sinus Problems* Self Care Fact Cards or other printed information for consumers is appropriate

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Assess patient's needs

A. Patient characteristics

The advice provided may depend on the patient's age (in particular, <18 years or >50 years), weight[1], and pregnancy or breastfeeding status.

B. Symptoms

There are different types of headache and a patient may be suffering from more than one type.[1–5] The most common types of primary headache are tension-type and migraine headaches.[5] Other types include sinus, cluster, ice-pick and medication over-use headache.[1–4]

Tension-type headache symptoms include[1,2,4]:

- bilateral location
- feeling of heaviness, pressure or tightness that may extend like a band around the head
- non-throbbing
- no aggravation with routine activity
- rarely severe enough to prevent simple activity
- photophobia or phonophobia (but not both)
- duration from 30 minutes to seven days.

Migraine headache symptoms include[1,2,4]:

- unilateral location (often)
- throbbing
- worsening pain with routine activity
- pain limiting activity
- nausea and/or vomiting
- photophobia and phonophobia
- duration commonly four to 72 hours.

Migraine may be preceded or accompanied by an aura. Aura symptoms may last for up to an hour and can include visual disturbance, 'pins and needles', numbness, dizziness and speech disturbances.[1,2,4]

Migraine symptoms may differ in children:

- Headache may be less pronounced, but other symptoms (e.g. nausea, stomach cramping, photophobia, phonophobia and diarrhoea) are more common.
- Children tend to have bilateral migraines.
- Migraine attacks in children are often shorter than in adults (may last as little as one to two hours).[2]

Medication over-use headache symptoms include[1–4]:

- headache on more than 15 days a month
- regular use of headache medication for more than three months
- simple analgesics used on 15 or more days a month
- any acute migraine drugs, including combination analgesics, used on 10 or more days a month.

Warning signs and symptoms that suggest secondary headache due to a serious underlying organic cause include[1,2,4]:

- confusion
- drowsiness
- vomiting
- neurological signs persisting between headaches
- fever
- sudden onset
- recent onset in a patient who is aged over 50 years or who is young and obese
- recent onset with cough, exertion or sexual activity
- headache that wakes patient
- head injury
- severe and debilitating pain.

C. Symptom frequency

Occasional tension and migraine headaches may be managed with simple analgesics and/or non-drug strategies (refer to G, K).[1,2,4]

Headaches increasing in frequency and headaches occurring on more than 15 days a month may require referral (refer to B, F).[2,4,7]

D. Trigger factors

Factors that can trigger migraines and other headaches include[2,4,6,8,9]:

- foods—including chocolate, citrus fruit, caffeine (intake or withdrawal), aspartame, food additives (e.g. monosodium glutamate, nitrites, phenylethylamine), tyramine-containing foods (e.g. red wine, aged cheese)
- Drugs—including analgesic overuse or withdrawal, calcium channel blockers, dipyridamole, nitrates, NSAIDs (esp. indomethacin), oestrogens (e.g. OCP), phosphodiesterase-5 inhibitors (sildenafil,

tadalafil, vardenafil), proton pump inhibitors, alcohol and nicotine
- head trauma
- stress, anxiety
- sensory stimulation—e.g. glare, smells, noise
- eye strain
- hormone changes—e.g. menstruation, pregnancy
- dehydration
- hypoglycemia (delayed or missed meals)
- strenuous physical activity
- inadequate sleep
- jaw tension and teeth grinding
- weather changes (barometric pressure)
- smoke, particularly from cigarettes
- poor posture
- infection.

Existing medical conditions should also be considered.

E. Prior treatment

Establish response to previous treatments. Optimal treatment for migraine may need to be refined over a series of attacks.[2]

Select appropriate action

F. The need to refer

Refer for further investigation in the following situation:[2,4,7–9]

- warning symptoms occur with headache
- medication over-use headache is suspected
- the frequency or severity of headaches is rapidly escalating
- a new or different type of headache occurs
- the patient is aged under 18 years.[2]

Recommend treatment

G. Treatment options

Consider patient characteristics, existing medical conditions and previous treatment response.

Tension-type or migraine headache

- Paracetamol, aspirin and NSAIDs are useful first-line treatments in adults. Soluble formulations may be preferable: patients with migraine have impaired absorption due to gastric stasis.[1–4,6,7]
- Avoid aspirin in children under 18 years. Use paracetamol or ibuprofen instead.[1–3]
- Avoid combination analgesics containing codeine. They may not be more effective than adequate doses of simple analgesics, may have more adverse effects and can slow absorption of other medications.[1–4,6]
- No studies have examined the use of antihistamines (e.g. doxylamine) in tension-type headache or migraine. A sedating antihistamine may be useful if bed rest is desired.[1,4]
- Consider a product containing metoclopramide for nausea or if simple analgesics do not reliably give relief from migraine.[1,3,4,6,7]
- Physical therapy such as massage, stretching, heat and postural correction can relieve tension-type headache.[1,2,4]
- Advise a patient with migraine to rest in a quiet, darkened room and avoid movement or activity (including reading or watching TV).[1–4]

If simple analgesics fail, a migraine-specific agent may be needed.[1–4,6,7]

Medication over-use headache

Treatment involves withdrawal of the over-used agent under medical supervision.[2,3,4]

Provide counselling supported by written information

H. How to use the medication

Once a medicine is selected the patient needs to know how to use it, the correct dose, and any specific precautions[3]:

- *Paracetamol.* Do not take more than 4 g/24 hours (8 x 500 mg tablets or 6 x 665 mg tablets). Paracetamol is contained in many products: overdosing may be prevented by carefully checking the ingredients in all products.
- *Aspirin and NSAIDs.* Use only one NSAID at a time (excluding low-dose aspirin). Response to NSAIDs varies and it may be necessary to try a number of agents to determine the one that is most effective; use the lowest effective dose for the shortest possible time.
- *Metoclopramide.* Available in combination preparations with paracetamol; avoid high doses in the elderly and adolescents (under

20 years of age) due to increased risk of adverse effects.

- *Sedating antihistamines.* Response to sedating antihistamines varies. It may be necessary to try a number of agents to determine the one that is most effective and best tolerated. The elderly are at greater risk of adverse effects and may require lower doses. Avoid alcohol and other sedating medications.

I. Adverse effects

The patient needs to know the most common and important adverse effects of the therapy selected[3]:

- *Paracetamol.* There is an increased risk of liver toxicity with doses greater than those recommended.
- *Aspirin and NSAIDs.* Gastrointestinal effects, headache, dizziness, salt and fluid retention, and hypertension are common. Cease therapy and see a doctor if there are signs of gastrointestinal ulceration or bleeding (black stools or dark, coffee-coloured vomit), NSAID-induced asthma (difficulty in breathing) or cardiovascular effects (swollen ankles).
- *Metoclopramide.* Drowsiness, dizziness, restlessness and headache are common.
- *Sedating antihistamines.* Sedation, dizziness, anxiety, tinnitus, blurred vision, tremor, gastrointestinal effects, dry mouth and cough are common.

J. Lifestyle modifications

- Patients may benefit from keeping a headache diary to help identify trigger factors, monitor headache frequency and severity, and monitor therapy.
- Avoiding trigger factors and engaging in behavioural interventions such as stress reduction, relaxation and cognitive behavioural therapy may help prevent tension-type headache and migraine.[2–4]

K. Follow-up

Advise patient to consult a doctor if[1,2,4,7–9]:

- Warning signs or symptoms develop.
- Migraine persists for more than three days.

Provision of the *Headache*, *Migraine*, and/or *Pain Relievers* Self Care Fact Cards or other printed information for consumers is appropriate.

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Head lice guide

Assess patient's needs

A. Patient characteristics

The age (in particular, whether >12 months) and pregnancy status of the patient should be determined because these will affect the advice provided.

B. Symptoms

Many cases of head lice (*Pediculus humanus capitis*) are asymptomatic. Pruritus, resulting from sensitisation to louse salivary or faecal antigens, is the most common symptom of infestation but does not necessarily indicate active infestation. Persistent scratching can cause lesions to develop, which may give rise to secondary infections and/or swollen lymph glands.

C. Lice detection

Diagnosis of lice infestation is confirmed by observing a louse on the scalp. Use the 'wet combing' method (also known as the 'conditioner and comb' method):

- Apply conditioner to dry hair, covering each hair from root to tip. The conditioner stuns the lice and immobilises them for about 20 minutes.
- Detangle the hair and evenly distribute conditioner using an ordinary comb.
- Divide the hair into 3–4 cm sections and comb each section using a fine-toothed comb.
- After each stroke wipe the conditioner off the comb onto a paper towel and inspect for head lice and eggs.
- Repeat the combing at least twice for each section.
- Thoroughly rinse the hair.

Head lice are 1–4 mm long, and their colour ranges from nearly colourless (when they hatch) to reddish brown (after feeding).

D. Egg detection

Eggs located within 6 mm of the scalp are usually viable, suggesting an active infestation. Most eggs found further than 1 cm from the scalp will be empty casings or dead. A viable egg will 'pop' when squashed between the fingers.

Dandruff and other objects in the hair can be distinguished from eggs by being easily removed from the hair.

E. Prior treatment

If live lice are found in combings after the correct application of a treatment, the head lice are either resistant to the product used or re-infestation has occurred. The person should be retreated as soon as possible, using a product with a different active ingredient.

Most treatment failures, however, are due to inappropriate contact times or application methods, or the use of unproven products.

Select appropriate action

F. The need to refer

Refer to a medical practitioner in the following situations:

- The diagnosis is unclear.
- There are signs of a secondary infection (e.g. weeping, crusting of skin, swollen glands, fever).
- Topical pediculicides have failed and antibiotics might be required.

Recommend treatment

G. Treatment options

Chemical preparations can be divided into four groups[2]:

- permethrin 1%—chemical treatment of choice in pregnancy and breastfeeding
- maldison—avoid in pregnancy and infants <12 months
- pyrethrins with piperonyl butoxide
- herbal products—essential oils such as melaleuca, lavender, eucalyptus and rosemary. One herbal product (*MOOV* head lice solution, containing eucalyptus oil 10%w/w) has been evaluated and registered by the Therapeutic Goods Administration for the treatment of head lice.

Permethrin and maldison are ovicidal as well as pediculicidal.

Preparations are available in a variety of formulations (e.g. foam, shampoo, lotion) which require specific application methods and contact times. Consumer preference should be considered when selecting a product.

If topical pediculicides are ineffective, trimethoprim+sulfamethoxazole may be prescribed.[3]

Non-chemical treatment options include:

- wet combing—must be continued for at least 10 days
- electronic combs—pediculicidal activity only.

Provide counselling supported by written information

H. General directions for using treatments

- Protect eyes with a towel or face cloth.
- Wear gloves when applying the product and wash hands thoroughly after use.
- Apply product all over head and coat all hairs from roots to tips.
- If using a lotion, apply to dry hair. If using a shampoo, wet hair with the least amount of water possible.
- Leave preparation on hair for the required time.
- Dry hair with a towel, not a hair dryer: heat may inactivate the product.
- Do not rewash hair for one to two days after treatment.
- Treatment should be repeated after seven to 10 days.
- In between treatments, wet combing should be done to remove eggs. Wet combing should be repeated weekly for several weeks after cure to detect recurrence.

Pharmacists should always refer to product-specific information when providing advice on how to use treatments.

If wet combing is the only treatment being undertaken, it needs to be repeated every two days until no head lice have been seen for 10 consecutive days.

I. Treatment expectations

Wet combing daily for 10 to 14 days has about a 40% success rate.[3]

Chemical resistance is common, so killing of lice should be checked the day following treatment. If successful, this treatment can be repeated as directed. If not successful, a different treatment should be used as soon as possible.

J. Adverse effects

The patient should be advised of the most common and important adverse effects of the treatment selected[2]:

- *All chemical treatments.* The itch, redness and swelling that normally accompany lice infestation may be temporarily increased; using more than the recommended amount increases the risk of irritation.
- *Maldison.* Using more than the recommended amount also increases the risk of systemic absorption and toxicity (e.g. gastrointestinal, and central nervous system effects, bradycardia, muscle twitching, pinpoint pupils).

K. Other action required

Head lice only live for up to 48 hours off the head. Eggs may survive for up to 10 days.

Wash pillow cases on hot cycle and combs and brushes in hot water (>60 °C). Place items that cannot be washed (e.g. hats) in a sealed plastic bag for at least two weeks.[4]

L. Prevention

Head lice treatments should not be used for prevention. When head lice are present in the community, simple measures for prevention include the following:

- Reduce head-to-head contact with other people.
- Carry out weekly hair and scalp checks.
- Comb frequently with nit combs.
- Avoid sharing brushes, combs, hats and pillows.
- Wash brushes and combs once a week in hot soapy water.
- Keep long hair tied back.
- Family and close contacts should be examined and treated if live lice are found.
- The school should be notified (but it is not necessary to exclude children from school after the initial treatment).

M. Additional information

It may be appropriate to reassure consumers:

- Head lice infestation is not a reflection of personal hygiene, home environment or social status. They do not prefer dirty hair.
- Head lice are not believed to be responsible for the spread of any infectious disease-causing organisms.

Provision of the *Head Lice* Self Care Fact Card or other printed information for consumers is appropriate.

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Smoking cessation guide

Assess patient's needs

A. Patient characteristics

The age (particularly if <12 years) and pregnancy and breastfeeding status of the person should be determined because these will affect the advice provided.

B. Assess nicotine dependence

Table E.4 Fagerström test for nicotine dependence[1]

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Questions	Answers	Score
1. How soon after waking up do you smoke your first cigarette?	Within 5 minutes	3
	6–30 minutes	2
	31–60 minutes	1
2. Do you find it difficult to abstain from smoking in public places?	Yes	1
	No	0
3. Which cigarette would you most hate to give up?	First one in the morning	1
	Any other	0
4. How many cigarettes a day do you smoke?	10 or less	0
	11–20	1
	21–30	2
	31 or more	3
5. Do you smoke more frequently in the morning?	Yes	1
	No	0
6. Do you smoke even though you are sick in bed for most of the day?	Yes	1
	No	0

Score: 0–2 = very low dependence.
3–4 = low dependence.
5 = medium dependence.
6–7 = high dependence.
8+ = very high dependence.

C. Prior attempts to quit

Awareness of the person's experience in previous attempts to quit will help to determine the advice provided.

D. Patient's readiness to quit

Determining a person's 'stage of change' enables a pharmacist to deliver the most appropriate assistance for a quit attempt. The stages of readiness to change are[1,2]:

- Pre-contemplation—unconcerned about smoking, not ready to change.

  Pharmacist: raise awareness of risks of smoking. Increased risk of:[1,3]

  – lung cancer
  – ischaemic heart disease
  – cerebrovascular disease
  – other cancers, including mouth, bladder, kidney, stomach, pancreas and cervix
  – respiratory problems, including COPD and emphysema
  – eye problems, including cataracts and age-related macular degeneration
  – wound infections and delayed healing.

- Contemplation—thinking about quitting.

  Pharmacist: emphasise benefits of quitting, risks of not quitting. Many adverse health effects from smoking decline rapidly after quitting[1,3]

  – 12 hours—almost all nicotine is out of the system.
  – 24 hours—blood level of carbon monoxide has dropped dramatically.
  – five days—most nicotine by-products are gone; sense of taste and smell improve.
  – one month—blood pressure returns to normal and immune system begins to recover.
  – two months—lungs no longer congested.
  – one year—risk of a heart attack is halved compared with that of a smoker.
  – 10 years—risk of lung cancer is less than half that of a smoker.
  – 15 years—risk of coronary heart disease is the same as a non-smoker.

- Preparation—planning to quit soon.

  Pharmacist: advise on quitting strategies.

- Action—has quit smoking in the past six months; high risk of relapse.

  Pharmacist: provide support; suggest strategies to prevent relapse.

- Maintenance—quit over six months ago.

  Pharmacist: provide counselling for long-term relapse prevention.

E. Medical history

- Cardiovascular disease, diabetes, and hepatic or renal impairment. If nicotine replacement therapy (NRT) is the chosen strategy, the person's doctor should be involved in the process.
- The presence of skin disorders, gastrointestinal disease, oral or pharyngeal inflammation, chronic throat disease, asthma, phenylketonuria or dentures may affect the form of NRT if NRT is the chosen quit strategy.

Select appropriate action

F. The need to refer

There are several triggers for referral[4]:

- The person has cardiovascular disease, diabetes, hepatic or renal impairment. NRT may be used but, because of the potential risks, the person's doctor should be involved in the process.
- The person is pregnant. For women unable to quit on their own, NRT may be recommended; the potential risks and benefits must be explained and understood and the doctor should be consulted.
- The person is <12 years of age.
- NRT is contraindicated or unsuitable and the person wishes to use an anti-smoking prescription medication (bupropion, varenicline). Contraindications for NRT include hypersensitivity to nicotine and age <12 years.

Recommend quit strategy

G. Consider options[1,2,4,5]

For NRT currently available in Australia, a Fagerström test score of:

- 1–3 = NRT may not be required (may consider 2 mg gum, lozenge or microtab)
- 4–5 = 2 mg gum, lozenge or microtab, patch or inhaler
- 6–7 = 4 mg gum, lozenge, microtab (x2) or patch
- 8+ = 4 mg gum, lozenge, patch or microtab (x2).

Patient characteristics influencing selection:

- *Pregnancy.* Oral forms of NRT are preferred; patches may be used if patient is suffering from nausea, but they should be removed at night.
- *Breastfeeding.* NRT can be used, but patches are not recommended; women should breastfeed just before using NRT.
- *Adolescents.* All forms of NRT can be used by smokers aged 12–18 years; pharmacist should check that the person is sufficiently nicotine dependent to warrant use of NRT, is committed to stopping smoking, and is willing to accept counselling. Maximum recommended duration of treatment is 12 weeks.
- Nicotine lozenges or sublingual tablets may be recommended for people who prefer an oral form of NRT but who cannot or do not wish to use nicotine gum.
- A nicotine inhaler may be useful for smokers who miss the hand-to-mouth action of smoking. Nicotine is absorbed through the oral mucosa, not the respiratory tract. Inhaler are contraindicated in people hypersensitive to menthol.

Medical conditions influencing selection:

- skin disorders (e.g. psoriasis, chronic dermatitis, urticaria)—patches are contraindicated
- gastrointestinal disease—swallowed nicotine may exacerbate symptoms of oesophagitis, gastric or peptic ulcers; patches may be preferred
- oral or pharyngeal inflammation—avoid nicotine gum
- chronic throat disease or asthma—avoid nicotine inhaler
- phenylketonuria—avoid nicotine lozenges, which contain aspartame (metabolised to phenylalanine)
- dentures—avoid nicotine gum.

Provide counselling supported by written information

H. Plan quit strategy[1,3]

- Pick a suitable quit date, ideally within the next two weeks.
- Practice quitting (e.g. quit for a day) try not smoking at the usual times, such as at the pub or during work breaks.
- Plan behavioral strategies to deal with cravings and withdrawal symptoms:
  - Avoid major triggers for smoking in the early stages of the quit attempt (e.g. alcohol, coffee, friends who smoke).

- Modify situations where there is an environmental cue (e.g. take the ashtray out of the car).
- Get support from family and friends.
- The 4Ds:

  Delay acting on the urge to smoke; after five minutes the urge to smoke weakens.

  Deep breathe; take a long, slow breath in and slowly release it; repeat three times.

  Drink water slowly and savour the taste.

  Do something else to distract (e.g. exercise).

I. How to use the medication[1,5]

Nicotine gum

- Most smokers require 8 to 12 pieces of the 2 mg gum or four to six pieces of the 4 mg gum per day; maximum daily recommended dose is 40 mg.
- Correct chewing technique is important: chew slowly (10–15 chews) until bitter taste or tingling sensation, then 'park' gum in cheek or under the tongue until taste or tingling sensation disappears; repeat cycle for about 30 minutes.
- The gum should be used for at least three months before gradual weaning is initiated. Treatment should be stopped when the dose is reduced to one to two pieces of gum a day.

Nicotine patch

- Starting dose:

  10 cigarettes a day and weight >45 kg → 21 mg/24 hr or 15 mg/16 hr patch

  <10 cigarettes per day or weight <45 kg or cardiovascular disease → 14 mg/24 or 10 mg/16 hr patch.

- Recommended duration:

  24 hr patches—21 mg for six weeks, 14 mg for two weeks, 7 mg for two to four weeks;

  16 hr patches—16 mg for 12 weeks, 10 mg for two weeks, 5 mg for two weeks.

- Patch should be applied to any area of non-hairy, clean, dry skin—e.g. upper thigh, hip, under arm, chest. Site of application should be rotated each day.
- If the user experiences vivid dreams with the 24-hour patch, the patch may be removed at bedtime or the user may switch to a 16-hour patch.

Nicotine inhaler

- Self-titrate dose according to withdrawal symptoms; usually six to 12 cartridges a day for three months, then reduce over six to eight weeks; maximum recommended duration is six months.
- Take shallow puffs approximately every two seconds or four deep inhalations a minute. Continue for up to 20 minutes.
- The cartridges in the inhaler should be regularly changed.

Nicotine lozenges

- Weeks 1–6: one lozenge every one to two hours, minimum nine a day; weeks 7–9: one lozenge every two to four hours; weeks 10–12: one lozenge every four to eight hours; weeks 12–24: when tempted to smoke; maximum recommended dose 15 lozenges a day
- Place lozenge in the mouth and allow to dissolve, periodically moving it from one side of the mouth to the other until it is completely dissolved (20–30 minutes).

Nicotine sublingual tablets (microtabs)

- Individualise dosage: low-dependence smokers → 1 tab every one to two hours (eight to 12 tabs daily). Highly dependent smokers → 2 tabs every one to two hours; maximum recommended dose 40 tabs daily.
- Use for at least two to three months then initiate gradual weaning. Stop using when dose is reduced to one to two tablets a day.
- Allow tablet to dissolve under tongue over 30 minutes.

Combination therapy using 2 mg gum and patches may be used by people who are unable to remain abstinent or continue to experience withdrawal symptoms using one type of therapy.[4]

Cut Down Then Stop (CDTS): nicotine gum or inhaler can be used while still smoking, with a view to reducing the amount smoked as a prelude to quitting.[4]

CDTS timeline:

- 0–6 weeks: cut down to 50% of baseline cigarette consumption.
- 6–9 months: stop smoking completely, continue NRT.
- Within 12 months: stop using NRT.

J. Impact on medications[4,5]

Tobacco smoking induces CYP1A2; smoking cessation may result in raised levels of drugs metabolised by CYP1A2 (e.g. theophylline, warfarin, clozapine, ropinirole, imipramine, haloperidol, olanzapine, clomipramine and fluvoxamine). People taking warfarin should closely monitor INR during smoking cessation. Smoking may reduce insulin absorption, and smoking cessation may result in increased absorption and the risk of hypoglycaemia. Careful monitoring of blood glucose is advisable.

K. Adverse effects[5]

- Usually minor and transient; some (e.g. sleep disturbance, dizziness, weight gain, headache, mouth ulcers) may be related to stopping smoking.
- All forms of NRT—dizziness, headache, nausea, vomiting, hiccups, indigestion, abdominal pain, myalgia, vivid dreams (especially 24-hour patch).
- Patches—application site reactions (redness, itch, rash); stop using if severe.
- Inhaler—coughing, throat irritation.
- Gum—jaw pain, dental problems.

L. Quitting resources

Provision of the *Smoking, Nicotine Replacement Therapy* and/or *Staying a Non-smoker* Self Care Fact Cards or other printed information for consumers is appropriate.

The Quitline can provide a free Quit Pack and telephone counselling (phone 13 78 48 or online at www.quit.org.au).

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Tinea guide

Assess patient's needs

A. Patient characteristics

The age and pregnancy status (if female and of child-bearing age) of the patient should be determined because these will affect the advice provided.

B. Symptoms

The location, appearance and severity of the lesions will help with deciding on the appropriate recommendation. Different presentations of tinea include:

- *Tinea pedis* (athlete's foot)[1–3]
  - interdigital—the most common form; starts with fissuring, maceration, erythema, scaling and itching between the fourth and fifth toes. It may eventually extend to the plantar surface (sole) of the foot
  - chronic hyperkeratotic—known as 'moccasin' *tinea pedis*. The soles, heels and sides of the feet become scaly and thickened. Itching, pain and inflammation may be slight or severe
  - vesiculobullous—characterised by painful, itchy vesicles, usually on the soles, with persistent redness and scaling after the vesicles rupture
  - ulcerative—rapidly spreading vesiculopustular lesions, ulcers and erosions, typically in the web spaces. Usually accompanied by a secondary bacterial infection. Occasionally large areas, even the entire sole, can be sloughed. Commonly seen in immuno-compromised and diabetic patients.
- *Tinea corporis* (ringworm)—single or multiple annular, scaly lesions with central clearing, a slightly elevated, reddened edge and sharp margination on the trunk, extremities or face. The border of the lesion may contain pustules or follicular papules. Itching is variable.[1]
- *Tinea cruris*—presents in the groin area as large patches of erythema with central clearing and pustules and vesicles at the active edge of the infected area. In acute infections, the rash may be moist and exudative, whereas chronic infections are usually dry. Patients complain initially of intense itching, but if maceration and superinfection occur, the lesions will become painful. May spread to the buttocks or lower thighs. The scrotum and penis are generally not affected, unlike candidal infections in this area.[1,3]
- *Tinea unguium* (onychomycosis)—a dermatophyte infection of the nails, which thicken and become chalky and dull. Brownish-yellow debris forms beneath the nail, causing it to separate from its bed. About half of those affected experience pain.[3]
- *Tinea capitis*—the most common dermatophytosis in children. Characterised by patches of alopecia and scaling on the scalp. An immune response termed a 'kerion', which is a boggy, sterile, inflammatory scalp mass, may also occur.[1,3]

C. Medical and lifestyle history

The presence of other medical conditions and other medications being taken will affect the advice provided. Risk factors for developing tinea include[2,4,5]:

- prolonged use of occlusive footwear
- a hot, humid, tropical environment
- hyperhidrosis (excessive perspiration)
- activities such as swimming and communal bathing
- contact with infected animals (e.g. cats, cattle)
- diabetes
- HIV or other conditions affecting the immune system
- medications affecting the immune system, (e.g. cyclosporin, azathioprine)
- occupation (e.g. farm worker, zookeeper, lab worker, vet)
- sports and hobbies (e.g. gardening, contact sports, use of sports facilities, animals).

D. Prior treatment

Prior use of, and the patient's response to, tinea medications will help determine either the need for referral or the type of treatment recommended.

Select appropriate action

E. The need to refer

Referral for systemic therapy is indicated if the infection is[4–7]:

- extensive
- inflamed
- recurrent
- unresponsive to topical therapy
- on the palms, soles or scalp
- in the nail matrix.

Recommend treatment

F. Treatment options[6–8]

- Most *Tinea corporis*, *cruris*, and *pedis* infections can be treated with topical agents.
- Oral therapy is recommended for tinea in hair-bearing areas, or on the palms and soles, or for tinea that is widespread, unresponsive to topical therapy, recurrent or has been previously treated with corticosteroids.
- Nail infections are difficult to cure with topical therapy because the infections usually occur under the nail and products penetrate poorly through the nail plate.
- Topical agents include:
  - imidazoles (azoles)—bifonazole, clotrimazole, econazole, ketoconazole, miconazole. Patients taking anticoagulants should avoid topical miconazole. Topical bifonazole and ketoconazole should be avoided during pregnancy
  - terbinafine
  - tolnaftate
  - undecenoic acid—may be an appropriate alternative; there is evidence that it is effective, but has not been compared with azoles or terbinafine
  - benzoic acid and salicylic acid (e.g. Whitfield's ointment)—less effective than the above classes of agents
  - amorolfine—may be considered for superficial or distal nail infection, but is not effective when the nail matrix is infected.

  Topical corticosteroids should not be used alone due to the potential for fungal proliferation and worsening of symptoms; combination antifungal–corticosteroids may be used for severely inflamed infections but should be substituted with a pure antifungal agent once symptoms are relieved and should not exceed two weeks for *Tinea cruris* and four weeks for *Tinea pedis* or *corporis*.[9]
- Prescription-only agents for systemic treatment include:
  - griseofulvin, which has a narrow spectrum of activity, so therefore accurate diagnosis is important. Treatment should continue for at least four weeks and if necessary up to several months until clinical resolution is achieved. Tablets should be taken with food or milk to optimise absorption. Concurrent use of topical azoles increases the cure rate
  - terbinafine, which requires shorter treatment duration and has better cure rates than griseofulvin, but is only PBS-approved (on authority prescription) for proximal or extensive onychomycosis where topical treatment has failed[10]
  - triazole antifungals (e.g. fluconazole, itraconazole), which may be used for dermatophyte infections that have not responded to topical therapy but are not PBS-approved for this indication.[10] Triazoles should be avoided during pregnancy
- Topical dosage forms are[3,6,8]:
  - cream—generally preferred; useful for dry, scaling tinea
  - lotion—drying; useful for tinea between the toes and on large and/or hairy areas
  - powder—can absorb moisture and decrease friction; may be used on the feet, and in the groin and intertriginous areas, either with creams or to prevent reinfection
  - spray—useful for large, hairy and/or painful areas
  - tincture—formulated for use on nails; should not be applied to open or inflamed lesions.

Provide counselling supported by written information

G. How to use the medication[6–8]

The patient should be told how to use the medicine, the frequency and duration of dosage or application and any specific precautions.

Table E.5 Topical treatments for tinea

Medication	Dosage	Duration of treatment	Comments
Bifonazole	Once daily	2–3 weeks; 14 days after symptoms resolve	The treatment of choice for mild localised infections.
Clotrimazole	2 or 3 times daily	2–4 weeks; 14 days after symptoms resolve	
Econazole	2 or 3 times daily	14 days after symptoms resolve	
Ketoconazole	Once or twice daily	2–6 weeks; 14 days after symptoms resolve	
Miconazole	Twice daily	One month; 14 days after symptoms resolve	
Terbinafine	Once daily	1 week	Produces a more rapid response than azoles; may be useful when patient compliance beyond 1 week cannot be ensured.
	One application (liquid)	*T. pedis*: apply once	Area should not be washed for 24 hours following application.
Tolnaftate	Two to three times daily	3–6 weeks; 14 days after symptoms resolve	Considered less effective than imidazoles and terbinafine.

H. Adverse effects[6–8]

The patient needs to know the most common and important adverse effects of the medicine.

- Topical preparations are generally well tolerated; may occasionally cause erythema, itching and irritation.
- With oral antifungal agents, common adverse effects include gastrointestinal problems and headaches.

I. Precautions[6–8,11]

- Terbinafine gel contains alcohol and should not be used on inflamed lesions or sensitive areas such as the face.
- Griseofulvin may reduce the efficacy of oral contraceptives: patients should take additional contraceptive precautions during treatment. It should not be taken during pregnancy, and additional contraception should be continued for four weeks after stopping therapy. It is also thought to affect sperm: men are advised not to father a child during and for six months after treatment. It may reduce the anticoagulant effect of warfarin.
- Oral terbinafine has rarely caused hepatic failure and neutropenia. Liver enzymes and blood count should be monitored if treatment exceeds six weeks. Patients should inform the doctor if they develop tiredness, nausea, anorexia, dark urine, pale faeces or jaundice.
- Triazoles have been associated with hepatotoxicity and hypokalaemia. Liver function and serum potassium should be monitored during therapy. Triazoles inhibit several CYP450 enzymes and may interact with many other drugs.

J. Prevention

A number of measures may be suggested to prevent tinea[2,4,5]:

- Maintain good hygiene and keep the skin and feet clean and dry.
- Wear loose-fitting cotton clothes.
- Wear clean cotton socks and shoes made of leather or breathable material.
- Avoid walking barefoot.
- Do not share clothes, hairbrushes or towels.
- If using communal showers at swimming centres, gyms, and soon, wear thongs, washable sandals or shoes.
- Children with *Tinea corporis* should be excluded from schools and swimming pools until at least 24 hours after starting treatment.

K. Additional information

Provision of the *Tinea* Self Care Fact Card or other printed information for consumers is appropriate.

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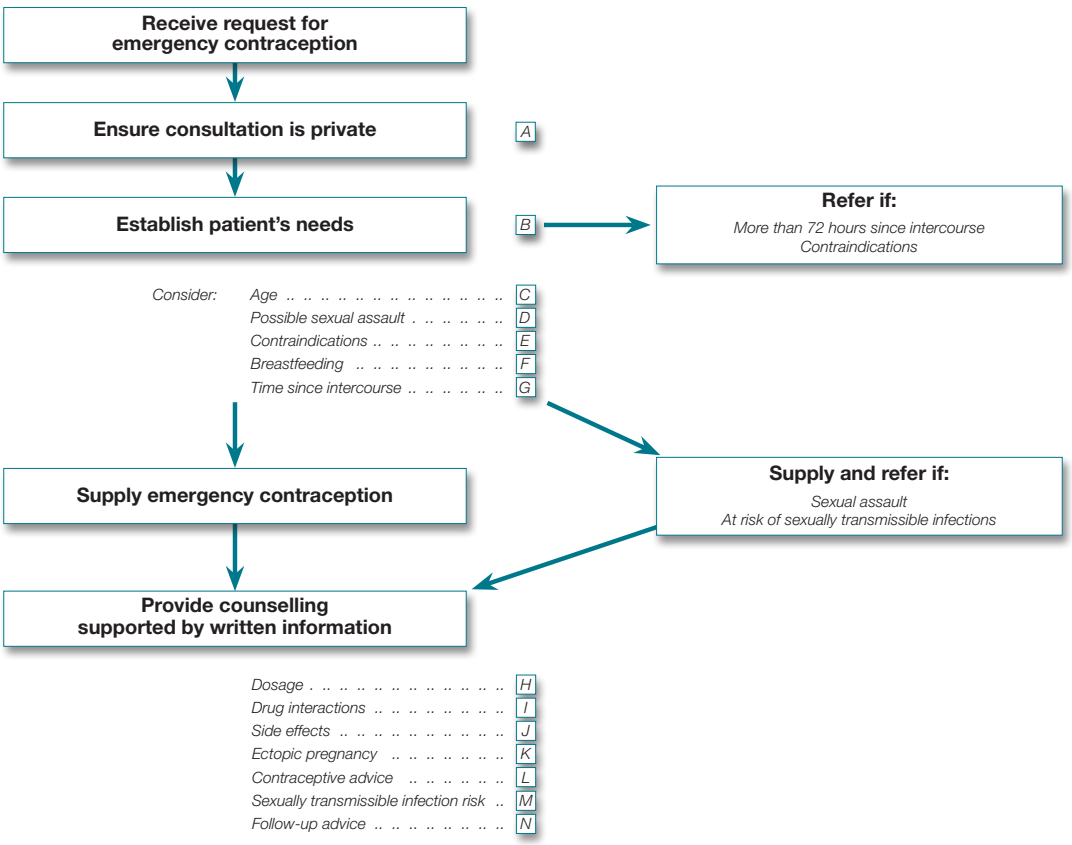
Supply of levonorgestrel as a Pharmacist Only medicine[1] for emergency contraception

October 2008



Explanatory notes

Pharmacists are expected to exercise professional judgment in adapting the guidance they provide to specific presenting circumstances.

A. Privacy

Pharmacists will be aware of their obligations in relation to respecting the patient's privacy and confidentiality in the provision of a Pharmacist Only medicine and associated patient counselling.[2]

B. Supply to a third party

Pharmacists must meet the relevant standard for the provision of Pharmacist Only medicines when a product for emergency contraception is requested through a third party.[2]

C. Age

There are limited data available on the use of levonorgestrel for EC in females of child-bearing potential aged 14–16 years.

It may be advisable to refer someone who is very young to a children's hospital, family planning clinic[3] or medical practitioner of her choice. In such cases it is part of the pharmacist's duty of care to assist with arranging an urgent appointment for the patient.

D. Sexual assault

Where sexual assault is suspected, the pharmacist should offer support and assistance with reporting the incident to the police and facilitating a referral to a medical practitioner or a sexual assault referral centre[4] for more comprehensive help and advice. One suggested approach if an assault is suspected

is for the pharmacist to ask if the sexual intercourse was consensual.

E. Contraindications

Levonorgestrel for EC should not be used if the patient is already pregnant.[5,6] However, pharmacists should note that this contraindication reflects a lack of benefit rather than any risk to the pregnancy, and it will not terminate an existing pregnancy.

The pharmacist should assess the likelihood of the patient already being pregnant (e.g. menstruation is late or was lighter than normal). If in doubt, a pregnancy test can be undertaken prior to the provision of EC, or the patient can be referred to a medical practitioner or family planning clinic.[3]

Other contraindications are unexplained vaginal bleeding and current breast cancer. Referral to a medical practitioner or family planning clinic[3] is advised.

F. Use in lactation

The use of levonorgestrel for EC is safe for nursing mothers.[6] The amount that can be transferred to the infant through breastfeeding is about 0.1% of the maternal dose.

G. Efficacy

Pharmacists must advise patients there is clear evidence that EC is not 100% effective. The time that has elapsed since intercourse is a critical factor and relates to percentage of expected pregnancies prevented as[7]:

<24 hours = 95%
24–48 hours = 85%
48–72 hours = 58%

Efficacy continues to decrease with time after 72 hours.

Overall, the frequency of unintended pregnancy with EC taken within 72 hours of unprotected sex is 1.5%. This can be compared with the frequency of pregnancy after unprotected sex without EC, which varies during the menstrual cycle from 2–4% to 20–30%.[6]

In some circumstances EC is unlikely to be effective. For example, where the patient:

- vomits within two hours of taking a tablet. In this case the 'lost' dose needs to be replaced as soon as possible
- has already engaged in unprotected sex prior to the event for which EC is being sought
- has further unprotected sex after taking EC.

H. Dosage and administration

EC can be taken at any time during the menstrual cycle. There are two approved regimens:

- one tablet containing 750 micrograms of levonorgestrel taken orally as soon as possible and within 72 hours of unprotected intercourse, followed by a second 750 microgram tablet 12 hours after the first dose
- one tablet containing 1.5 mg of levonorgestrel taken orally as soon as possible and within 72 hours of unprotected intercourse.

Recent published research showed that a single dose of 1.5 mg levonorgestrel (i.e. two 750 microgram tablets taken at once within 72 hours of unprotected intercourse) was as effective as the 12-hourly dose.[8]

If the two-dose regimen is supplied, the doses should be timed for optimum convenience to the patient in order to minimise the risk of missing the second dose.

I. Drug interactions[5] and other considerations

- *Warfarin.* The use of levonorgestrel for EC has been associated with a marked increase in INR within three days of administration. Therefore, close monitoring of INR is recommended and adjustment to the dose of warfarin may be required.
- *Hepatic enzyme-inducing drugs.* Medicines such as primidone, phenytoin, carbamazepine, rifampicin, ritonavir, griseofulvin and St John's Wort can increase the metabolism (and therefore reduce the efficacy) of levonorgestrel. See Table D.1 in 'Clinically important drug interactions', Section D, for a full list of CYP3A4-inducing drugs.
- *Crohn's disease and irritable bowel syndrome.* EC can be used but may be less effective due to reduced absorption.

If the patient has current or ongoing acute diarrhoea or vomiting, the efficacy of EC may be reduced.

J. Side effects[6,7]

The most commonly reported side effects are nausea (23%) and vomiting (5–6%). Less common effects include breast tenderness, vaginal bleeding and headache.

There are no known reports of adverse effects on foetal development where EC has failed.[5]

No statistically or clinically significant differences in side effects between the two dosing regimens have been observed, except for more cases of headache with the single-dose regimen.[9]

K. Ectopic pregnancy

There may be a slightly increased risk of ectopic pregnancy following the use of EC.

Severe abdominal cramping following EC treatment requires immediate referral to a medical practitioner.

The patient must be advised that if pregnancy does result she should inform a medical practitioner as soon as possible that she has taken EC during the last cycle.

L. Contraceptive advice

While no adverse effects have been reported, the use of EC products as a 'routine' method of contraception is not recommended.

Where appropriate, the pharmacist should offer the patient general information about the appropriate use of contraception or facilitate referral to a medical practitioner.

M. Sexually transmissible infection risk

The use of a product for EC does not protect against sexually transmissible infections.

Undiagnosed or untreated STIs can lead to serious complications (including infertility) and/or the need for more intensive treatment after diagnosis.[10] For these reasons, all patients at risk of STIs—this includes anyone requesting EC who is not in a monogamous STI-free relationship—should be encouraged to visit their doctor or a sexual health service for testing within two to three weeks of having unprotected sex, rather than waiting to see if symptoms develop.[11]

N. Follow-up advice

It is important that pharmacists provide to the patient information about what follow-up actions should be taken. These include the following:

- After a course of EC, the patient's menstrual period should occur around the (previously) anticipated date but can be up to one week earlier or later.
- If menstruation does not occur within one week after the expected date or if the period is lighter than normal or intermittent, the patient should conduct a pregnancy test and/or consult a medical practitioner or family planning clinic.
- A course of EC does not provide ongoing protection against pregnancy. Other forms of contraception (e.g. abstinence, barrier method, continuation of the oral contraceptive pill within 12 hours of taking EC) must be employed until the next period starts and regular contraception can be instituted. If the patient continues the oral contraceptive pill (i.e. does not wait until the next menstrual cycle before starting it), she should conduct a pregnancy test in three weeks to ensure the EC was effective.[11]

Notes/references

1. At the time of publication, products available in Australia for EC are a two-tablet pack (each tablet containing 750 micrograms of levonorgestrel) and a one-tablet pack (the tablet containing 1.5mg levonorgestrel).
2. Pharmaceutical Society of Australia. Standards for the provision of pharmacy medicines and pharmacist only medicines in community pharmacy. In: Professional Practice Standards (version 3). Canberra: PSA, 2006.
3. The contact details for Family Planning Australia are as follows. Pharmacists may also find local family planning clinics which would be more convenient for the patient to access.

ACT	Sexual Health Family Planning ACT 02 6247 3077
NSW	FPA Health 02 8752 4300 or Health line 1300 658 886
NT	Family Planning Welfare Association of NT 08 8948 0144
Qld	Family Planning Qld 07 3250 0240
SA	Sexual Health Information Networking and Education (Shine SA) 08 8431 5177 or Sexual Healthline 1800 188 171
Tas	Familiy Planning Tasmania Inc. 03 6228 5244 or Healthline 1300 358 886
Vic	Family Planning Victoria Inc. 03 9257 0100
WA	Family Planning Western Australia 08 9227 6177

4. The telephone numbers for sexual assault centres are as follows. Pharmacists may also find local centres which would be more convenient for the patient to access.

ACT	Rape Crisis Centre 02 6247 2525
NSW	Rape Crisis Centre 02 9819 7357 or Counselling Line Freecall 1800 424 017
NT	Darwin Centre Against Rape 08 8945 0155
Qld	Sexual Assault Helpline 1800 01 01 20
SA	Rape and Sexual Assault Service 1800 817 421
Tas	Sexual Assault Support Service 03 6231 1811
Vic	Centre Against Sexual Assault (CASA) 1800 806 292
WA	Sexual Assault Resource Centre 1800 199 888

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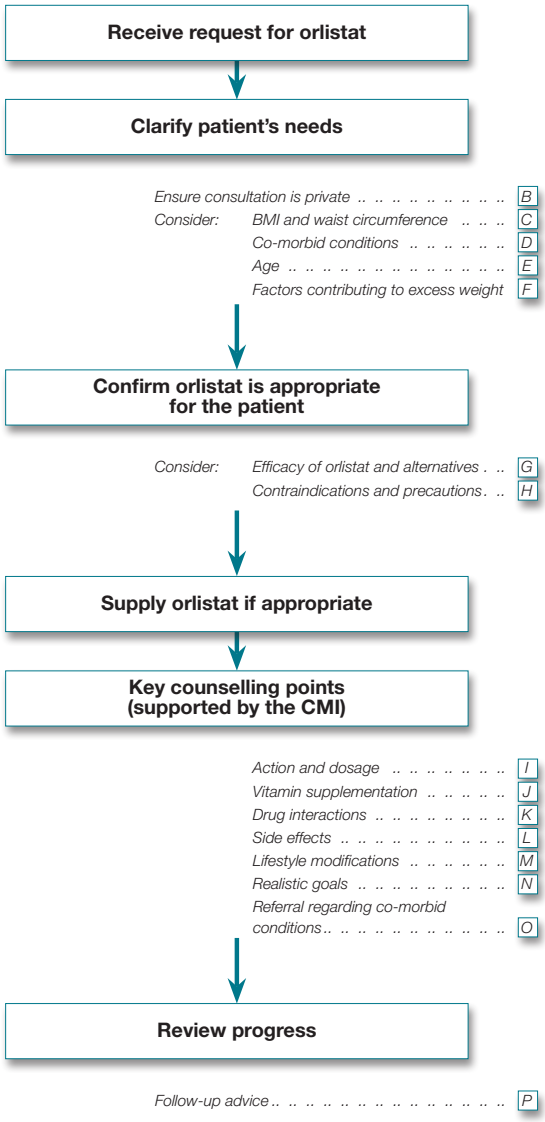
Provision of orlistat as a Pharmacist Only medicine

The decision to supply any weight loss product should involve consideration of all aspects of a weight management service [A]—January 2006



Explanatory notes

Pharmacists are expected to exercise professional judgment in adapting the guidance they provide to specific presenting circumstances.

A. Weight management service

- For details, see the Pharmaceutical Society of Australia's *Essential CPE: weight management*.

B. Privacy issues

- Pharmacists will be aware of their obligations in relation to respecting the patient's privacy and confidentiality in the provision of a Pharmacist Only medicine and associated patient counselling.[1]

C. BMI and waist circumference

- Orlistat is indicated for treatment of obese patients with a body mass index (calculated as

weight (kg) divided by height (m) squared) of ≥30 or overweight patients with a BMI of ≥27 and the presence of one or more co-morbidities.[2]

- Substantially increased disease risk due to obesity and overweight in adults is associated with a waist circumference of ≥102 cm in men and ≥88 cm in women.[3]

D. Co-morbid conditions

- Co-morbid conditions associated with overweight and obesity may be caused by metabolic conditions and/or the excess weight itself. The conditions' presence may assist in determining the patient's need to lose weight. Co-morbid conditions include Type 2 diabetes, gallbladder disease, hypertension, dyslipidaemia, sleep apnoea, breathlessness, osteoarthritis, gout and psychological problems.[4] For a full list and their relative risk, see the Pharmaceutical Society of Australia's *Essential CPE: weight management*.

E. Age

- Studies have not been done in children <18 years or adults >74 years of age. The safety and efficacy of orlistat in these patient groups has not been established. Referral to a medical practitioner is recommended.[2]

F. Factors contributing to excess weight

- Increased body weight results from an imbalance between energy intake (food) and expenditure (basal rate metabolism, thermogenesis and physical activity). Factors that may be influencing this imbalance include genetic influences, life stages and events, and medical conditions and treatments.

G. Efficacy of orlistat and alternatives

- When combined with lifestyle modification, orlistat can produce weight losses of 6–13 kg (1.1–4.5 kg more than placebo) over one to two years, sibutramine can produce weight losses of 5–17 kg (4–5 kg more than placebo) over one to two years, and phentermine and diethylpropion can produce weight losses of 6–7 kg (3–3.6 kg more than placebo) over three months.
- There is no good evidence of weight loss benefits from the use of any complementary medicines currently on the market.[5]

H. Contraindications and precautions

- The use of orlistat is not recommended in patients with the following medical conditions:
  - cholestasis
  - major gastrointestinal surgery
  - chronic malabsorption syndrome
  - pancreatic enzyme deficiency
  - chronic pancreatitis.
- Precautions should also be taken in patients with the following medical conditions:
  - bulimia
  - laxative abuse
  - fat-soluble vitamin deficiency (vitamins A, D, E and K)
  - nephrolithiasis (renal stones)
  - active peptic ulcer disease
  - chronically treated psychiatric or neurological disorders
  - symptomatic cholelithiasis.
- Pregnant and lactating women should postpone weight loss.
- There is limited information about the safety and efficacy of using a combination of weight-loss agents. One small study showed no additive effect by combining sibutramine with orlistat.[4]

I. Action and dosage[2,4]

- Orlistat inhibits the absorption of approximately one-third of dietary fat. The effect is seen 24–48 hours after dosing. It does not suppress appetite.
- Orlistat also produces improvements in some co-morbid conditions.
- The recommended dose is one 120 mg capsule with each main meal (during or up to one hour after the meal). If a meal is missed or contains no fat the dose may be omitted.
- Safety and efficacy have been shown for up to four years.

J. Vitamin supplementation

- Orlistat reduces the absorption of fat-soluble vitamins (A, D, E and K). Vitamin supplements should be administered two hours before or two hours after orlistat.

K. Drug interactions[2]

- Approximately 97% of orlistat and its metabolites are eliminated faecally, suggesting minimal absorption and therefore minimising the opportunity for interactions.
- Due to the reduced absorption of vitamin K, concurrent use of orlistat with anticoagulants

may result in an increased INR value. Caution and close monitoring are recommended.

- Concurrent use of cyclosporin with orlistat leads to decreased cyclosporin plasma concentrations. Plasma levels need to be monitored more frequently.
- The improved metabolic control in diabetics observed during long-term treatment with orlistat may mean a reduced dosage of hypoglycaemics is possible.

L. Side effects[2]

- Gastrointestinal symptoms are related to orlistat's mechanism of action; most are mild and transient.
- The most common side effect is fatty or oily stools, resulting from unabsorbed fat in the diet.
- Abdominal pain, diarrhoea, dyspepsia, faecal incontinence, flatulence and headache require medical attention only if they continue or are bothersome.
- Those effects requiring medical attention include blood in stools, cholethiasis, cholecystitis, diverticulitis, enteritis and hypoglycaemia.

M. Lifestyle modifications

- The patient should be on a nutritionally balanced, mildly hypocaloric diet that contains approximately 30% of calories from fat. A multivitamin containing fat-soluble vitamins, taken two hours before or after the orlistat dose, may be necessary to ensure adequate nutrition.[6]
- Long-term weight loss is more likely to be maintained if patients participate in a regular level of increased physical activity. With physical activity, health benefits may be gained even in the absence of weight loss.
- 30 minutes of moderate-intensity physical activity on most days of the week has a demonstrated health benefit.[4]
- 60 minutes of light- to moderate-intensity physical activity on most days of the week is needed to achieve weight loss; 60–90 minutes on most days of the week is best to maintain weight following weight loss.[4]
- Patients may need to build up to these durations to avoid any ill-effects from a sudden increase in activity.[4]

N. Realistic goals[4]

- Most patients' expectations for weight loss are unrealistic. A loss of up to 35% of initial body weight is often expected. See Table E.6.

Table E.6 Realistic goals for weight loss

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Duration	Weight	Waist circumference
Short term	1–4 kg/month	1–4 cm/month
Medium term	10% of initial weight	5% after six weeks
Long term	10–20% of initial weight	≤88 cm (females) ≤102 cm (males)

- The main goal of any weight loss should be an improvement in health.
- A reduction of 5–10% in initial body weight can result in significant improvements in metabolic health. Therefore, other goals may include a reduction in blood pressure or improved glycaemic control.
- Process goals may include a reduction of food or fat intake or an increase in the number of steps walked per day (e.g. using a pedometer).

O. Co-morbid conditions

- Patients should be referred to their medical practitioner for the treatment and monitoring of any co-morbid conditions.

P. Follow-up advice

- Weight loss maintenance is required for life in post-obese or overweight patients. Initially, fortnightly reviews may be necessary, then monthly. Even after weight is normalised occasional reviews may be necessary to maintain weight.

References

1. Pharmaceutical Society of Australia. Standards for the provision of pharmacist only and pharmacy medicines in community pharmacy. In: Professional Practice Standards (version 3) Canberra: PSA, 2006.
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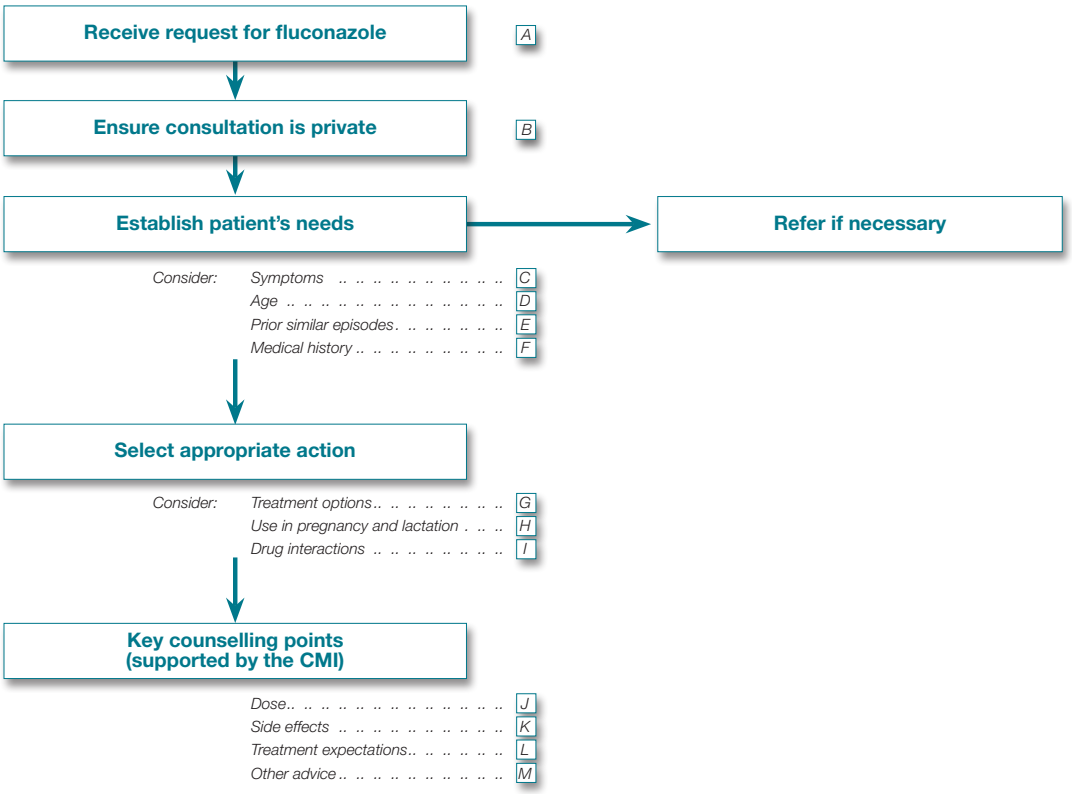
Released by PSA May 2004; revised October 2005

Provision of oral fluconazole as a Pharmacist Only medicine

for the treatment of vaginal candidiasis—January 2006



Explanatory notes

Pharmacists are expected to exercise professional judgment in adapting the guidance they provide to specific presenting circumstances.

A. Professional standards

The professional standards[1] outline the appropriate actions to be taken by pharmacists and trained pharmacy staff in response to a direct product or symptom-based request.

B. Privacy

Pharmacists will be aware of their obligations in relation to respecting the patient's privacy and confidentiality in the provision of a Pharmacist Only medicine and associated patient counselling.[1]

Particular care is needed for conditions which may be difficult for the patient to discuss.

C. Symptoms

Vulvovaginal candidiasis (VVC) is a common cause of vulvitis and vaginitis. However, there are other common conditions that can produce similar symptoms; e.g. bacterial vaginosis, trichomoniasis, genital herpes, atrophic vaginitis and dermatitis.[2,3]

Symptoms typical of VVC include itching of the vulval area, vulvar erythema, and vaginal discharge that is thick, white (cottage cheese–like) and odourless.[2–4]

Referral to a medical practitioner is necessary if symptoms include fever, discharge with unusual colour or smell, abnormal or irregular menstrual bleeding, blood-stained discharge, vaginal or vulval sores or blisters, pain in the lower abdomen, or burning on urination.

D. Age

Individuals <16 and >60 years old should be referred to a medical practitioner.[5]

Although girls <16 may present with vulvar itching and discomfort, candidiasis is rare pre-puberty. Poor hygiene, contact dermatitis, threadworms, diabetes, an altered immune status, bacterial infections, and sexual abuse may all need to be considered by a medical practitioner.[6]

Elderly patients are more prone to skin infections, and have an increased risk of malignancy. Therefore diagnosis and appropriate treatment should be undertaken by a medical practitioner.[7]

E. Prior similar episodes

VVC is considered recurrent when the individual experiences four specific episodes, or at least three episodes unrelated to antibiotic therapy, in one year. Physical examination and a vaginal swab by a medical practitioner are essential for individuals experiencing symptoms for the first time or experiencing recurrent symptoms to ensure there are not other causes or concurrent infections.[2,4]

F. Medical history

The risk of VVC is increased in women who[3]:

- have diabetes
- are immunocompromised
- are pregnant
- use the oral contraceptive pill, a diaphragm and spermicide, or an IUD
- are taking antibiotics.

In these instances, evaluation by a medical practioner may be warranted. Physical examination by a medical practitioner is essential for individuals who have a history of a sexually transmitted infection, or exposure to a partner with an STI.

G. Efficacy of treatment options

No statistically significant differences have been shown between oral and topical antifungal treatment for clinical cure at short-term (five to 15 days) and long-term (two to 12 weeks) follow-up.[8]

Treating a woman's male sexual partner has not been shown to improve resolution of a woman's symptoms or reduce the rate of symptomatic relapse.[9]

H. Use in pregnancy and lactation

Fluconazole is rated Australian Drug Evaluation Committee Category D and should not generally be used in pregnancy. However, the single dose therapy (150 mg) does not appear to cause adverse effects in pregnancy.[11] Topical therapies are generally recommended, but care should be taken when using an applicator in late pregnancy.

Fluconazole is excreted in breast milk, although the single 150 mg dose appears to be safe to use.[11]

I. Drug interactions

Clinical drug interactions have not been reported with single-dose use of fluconazole, but a range of interactions are possible, particularly with multiple doses.[12]

Fluconazole inhibits CYP2C, and to a lesser extent 3A isoforms, and so may affect the metabolism of other drugs. In vitro studies demonstrate that the extent of inhibition of 3A isoforms is lowest with fluconazole when compared with ketoconazole and itraconazole.[10]

Although interactions are unlikely to be clinically significant with a single dose, monitoring may be required when taking[10,11]:

- phenytoin, sulphonylureas, cyclosporin, warfarin, theophylline—levels may be increased by concomitant administration with fluconazole
- rifamycins—fluconazole levels may be reduced and rifampicin and rifabutin levels may be increased
- celecoxib, parecoxib—levels may be increased by concomitant administration with fluconazole.

J. Dose

Fluconazole 150 mg is administered as a single oral dose, with or without food.

Although fluconazole is predominantly renally excreted, no dose adjustment is necessary for single-dose therapy in individuals with renal impairment.[10]

A two-dose regimen (150 mg on day one followed by 150 mg 72 hours later) has been trialled in the united states.[13] However, this regimen is currently not approved in Australia by the Therapeutics Goods Administration.

K. Side effects

Common side effects (with an incidence of >1%) include nausea, vomiting, abdominal pain, constipation, headache and dizziness.[11]

L. Treatment expectations

Onset of symptom relief may be expected within one day, with complete relief possible in two days.[14]

Within five to 16 days, 85% of women can expect mycological cure and 99% can expect a favourable clinical response.[14] If symptoms persist the individual should be referred to doctor for a physical examination and vaginal swab.

M. Other advice

A topical antifungal cream concomitantly applied externally may be appropriate to help relieve local symptoms.[5]

Provision of the *Thrush* Self Care Fact Card or other printed information for consumers is appropriate.

References

1. Pharmaceutical Society of Australia. Standards for the provision of pharmacy medicines and pharmacist only medicines in community pharmacy. In: Professional Practice standards (version 3). Canberra: PSA, 2006.
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Released by PSA June 2004; revised October 2005

Section F

Health information

National medicines policy and therapeutic goods regulation in Australia

This section provides a brief overview of national policy and regulations that affect on the availability and use of medicines in Australia.

State regulations and policies are beyond the scope of this publication and are not considered.

Further information on the National Medicines Policy can be found on the Department of Health and Ageing's website at www.health.gov.au; follow the links to publications to find more on the NMP. Information about the regulation of therapeutic goods is available at www.tga.gov.au.

National Medicines Policy

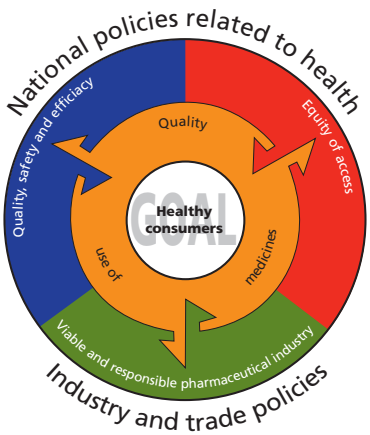
The National Medicines Policy[1] (NMP) is a framework based on the cooperation, contribution and collaboration of all partners in order to bring about better health outcomes for Australians, focusing especially on people's access to, and wise use of, medicines.

Aim

The NMP aims to meet medication and related service needs, so that both optimal health outcomes and economic objectives are achieved for Australians.

Objectives

The NMP has four central objectives based on active and respectful partnerships, taking into account elements of social and economic policy. The objectives are outlined in detail below. The diagram here illustrates the interdependence of the four components, with the central goal of optimising health outcomes. The diagram also shows that public policy concerning medicines must be integrated within the broader health and trade policies.



The four central objectives of the NMP are:

1. **Timely access to the medicines that Australians need, at a cost individuals and the community can afford**

   The Australian Government's Pharmaceutical Benefits Scheme helps improve the health of all Australian residents by ensuring they have timely access to necessary and cost-effective medicines at an affordable price.

2. **Medicines meeting appropriate standards of quality, safety and efficacy**

   The Australian community expects that medicines and medical devices in the marketplace are safe and of high quality, to a standard at least equal to that of comparable countries. The Therapeutic Goods Administration provides a national framework for the regulation of therapeutic goods in Australia. It also ensures the quality, safety and efficacy of therapeutic goods.

3. **Quality use of medicines**

   Australia has a National Strategy for Quality Use of Medicines[2] (QUM), which is central to Australia's NMP. The National Strategy is intended to assist the QUM partners—health care consumers, health practitioners and educators, health care facilities, the medicines industries, the media, health care funders and purchasers, and governments—in becoming more aware of the QUM framework and approach. This will enable them to integrate their own activities with the National Strategy.

4. **Maintaining a responsible and viable medicines industry**

   The preceding three NMP objectives can be achieved through the existence of a responsible and viable medicines industry.

Definition of quality use of medicines

'Quality use of medicines' means[3]:

- selecting management options wisely by
  - considering the place of medicines in treating illness and maintaining health
  - recognising that non-drug therapies may be the best option for the management of many disorders

- choosing suitable medicines, if a medicine is considered necessary, so that the best available option is selected by taking into account
  - the individual
  - the clinical condition
  - risks and benefits
  - dosage and length of treatment
  - any co-existing conditions
  - other therapies
  - monitoring considerations
  - costs for the individual, the community and the health system as a whole
- using medicines safely and effectively to achieve the best possible results by
  - monitoring outcomes
  - minimising misuse, over-use and under-use
  - improving people's ability to solve problems related to medication, such as adverse effects or managing multiple medicines.

The definition of QUM applies equally to decisions about medicine use by individuals and decisions that affect the health of the population.

National Medicines Policy groups

Many national and local groups are involved in the implementation of NMP. The government has established a structure through which it will be advised on the development of the NMP. This structure includes:

- a National Medicines Policy Executive
- a National Medicines Policy Committee
- an annual National Medicines Policy Partnerships Forum.

For further information see www.health.gov.au/internet/main/publishing.nsf/content/nmp-news.htm-copy2.

Therapeutic goods regulation

The Therapeutic Goods Act

The main objective of the *Therapeutic Goods Act 1989*[4] (the Act) is to establish and maintain a national system of controls relating to the quality, safety, efficacy and timely availability of therapeutic goods. The term 'therapeutic good' refers to ant product that claims to provide therapeutic benefit and includes medicines, medical devices and blood products. The Act provides for the setting of standards (including labelling, and recall procedures), licensing of manufacturers and inclusion of the goods in the Australian Register of Therapeutic Goods (ARTG).

The Act is administered by the Therapeutic Goods Administration and applies to things done by:

- corporations; and
- natural persons or corporations
  - in the course of interstate or international trade
  - in relation to the Pharmaceutical Benefits or Repatriation Pharmaceutical Benefits Schemes
  - in relation to the Commonwealth or any Commonwealth authority.

The Act is intended to operate in concert with state laws. Complementary therapeutic goods laws operate in Victoria, New South Wales and Tasmania. The effects of these laws are to:

- bring unincorporated manufacturers and sponsors of therapeutic goods who trade only in their own jurisdictions into the federal regime
- require wholesalers to comply with the code of good wholesaling practice
- impose controls on the supply of therapeutic goods by retail or in circumstances corresponding to retail supply, such as vending machines.

The Australian Register of Therapeutic Goods

Therapeutic goods that are manufactured or supplied in Australia must be entered in the ARTG or be included in one of several categories of goods that are exempted by the Therapeutic Goods Regulations 1990 from the need to be included in the ARTG. Personal imports, clinical trial drugs and extemporaneously prepared medicines for particular persons (for application to that person) are common examples of exempt goods. Unless exempt, medicines are entered as either 'registered' or 'listed' medicines, and medical devices must be included before they may be supplied in or exported from Australia.

Information on therapeutic goods is held on the database and in hard copy format. The ARTG can be accessed through the TGA's website (www.tga.gov.au/docs/html/artg.htm), although the information made available to the public is limited (as specified by the Therapeutic Goods Regulations 1990). The TGA is in the process of extending the range of information generally available to consumers on the public-access part of the ARTG.

Listed medicines

Listed medicines are generally recognised as low risk products. Listed medicines may only contain substances evaluated by the TGA as being low risk and must be manufactured under good manufacturing principles.

Listed medicines include sunscreens, herbal substances, minerals, vitamins, homoeopathic substances, and aromatherapy oils. Applications are self-assessed by the sponsor in accordance with a set of guidelines and submitted electronically using the Electronic Lodgement Facility (ELF). Sunscreen products must provide evidence of SPF testing with the application. Sponsors of other listed medicines are required to hold information to substantiate any claims that are made for the product. Labels of listed medicines must include the symbol AUST L followed by a unique number.

Registered medicines

Applications for registered goods are fully evaluated by the TGA, usually on the advice of one of several independent expert advisory committees. The evaluation considers all aspects of quality, safety and efficacy, including clinical trial data, pharmaceutical stability and the content of labels, package inserts and approved Product Information. Registered goods are recognised by the symbol AUST R followed by an individual number printed on the main label.

Government committees

This section provides brief information on some of the committees associated with the regulation of therapeutic goods in Australia. Further detail can be found through the relevant website.

Australian Drug Evaluation Committee

www.tga.gov.au/docs/html/adec/adec.htm

The Australian Drug Evaluation Committee (ADEC) provides advice on:

- the quality, risk–benefit, effectiveness and access within a reasonable time of any drug referred to it for evaluation
- medical and scientific evaluations of applications for registration of prescription drugs (e.g. new chemical entities, new forms of previously registered drugs and therapeutic variations to registered drugs).

ADEC subcommittees include:

- the Adverse Drug Reactions Advisory Committee (ADRAC)—see www.tga.gov.au/adr/adrac.htm
- the Pharmaceutical Subcommittee.

Medicines Evaluation Committee

www.tga.gov.au/docs/html/mecinfo.htm

The Medicines Evaluation Committee (MEC) provides independent scientific and policy advice on over-the-counter medicines. It evaluates applications for conventional non-prescription medicines and other medicines that are not assessed by either the ADEC or the CMEC (see below). The MEC provides advice on the safety, effectiveness and quality of any OTC medicine or ingredient (including excipients).

Complementary Medicines Evaluation Committee (CMEC)

www.tga.gov.au/docs/html/cmec/cmec.htm

The Complementary Medicines Evaluation Committee (CMEC) provides scientific and policy advice relating to controls on the supply and use of complementary medicines, with particular reference to the safety and quality of products and, where appropriate, efficacy relating to the claims made for products. The CMEC also evaluates ingredients used in complementary medicines, evaluates complementary medicines that are not eligible for listing, and recommends active substances used in complementary medicines that should be eligible for listing.

National Drugs and Poisons Schedule Committee (NDPSC)

www.tga.gov.au/ndpsc/index.htm

The main functions of the National Drugs and Poisons Schedule Committee (NDPSC) are to:

- make decisions in relation to the classification and scheduling of substances
- provide advice on restrictions on accessibility and availability of particular substances
- provide advice on policies relating to labelling, packaging and advertising of substances
- compile and maintain the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). Note that the decisions of the NDPSC in relation to the SUSDP have no force in Australian law but are recommended for incorporation in state and territory drugs or poisons legislation (i.e. they are usually adopted in full or in part by the states and territories)
- facilitate the harmonisation between Australia and New Zealand, of legislative provisions relating to the classification and scheduling of substances.

National Coordinating Committee on Therapeutic Goods

www.tga.gov.au/docs/html/ncctg.htm

The National Coordinating Committee on Therapeutic Goods takes action necessary to coordinate legislative and administrative controls on therapeutic goods and poisons and makes recommendations to the Australian Health Ministers' Advisory Council as necessary.

Therapeutic Goods Committee

www.tga.gov.au/docs/html/tgc.htm

The Therapeutic Goods Committee provides advice on standards for therapeutic goods, including labelling and packaging, and on principles to be observed in the manufacture of therapeutic goods for human use.

Medical Devices Evaluation Committee

www.tga.gov.au/docs/html/mdec/index.htm

Known as the Therapeutic Devices Evaluation Committee until October 2002, the Medical Devices Evaluation Committee provides independent medical and scientific advice on the safety, quality and performance of medical devices supplied in Australia.

The Australia New Zealand Therapeutic Products Authority

In December 2003 the Australian and New Zealand Governments signed an agreement to establish a joint regulatory scheme for therapeutic products. The key objectives in establishing a trans-Tasman therapeutic products agency were to:

- establish a trans-Tasman scheme to regulate therapeutic products that will safeguard public health and safety in Australia and New Zealand
- facilitate trans-Tasman trade and enhance closer economic relations between Australia and New Zealand, consistent with the Trans Tasman Mutual Recognition Arrangement.

Establishment of the Australia New Zealand Therapeutic Products Authority was postponed in July 2007, when the New Zealand Government announced it would not be proceeding with the legislation designed to enable the joint agency. The Australian Government has indicated it will continue to work towards the same goals and standards and will be identifying areas of possible harmonisation outside the joint scheme. Relevant information can be found at:

- www.tga.gov.au/tta/index.htm
- www.anztpa.org.

References

1. Australian Government Department of Health and Ageing. National Medicines Policy 2000. Canberra: Commonwealth of Australia, 1999. At: www.health.gov.au/internet/main/publishing.nsf/Content/National+Medicines+Policy-2.
2. Australian Government Department of Health and Ageing. The National Strategy for Quality Use of Medicines. Canberra: Commonwealth of Australia, 2002.
3. Australian Government Department of Health and Ageing. The National Strategy for Quality Use of Medicines: executive summary. Canberra: Commonwealth of Australia, 2002. At: www.health.gov.au/internet/main/publishing.nsf/Content/4CCAC8550BA36A52CA256F1800468A6E/$File/execsumbro.pdf.
4. All current legislation can be accessed through the Australian Government Attorney-General's Department Commonwealth legislation website at www.comlaw.gov.au.

Australian guidelines for drug donations to developing countries

Australian guidelines for drug donations to developing countries is endorsed by the Australian Pharmaceutical Advisory Council, November 1996. Amended November 2000.

Introduction

These Australian guidelines are based on the international Guidelines for Drug Donations developed by the World Health Organization (WHO) in 1996. The WHO guidelines reflect a consensus between the major international agencies active in humanitarian emergency relief: WHO, Office of the United Nations High Commission for Refugees (UNHCR), United Nations Children's Fund (UNICEF), International Committee of the Red Cross, Médecins sans Frontières, Churches Action for Health and the World Council of Churches. They aim to improve the quality of drug donations and are intended to serve as a basis for national and institutional guidelines.

Scenarios associated with drug donations range from acute emergencies to non-emergency development programs. Although there are differences between these scenarios, there are basic rules for an appropriate response that apply to all.

As with the guidelines prepared by WHO, this Australian document starts with a discussion on the need for guidelines, followed by the presentation of the core principles for appropriate donations.

The Australian guidelines have been endorsed by the Australian Pharmaceutical Advisory Council (APAC). APAC expresses its appreciation to the Society of Hospital Pharmacists of Australia for its assistance in developing these guidelines.

Why do we need guidelines for donations of drugs to developing countries?

The contribution of medicines in the form of donations to developing countries or in disaster situations is often viewed by communities in developed countries, such as Australia, as a useful way to provide much needed pharmaceutical supplies. Televised pictures of refugee camps or rural areas lacking the most basic health services often give rise to emotional appeals to 'do something'. As the lack of medicines is often presented as a pressing problem, an immediate donation of drugs is often perceived as the most pragmatic and direct response. Unfortunately, not all drug donations are helpful and inappropriate drug donations can be dangerous or useless, and a source of problems for the recipients as the following examples illustrate.

Guatemala, 1976

In the first week after the earthquake in Guatemala, 7,000 cartons of mixed drugs arrived. These were sorted by a group of 40 pharmacy students at a rate of 25–50 boxes per day (it took about six months to finish the job). Only 10% of the drugs sent were relevant to the health needs in Guatemala and were adequately labelled.

Sudan, 1990

A large consignment of drugs was sent from France to war-devastated southern Sudan. Each box contained a collection of small packets of drugs, some partly used. All were labelled in French, a language not spoken in Sudan. Most were inappropriate, some could be dangerous. There were: contact lens solutions, appetite stimulants, antidepressants and expired antibiotics. Of 50 boxes, 12 contained drugs of some use. It would have been much better to use the money spent on transport to purchase penicillin and other essential drugs from Kenya and to have then sent from there.

Eritrea, 1980s

During the war for independence, despite the careful wording of appeals, much time and energy had to be spent on sorting drug consignments. Examples of inappropriate donations were: seven truck loads of expired aspirin tablets that took six months to burn; a whole container of unsolicited cardiovascular drugs with two months to expiry; and 30,000 half-litre bottles of expired amino acid infusion that could not be disposed of anywhere near a settlement because of the smell.

How else can drug donations cause problems?

Most developing countries have national essential drugs lists covering major health problems. Training programs for health personnel focus on the correct use of these drugs. Such developments need support. Donated drugs can frustrate and undermine national drug policies which aim to secure reliable supplies of appropriate, good quality, essential drugs and to promote standard treatment guidelines as a tool to encourage rational drug use.

There are also problems with the quality of donated drugs, donation of expired drugs being a common practice. This practice is not acceptable. If the quality of drug is not suitable for use in Australia, it is not suitable for donation to an overseas country.

Apart from the issues of the quality of the products, e.g. expired/damaged drugs, and the relevance of the drugs to the situation, logistical difficulties can also arise. These difficulties are associated with sorting, storage and distribution which may waste valuable human and financial resources. In addition, transport costs may be higher than the value of the drugs, and local purchase can be more cost effective.

Guidelines for donating drugs

Core principles

- A donation is intended to assist the recipient. Donations should be based on an expressed need. Donor-initiated donations where the recipient's advice has not been sought are unhelpful.
- Donations must support essential drug policies. Respect must be given for the authority of the recipient and the receiving country's administrative arrangements.
- There should be no double standards. If the quality of an item is not acceptable in Australia, it is unacceptable as a donation. Therefore the collection and redistribution of patients' unused medicines is not permitted.

Selection of drugs

1. All drug donations should be based on an expressed need.
   - Drugs should not be sent without prior clearance by the recipient.
   - A written request should be obtained from a competent authority in the recipient country.
   - The health facility receiving the drugs should be required to acknowledge receipt of the donated medicines.

   Justification

   This provision excludes donor-driven donations, or donations which arrive unannounced and unwanted. It encourages recipients to specify their needs, and empowers them to refuse unwanted gifts.

2. All donated drugs should be on the national list of essential drugs of the recipient country or, if such a national list is not available, on the WHO Model List of Essential Drugs.

   Justification

   This provision ensures that drug donations comply with existing government policies and with the essential drugs concept. It aims at maximising the positive impact of the donation, and excludes the donation of unnecessary or dangerous drugs, and drugs which are not specified for use in that country.

   Copies of the WHO Model List of Essential Drugs are available from: Hunter Publications, 58 Gipps Street, Collingwood, 3066. Telephone: 03 9417 5361[a]

3. The presentation and strength of donated drugs should, as much as possible, be similar to those commonly used in the recipient country.

   Justification

   Most staff working at different health care levels in the recipient country have been trained to use a certain dosage schedule and dosage forms. Treatment guidelines cannot be constantly changed.

   Note: Vaccine donations

   The donation of vaccines is not appropriate because of the logistical problems associated with transport and storage. Donations of money for purchasing vaccines are more helpful, so cold chain facilities can be put in place, and the right quantity and type of vaccine and associated supplies can be ordered at the right time. Donations for vaccine purchase should only be directed to a responsible agency which has an accepted role in immunisation programs such as Australian Red Cross, Médecins Sans Frontières, UNICEF, Save The Children and World Vision Australia.

Quality and shelf life

4. All donated drugs should comply with quality standards in both the donor and recipient country.

   Justification

   This provision prevents double standards. For example, donations of unused drugs (returned drugs from patients or doctors' free samples) which would not be acceptable for use in Australia should not be donated to another country.

5. All donated drugs should have a remaining shelf-life of at least one year after the arrival in the recipient

a. Copies of WHO Model List of Essential Drugs available from: www.who.int/medicines/publications/essentialmedicines/en or Publisher Relations, DA information Services, 648 Whitehorse Road, Mitcham, 3132. Telephone: (03) 9210 7777, Fax: (03) 9210 7788. Email: service@dadirect.com. Web: www.dadirect.com.

country, with an exception for direct donations to a specific health program in response to an urgent and special request. This exception may be made provided; the date of arrival and the expiry dates of the drugs is advised to the responsible recipient professional, and that they acknowledge that they are aware of the shelf-life; and, that prior to expiration, the quantity and remaining shelf-life allow for proper administration.

Justification

Considerable periods of time may elapse before donated drugs are transported, cleared through customs, relocated to a warehouse, contents identified and recorded, and the drugs dispatched to the place of use. Distribution may take many months as drugs are moved from a central store, to provincial stores, to district hospitals and other peripheral health facilities. Very few possibilities for immediate distribution exist.

Presentation, packing and labelling

6. All drugs should be labelled in a language that is easily understood in the recipient country. The label should contain at least the International Non-proprietary Name (generic name), dosage form, strength, name of manufacturer, storage conditions and expiry date.

   Product Information and Consumer Product Information (where available) should be included for each of the drugs sent.

   Justification

   Generic names can be understood in any country where Roman script is being used. Training programs are based on the use of generic names. Receiving the same drug under many different and often unknown brand names is very confusing to the health workers and can even be dangerous. The use of generic names also prevents brand-name loyalty being inadvertently promoted by the donor.

   Many health facilities in developing countries do not have access to current, complete and accurate drug information. Where national treatment guidelines are not in use, it is important that prescribers and dispensers are provided with this information to ensure safe use.

7. As much as possible, donated drugs should be presented in larger quantity units.

   Justification

   Larger quantity packs are more cost-effective as they are cheaper and less bulky to transport. This should not be taken as encouragement to repack drugs from different batch lots and with different expiry dates into one container.

Export and transport

8. All drug donations should be packed in strong outer cartons and be accompanied by a detailed packing list which should specify the contents of each carton by generic name, quantity and expiry date. Cartons should be numbered and the contents of each carton listed in detail in the accompanying documents. In addition, cartons should be marked on the outside with their contents, preferably using a code system.

   Justification

   In addition to knowing what is coming, the recipient is assisted when the consignment arrives. S/he will know just where to find items which may be needed urgently (instead of having to unpack the whole shipment) and will be able to decide where to direct items that may be intended for different centres. A code numbering system for listing contents on the outside of packs is better than the use of the names of items which can facilitate pilferage.

9. Preparation for consignment of goods must be undertaken in close cooperation with the recipient to determine the transport and clearance arrangements, documents needed by the recipient, and the costs that need to be met by the donor. The recipient will require advance details of the content of the shipment and its time of arrival. In most cases, international transport, customs warehousing, clearance costs and internal transport will need to be paid by the donor. However, in some cases, the recipient is able to cover the cost of clearance and internal transport. Agencies should make their own arrangements to comply with customs documentation requirements at all dispatch, transit and entry points.

   Justification

   The recipient will know the local requirements for receiving and clearing consignments and will be able to make preparatory arrangements for prompt clearance in advance. It is most important that shipments are met on arrival. Having a consignment lying on the docks or in a store somewhere, without attention, is also potentially disastrous, and can be very expensive. In addition, these provisions prevent the recipient having to spend effort and money on the clearance and transport of unannounced consignments of unwanted items and enables the recipient to review the list of donated items at an early stage. However, it does not exclude costs being paid by the recipient, if prior notice has been given and agreement has been reached.

Federal permits

10. The export of certain drugs, including drugs of addiction, i.e. drugs listed in Schedule 8 of the Standard for the Uniform Scheduling of Drugs and Poisons, psychotropic substances such as stimulants, barbiturates and benzodiazepines as well as drugs and chemicals of concern such as ephedrine and pseudoephedrine, requires a written permission to export from the Commonwealth Department of Health and Ageing. This written permission must be obtained prior to the shipment leaving Australia. Special conditions apply to the issue of a written permission to cover an immediate response to an emergency situation. The person responsible for shipping the donation should contact:

    The Assistant Director
    Treaties and Monitoring Secretariat Section
    Department Health and Ageing
    PO Box 100
    WODEN ACT 2606
    Telephone: (02) 6270 4331[a]

    – with a list of drugs proposed to be donated, to confirm whether a licence and export permit is required.

    If the items do not require an export permit, and provided that the drugs have been legally acquired within Australia, are not for commercial supply and are not intended for use in clinical trials, there is no requirement to provide any documentation to the federal authorities.

How can Australians help?

The most appropriate response to appeals for help or ongoing assistance to developing countries is a financial contribution.

It is usually cheaper for drugs to be purchased locally, or from specialist non-profit procuring agencies which are closer to the scene. Local procurement, which involves only a fraction of the transport costs, encourages locally sustainable drug availability and support for local industry is a more development-oriented approach. Provision of funds for direct procurement from specialist non-profit agencies, such as the International Dispensary Association (IDA), is the most helpful strategy when supplies are not available locally.

In emergencies, the most appropriate action may be the purchase of World Health Organization Emergency Health Kits which include drugs and medical supplies for a population of 10,000 people for three months. Delivery within 48 hours can be arranged through:

1. IDA - International Dispensary Association
   PO Box 37098
   1030 AB Amsterdam
   THE NETHERLANDS
   Telephone: 31-20-403-3051
   Facsimile: 31-20-403-1854
   Email: ida_sale@euronet.nl

or

2. UNICEF - United Nations Children's Fund
   Unicef Plads - Freeport
   DK-2100 Copenhagen 0
   DENMARK
   Telephone: 45-35-273-527
   Facsimile: 45-35-269-421
   Email: supply@unicef.dk

Donations of funds for purchase of these kits can be very helpful.

Donors wishing to identify the coordinating agency for a current emergency can find information on the internet through the United Nations Departments UNDHA - UN Department of Humanitarian Affairs:

UNDHA www.un.org/Depts/dha
Relief www.reliefnet.org

Alternatively information can be sought from:

- Medical Advisor, Australian Red Cross National Office, telephone: (03) 94180 5200b
- Medical Advisor, Médecins sans Frontières, National Office, telephone: (02) 9319 3500c
- Emergency Program Officer, AusAID Human Relief Programs, telephone: (02) 6206 4586

Further information

WHO. Guidelines for drug donations. Geneva: WHO, 1996. (WHO/DAP/96.2)

Interagency Guidelines for Drug Donations, 1999. Published on behalf of agencies by the World Health Organization.

Guidelines for donors and recipients of pharmaceutical donations. Geneva: Christian Medical Commission of the World Council of Churches, 1990.

The New Emergency Health Kit. Geneva: World Health Organization, 1990.

The use of essential drugs. Geneva: World Health Organization, 1992. Technical Report Series 825.

a. Contact details have changed. Contact: Treaties and Compliance Section, Office of Chemical Safety, Office of Health Protection, Department of Health and Ageing, GPO Box 9848, Canberra ACT 2601 MDP 88. Telephone: (02) 6160 3258. Fax (02) 6160 3260.

b. Contact details have changed. Telephone (03) 9345 1850.

c. Contact details have changed. Telephone (02) 9552 4933.

Evidence-based medicine: the basics

Australian pharmacists obtain much of their clinical information from a trusted hierarchy of publishers such as the Therapeutic Guidelines Group and the *Australian Medicines Handbook* and bodies such as the Pharmaceutical Society of Australia, the National Prescribing Service and the Department of Veterans' Affairs. Information from these sources and peak body clinical guidelines has been critically appraised using evidence-based medicine (EBM) principles and is presented in a manner that facilitates its application to individual patients.

Clinical decisions should not be based solely on evidence, however; they should be an integration of:

- the best available evidence
- professional judgment to interpret the relationship between clinical trial participants and individuals in your care
- consideration of patient factors.

Following are some definitions and principles of EBM to assist in the interpretation of trusted clinical information.

Levels of evidence[1,2]

Evidence can be graded according to its level, quality, relevance and strength. The 'level' of evidence refers to the design of the study used to obtain the evidence. The National Health and Medical Research Council's levels of evidence have been interpreted as:

I	a quality systematic review of two or more randomised control trials
II	well designed randomised controlled trial
III-1	well-designed pseudo-randomised controlled trials
III-2	cohort studies
III-3	comparative studies
IV	case series.

Study types[3]

Randomised controlled trial

A Randomised Controlled Trial (RCT) with adequate statistical power is considered the gold-standard study design to measure the effects of an intervention. Subjects are randomly allocated to receive either an intervention or a control (e.g. placebo or standard treatment). Randomisation minimises the likelihood that the effects observed are due to factors other than the intervention. Clinical trials are designed to have one or more endpoints. An endpoint is a measure that determines whether the intervention under study has an effect (e.g. whether a tumour shrinks after receiving chemotherapy).

Blinded study

One commonly used RCT is a blinded study. Blinding is a measure taken to avoid bias. It involves not disclosing which subjects in a study are allocated to which procedure (treatment). If both the experimenter and the subjects are unaware of the treatment allocation, the study is double blind. If, in addition, the statistical analysis is done in ignorance of the group to which subjects belong, the study is sometimes described as triple blind.

Systematic review

Systematic review involves the systematic location and appraisal of studies to allow the evidence from multiple studies to be combined. Systematic reviews are distinct from traditional literature reviews in that they are based on a strict scientific design to minimise bias and ensure reliability. When studies are similar in terms of the study question addressed and methods used, and are not statistically heterogeneous, results from the studies may be combined to calculate a summary estimate of effect.

Systematic review is particularly useful when no large RCTs exist, but a number of small RCTs have been conducted. Systematic reviews that use good quality RCTs are considered high-level evidence.

Not all published systematic reviews have been produced with meticulous care; therefore the findings may sometimes be misleading.

Meta-analysis

Meta-analysis is statistical technique that uses quantitative methods to synthesise and summarise the results of several studies in a single weighted estimate, in which more weight is given to results from higher quality studies. It is the statistical method usually used in systematic review.

Cohort study

A cohort study involves two groups (cohorts) of patients, one which receive the exposure of interest (e.g. smoking) and one which does not, then following these cohorts to observe for the outcome of interest (e.g. lung cancer). Cohort studies are useful when trying

to ascertain whether exposure to a certain factor is likely to cause specified events. Prospective cohort studies (which track participants forward in time) are more reliable than retrospective cohort studies.

Case-control study

A case-control study involves identifying people with a disease or condition (cases) and people from the same population who do not have that disease or condition (controls) and looking at how exposure to a suspect agent differed between the two groups. The exposure could be an environmental factor, a behavioural factor, or exposure to a drug or other therapeutic intervention. Case-control studies are retrospective (i.e. look back in time), whereas cohort studies are usually prospective (i.e. look forward in time).

A case-control study can be used to identify risks and trends and suggest possible causality for a disease or a particular outcome (e.g. adverse drug effect).

Case-control studies can generate odds ratios (ORs) only, not relative risk (RR).

Terminology[4–7]

Absolute risk

Absolute risk is the probability that a person will experience a specified outcome during a specified period.

In contrast with common usage, the word 'risk' may refer to adverse events (such as myocardial infarction) or desirable events (such as cure).

Absolute risk difference

Absolute risk difference is the difference in absolute risk of an outcome between the control group and the treatment group. This may be an absolute risk increase (ARI) or an absolute risk reduction (ARR).

An absolute risk difference of zero indicates no difference between the groups.

ARI is used when the risk in the treatment group exceeds the risk in the control group. It is calculated by subtracting the AR in the control group from the AR in the treatment group.

ARR is used when the risk in the control group exceeds the risk in the treatment group. It is calculated by subtracting the AR in the treatment group from the AR in the control group

Bias

Bias refers to systematic deviation of study results from the true results due to the way(s) in which the study is conducted. It can arise from systematic differences in the groups that are compared (selection bias); the care that is provided or exposure to other factors apart from the intervention of interest (performance bias); withdrawals or exclusions of people entered into the study (attrition bias); or how outcomes are assessed (detection bias). Bias does not necessarily carry an imputation of prejudice, such as the investigators' desire for particular results.

Confidence interval

The range of values within which the true value for a population (as estimated by subjects in studies) is likely to lie is called the confidence interval (CI). Most often a 95% confidence interval is calculated. If, for example, the relative risk (as measured in a study) of breast cancer after five years' HRT use is calculated as RR = 3.0 (95% CI: 2.5–3.8), this is interpreted as meaning that there is a 95% chance that the true relative risk lies somewhere in the CI range of 2.5–3.8. If the CI includes 1.0 in its range—e.g. RR = 3 (95% CI: 0.8–3.4)—the estimated RR is not statistically significant at that probability.

Cost–benefit analysis

Cost–benefit analysis assesses whether the cost of an intervention is worth the benefit by measuring both in monetary units.

Cost-effectiveness analysis

Cost-effectiveness analysis measures both costs and benefits of alternatives that have a common health outcome (e.g. stroke) to find the strategy with the best ratio of benefits to costs. Results are reported as cost per unit effect (e.g. cost per episode of stroke prevented).

Cost-minimisation analysis

Cost-minimisation analysis calculates the cost of two or more alternatives that have the same outcome in order to identify the lowest cost option. With medicines, this type of evaluation usually involves comparing efficacy and safety.

Cost–utility analysis

Cost–utility analysis provides a common unit of measurement when options being compared have different outcomes. Outcome measures involving length and quality of life such as quality-adjusted life-years (QALYs) are used. Results are often expressed as cost per QALY gained.

Direct and indirect costs

Direct costs can be directly associated with resource use for a health service or commodity. 'Indirect costs' often refers to productivity losses.

Economic evaluation

Economic evaluation involves methods by which the costs and consequences of health interventions are identified, measured and analysed. It encompasses cost-benefit, cost-minimisation, cost–utility and cost-effectiveness analyses.

Effectiveness

Effectiveness is the extent to which an intervention does 'good relative to harm'. An effective treatment or intervention is effective in real-life circumstances, not just in an ideal situation.

Efficacy

Efficacy is the extent to which an intervention improves the outcome for people under ideal circumstances. Testing efficacy means finding out whether something is capable of causing an effect at all.

Hazard ratio

Hazard ratio measures relative hazard between two groups. This is broadly equivalent to relative risk, the hazard ratio (HR) is useful when the risk is not constant with respect to time. It uses information collected at different times. The term is typically used in the context of survival over time. For example, if the HR is 0.5 then the relative risk of dying in one group is half the risk of dying in the other group.

Health economic modelling

Health economic modelling applies evidence from randomised trials to real-life settings in order to better judge a drug's clinical and economic performance. It may be used to extend surrogate outcomes (such as blood pressure reduction) to clinical end points (cardiovascular events prevented), to extend findings of studies to likely duration of use, and to examine the impact of differences between study subjects and patients likely to receive the drug in clinical practice.

Heterogeneity

In the context of meta-analysis, heterogeneity means dissimilarity between studies. It can be because of the use of different statistical methods (statistical heterogeneity) or evaluation of people with different characteristics, treatments or outcomes (clinical heterogeneity). Heterogeneity may render pooling of data in meta-analysis unreliable or inappropriate.

Intention to treat

Intention to treat is a method of analysis for randomised trials in which all patients who are randomised to a treatment arm are analysed together, regardless of whether or not they completed or received that treatment, in order to preserve randomisation.

Number needed to harm

Number needed to harm (NNH) is an epidemiological measure that indicates how many patients need to be exposed to a risk factor to cause harm in one patient that would not otherwise have been harmed. It is defined as the inverse of the attributable risk (i.e. NNH = 1/ARI). The lower the NNH, the worse the risk factor.

Number needed to treat

Number needed to treat (NNT) is an estimate of how many people need to receive a treatment for a certain period before one person would experience the outcome measured. For example, if you need to give a stroke prevention drug to 20 people before one stroke is prevented, the NNT for that stroke prevention drug is 20. It can be calculated in a number of ways; the simplest is to calculate the reciprocal of absolute risk reduction, with ARR expressed as a decimal.

Odds

'Odds' refers to the probability that an event will occur, expressed as a proportion of the probability that the event will not occur.

Odds ratio (OR)

The Odds ratio (OR) is a measure of treatment effectiveness. It is the odds of an event happening in the experimental group expressed as a proportion of the odds of an event happening in the control group. The closer the OR is to one, the smaller the difference in effect between the experimental intervention and the control intervention. If the OR is greater (or less) than one, the effects of the treatment are more (or less) than those of the control treatment. The effects being measured may be adverse or desirable.

For most clinical trials where the event rate is low (i.e. less than 10% of all participants have an event), the odds ratio and relative risk can be considered interchangeable. The relative risk and odds ratio will also be closer together when the treatment effect is small (i.e. OR and RR are close to 1) than when treatment effect is large. However, as the event rate increases above 15% or as the treatment effect becomes large, the OR will progressively diverge from the RR.

Power of a study

The power of a study is the probability of detecting a pre-specified difference between treatments if that difference truly exists.

P-value

The p-value is probability that an observed or greater difference occurred by chance, if it is assumed that there is in fact no real difference between the effects of the interventions. The lower the p-value the more likely it is that the difference between groups was caused by the intervention. If this probability is less than 1 in 20 (i.e. the p-value is less than 0.05) the result is conventionally regarded as being 'statistically significant'.

Quality-adjusted life-years

Quality-adjusted life-years is a common measure of health status that includes both duration and quality of life.

Relative risk

Also called the risk ratio, the relative risk (RR) is the number of times more likely (RR>1) or less likely (RR<1) an event is to happen in one group compared with another. For example, if RR = 3.0, the effect is about three times more likely to happen, and 0.3 means it is three times less likely to happen. An RR of 1.0 means there is no apparent effect on risk.

RR is derived by dividing the absolute risk in the intervention group by the absolute risk in the control group. RR should be expressed with confidence intervals—e.g. RR 3.0 (95% CI: 2.5–3.8.

Relative risk reduction

The relative risk reduction (RRR) is the amount by which the relative risk has been reduced by treatment; it is calculated as 1 – relative risk. (RRR = 1 – RR) and is often expressed as a percentage. RRR may sometimes lead to overestimation of treatment effect. Using absolute risk reduction to represent an identical outcome will result in a lesser numerical value than RRR.

Sensitivity analysis

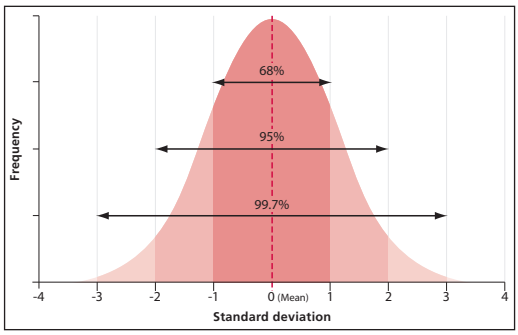
Sensitivity analysis assesses whether variations in the assumptions made in the modelling affect the results of an economic evaluation by testing how much the result changes when important parameters are varied.

Standard deviation

Standard deviation is a statistical measure of the distance a quantity is likely to lie from its average value (i.e. a measure of dispersion).

Plotting the frequency of variables such as height or weight in a large, random sample of people will result in a curve the shape of an inverted bell, known as a pattern of normal distribution. Approximately 70% of the people will fall within one standard deviation above and below the mean (see F.1). The more widely the scores are spread out, the greater the standard deviation and the greater the range (difference between the highest and lowest values) of values within the sample.[8]

Figure F.1 The normal distribution (bell curve)



The larger standard deviation indicates more scatter and less precision in the results. A smaller standard deviation indicates less scatter. Both sets of results have the same mean.

Statistical significance

'Statistically significant' means that the findings of a study are unlikely to be due to chance. Significance at the commonly cited 5% level (p <0.05) means that the observed result would occur by chance in only 1 in 20 similar studies. Statistically significant does not necessarily mean clinically important. It is the size of the effect that determines the importance, not the presence of statistical significance. Conversely, non-significance does not mean 'no effect'. Small studies often report non-significance even when there are important, real effects.

Surrogate outcomes

Surrogate outcomes are substitute measures of effect that may be easier, cheaper or quicker to measure than the most meaningful outcomes (e.g. blood pressure instead of cardiovascular events such as heart attack). Studies that use surrogate outcomes that are not validated as being appropriate replacements for particular end points should be interpreted as less convincing compared with studies that use morbidity and/or mortality measures.

Calculating risks and ratios from clinical trial outcomes[9]

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Example 1

In a trial of 441 patients at risk of developing pressure ulcers, patients were randomised to receive a sheepskin mattress overlay (intervention group) or usual treatment (control group) during their hospital stay. The results after 20 days of observation are shown in Table F.1.

Table F.1 Trial data of patients developing pressure ulcers

	Patients with ulcers	Patients with no ulcers	Total patients
Sheepskin group	21	197	218
Control group	37	186	223

The absolute risk reduction can be calculated by subtracting the proportion of patients with ulcers in the sheepskin group from that in the control group:

$$(37 / 223) - (21 / 218) = 0.07 \text{ (or } 50\%)$$

That is, the absolute risk of developing ulcers in the sheepskin group was 7% less than in the control group.

Relative risk can also be calculated from the data in the table:

$$(21 / 218) \div (37 / 223) = 0.58$$

In the trial 10% of patients in the sheepskin group developed ulcers compared with 17% in the control group. So the risk of getting ulcers with a sheepskin overlay was 0.58 of that in the control group.

The relative risk reduction in the trial was:

$$1 - 0.58 = 0.42$$

Sheepskin overlays reduced the risk of patients getting ulcers by 42%.

The odds ratio can be calculated by dividing the odds of getting an ulcer in the sheepskin group by the odds in the control group:

$$(21 / 197) \div (37 / 186) = 0.54$$

Therefore the odds of developing an ulcer in the sheepskin group were 0.54 of that in the control group, i.e. patients with a sheepskin overlay were half as likely to develop ulcers as patients given usual treatment.

The number needed to treat can be calculated as the reciprocal of absolute risk reduction:

$$1/0.07 = 14$$

That is, 14 patients need to have a sheepskin overlay for 20 days to prevent one of them from getting an ulcer.

Example 2

In an overview of randomised controlled trials of hypertension management, rates of stroke were measured in patients randomised to receive the experimental treatment or control. Results were analysed according to the severity of hypertension. This is shown in table F.2.

References

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9. Scott I. Interpreting risks and ratios in therapy trials. Aust Prescr 2008;31:12–16. At: www.australianprescriber.com/magazine/31/1/12/6.

Further information

See 'Information from the world wide web', Section F, for other relevant EBM internet sites.

Table F.2 Relation between relative risk, absolute risk and odds ratio

Disease severity	Event rate in control group (AR)	Event rate in experimental group (AR)	RR (RRR)	ARR	NNT	OR
Moderate hypertension	20%	12%	0.60 (0.40)	8%	13	0.54
Mild hypertension	1.5%	0.9%	0.60 (0.40)	0.6%	167	0.60

AR absolute risk RR relative risk RRR relative risk reduction ARR absolute risk reduction
NNT number needed to treat to prevent one stroke OR odds ratio

Information from the world wide web

The following list of websites is a starting point for locating information on the internet. It is not exhaustive. Note the following:

- Not all listed websites are peer reviewed.
- Some sites may be supported or sponsored by the pharmaceutical industry.
- Some sites have been developed by individuals or organisations not related to academic institutions, government or research agencies.
- Website addresses were correct and active at the time of printing.

Searching the internet

To effectively locate evidence-based clinical information, do three things:

- Use the right search tool.
- Plan a good search strategy.
- Use the best combination of keywords to search.

Google

www.google.com.au

A commonly used search engine. Results can be limited to Australian content by selecting the appropriate option.

Google Scholar

http://scholar.google.com.au

Locate clinical papers and abstracts in nominated libraries.

Internet Pharmacist

www.vts.intute.ac.uk/he/tutorial/pharmacist

A tutorial to help pharmacists learn about sources of evidence-based information available on the internet.

Medical Matrix

www.medmatrix.org/index.asp

The Medical Matrix Project (US) ranks internet resources based on their utility for point-of-care clinical application. Registration required.

Pharmacist-relevant sites

www.auspharmacist.net.au

A comprehensive directory of Australian and overseas websites such as pharmacy and medical resources, pharmacy organisations, search engines, and a range of useful links. Can be used as an internet browser 'home page'.

ToxSeek

http://toxseek.nlm.nih.gov

ToxSeek is a meta-search engine that enables simultaneous searching of different information resources.

TRIP database

www.tripdatabase.com/index.html

A specialised search engine to locate evidence-based medicine information. Simultaneously searches over 50 sources such as the Cochrane Database, the National Prescribing Service, POEMS, and Clinical Knowledge Summaries (CKS—previously PRODIGY).

Virtual Library—Pharmacy (International)

www.pharmacy.org

A comprehensive directory of pharmacy-related websites.

Virtual Pharmacy Centre: pharmacy, pharmacology, clinical pharmacology and toxicology (international)

www.martindalecenter.com/Pharmacy.html

University of California, Irvine Science Library. Medical dictionaries and glossaries, interactive anatomy browser, online journals, pharmacy courses, tutorials and lectures, drug databases, pharmacy and pharmacology databases, pharmacy schools and associations, and so on. Some links may require subscription.

Where's the Evidence?

www.nhmrc.gov.au/nics

The National Institute of Clinical Studies (NICS). A tutorial and concise guide that lists reliable sources of free evidence-based online information.

Professional organisations—Australia

Association of Professional Engineers, Scientists and Managers, Australia

www.apesma.asn.au

The largest national non-profit organisation representing professional employees. The Pharmacist Division of APESMA represents both the industrial and the professional interests of community employee pharmacists.

Australian Academy for the History of Pharmacy

www.psa.org.au/site.php?id=56

The history of Australian pharmacy.

Australian Association of Consultant Pharmacy

www.aacp.com.au

Develops and administers the accreditation of pharmacists wishing to provide professional pharmacy services such as medication management reviews.

Australian College of Pharmacy Practice and Management

www.acp.edu.au

Formed by the amalgamation of the Australian College of Pharmacy Practice and the Australian Institute of Pharmacy Management. It develops and delivers education, training and research programs to contribute to the advancement of practice and management within the pharmacy and pharmaceutical industries.

Australian Self-Medication Industry

www.asmi.com.au

The peak industry body for the Australian self-care industry. Promotes the role of non-prescription medicines, both over-the-counter (OTC) and complementary.

Medicines Australia

www.medicinesaustralia.com.au

Represents pharmaceutical companies involved in the discovery, development and manufacture of prescription medicines. The site includes the pharmaceutical industry code of conduct.

Pharmaceutical Society of Australia

www.psa.org.au

Represents the professional interests of Australia's pharmacists. The website describes the activities and charter of the PSA, provides contact details for PSA officials and office bearers, and describes professional standards, policies and guidelines, programs, activities, conferences and educational events.

Rural and remote pharmacy

www.ruralpharmacy.com.au

The aim of the Rural and Remote Pharmacy Workforce Development Program is to implement strategies to strengthen and support the rural and remote pharmacy workforce in Australia. The site contains links to programs being supported by the third and fourth Community Pharmacy Agreement under the Rural Pharmacy Allowance and Support Program.

The Society of Hospital Pharmacists of Australia

www.shpa.org.au

The professional body representing pharmacists practising in Australian hospitals and similar institutions.

The National Aboriginal Community Controlled Health Organisation

www.naccho.org.au

NACCHO represents the health interests of Aboriginal communities at the national level. It promotes holistic and culturally appropriate health.

The Pharmacy Guild of Australia

www.guild.org.au

The organisation representing community pharmacy owners. The website contains information on programs funded under Community Pharmacy Agreements and links to the websites for each state branch.

Professional organisations—international

American Institute of the History of Pharmacy

www.pharmacy.wisc.edu/aihp

A non-profit organisation devoted to advancing knowledge and understanding of the place of pharmacy in history.

American Pharmacists Association

www.pharmacist.com

The largest association of pharmacists in the United States. This site provides specific continuing education, drug information and publications; see also APhA's consumer site, www.pharmacyandyou.org.

American Society of Consultant Pharmacists

www.ascp.com

Articles and information about consultant pharmacy, senior care pharmacy and clinical issues.

Canadian Pharmacists Association

www.pharmacists.ca/content/about_cpha/index.cfm

The national voluntary organisation of pharmacists. The website has details of the organisation's programs and services, including professional standards.

Drug Information Association

www.diahome.org

A non-profit multidisciplinary scientific association which provides a global forum for the exchange and dissemination of information on the discovery, development, evaluation and utilisation of medicines and related health care technologies.

International Pharmaceutical Federation

www.fip.org

A world-wide federation of national pharmaceutical (professional and scientific) associations.

National Community Pharmacists Association

www.ncpanet.org

Represents pharmacy owners, managers, and employees of independent community pharmacies in the United States.

National Pharmaceutical Association

www.npa.co.uk

The national body of Britain's community pharmacy owners.

Pharmacy Council of New Zealand

www.pharmacycouncil.org.nz

Responsible for the registration of pharmacists, and the setting of standards for pharmacists' education, and for scopes of practice and conduct.

Pharmacy Guild of New Zealand

www.pgnz.org.nz

Represents the interests of retail pharmacy in New Zealand.

Pharmaceutical Society of New Zealand

www.psnz.org.nz

The professional body for pharmacists in New Zealand. The website contains information on practice standards, and educational programs, as well as pharmacy-related links.

Royal Pharmaceutical Society of Great Britain

www.rpsgb.org.uk

The professional body for pharmacists in the United Kingdom. The website contains information on education, practice, practice research, law and ethics, plus links to related organisations and publications such as the *Pharmaceutical Journal* and the British National Formulary.

Professional discussion forums

AACP discussion forum

www.aacp.com.au

Members of the Australian Association of Consultant Pharmacy may enter via the 'Members resources' section and communicate with other accredited pharmacists.

AusPharmList

www.auspharmlist.net.au

An active internet discussion group for Australian pharmacists and pharmacy students. Basic content is free to all registered users. Premium-level content requires subscription. Undergraduate pharmacy students are eligible for free access to premium content.

E-Drug

http://list.healthnet.org/mailman/listinfo/e-drug

Health care professionals, researchers and policy makers discuss current information on essential drugs, policy, program activities, education and training.

PSA e-Communities

www.psa.org.au

Pharmaceutical Society of Australia special interest group interactive forums for accredited pharmacists and rural pharmacists are available via the 'Pharmacist members' pages.

Government and regulatory bodies—Australia

Adverse Drug Reactions Advisory Committee

www.tga.gov.au/adr/adrac.htm

A subcommittee of the Australian Drug Evaluation Committee that advises the Therapeutic Goods Administration on the safety of medicines. Provides the *Australian Adverse Drug Reactions Bulletin* at www.tga.gov.au/adr/aadrb.htm and drug recall alerts at www.tga.gov.au/recalls/index.htm.

Australian Healthcare Association

www.aha.asn.au

The national body for publicly funded hospitals and health care organisations, including aged and extended care, primary care and community health.

Australian Institute of Health and Welfare

www.aihw.gov.au

Australia's national agency for health and welfare statistics and information.

Consumers' Health Forum of Australia

www.chf.org.au

Represents and involves consumers in health policy and program development, with a membership of about 100 health consumer organisations.

Department of Health and Ageing

www.health.gov.au

Website provides access to information on government health programs and initiatives, including the Pharmaceutical Benefits Scheme, and departmental contact details.

Department of Veterans' Affairs

www.dva.gov.au

Provides information pertaining to the care of veterans in the Australian health and social systems.

National Centre for Classification in Health

www2.fhs.usyd.edu.au/ncch

The National Centre for Classification in Health is the Australian centre of excellence in health classification theory and an expert centre in coding systems (especially ICD-10).

National Drugs and Poisons Schedule Committee

www.tga.health.gov.au/ndpsc

A subcommittee of the Therapeutics Goods Administration, responsible for the scheduling of chemical substances in the Standard for Uniform Scheduling of Drugs and Poisons. Website contains gazette notices, results of committee decisions and records of reasons.

National Health and Medical Research Council

www.nhmrc.gov.au

Promotes the development and maintenance of public and individual health standards in Australia.

National Medicines Policy

www.health.gov.au/internet/main/publishing.nsf/Content/National+Medicines+Policy-2

Website details the objectives and strategies of the National Medicines Policy (including quality use of medicines policies and evaluation). It has links to most other Government, medical and consumer bodies.

NSW Department of Health Clinical Information Access Project

www.clininfo.health.nsw.gov.au

provides evidence-based medicine reviews, *MIMS*, Medline, CINAHL, full Cochrane Library, Healthstar, Nursing, mental health journals, Micromedex, clinical policies, guidelines and procedures, and much more. Password access required for most content and generally limited to health professionals working in the NSW Department of Health.

Pharmaceutical Benefits Advisory Committee

www.health.gov.au/internet/main/publishing.nsf/Content/Pharmaceutical+Benefits+Advisory+Committee-1

Decides whether and how medicines should be subsidised in Australia.

Pharmaceutical Benefits Advisory Committee Public Summary Documents

www.health.gov.au/internet/main/publishing.nsf/Content/pbac-outcomes-and-public-summary-documents

Documents providing the rationale for specific PBAC recommendations, and information on the PBS listing process.

Pharmaceutical Benefits Schedule [online]

www.pbs.gov.au/html/home

Search all of the drugs listed on the Pharmaceutical Benfits Scheme, and regulations relating to the scheme.

Quality Use of Medicines Mapping Project

www.qummap.net.au

Maps Australian QUM activities.

Therapeutic Goods Administration

www.tga.gov.au

A division of the Commonwealth Department of Health and Ageing. The TGA aims to ensure that therapeutic goods are assessed for safety, quality and efficacy at a standard equal to that of comparable countries and that the Australian community has access, within reasonable time, to modern therapeutic advances.

Government and regulatory bodies—international

Canadian Adverse Drug Reaction Database

www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index-eng.php

Provides information about adverse drug reaction reports from Health Canada's CADRMP (Canadian Adverse Drug Reaction Monitoring Program) database.

National Institutes of Health

www.nih.gov

Provides US health information such as publications, clinical trials, health hotlines, special programs and clinical alerts.

The European Agency for the Evaluation of Medicinal Products

www.emea.europa.eu

European pharmaceutical regulatory website.

United Nations Office for the Coordination of Humanitarian Affairs

www.reliefweb.int/rw/dbc.nsf/doc100?OpenForm

ReliefWeb has information (documents and maps) on humanitarian emergencies and disasters. Designed to assist the international humanitarian community in the delivery of emergency assistance.

US Food and Drug Administration, Centre for Drug Evaluation and Research

www.fda.gov/cder

Provides US drug information, regulatory guidelines, new and generic drug approvals, consumer drug information and adverse drug reaction systems.

World Health Organization

www.who.int/en

WHO's objective is the attainment by all peoples of the highest possible level of health. This site has links to all areas of health management and research.

Medication safety

Guiding Principles to Achieve Continuity in Medication Management

www.health.gov.au/internet/main/publishing.nsf/Content/nmp-guiding

Document aimed at improving the safe and effective use of medicines as consumers move through different health care situations, including hospitals and residential and community care.

MedWatch

www.fda.gov/medwatch

An internet gateway for safety information on the drugs and other medicinal products regulated by the United States Food and Drug Administration.

Australian Commission on Safety and Quality in Health Care

www.safetyandquality.gov.au/internet/safety/publishing.nsf/Content/home

Aims to improve the safety and quality of health care provision in Australia. Provides links and resources for consumers and health care professionals.

Australian Patient Safety Foundation

www.apsf.net.au

A non-profit, independent organisation that provides leadership in the reduction of harm to patients in all health care environments.

The Institute for Safe Medicine Practices

www.ismp.org

A non-profit organisation that works closely with health care practitioners and institutions, regulatory agencies, professional organisations and the pharmaceutical industry to provide education about adverse drug events and their prevention.

University of Michigan Health System Patient Safety Toolkit

www.med.umich.edu/patientsafetytoolkit

Toolkit designed to assist best practice in patient safety.

Health statistics—Australia

Australian Institute of Health and Welfare

www.aihw.gov.au/index.cfm

Australia's national agency for health and welfare statistics and information.

Department of Health and Ageing Health Statistics

www.health.gov.au/internet/main/publishing.nsf/Content/Statistics-1

Australian government links to various types of federal health data.

Health statistics—international

Statistics at Square One

www.bmj.com/statsbk

One of the more comprehensive and easy to follow explanations of statistics published by the *British Medical Journal*.

WHO Collaborating Centre for Drug Statistics Methodology

www.whocc.no/atcddd

WHO explanations of anatomical therapeutic chemical coding and defined daily doses.

Epidemiology

Epidemiology for the Uninitiated

www.bmj.com/collections/epidem

The *British Medical Journal* provides a simple introduction to concepts and terminology in epidemiology.

Epidemiology Supercourse

www.pitt.edu/~super1

A global repository of lectures on public health and illness prevention, targeting educators around the world.

Informed Health Online

www.informedhealthonline.org/index.2.en.html

Cochrane Collaboration dictionary of epidemiology terms for consumers.

Seattle Epidemiologic Research and Information Centre

www.eric.seattle.med.va.gov/resources/external.html

Links to various epidemiology sites.

WWW Virtual Library: Epidemiology

www.epibiostat.ucsf.edu/epidem/epidem.html

Links to a wide range of epidemiology sites.

Evidence-based research

Bandolier

www.jr2.ox.ac.uk/bandolier/bandlink.html

Provides evidence-based advice about particular treatments or diseases.

British Medical Journal Clinical Evidence

www.clinicalevidence.bmj.com/ceweb/index.jsp

A medical resource for informing treatment decisions and improving patient care. Subscription required.

Cochrane Collaboration

www.cochrane.org

Prepares, maintains and promotes accessible systematic reviews of the effects of health care interventions.

Community Pharmacy Research Support Centre

www.communitypharmacyresearch.org

A database of Australian and international literature relating to community pharmacy practice research and the economics of professional pharmacist services.

Monash University Centre for Clinical Effectiveness

www.mihsr.monash.org/cce

Aims to improve health care by enabling evidence-based decision making. Site provides resources and links to databases and guidelines.

National Guidelines Clearinghouse

www.ngc.org

An initiative of the Agency for Healthcare Research and Quality and the United States Department of Health and Human Services. A resource for evidence-based clinical practice guidelines.

National Institute for Clinical Excellence

www.nice.org.uk

An independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill-health.

National Institute of Clinical Studies

www.nicsl.com.au

Works in partnership with consumers, health professionals and organisations, researchers and governments to close the gaps between evidence and clinical practice.

National Prescribing Service

www.nps.org.au

An independent, non-profit organisation funded by the Australian Government Department of Health and Ageing that provides accurate, balanced evidence-based information and services to health professionals and the community on quality use of medicines.

NPS RADAR

www.npsradar.org.au

Rational Assessment of Drugs And Research, an online service designed for health professionals and consumers. Provides timely and independent information on new medicines, revised PBS listings and commentary on newly published research relating to primary care. Free to register.

Oxford Centre for Evidence-Based Medicine

www.cebm.net/index.asp

Promotes evidence-based health care. Website contains a range of resources and links.

Patient Oriented Evidence that Matters (POEMS)

www.pharmj.com/noticeboard/series/poem.html

Website has a series of POEMS available free.

Users' Guides to Evidence-Based Practice

www.cche.net/usersguides/main.asp

The guides were originally published in the *Journal of the American Medical Association*. Provided by the Centre of Health Evidence.

Evidence-based product review

Healthy Skepticism

www.healthyskepticism.org

A non-profit organisation that aims to improve health by reducing harm from misleading drug promotion.

Quackwatch

www.quackwatch.com

A non-profit corporation whose purpose is to combat health-related fraud, myths, fads and fallacies.

Electronic journals

Many other major journals are available via the internet but mainly through subscription services. Check with the journal publisher for on-line information.

Australian Pharmacist

www.psa.org.au/site.php?id=41

Official journal of the Pharmaceutical Society of Australia. Table of contents and selected articles available to the public but PSA membership required for full online access.

Australian Prescriber

www.australianprescriber.com

Independent therapeutic information. Current and back issues are searchable. Consumer information and extensive links to other pharmacy and medical journals.

British Medical Journal

www.bmj.com

Original research papers free; remaining content free after one year.

Corey Nahman Free Pharmacy Journals

www.coreynahman.com/pharmacyjournals.html

Links to many free online pharmacy journals.

Journal of Pharmacy Practice and Research

www.shpa.org.au/docs/jppr_current.html

Official journal of the Society of Hospital Pharmacists of Australia.

Lancet

www.thelancet.com

Requires registration for limited access to articles if a non-subscriber.

Medical Journal of Australia

www.mja.com.au

Clinical articles and many guidelines.

Medscape

www.medscape.com

Provides clinical information and electronic notification. Free but requires registration.

Pharmaceutical Journal

www.pjonline.com

Official journal of the Royal Pharmaceutical Society of Great Britain. Free access to all research and education articles.

Free Medical Journals

www.freemedicaljournals.com

Dedicated to the promotion of free internet access to medical journals.

The New England Journal of Medicine

www.nejm.com

Subscription required for full-text articles but free registration allows access to articles older than six months.

US Pharmacist

www.uspharmacist.com

Free access to all research and education articles.

Therapeutic advice and information

Allergy

Australasian Society of Clinical Immunology and Allergy.

www.allergy.org.au

Allergy Society of South Africa. Up-to-date medical literature and information for consumers.

www.allergysa.org/allsa.htm

Arthritis/rheumatology

Arthritis Australia.

www.arthritisaustralia.com.au

Arthritis Foundation of America. Conventional and alternative therapies for the treatment of rheumatic diseases.

www.arthritis.org

Australian Rheumatology Association. Contains links to many rheumatological sites of interest to doctors and consumers.

www.rheumatology.org.au

American College of Rheumatology. Patient information, publications and press releases.

www.rheumatology.org/index.asp

National Health Priorities and Quality: arthritis and musculoskeletal conditions.

www.health.gov.au/internet/main/publishing.nsf/Content/pq-arthritis

Asthma

National Asthma Council Australia. Resources for health professionals and consumers, including the *Asthma Management Handbook*.

www.nationalasthma.org.au

Represents all the asthma foundations of Australia.

www.asthmaaustralia.org.au

Asthma Foundation of Victoria. Provides a range of resources about asthma.

www.asthma.org.au

The Australian Lung Foundation's *Guide to Lung Health & Respiratory Medicine*.

www.lungnet.org.au

National Health Priorities and Quality: asthma awareness campaign.

www.health.gov.au/internet/main/publishing.nsf/Content/health-pq-asthma-index.htm

Cancer

Australian Government National Health Priority Area: cancer. The site contains many links.

www.health.gov.au/internet/main/publishing.nsf/Content/pq-cancer

Promotes cancer research, prevention, early detection, treatment and education initiatives. Site lists patient support agencies and treatment guidelines in the 'Health professionals' section.

www.cancerinstitute.org.au

Memorial Sloan-Kettering Cancer Center. A United States institution devoted to patient care, education, and research into cancer. Site provides resources for consumers and health care professionals.

www.mskcc.org

Cardiovascular

National Heart Foundation of Australia. Information for consumers and health professionals.

www.heartfoundation.com.au

National Health Priorities and Quality: cardiovascular health.

www.health.gov.au/internet/main/publishing.nsf/Content/portal-Cardiovascular%20diseases

Wake Forest University Baptist Medical Centre. Hypertension and vascular disease.

www1.wfubmc.edu/hypertension

American Society of Hypertension.

www.ash-us.org

World Hypertension League. Dedicated to the control of arterial hypertension.

www.worldhypertensionleague.org/Pages/Home.aspx

National Stroke Foundation, Australia. Information for consumers and carers.

www.strokefoundation.com.au

Chronic Obstructive Pulmonary Disease

The Australian and New Zealand COPD reference site. Contains the COPD-X management guidelines.

www.copdx.org.au

The Australian government website. Contains links to articles and research.

www.healthinsite.gov.au/topics/Chronic_Obstructive_Pulmonary_Disease__COPD_

Site contains specific information on pharmacy-related smoking cessation and tobacco-control activities.

www.fip.org/projectsfip//pharmacistsagainsttobacco

Complementary medicine

United States National Centre for Complementary and Alternative Medicine. Dedicated to exploring complementary and alternative healing practices in the context of rigorous science and providing authoritative information to the consumer and health care professional.

www.nccam.nih.gov

The American Botanical Council. A non-profit organisation that aims to educate the public about beneficial herbs and plants, and to promote the safe and effective use of medicinal plants.

http://abc.herbalgram.org/site/PageServer

The European Scientific Cooperative on Phytotherapy. Represents national phytotherapy associations across Europe with the aim of advancing the scientific status of phytomedicines.

www.escop.com

HerbMed. Provides access to scientific data on the use of herbs for health. An evidence-based information resource for professionals, researchers and consumers.

www.herbmed.org

The Research Council for Complementary Medicine. Promotes and facilitates research in to complementary medicine to encourage safe and effective practice and improved patient care.

www.rccm.org.uk

The Therapeutic Goods Administration. Conducts assessment and monitoring to ensure complementary medicines available in Australia are of an acceptable standard.

www.tga.gov.au/cm/cm.htm

The Complementary Medicines Evaluation Committee. Provides scientific and policy advice relating to controls on the supply and use of complementary medicines. Also provides advice with particular reference to the safety and quality of products and, where appropriate, efficacy relating to claims made for products.

www.tga.gov.au/docs/html/cmec/cmec.htm

Dermatology

Eczema Association of Australia.

www.eczema.org.au

The New Zealand Dermatological Society.

www.dermnetnz.org

Diabetes

Diabetes Australia.

www.diabetesaustralia.com.au

American Diabetes Association. Up-to-date reviews and guidelines.

www.diabetes.org/homepage.jsp

Diabetes UK (formerly British Diabetes Association). Online support for people living with diabetes.

www.diabetes.org.uk

International Diabetes Institute, Australia. Information for doctors, health professionals and people with diabetes.

www.diabetes.com.au

The National Institute of Diabetes (United States) and Digestive and Kidney Diseases. Guidelines and patient education materials.

www2.niddk.nih.gov

National Health Priorities and Quality: diabetes.

www.health.gov.au/internet/main/publishing.nsf/Content/portal-Diabetes

Diabetes Centre. Centre for diabetes located at the Queen Elizabeth Hospital in South Australia. Resource for diabetes information and links to other diabetes-related sites.

www.diabetes.org.au/index.html

Drugs in sport

Australian Sports Anti-Doping Authority. Policy, trends and prohibitions on drugs in sports.

www.asada.gov.au

World Anti-doping Agency.

www.wada-ama.org

Epilepsy

Epilepsy Action Australia.

www.epilepsy.org.au

National Epilepsy Society, United Kingdom.

www.epilepsynse.org.uk/homepage

American Epilepsy Society.

www.aesnet.org

British Epilepsy Action.

www.epilepsy.org.uk/info

Incontinence

Continence Foundation of Australia.

www.contfound.org.au

Family planning

Comprehensive family planning site based at the Johns Hopkins University.

www.reproline.jhu.edu

Sexual health and family planning in NSW.

www.fpahealth.org.au

Sexual Health information from South Australia. Information on safer sex, relationships, contraception or sexually transmitted infections.

www.shinesa.org.au

International Planned Parenthood Federation. Contains statements on contraceptive methods and safe use.

www.ippf.org

Planned Parenthood. Concentrates mainly on emergency contraception, abortion and teenage pregnancy.

www.plannedparenthood.org/index.htm

Healthy living

Mayo Clinic. Information for a healthier life.

www.mayoclinic.com/index.cfm?

National Women's Health Resource Center. A non-profit organisation dedicated to helping women make informed decisions about their health; encourages women to embrace healthy lifestyles to promote wellness and prevent disease.

www.healthywomen.org

Better Health Channel. Health information from the Victorian Department of Human Services. Site contains healthy recipes and many articles about health.

www.betterhealthchannel.com.au/bhcv2/bhcsite.nsf

NSW Health site. The mental health section enables quick location of health services.

www.health.nsw.gov.au

HealthInsite. An Australian government initiative funded by the Department of Health and Ageing, it aims to improve the health of Australians by providing easy access to quality information.

www.healthinsite.gov.au

Immunisation

The *Australian Immunisation Handbook*, 9th edition.

www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/handbook-home

National Immunisation Advisory Structures. Weblinks to the policies and schedules for immunisation in Australia.

www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/atagi

National Immunisation Program Schedule. Guidelines outlining the recommended vaccine plan for the Immunise Australia Program.

www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/nips

Centers for Disease Control and Prevention.

www.cdc.gov/az/a.html

Infectious diseases

National Health and Medical Research Council. Recommended minimum periods of exclusion from school, preschool and childcare centres for cases of and contact with infectious diseases.

www.nhmrc.gov.au/publications/synopses/_files/ch43poster4.pdf

Communicable disease control, including advice on immunisation, travel and quarantine.

www.health.gov.au/internet/main/publishing.nsf/Content/Communicable%20Disease%20Control-4

United States National Foundation for Infectious Diseases.

www.nfid.org

Communicable Diseases Australia.

www9.health.gov.au/cda/Source/CDA-index.cfm

World Health Organization communicable disease surveillance and response.

www.who.int/csr/don/en

Injury prevention

Australian Injury Prevention Network.

www.aipn.com.au

National Health Priorities and Quality: injury prevention.

www.health.gov.au/internet/main/publishing.nsf/Content/portal-Injury%20prevention

Menopause

North American Menopause Society. Comprehensive site for information for both consumers and health professionals.

www.menopause.org

Australian Menopause Society. Aimed mainly at health professionals but does contain some information that can be used for patient printouts.

www.menopause.org.au

Mental health

Australian Alzheimer's Association.

www.alzheimers.org.au

Internet Mental Health. Major Depressive Disorder.

www.mentalhealth.com/dis/p20-md01.html

National Health Priorities and Quality: Mental Health and Wellbeing.

www.health.gov.au/internet/main/publishing.nsf/Content/portal-Mental%20health

Royal College of Psychiatrists. Mental Health Information.

www.rcpsych.ac.uk/mentalhealthinformation.aspx

SANE Australia. Focus on providing information about psychotic illnesses such as schizophrenia.

www.sane.org

Multiple sclerosis

Multiple Sclerosis Australia.

www.msaustralia.org.au

Muscular dystrophy

Muscular Dystrophy Association of Australia.

www.mda.org.au

Osteoporosis

Osteoporosis Australia.

www.osteoporosis.org.au

American National Osteoporosis Foundation.

www.nof.org

National Institutes of Health: Osteoporosis and Related Bone Diseases.

www.niams.nih.gov/Health_Info/Bone

Osteoporosis Centre. Endocrinology and Department of Nuclear Medicine at The Queen Elizabeth Hospital.

www.osteoporosis-centre.org

Palliative care

Palliative Care Australia. General palliative care information.

www.palliativecare.org.au

Cancer Council Australia. Information on palliative care.

www.cancer.org.au/Home.htm

Peter McCallum Cancer Centre.

www.petermac.org

Growth House. San Francisco based: provides information and referral services.

www.growthhouse.org

Canadian Hospice Palliative Care Association.

www.chpca.net/index.htm

Pathology

Labtests online. Information on laboratory tests and how they are used.

www.labtestsonline.org.au

Reference manual on the use and interpretation of pathology tests.

www.rcpamanual.edu.au

Poisons

Poisons prevention and education—New Zealand National Poisons Centre.

www.poisons.co.nz

Resources for consumers

National Prescribing Service. Search for consumer medicines information leaflets.

www.nps.org.au/site.php?page=2

Health Translations Directory. Victorian government health information. Search for online multilingual health resources from government departments, peak health bodies, hospitals, community health centres and welfare agencies.

www.healthtranslations.vic.gov.au/bhcv2/bhcht.nsf

Patient UK. A directory of UK health, disease and related websites. The site contains many information leaflets for consumers.

www.patient.co.uk

Sexually transmitted infections

International Herpes Management Forum. Management of herpes virus infection.

www.ihmf.org

Australian Herpes Management Forum. Management and control of herpes virus infection.

www.ahmf.com.au

American Herpes Foundation. Patient and physician information on herpes virus infection.

www.herpes-foundation.org

Clinic 275 (Royal Adelaide Hospital). Has section on genital herpes.

www.stdservices.on.net/clinic275/Default.htm

Australian Federation of AIDS Organisations.

www.afao.org.au

Toxicology

Toxicology Data Network includes databases on toxicology, hazardous chemicals, environmental health and related areas.

http://toxnet.nlm.nih.gov

Travel medicine

Communicable disease control, including advice on immunisation, travel and quarantine.

www.health.gov.au/internet/main/publishing.nsf/Content/Communicable%20Disease%20Control-4

United States Centers for Disease Control and Prevention. 'Traveller's health' section covers reference materials, outbreaks, travelling with children, special needs of travellers and vaccinations.

wwwn.cdc.gov/travel/default.aspx

The official Department of Foreign Affairs and Trade travel advisory service, to be read in conjunction with specific travel health sites information.

www.smartraveller.gov.au

The Travel Doctor.

www.tmvc.com.au/about.html

Medical Advisory Services for Travellers Abroad Australia. Basic overview of travel-related diseases. Need a password for the professional section of the site.

www.masta.org

International Society of Travel Medicine. Up-to-date news on disease outbreaks around the world.

www.istm.org

Shoreland's Travel Health Online. Comprehensive details on travel and health-related concerns for individual countries.

www.tripprep.com

World Health Organization. Reproduction of the *International Travel and Health Vaccination Requirements and Health Advice* book.

www.who.int/ith

Australian government advice about taking medicines out of Australia either for self-use or for humanitarian aid.

www.tga.gov.au/consumer/travellers.htm

References and databases—Australia

Australian Medicines Handbook

www.amh.net.au

Sample Product Information only. Requires subscription.

MIMS Online

www.mims.com.au

The MIMS range of publications covers an array of subjects and specialities. Requires subscription.

Therapeutic Guidelines

www.tg.com.au/home/index.html

Demonstration site. Subscription required for full-text or CD version.

References and databases—international

British National Formulary

www.bnf.org/bnf

Provides UK health care professionals with authoritative and practical information on the selection and clinical use of medicines. Registration required.

British Pharmacopoeia

www.pharmacopoeia.co.uk

Subscription required.

Clinical Trials.gov

www.clinicaltrials.gov

Provides information about federally and privately supported clinical research in human volunteers.

Merck

www.merck.com

Full text access to several of the Merck Manual series.

Micromedex

www.micromedex.com

Access to database on 1300 medicines plus alternative medicines database. Subscription required.

National Library of Medicine

www.nlm.nih.gov

Offers free access to Medline through PubMed, an abstracting database that allows searching of the biomedical literature.

www.ncbi.nlm.nih.gov/PubMed

Pharmaceutical Press

www.pharmpress.com

Publishers of *Martindale*, *Stockley's Drug Interactions*, *British National Formulary*, *Herbal Medicines* and others. Offers free online trials.

US Pharmacopoeia

www.usp.org

Subscription required but some information accessible.

Immunisation and cold chain management

Immunisation protects individuals against harmful infections. It also protects others in the community by increasing the general level of immunity and minimising the spread of infection.[1] Health professionals should take every opportunity to promote the proven effectiveness of immunisation in saving lives and preventing serious illness.[1]

Immunisation is not compulsory but is highly recommended for adults and children. Recommendations are often based on patient age, although some groups of people are at higher risk for acquiring certain infections (e.g. Aboriginal and Torres Strait Islander people, overseas travellers, people with an occupational risk) and so will have special vaccination requirements. Other groups of people may be more at risk of adverse events (e.g. pregnant women) or more at risk of having a suboptimal response to vaccination (e.g. people with impaired immunity due to disease or treatment) and will also have special vaccination requirements. All people, including parents and guardians, should have access to information to be able to make an informed choice about vaccination. Pharmacists can play a vital role in immunisation programs by being a source of current information.

Immunisation schedules and guidelines are, of their nature, dynamic and reflect the situation at any given time. The Immunise Australia Program website provides the most up to date information about Australian immunisation standards, including the latest edition of the National Health and Medical Research Council's *Australian Immunisation Handbook*.
See: www.immunise.health.gov.au.

Cold chain management in community pharmacy

The cold chain is the system of transporting and storing vaccines within the temperature range of +2 °C and +8 °C from the place of manufacture to the point of administration.[1]

In order to maintain the efficacy of vaccines, it is essential that they be stored under preferred conditions at all times. Both heat and freezing (≤0 °C) can adversely affect a vaccine. Freezing can cause an immediate loss of potency in cold- or freeze-sensitive vaccines. Exposure to repeated episodes of heat can cause a cumulative loss of potency that is irreversible.[1] Pharmacists should ensure maintenance of the cold chain (as outlined) in the storage and transport of vaccines.

Storage of vaccines

Pharmacists should be familiar with and adhere to the *National Vaccine Storage Guidelines: strive for 5*. These guidelines state that for vaccine storage, pharmacies require the following[2]:

- a reliable and stable refrigerator with adequate capacity
- accurate and reliable temperature monitoring equipment
- a written process for monitoring and recording temperatures
- an appropriately placed temperature probe
- education and information for everyone handling vaccines
- a maintenance schedule for temperature monitoring equipment, checking the accuracy of the thermometer and changing of the batteries
- a written process for dealing promptly with a cold chain breach
- a written process for ordering and rotating stock
- a written process for receiving vaccines
- a written process for managing a power failure.

Purpose-built vaccine refrigerators

The following are the recommended features of a purpose-built vaccine refrigerator[2]:

- It maintains a stable, uniform and controlled cabinet temperature unaffected by ambient temperature.
- It has defrost cycles that allow defrosting without rises in cabinet temperature.
- It has standard alarm and safety feature alerts.
- It has good temperature recovery.
- Nearly all the internal space can be used for storing vaccines.

Within a purpose-built vaccine refrigerator, vaccines can be stored in shallow plastic baskets or trays. To allow for air circulation, shelves should not be overfilled. Temperatures need to be monitored and recorded daily, even with purpose-built vaccine refrigerators.

Pharmacies wishing to comply with mandatory Quality Care Pharmacy Program (QCPP) standards must have an approved vaccine refrigerator. Further information can be found at www.guild.org.au/qcpp/content.asp?id=483.

Transporting vaccines

Cold chain monitors should accompany all vaccines during transport. These should be checked for colour change and the temperature recorded when a vaccine delivery arrives. There are dual time–temperature indicators that allow estimation of the duration of time the temperature exceeds a set threshold and freeze indicators that are activated at 0 °C. Freeze indicators are particularly recommended in Australia.[2]

If a cooler (e.g. *Esky, Willow*) is to be used for storing or transporting vaccines, be aware of the following[2]:

- These are not adequate for transporting vaccines over prolonged periods (more than eight hours) or in extreme conditions (specialised cold boxes are required in these situations).
- Freezing episodes occur easily, usually in the first two hours of packing.
- Only conditioned ice or gel packs should be used (i.e. packs that have been left at room temperature to allow the ice or gel at the core to rise to about 0 °C).
- Contents should be packed securely, and vaccines should be insulated so they do not come into contact with ice or gel packs.
- An insulated foil bag may be provided to patients when vaccines are to be transported directly to the general practitioner for immediate administration.
- The cooler should be kept out of direct sun.
- The temperature of the vaccines needs to be monitored.

A person purchasing a vaccine should be advised to obtain it immediately before attending their GP or clinic. If this is not possible, they need to be made aware of the risks of freezing and warming the vaccine and of safe storage procedures.

References

1. National Health and Medical Research Council. The Australian immunisation handbook. 9th edn. Canberra: NHMRC, 2008. At: www.immunise.health.gov.au.
2. Department of Health and Ageing. National Vaccine Storage Guidelines: Strive for 5. Canberra: Department of Health and Ageing, 2005. At: www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/provider-store.

Exclusion periods for infectious conditions

Children are reasonably well protected from infectious diseases at home because they do not come into contact with many people. The adults they do come into contact with are often immune to many childhood illnesses and so do not transmit the infection to children.

In childcare centres, preschools and schools, children are exposed to a large number of other children, providing an opportunity for infectious diseases to be spread. The spread of infectious diseases can be reduced by excluding a person who is known to be infectious from contact with others who are at risk of acquiring the infection.

The National Health and Medical Research Council has recommended minimum exclusion periods from schools, preschools and childcare centres for specific infectious conditions (see Table F.3).

The need for exclusion is dependent on the ease with which the infection can be spread, the ability of the infected person to follow hygiene precautions, and the severity of the disease.[1] The exclusion periods are based on the time that a person is likely to be infectious. They are *minimum* periods of exclusion and may need to be modified in individual cases as circumstances warrant.

In cases of doubt, or for guidance in cases of conditions not mentioned in Table F.3, advice should be sought from the appropriate clinician, school medical officer or medical officer of public health in your state or territory department of health. Similarly, advice on possible preventive measures should be sought if cases occur in boarding institutions among children housed in dormitory-type accommodation.

More information about preventing infectious diseases in children can be found on the National Health and Medical Research Council website (www.nhmrc.gov.au/publications/synopses/ch43syn.htm).

Child and youth health parent helplines can also provide information. The contact details for 24-hour parent helplines in Australia are as follows:

ACT
Parentline: (02) 6287 3833
Tresillian Parent Help Line: 1800 637 357
NSW
Parentline: 13 20 55
Tresillian Parent Help Line: (02) 9787 0855 (Sydney metro area) or 1800 637 357
Karitane Care Line: (02) 9794 1848 (Sydney metro area) or 1300 227 464
NT
Parentline: 1300 30 1300
QLD
Parentline: 1300 30 1300
Child Health Line: (07) 3862 2333 (Brisbane metro area) or 1800 177 279
SA
Parent Helpline: 1300 364 100
TAS
Parenting Line: 1800 808 178
VIC
Parentline: 13 22 89
WA
Parenting Line: (08) 6279 1200 or 1800 654 432

Table F.3 Recommended minimum exclusion periods for infectious conditions for schools, preschools and childcare centres[1]

This table was developed by the National Health and Medical Research Council. Copyright Commonwealth of Australia, reproduced by permission.

Condition	Exclusion of case	Exclusion of contacts
Amoebiasis (Entamoeba histolytica)	Exclude until there has not been a loose bowel motion for 24 hours	Not excluded
Campylobacter	Exclude until there has not been a loose bowel motion for 24 hours	Not excluded
Candidiasis	See 'Thrush'	
Chickenpox (Varicella)	Exclude until all blisters have dried. This is usually at least 5 days after the rash first appeared in unimmunised children and less in immunised children.	Any child with an immune deficiency (for example, leukaemia) or receiving chemotherapy should be excluded for their own protection. Otherwise, not excluded.
CMV (Cytomegalovirus infection)	Exclusion is NOT necessary	Not excluded
Conjunctivitis	Exclude until the discharge from the eyes has stopped unless doctor has diagnosed a non-infectious conjunctivitis.	Not excluded
Cryptosporidium infection	Exclude until there has not been a loose bowel motion for 24 hours	Not excluded
Diarrhoea (No organism identified)	Exclude until there has not been a loose bowel motion for 24 hours	Not excluded
Diphtheria	Exclude until medical certificate of recovery following at least 2 negative throat swabs, the first not less than 24 hours after finishing a course of antibiotics followed by another swab 48 hours later.	Exclude contacts that live in the same house until cleared to return by an appropriate health authority.
German measles	See 'Rubella'	
Giardiasis	Exclude until there has not been a loose bowel motion for 24 hours	Not excluded
Glandular fever (Mononucleosis, EBV infection)	Exclusion is NOT necessary	Not excluded
Hand, foot and mouth disease	Excluded until all blisters have dried	Not excluded
Haemophilus influenzae type b (Hib)	Exclude until the person has received appropriate antibiotic treatment for at least 4 days.	Not excluded
Head lice (Pediculosis)	Exclusion is NOT necessary if effective treatment is commenced prior to the next day at child care (i.e. the child doesn't need to be sent home immediately if head lice are detected).	Not excluded
Hepatitis A	Exclude until a medical certificate of recovery is received, but not before seven days after the onset of jaundice.	Not excluded
Hepatitis B	Exclusion is NOT necessary	Not excluded
Hepatitis C	Exclusion is NOT necessary	Not excluded
Herpes simplex (cold sores, fever blisters)	Exclusion is not necessary if the person is developmentally capable of maintaining hygiene practices to minimise the risk of transmission. If the person is unable to comply with these practices they should be excluded until the sores are dry. Sores should be covered by a dressing where possible.	Not excluded
Human Immunodeficiency Virus (HIV/AIDS)	Exclusion is NOT necessary. If the person is severely immunocompromised, they will be vulnerable to other people's illnesses.	Not excluded
Hydatid disease	Exclusion is NOT necessary	Not excluded
Impetigo (school sores)	Exclude until appropriate antibiotic treatment has commenced. Any sores on exposed skin should be covered with a watertight dressing.	Not excluded

Table F.3 Recommended minimum exclusion periods for infectious conditions for schools, preschools and childcare centres[1] (continued)

Condition	Exclusion of case	Exclusion of contacts
Influenza and influenza-like conditions	Exclude until well	Not excluded
Legionnaires' disease	Exclusion is NOT necessary	Not excluded
Leprosy	Exclude until approval to return has been given by an appropriate health authority	Not excluded
Measles	Excluded for 4 days after the onset of the rash	Immunised and immune contacts are not excluded. Non-immunised contacts of a case are to be excluded until 14 days after the first day of appearance of rash in the last case, unless immunised within 72 hours of first contact during the infectious period with the first case. All immunocompromised children should be excluded until 14 days after the first day of appearance of rash in the last case.
Meningitis (bacterial)	Exclude until well and has received appropriate antibiotics	Not excluded
Meningitis (viral)	Exclude until well	Not excluded
Meningococcal infection	Exclude until appropriate antibiotic treatment has been completed	Not excluded
Molluscum contagiosum	Exclusion is NOT necessary	Not excluded
Mumps	Exclude for nine days after onset of swelling	Not excluded
Norovirus	Exclude until there has not been a loose bowel motion or vomiting for 48 hours	Not excluded
Parvovirus infection (fifth disease, erythema infectiosum, slapped cheek syndrome)	Exclusion is NOT necessary	Not excluded
Pertussis	See 'Whooping cough'	
Respiratory Syncytial virus	Exclusion is NOT necessary	Not excluded
Ringworm/tinea	Exclude until the day after appropriate antifungal treatment has commenced	Not excluded
Roseola	Exclusion is NOT necessary	Not excluded
Ross River virus	Exclusion is NOT necessary	Not excluded
Rotavirus infection	Children are to be excluded until there has not been a loose bowel motion or vomiting for 24 hours	Not excluded
Rubella (German measles)	Exclude until fully recovered or for at least four days after the onset of the rash	Not excluded
Salmonella infection	Exclude until there has not been a loose bowel motion for 24 hours	Not excluded
Scabies	Exclude until the day after appropriate treatment has commenced	Not excluded
Scarlet fever	See 'Streptococcal sore throat'	
School sores	See 'Impetigo'	
Shigella infection	Exclude until there has not been a loose bowel motion for 24 hours	Not excluded
Streptococcal sore throat (including scarlet fever)	Exclude until the person has received antibiotic treatment for at least 24 hours and feels well	Not excluded
Thrush (candidiasis)	Exclusion is NOT necessary	Not excluded
Toxoplasmosis	Exclusion is NOT necessary	Not excluded

Table F.3 Recommended minimum exclusion periods for infectious conditions for schools, preschools and childcare centres[1] (continued)

Condition	Exclusion of case	Exclusion of contacts
Tuberculosis (TB)	Exclude until medical certificateis produced from an appropriate health authority	Not excluded
Typhoid, paratyphoid	Exclude until medical certificateis produced from an appropriate health authority	Not excluded unless considered necessary by public health authorities
Varicella	See 'Chickenpox'	
Viral gastroenteritis (viral diarrhoea)	Children are to be excluded until there has not been a loose bowel motion for 24 hours	Not excluded
Warts	Exclusion is NOT necessary	Not excluded
Whooping cough (pertussis)	Exclude until five days after starting antibiotic treatment or for 21 days from the onset of coughing	Contacts that live in the same house as the case and have received less than three doses of pertussis vaccine are to be excluded until they have had 5 days of an appropriate course of antibiotics. If antibiotics have not been taken, these contacts must be excluded for 21 days after their last exposure to the case while the person was infectious.
Worms	Exclusion not necessary if treatment has occured	Not excluded

References

1. National Health and Medical Research Council. Staying healthy in child care: preventing infectious diseases in childcare. 4th edn. Canberra: NHMRC, 2005. At: www.nhmrc.gov.au/publications/synopses/_files/ch43.pdf.

First aid for poisoning

Poisons information centres

It is recommended that pharmacists use the expertise available from Poisons Information Centres when they are asked for assistance in the event of accidental or intentional poisoning. Information on the management of poisoning changes over time, and Poisons Information Centres have access to current information.

Poisons information centres

	Telephone
Australia:	13 11 26
New Zealand:	0800 POISON (0800 764 766)

Poisons Information Centres provide:

- telephone assessment for patients exposed to suspected poisons, including advice on first aid, with referral to a medical facility where appropriate
- information for health professionals on the content of products and the management of poisoned patients
- advice on the initial management of bites and stings by venomous animals, insects and marine creatures
- information for the public on all aspects of poisoning.

Assessment of the likely severity of poisoning is difficult in both accidental and deliberate poisoning situations. Contact a Poisons Information Centre or a medical practitioner for guidance.

The following information may be required by the Poisons Information Centre to enable an accurate assessment of likely toxicity:

- substance involved in suspected poisoning (including ingredients and manufacturer, if available)
- type of exposure to the poison (e.g. ingested, inhaled, skin or eye contact, bite or sting)
- quantity of suspected poison taken or amount of exposure (may include dose form, strength of product and size of container)
- length of time since the exposure occurred
- patient details (e.g. age, weight, existing illnesses and current medication)
- any current signs or symptoms
- first aid treatment already given (if any).

Accidental poisoning

The great majority of accidental poisoning occurs in children under the age of five years, with 83% of childhood exposures reported in this age group.[1] Most children ingesting poisons do so in small quantities and suffer only minor symptoms. However, a small number of serious and in some cases life-threatening poisonings occur.[2,3] Some accidental poisoning occurs in adults through occupational exposures or through inappropriate use of or inadvertent exposure to domestic chemicals.

Therapeutic errors

Some accidental poisonings can result from medication errors in hospitals, residential facilities and individual homes. These may relate to prescribing, dispensing or administration of medicines. Commonly, an excessive dose of medication is taken or the patient receives medication intended for someone else—e.g. duplicate doses received from co-administration of paracetamol contained in cold and flu and pain preparations.

Intentional poisoning

Intentional poisoning is largely confined to adolescents and adults and commonly involves the ingestion of one or more medicinal products, frequently in association with alcohol. All such cases should be referred to a hospital or medical practitioner. Histories related by these patients (of substances, quantities and time since ingestion) may be inaccurate. Recreational poisoning may occur following the intake of alcohol and/or various illicit drugs or chemicals.

Immediate first aid

Immediate first aid treatment is aimed at prevention or reduction of harm for the patient.

In significant poisonings, this will be carried out in a hospital environment with access to appropriate resuscitation facilities and expertise.

The management of poisoning episodes should be based on a risk assessment using the patient's history and poison exposure.[4]

If the patient is unconscious and not breathing

- Ring, an ambulance.
- See basic life support for a person who collapses in 'Medical and surgical emergencies', Section F.

If the patient is unconscious but breathing

- Roll the patient on their side, with head down slightly to reduce the potential for choking should vomiting occur.
- Remove any obstructions to breathing and hold the person's jaw forward.
- Ring for an ambulance and transport the patient to hospital immediately.

If poison is in contact with skin

- Remove contaminated clothing.
- Wash the affected area thoroughly with cold or tepid water (not warm or hot).
- Call the Poisons Information Centre (13 11 26) with details of the product and seek advice.
- Do not attempt to neutralise the contaminant with another chemical.
- Do not apply lotions, ointments or creams unless instructed to do so by the Poisons Information Centre.

If poison is in the eyes

- Irrigate with gently running water for 15 minutes.
- Do not instil drops or apply ointments.
- If irritation persists or vision is affected, or as advised by the Poisons Information Centre, cover the eye and send the patient to hospital or a medical practitioner.

If poison is inhaled

- Remove the patient from exposure and place in fresh air if safe to do so.
- Remove any obstruction to breathing and use artificial respiration if necessary. Rescuers should take care not to be overcome by gas or fumes themselves. If mouth-to-mouth resuscitation is indicated, care should be taken not to inhale the expired air or to contaminate the mouth with highly toxic material (e.g. corrosive substances, cyanide).
- If the patient has obvious breathing difficulties ring for an ambulance and transport the patient to hospital as soon as possible.
- Call the Poisons Information Centre with details of the substance for further advice.
- Inhalation of some poisons can result in increasing respiratory symptoms over a number of hours. Patients with delayed or increasing respiratory symptoms should be referred to a medical practitioner.

If the poison has been taken by mouth

- Do not induce vomiting.
- In the case of corrosive or irritant substances, prompt dilution (with a small amount of water given slowly) may help reduce the severity of burns to the mouth, throat and oesophagus.

Gastrointestinal decontamination

Prevention of absorption of the poison is often employed in reducing the risk of serious toxicity. Gastrointestinal decontamination procedures are not without risk and should be reserved for cases where severe toxicity is anticipated.[5] In many cases supportive care in an appropriate medical facility is all that is required.

Telephone the Poisons Information Centre (13 11 26) to determine appropriate management.

Activated charcoal

The preferred dosage form is activated charcoal slurry in a dose of 1–2 g/kg body weight for children and 50–100 g for adults.

Activated charcoal will adsorb a range of commonly ingested poisons and reduce their absorption from the gastrointestinal tract. Activated charcoal tablets are not an effective adsorbent for poisoning situations and should not be used.

In rare circumstances, endotracheal intubation may be required before activated charcoal is administered. There is a substantial risk of charcoal aspiration (which can be fatal) if the patient's level of consciousness is depressed.

Activated charcoal should not be administered to patients in whom bowel sounds are absent.

Small or highly charged molecules bind poorly to charcoal, and charcoal is *not* indicated in poisoning by the following substances:

- acids
- alkalis
- button batteries
- cyanide
- ethanol
- fluoride preparations
- glycols and esters
- heavy metals
- iron salts
- lithium salts
- methanol
- potassium salts.

Activated charcoal may be indicated with these agents in situations where other substances are thought to also have been ingested.

Administering cathartics with activated charcoal has no proven benefit.[6] They should not be used routinely.

Whole-bowel irrigation

Whole-bowel irrigation is an alternative means of gastric decontamination. It involves administration of a large volume of iso-osmotic colonic lavage solution and it is useful in managing life-threatening poisoning involving sustained-release medications and medications not adsorbed by activated charcoal. This procedure should only be undertaken in a hospital setting. Details are available from Poisons Information Centres (13 11 26).

Gastric emptying

There is no added benefit from using gastric emptying plus activated charcoal over the use of activated charcoal alone.[7,8]

The use of ipecacuanha (ipecac) syrup to induce emesis is no longer recommended. It is less effective than activated charcoal in prevention of absorption of many common poisons and its use can interfere with subsequent patient management.

Ipecac syrup is still occasionally used. It would not be indicated for any patients located within 60 minutes of a medical facility or if activated charcoal was available and not contraindicated (this would include almost all patients presenting to pharmacies). In remote situations, the absence of appropriate alternatives and lack of medical facilities may support the use of ipecac syrup in limited circumstances.

Ipecac syrup should *only* be given on the specific advice of a medical practitioner or Poisons Information Centre.

Ipecac syrup is contraindicated when corrosive agents, hydrocarbon-based products or agents likely to produce seizures are ingested or if the patient is drowsy or likely to become so within 30 minutes.

Poisons Information Centre advice should be sought in determining appropriate management of all cases of poisoning.

Table F.4 Contact details for Poisons Information Centres

Australia, all states and territories—telephone (24/7): 13 11 26

New Zealand—telephone: 0800 POISON (0800 764 766)

Note: Urgent inquiries should not be forwarded by email or facsimile as there may be a delay in transmission.

New South Wales

The Children's Hospital at Westmead
Hawkesbury Road, Westmead, 2145
Fax: (02) 9845 3597
Internet: www.chw.edu.au/poisons

Queensland

Royal Children's Hospital, Brisbane
Herston Road, Herston, 4029
Fax: (07) 3252 1903
Email: poison_info@health.qld.gov.au
Internet: www.health.qld.gov.au/poisonsinformationcentre

Western Australia

Sir Charles Gairdner Hospital 2nd Floor, R Block,
Verdun St, Nedlands, 6009
Fax: (08) 9346 3493

Victoria

Austin Hospital
Studley Road, Heidelberg, 3084
Fax: (03) 9496 4912
Internet: www.austin.org.au/poisons

New Zealand

National Poisons Centre
PO Box 913, Dunedin, New Zealand
Telephone: 0800 POISON (0800 764766) [NZ only]
Fax: +64 3 477 0509
Email: poisons@otago.ac.nz
Internet: www.poisons.co.nz or www.toxinz.com

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Medical and surgical emergencies

All pharmacists should be familiar with the methods used to sustain life and prevent further injury in a variety of situations. Programs for training and maintenance of skills in first aid are readily available. Pharmacists are encouraged to maintain up-to-date training in this area.

As a trained observer, a pharmacist may be in a unique position to record information for a medical practitioner. Paramedics in all states and territories are skilled in advanced life support, including administration of drugs for resuscitation and cardiac defibrillation.

Basic life-support for a person who collapses

When someone collapses, irrespective of the apparent cause, look for and correct abnormalities in the sequence shown in Figure F.2, p. 453, while awaiting the arrival of an ambulance.

Ensure that all 'rescuers' are safe from danger. If there are two or more 'rescuers' available, have one person call immediately for an ambulance before providing direct assistance to the patient.

Take standard precautions to reduce the risk of acquiring transmissible diseases (e.g. wearing gloves, using a resuscitation mask).

Stimulate the person to see if there is any response (i.e. physically rouse firmly, but not violently, and shout).

Basic life-support technique

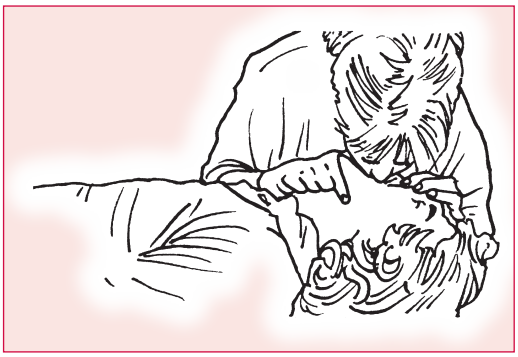
A—Airway

Inspect the mouth for foreign material and gently clear the airway by removing anything foreign and visible. Do not sweep a finger blindly about inside the mouth.

Check by looking at and feeling the chest wall for any evidence of spontaneous breathing. If there is none, tilt the head back and lift the jaw forward to open the airway. If this is ineffective, the jaw thrust manoeuvre should be used. Kneel down at the head of the person and grasp the angles of the mandible with both hands. Lift the mandible forward then, when the airway is open, rest the elbows on the surface on either side of the patient's head. Two rescuers will be required to perform ventilation when the jaw-thrust technique is used.[1]

B—Breathing

If the person is not breathing, for expired air resuscitation or mouth-to-mouth breathing, place the person on their back, open the airway, pinch the person's nostrils closed with one hand, and slightly open the mouth with the other. Breathe in, seal your mouth around the person's mouth, then breathe out, watching the chest rise as you do so. Take your mouth away, watch the chest fall, and feel the air being exhaled. For children, less volume and force are required. For infants, your mouth should cover the infant's mouth and nose. Mouth-to-mask may also be used. The breath rate recommended for expired air resuscitation only in adults and children is 12 per minute. When combined with external cardiac compression it is two breaths for every 30 compressions.[2]



C—Circulation

Check for a pulse. If the pulse is absent or cannot be confidently identified, begin external cardiac compression by placing the person on their back and depressing the lower half of the sternum 4–5 cm with the heels of both hands, at a rate of approximately 100 compressions per minute. Use the heel of one hand for children and two fingers for infants. Alternate

two breaths with 30 chest compressions.[3] The elbows should be straight and a rocking motion of the torso of the rescuer should be used to deliver effective compressions whilst minimising fatigue. In children, less force is required. It is very important that interruption of chest compressions is avoided whenever possible.[4]

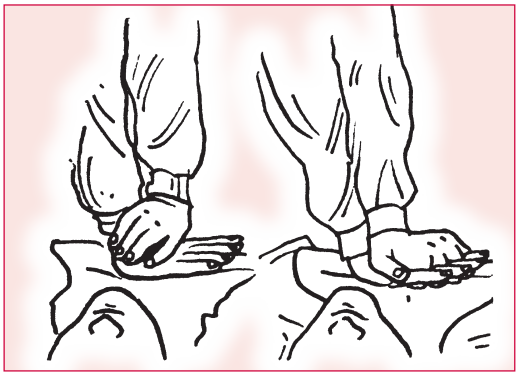
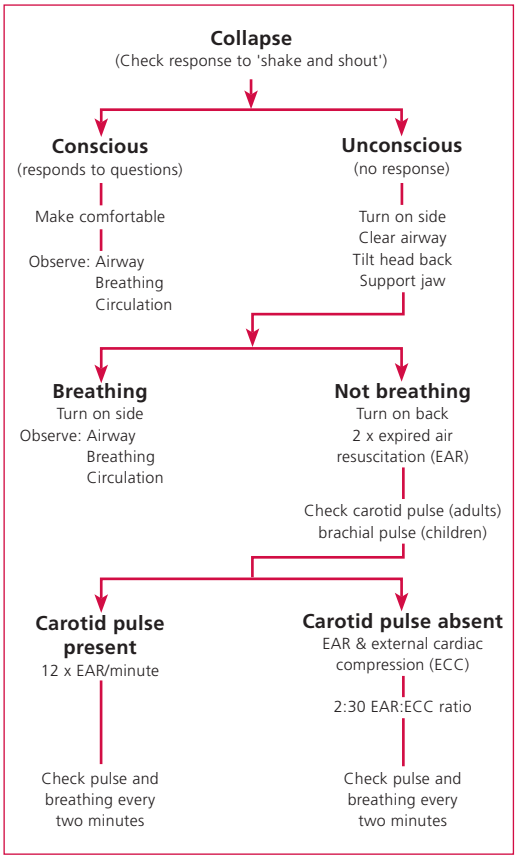


Figure F.2 Basic life-support technique



Guide to basic first aid

Accident victims

Any person involved in a high-velocity impact accident or the victim of any penetrating trauma (e.g. shooting or stabbing) needs ambulance and/or medical assessment.

First aid consists of maintaining the airway and breathing (see Figure F.2) and stopping external bleeding by the application of direct pressure to wounds. If the patient is unconscious, protect the neck to avoid spinal cord damage, although keeping the airway open takes precedence over spinal immobilisation. Jaw thrust is the preferred method for keeping the airway open. Head tilt and jaw lift should only be used if jaw thrust is ineffective.

Amputated parts

All amputated parts should be wrapped in saline soaked gauze then placed in a clean container. This container should be sealed and placed in another container of iced water while transport to hospital is arranged. Do not place ice directly against the amputated part and do not immerse the part in saline.

Bites and stings

In the event of bites by snakes, funnel-web spiders or blue-ringed octopus, immobilise the limb and apply a firm pressure bandage over the whole length of the limb in order to reduce lymph flow.[5] The exception is in the event of a red-back spider bite: in this case, a pressure bandage should *not* be applied as this only makes the pain worse.[6] The blue-ringed octopus (and some snakes) kill by causing muscle paralysis. Expired air resuscitation alone may be all that is required to keep the person alive until ambulance or medical help arrives. Symptoms arising from minor stings (bees, wasps, and so on) may be relieved by the application of ice or proprietary preparations. Medical attention should be sought for allergic reactions or multiple stings (more than 20 in an adult).

Burns

See 'Burns' in 'Wound management', Section D.

Chest pain

Cardiac pain is often dull or crushing in nature and may radiate to the arms, jaw, upper abdomen or back. Immediate medical attention should be sought if pain is suspected to be of cardiac origin and is new in onset, or increasing in duration, frequency or severity.[7] Suspected cardiac chest pain not relieved by two doses

of sublingual nitrates or with a duration of greater than 15 minutes is an indication for immediate ambulance transport to hospital. Many other serious causes of chest pain exist, somedical review should always be sought.

Choking

If a person who is choking is conscious, encourage coughing. Examine the mouth for a foreign body, which can be removed. If the person is losing consciousness deliver up to five back blows between the patient's scapula with the heel of the hand. Infants should be held face down over one arm or thigh whilst this is performed. Up to five chest thrusts should be used if back blows are ineffective. Chest thrusts are performed using the same technique as for external cardiac compression, but sharper and delivered at a slower rate. The airway should be checked after each chest thrust to see if the obstruction is relieved. If not, alternate five back blows and five chest thrusts.[1]

If the person stops or is not breathing, start expired air resuscitation.

Eye injuries

If chemicals have entered the eye, first remove any solid particles, then wash with copious quantities of water. This should continue for at least 30 minutes. The eye should then be covered with a pad strapped in place with adhesive tape. If there is physical trauma to the eye, cover the eye with an eye shield. Direct pressure on the globe itself should be avoided as this may worsen damage if ocular penetration has occurred.[8]

Medical attention should always be sought for eye injuries.

Fainting

Prior to fainting, a person typically feels unwell, or weak, turns pale or ashen, and has a slow pulse. A person with hypoglycaemia may faint, become confused or disorientated, or act as if drunk. Sweating may be present. If conscious, a glucose drink should be given. If unconscious, urgent medical help is required.

Fractures

Possible fractures should be immobilised with a splint and bandage. If the limb is deformed and the fingers or toes are white, urgent transport to hospital is required.

Pain

Severe pain is always potentially serious, and it is often difficult to distinguish a life-threatening condition from a harmless one. Therefore, referral to a medical practitioner is required.

Eye pain and earache need medical assessment regardless of severity.

Poisoning

See 'First aid for poisoning', Section F.

Respiratory distress

Any person who claims to be or appears to be having difficulty breathing requires close monitoring and referral to a medical practitioner. Sit the person comfortably upright; be calm and reassuring. Some conditions requiring medical assessment are:

- croup, epiglottitis or inhaled foreign body
- sudden swelling of face and neck, usually due to allergy. If the person has an adrenaline syringe for self-administration and/or a reliever inhaler and has difficulty breathing, these should be used
- asthma. If the person has a reliever inhaler, use the "4 x 4 x 4" first aid protocol. Give four puffs, one puff at a time, with four breaths after each puff. Use a spacer if available. Wait four minutes and then repeat. If there is little or no improvement, call an ambulance immediately and say the person is having an asthma attack. Keep administering the reliever until the ambulance arrives. For children, four puffs every four minutes is a safe dose. For adults, up to six to eight puffs may be given every five minutes for a severe attack.[9]

Seizures

The most common form of seizure is a generalised tonic-clonic seizure. The person may experience an 'aura' or warning of the attack prior to onset. They may then cry out and collapse at the onset of the seizure. A generalised seizure has a characteristic tonic (stiff) phase, and a clonic (alternating stiffness and relaxation) phase with jerky movements that usually last one to two minutes. There may be frothing of the mouth, cyanosis (blueness) or loss of bowel or bladder control.[10] This is followed by a period of unconsciousness, which usually resolves within 30 minutes. An accurate history of the sequence of events is an important part of the medical assessment.

Treatment is aimed at preventing injury and maintaining the Airway and Breathing. Roll the person onto their side in a 'coma' position until they awaken. Do not force the mouth open during the seizure nor attempt to insert anything in the mouth. An ambulance should be called for all people with seizures as some will have multiple seizures or require anticonvulsant drugs to terminate the seizure.

Tooth dislodgment (avulsion)

Replace the tooth in its socket and obtain immediate dental advice. If the tooth cannot be placed into the socket, then store in the person's mouth between the lower lip and the jaw until dental review.

A permanent tooth that is replaced within 30 minutes of being dislodged (avulsed) can often be successfully reimplanted. Replacing a baby (deciduous) tooth however, may damage the developing permanent teeth and should be avoided.[11]

If it is impossible to obtain immediate dental advice, place the tooth gently back into its socket:

- handle the tooth by its crown—not its root
- rinse tooth in saliva or milk if it is dirty—do not scrub
- place tooth gently back in place and hold it there (check it's the correct way round, and if it does not go back into place easily and without pressure, then store carefully to prevent it drying out)
- contact the dentist immediately—time is critical.

To store a dislodged tooth (in descending order of preference):

- store the tooth in milk (not water)
- hold it in the mouth between the cheek and gum (young children who may swallow the tooth should be asked to spit into a container in which to store the tooth)
- wrap the tooth in plastic ('cling') wrap (not tissue).

Unconsciousness

Unconsciousness may be due to many causes. In most cases, attention to Airway and Breathing is all that is required. Observation of the sequence of events leading to loss of consciousness is important. Take note of skin colour, sweating, paralysis, seizure activity, respiratory rate and character, and pulse rate and character.

Treatment consists of lying the person flat and elevating their legs, which usually results in return of consciousness within a minute and full recovery usually within 5–10 minutes. If the person is in the latter half of pregnancy, roll to the left side to avoid compression of the vena cava by the uterus.[7]

Referral for medical attention is recommended.

Violence

A person who behaves irrationally, is confused, appears 'drunk', or is aggressive or violent may have a medical (e.g. hypoglycaemia) or psychiatric condition contributing to this behaviour. If possible, talk to them calmly and reassuringly while assistance is obtained. Maintain a safe distance and do not approach or touch the person. Retreat if threatened whilst keeping the person within your view.[12]

Vomiting and diarrhoea

Vomiting and diarrhoea may lead to dehydration and severe illness requiring medical attention. Dehydration can occur over a period of 6–12 hours if fluid loss is severe. Use correctly formulated oral rehydration solutions where appropriate. Signs of dehydration include listlessness, pallor, dry mouth, reduced skin turgor, and depressed fontanelle in infants.

See 'Gastroenteritis in children', Section D.

Wounds

See 'Wound management', Section D.

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Further Information

First aid information is available via the St John Ambulance website at: www.stjohn.org.au/index.php?option=com_content&task=view&id=22&Itemid=34.

Travel medicine

At present over 5 million Australians travel overseas each year. Travel medicine encompasses the wide range of health and environmental issues that arise with the movement of large numbers of people, possibly with pre-existing illnesses, across borders into countries that have differing public health conditions, drug regulations, diseases and vectors. In addition, there can be inherent health problems in the travel process due to minimal mobility for long periods. Travel medicine is therefore an important area of health that requires the pharmacist to remain current in practice.

Preparation

Before undertaking short or long periods of travel it is ideal that the traveller identify what their likely destinations will be and whether they will be in urban or rural settings. Consideration of possible exposures is important for the medical practitioner to formulate likely risks of disease (e.g. infective diarrhoea, exacerbations of asthma or altitude sickness). The traveller must also identify any diseases or conditions (e.g. asthma, hypertension, pregnancy) that may interfere with therapy selection or may in themselves pose problems when travelling. The general practitioner may need to refer patients to a travel clinic or other specialist (e.g. to assess suitability to travel) but will need to provide a medical and medication history for optimal management. The pharmacist may be asked to provide a current medication history for the patient to carry for proof of medication legality. Complete labelling of each medication is essential for the patient and relevant authorities, including health professionals who may have contact with the patient while overseas.

Whenever possible, transportation of medications should be in the original labelled containers. It is important to keep the medications accessible in hand luggage. Some medications that usually require refrigeration can be used for a reduced period of time if not refrigerated (e.g. thyroxine, insulin): check the company-provided literature. A Medic Alert bracelet should be worn if there is a risk of loss of consciousness.

Travellers should also be alerted to the availability of counterfeit medications overseas.

All travellers should take out travel insurance: the costs of health care overseas can be prohibitive. If medical assistance is needed overseas the International Association for Medical Assistance to Travellers publishes a directory of English-speaking doctors and advice for travellers (www.iamat.org). In urgent situations people can seek help from the Department of Foreign Affairs and Trade's 24-hour consular service (tel: +61 2 6261 3305).

In addition to health factors, differing customs regulations between countries may cause problems when patients travel with medicines. Proof of need may be required in the form of a health summary provided by the medical practitioner. The patient will need to take sufficient quantities of their regular medicines. There are, however, legal restrictions on the quantity of PBS drugs a traveller can take overseas. The Medicare Australia website can aid in this calculation:

- www.medicareaustralia.gov.au/public/migrants/travelling/medicines.jsp
- www.medicareaustralia.gov.au/public/migrants/travelling/index.jsp
- www.tga.gov.au/consumer/travellers.htm.

Alternatively, call the 'Travelling with PBS medicine' inquiry line on 1800 500 147.

Vaccination

Vaccination for overseas travel is done to provide protection against certain infectious diseases that are more prevalent in overseas countries and occasionally to meet quarantine requirements. It is important that international travellers are aware that immunisation plays only a limited role in protection against travel-related infection, and they should be aware of other important means of protecting themselves. Specific vaccine requirements depend on a range of factors, such as destination, length and season of travel, intended activities and accommodation, specific exposures, and the medical history of the traveller.

Older travellers and those at risk should also consider influenza and pneumococcal vaccinations. Influenza vaccination is indicated annually for those aged 65 years or more and people with chronic diseases. Those travelling where they will be in confined spaces with other travellers such as buses and cruise trips are at greater risk. Pneumococcal vaccine is indicated every five years for everyone over 65 years of age, people with chronic diseases and post-splenectomy: www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/about.

Detailed information on immunisation for overseas travel can be obtained from organisations that have the

resources to update their information daily if required. It is important to consult the most recent information available, as specific recommendations can change in response to emerging disease patterns—e.g. www.tripprep.com/scripts/main/default.asp, www.cdc.gov.

In the event of a traveller becoming exposed to an unexpected infection (e.g. rabies), post-exposure vaccination may be required. In urgent situations people can seek help from the Department of Foreign Affairs and Trade's 24-hour consular service (tel: +61 2 6261 3305).

Education

Up-to-date travel medicine advice is particularly important for travellers with special needs, such as children, pregnant women, and people with immune suppression or chronic systemic diseases. It is important that travellers discuss with their health professionals how they will manage the long travel required to travel overseas from Australia, as well as management of their general health and wellbeing whilst they are away.

Those with a specific past medical history (e.g. deep vein thrombosis, chronic lung conditions, diabetes, cardiovascular disease, and immunocompromised patients) face particular challenges when travelling.

For most people, the baseline risk of a venous thrombo-embolism (VTE) event is very low. The average VTE risk for a middle-aged traveller is about one per 40,000 flights, with a risk of death from flight-related pulmonary embolism (PE) after an overseas trip of about one in every 2 million flights. For a traveller taking one overseas trip a year, this means the annual risk of death from flight-related VTE is some 100 times less than the average annual risk of death from a motor vehicle accident in Australia (www.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-strateg-communic-factsheets-vte.htm).

If travellers have one or more other risk factors (e.g. heart failure, obesity, old age), it is worth considering compression stockings and perhaps other interventions. Referral to their medical practitioner is required for risk–benefit assessment. All travellers should heed the advice to avoid too much alcohol, keep hydrated, perform simple exercises, and break the journey if possible.

Any person intending to travel overseas should be referred to the Department of Foreign Affairs and Trade's, Travel Advisory and Consular Assistance Service. This service offers comprehensive travel advice, including detailed information and numerous publications on staying healthy whilst travelling (e.g. *Travelling Well,* which includes information on taking prescription medicines overseas, vaccinations, and so on), travel advisories, information on travel insurance, embassies and consulates. This information can be accessed at www.smartraveller.gov.au/tips/travelwell.html or via the Smartraveller phone service tel: 1300 555 135.

Consider providing the PSA Pharmacy Self Care Fact Card *Travel Health* to any person intending to travel overseas.

Preventative medications

When vaccination is not available for infectious diseases there is a requirement for travellers to take preventative medications before entering an endemic area and for a period after leaving the area. Diseases such as malaria are prevalent in many countries that are popular with Australian holidaymakers. Each year it is estimated that 30,000 cases of malaria occur in non-immune travellers worldwide. The estimated mortality rate for falciparum malaria in non-immune adults is up to 5%, so prophylaxis is an important consideration for travellers.

The choice of chemoprophylaxis depends on prevalent endemic malarial species, susceptibility of the malarial parasites, intensity of transmission, risk of exposure, duration of stay, seasonal pattern, availability of reliable diagnostic tests and care for patients with malaria, potential adverse effects of medications, compliance issues, and the traveller's personal characteristics (e.g. diseases, age and pregnancy) and preferences.

Pharmacists should spend time with the traveller, explaining potential adverse effects and strategies to minimise them (e.g. sun protection for photosensitivity). Reference to the Consumer Medicine Information and the *Australian Medicines Handbook* will aid complete counselling.

For current recommended prophylaxis and treatment of malaria see:

- www.rph.wa.gov.au/malaria/prophylaxis.html
- www.iamat.org
- www.tripprep.com/scripts/main/default.asp
- www.cdc.gov.

Behavioural change

Some simple precautions can be taken in order to minimise risks associated with travel:

- Seek specialist travel health advice before travel.
- Eat only well-cooked foods; avoid raw or rewarmed food.
- Drink safe water, boiled or bottled only; do not drink local water from taps.
- Avoid unpasteurised dairy products.
- Wash and air-dry hands before eating.
- Choose safe modes of transport.
- Wear shoes or sandals.
- Avoid unprotected sexual contact.
- Avoid getting tattoos or body piercing.
- Avoid illicit drugs.
- Obtain travel insurance.
- Avoid contact with animals.
- Reduce exposure to mosquitoes and the risk of contracting malaria by:
  - minimising outdoor activities at the vector's feeding times (from dusk to dawn)
  - sealing off access to living and sleeping areas
  - limiting the use of perfumes, aftershaves and dark clothing
  - using insecticides and repellents.

For useful travel tips go to: www.smartraveller.gov.au/tips.

Further information

Centres for Disease Control. Health information for international travel 2005–2006. Atlanta US: Dept of Health and Human Services, Public Health Service. At: www.cdc.gov/travel.

Department of Foreign Affairs and Trade website: www.smartraveller.com.au.

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Drugs in sport

The use of drugs to enhance sporting performance is termed 'doping'. Athletes who may be tested by a doping control agency should ensure all medicines they take, prescription-only and over-the-counter, do not contain substances included in the World Anti-Doping Code list of prohibited substances (prohibited list).[1] The World Anti-Doping Authority has been responsible for preparing the list since 2004.

Athletes should take only medicines prescribed by a practitioner familiar with the list of prohibited medicines for the individual athlete's sport. To avoid inadvertent doping, athletes should be made aware that many nutritional supplements contain banned substances. Extreme caution should be used when considering the use of supplements of unknown quality or origin.[2,3]

Prohibited substances

A substance is included in the list of prohibited substances if it satisfies any two of the following criteria[4,5]:

- potential to enhance sport performance
- actual or potential risk to health
- violation of the spirit of sport.

The use of listed substances and practices are prohibited[1]:

- at all times—i.e. both during competition and out of competition (e.g. anabolic agents, hormones, beta$_2$ agonists, substances with anti-estrogenic activity and diuretics and other masking agents)
- during competition—those prohibited at all times in addition to listed stimulants, narcotics, cannabinoids and glucocorticosteroids
- in particular sports—e.g. archery and motor sports (alcohol); and shooting and billiards (beta-blockers).

The prohibited list also identifies specific substances and doping practices which are particularly susceptible to unintentional anti-doping rule violations because of their general availability in medicinal products.

Links to the current prohibited list can be found on the Australian Sports Anti-Doping Authority (ASADA) website (www.asada.gov.au). ASADA, an Australian government authority, deters athletes and sports officials from engaging in doping practices through education, drug and doping testing, advocacy, investigation and coordination of Australia's anti-doping program. It also has powers to investigate suspected cases of doping.

It is recommended that reference is always made to the current prohibited list, the ASADA *Anti-doping Handbook*[6], and/or the relevant national sporting organisation for sport-specific variations and newly listed substances or changes to the World Anti-Doping Code.

Further anti-doping information or confirmation of permitted use may be obtained by phoning the ASADA Anti-doping Hotline on 1800 020 506 (8 am – 8 pm, Australian Eastern Standard Time, seven days a week).

Therapeutic use exemption[6]

The use of some medications is permitted under specified conditions. The Australian Sports Drug Medical Advisory Committee (ASDMAC) is the body which grants such exemptions. If an athlete requires treatment with prohibited substances an athlete can apply to ASDMAC for a therapeutic use exemption form by mail or at www.asdmac.org.au.

For example, athletes using the beta agonists eformoterol, salbutamol, salmeterol or terbutaline must have a medical practitioner sign an exemption form specifying the substance, dosage, and duration of treatment and the diagnosis of asthma or exercise-induced bronchospasm.

Authorities should also be notified where glucocorticoids are:

- inhaled (for the treatment of asthma and/or allergic rhinitis)
- injected into joints, bursae or lesions but not intravenously or by intramuscular injection
- applied topically to the ear, the eye or the skin.

The athlete's state and national sporting organisation must be notified well in advance of any competition, and the onus is on the athlete to ensure that documentation is appropriate and timely.

Where a prohibited substance has been used appropriately during a medical emergency such as a hospital admission, a provisional therapeutic use exemption may be granted after the event. An application should be made as quickly as possible.

Process for athletes subject to doping control who are prescribed prohibited medications[6]:

1. Call the ASADA Anti-Doping Hotline on 1800 020 506, 8 am – 8 pm Australian Eastern Standard Time and check the status of the medication.
2. Check with the doctor and see if there is an alternative medication permitted that may be used.
3. If there is NO alternative medication permitted, the athlete and the doctor must complete a therapeutic use exemption form.
4. Obtain a therapeutic use exemption form via the ASDMAC website at www.asdmac.gov.au.
5. Complete and submit the therapeutic use exemption form with supporting medical evidence to the ASDMAC (NOT ASADA).
6. The therapeutic use exemption application is considered by ASDMAC, and it will notify the athlete whether the application has been approved or rejected.

ASADA advises athletes not to use a prohibited medication before to receiving the ASDMAC decision, unless it is in an emergency medical situation.

References

1. World Anti-Doping Authority. Prohibited list international standard. At: www.wada-ama.org. List is updated at least once a year.
2. Australian Sports Commission. AIS Sports Supplement Program. At: www.ais.org.au/nutrition/Supplements.asp.
3. Burke L, Deakin V, eds. Clinical sports nutrition. 3rd edn. Sydney: McGraw-Hill, 2006. At: Australian Institute of Sport. Supplements and Sports Foods—www.ausport.gov.au/ais/nutrition/publications/books/clinical_sports_nutrition.
4. Fricker PA. The anti-doping code in sport—update for 2004. Aust Prescr 2004;27:84–7.
5. Orchard JW, Fricker PA , White SL, Burke LM, Healey DJ. The use and misuse of performance-enhancing substances in sport. MJA 2006;184(3):132–6.
6. Australian Sports Anti-Doping Authority. 2008 ASADA anti-doping handbook. 11th edn. Canberra: ASADA, 2008. At: www.asada.gov.au/resources.

Food additives

The Australia New Zealand Food Standards Code is intended to implement uniform food standards across all Australian states and territories and New Zealand. One of its requirements is for food labels to list all ingredients in descending order of proportion by weight. More information on the Code can be found at www.foodstandards.gov.au.[1]

Food additives are usually intentionally added to achieve certain technological functions. They are required to be identified by their class or functional name (e.g. thickener, antioxidant, colour) and by an individual name or code number. The numbers used are based on an international system for identifing food additives; they replace long names on labels while still providing consumers with adequate information about the food additive's presence.[1]

Adverse reactions to additives in foods or medicines may include hives, headaches, mouth ulcers, nausea and asthma. Pharmacists can use the following list when assisting people with known hypersensitivities to identify products which are likely to cause reactions.[2]

Table F.5 List of food additives

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Code number	Prescribed name
100	Curcumin or Turmeric (colour)
101	Riboflavin or Riboflavin 5'-phosphate sodium (colour)
102	Tartrazine (colour)
103	Alkanet or Alkannin (colour)
104	Quinoline yellow (colour)
110	Sunset yellow FCF (colour)
120	Carmines or Carminic acid or Cochineal (colour)
122	Azorubine or Carmoisine (colour)
123	Amaranth (colour)
124	Ponceau 4R (colour)
127	Erythrosine (colour)
129	Allura red AC (colour)
132	Indigotine (colour)
133	Brilliant blue FCF (colour)
140	Chlorophyll (colour)
141	Chlorophyll-copper complex (colour)
142	Green S (colour)
143	Fast green FCF (colour)
150a	Caramel I (colour)
150b	Caramel II (colour)
150c	Caramel III (colour)
150d	Caramel IV (colour)
151	Brilliant black BN or Brilliant black PN (colour)
153	Carbon black or vegetable carbon (colour)
155	Brown HT (colour)
160a	Carotene (colour)
160b	Annatto extracts (colour)
160c	Paprika oleoresins (colour)
160d	Lycopene (colour)
160e	β-apo-8' Carotenal (colour)
160f	β-apo-8' Carotenoic acid or methyl ethyl ester (colour)
161a	Flavoxanthin (colour)
161b	Lutein (colour)
161c	Kryptoxanthin (colour)
161d	Rubixanthin (colour)
161e	Violoxanthin (colour)
161f	Rhodoxanthin (colour)
162	Beet red (colour)
163	Anthocyanins or Grape skin extract or Blackcurrant extract (colour)
164	Saffron or Crocetin or Crocin (colour)
170	Calcium carbonate (colour, anti-caking agent)
171	Titanium dioxide (colour)
172	Iron oxide (colour)
173	Aluminium (colour)
174	Silver (colour)
175	Gold (colour)
181	Tannic acid or tannins (colour, emulsifier, stabiliser, thickener)
200	Sorbic acid (preservative)
201	Sodium sorbate (preservative)
202	Potassium sorbate (preservative)
203	Calcium sorbate (preservative)
210	Benzoic acid (preservative)
211	Sodium benzoate (preservative)
212	Potassium benzoate (preservative)
213	Calcium benzoate (preservative)
216	Propylparaben or Propyl-p-hydroxy-benzoate (preservative)
218	Methylparaben or Methyl-p-hydroxy-benzoate (preservative)
220	Sulfur dioxide (preservative)
221	Sodium sulphite (preservative)

Table F.5 List of food additives (continued)

Code number	Prescribed name
222	Sodium bisulphite (preservative)
223	Sodium metabisulphite (preservative)
224	Potassium metabisulphite (preservative)
225	Potassium sulphite (preservative)
228	Potassium bisulphite (preservative)
234	Nisin (preservative)
235	Natamycin or Pimaricin (preservative)
242	Dimethyl dicarbonate (preservative)
249	Potassium nitrite (preservative, colour fixative)
250	Sodium nitrite (preservative, colour fixative)
251	Sodium nitrate (preservative, colour fixative)
252	Potassium nitrate (preservative, colour fixative)
260	Acetic acid, glacial (acidity regulator)
261	Potassium acetate or Potassium diacetate (acidity regulator)
262	Sodium acetates (acidity regulator)
263	Calcium acetate (acidity regulator)
264	Ammonium acetate (acidity regulator)
270	Lactic acid (acidity regulator)
280	Propionic acid (preservative)
281	Sodium propionate (preservative)
282	Calcium propionate (preservative)
283	Potassium propionate (preservative)
290	Carbon dioxide (propellant)
296	Malic acid (acidity regulator)
297	Fumaric acid (acidity regulator)
300	Ascorbic acid (antioxidant)
301	Sodium ascorbate (antioxidant)
302	Calcium ascorbate (antioxidant)
303	Potassium ascorbate (antioxidant)
304	Ascorbyl palmitate (antioxidant)
306	Tocopherols concentrate, mixed (antioxidant)
307	α-Tocopherol (antioxidant)
308	γ-Tocopherol (antioxidant)
309	δ-Tocopherol (antioxidant)
310	Propyl gallate (antioxidant)
311	Octyl gallate (antioxidant)
312	Dodecyl gallate (antioxidant)
315	Erythorbic acid (antioxidant)
316	Sodium erythorbate (antioxidant)
319	tert-Butylhydroquinone (antioxidant)
320	Butylated hydroxyanisole (antioxidant)
321	Butylated hydroxytoluene (antioxidant)
322	Lecithin (antioxidant, emulsifier)
325	Sodium lactate (acidity regulator, humectant, bulking agent)
326	Potassium lactate (acidity regulator, humectant, bulking agent)
327	Calcium lactate (acidity regulator)

Code number	Prescribed name
328	Ammonium lactate (acidity regulator)
329	Magnesium lactate (acidity regulator)
330	Citric acid (acidity regulator, antioxidant)
331	Sodium citrates (acidity regulator, emulsifier, stabiliser)
332	Potassium citrates (acidity regulator, stabiliser)
333	Calcium citrates (acidity regulator, stabiliser)
334	Tartaric acid (acidity regulator, antioxidant)
335	Sodium tartrates (acidity regulator)
336	Potassium tartrate or Potassium acid tartrate (acidity regulator, stabiliser)
337	Potassium sodium tartrate (acidity regulator, stabiliser)
338	Phosphoric acid (acidity regulator)
339	Sodium phosphates (acidity regulator, emulsifier, stabiliser)
340	Potassium phosphates (acidity regulator, emulsifier, stabiliser)
341	Calcium phosphates (acidity regulator, emulsifier, stabiliser, anti-caking agent)
342	Ammonium phosphates (acidity regulator)
343	Magnesium phosphates (acidity regulator, anti-caking agent)
349	Ammonium malate (acidity regulator)
350	Sodium malates (acidity regulator, humectant)
351	Potassium malates (acidity regulator)
352	Calcium malates (acidity regulator)
353	Metatartaric acid (acidity regulator)
354	Calcium tartrate (acidity regulator)
355	Adipic acid (acidity regulator)
357	Potassium adipate (acidity regulator)
359	Ammonium adipates (acidity regulator)
363	Succinic acid (acidity regulator)
365	Sodium fumarate (acidity regulator)
366	Potassium fumarate (acidity regulator)
367	Calcium fumarate (acidity regulator)
368	Ammonium fumarate (acidity regulator)
380	Ammonium citrate or triammonium citrate (acidity regulator)
381	Ferric ammonium citrate (acidity regulator, anti-caking agent)
385	Calcium disodium ethylenediaminetetraacetate or Calcium disodium EDTA (preservative, antioxidant)
400	Alginic acid (thickener, stabiliser)
401	Sodium alginate (thickener, stabiliser, gelling agent)
402	Potassium alginate (thickener, stabiliser)
403	Ammonium alginate (thickener, stabiliser)
404	Calcium alginate (thickener, stabiliser, gelling agent)
405	Propylene glycol alginate (thickener, emulsifier)
406	Agar (thickener, gelling agent, stabiliser)
407	Carrageenan (thickener, gelling agent, stabiliser)
407a	Processed eucheuma seaweed (thickener, gelling agent, stabiliser)

Table F.5 List of food additives (continued)

Code number	Prescribed name
409	Arabinogalactan or Larch gum (thickener, gelling agent, stabiliser)
410	Locust bean gum or Carob bean gum (thickener, stabiliser)
412	Guar gum (thickener, stabiliser)
413	Tragacanth gum (thickener, stabiliser)
414	Acacia or gum Arabic (thickener, stabiliser)
415	Xanthan gum (thickener, stabiliser)
416	Karaya gum (thickener, stabiliser)
418	Gellan gum (thickener, stabiliser, gelling agent)
420	Sorbitol or Sorbitol syrup (sweetener, humectant, emulsifier)
421	Mannitol (sweetener, humectant)
422	Glycerin or Glycerol (humectant)
431	Polyethylene (40) stearate (emulsifier)
433	Polysorbate 80 or Polyoxyethylene (20) sorbitan monooleate (emulsifier)
435	Polysorbate 60 or Polyoxyethylene (20) sorbitan monostearate (emulsifier)
436	Polysorbate 65 or Polyoxyethylene (20) sorbitan tristearate (emulsifier)
440	Pectins (thickener, stabiliser, gelling agent)
442	Ammonium salts of phosphatidic acid (emulsifier)
444	Sucrose acetate isobutyrate (emulsifier, stabiliser)
445	Glycerol esters of wood rosins (emulsifier, stabiliser)
450	Potassium pyrophosphate or Sodium acid pyrophosphate or Sodium pyrophosphate (emulsifiers, acidity regulators, stabilisers)
451	Potassium tripolyphosphate or Sodium tripolyphosphate (acidity regulator)
452	Potassium polymetaphosphate or Sodium metaphosphate, insoluble or Sodium polyphosphates, glassy (emulsifier, stabiliser)
460	Cellulose microcrystalline and powdered (anti-caking agent)
461	Methyl cellulose (thickener, stabiliser, emulsifier)
463	Hydroxypropyl cellulose (thickener, stabiliser, emulsifier)
464	Hydroxypropyl methylcellulose (thickener, stabiliser, emulsifier)
465	Methyl ethyl cellulose (thickener, stabiliser, emulsifier, foaming agent)
466	Sodium carboxymethylcellulose (thickener, stabiliser)
470	Aluminium, calcium, sodium, magnesium, potassium and ammonium salts of fatty acids (emulsifier, stabiliser, anti-caking agent)
471	Mono- and di-glycerides of fatty acids (emulsifier, stabiliser)
472a	Acetic and fatty acid esters of glycerol (emulsifier, stabiliser)
472b	Lactic and fatty acid esters of glycerol (emulsifier, stabiliser)
472c	Citric and fatty acid esters of glycerol (emulsifier, stabiliser)
472e	Diacetyltartaric and fatty acid esters of glycerol (emulsifier)
472f	Mixed tartaric, acetic and fatty acid esters of glycerol (emulsifier, stabiliser)
473	Sucrose esters of fatty acids (emulsifier)
475	Polyglycerol esters of fatty acids (emulsifier)
476	Polyglycerol esters of interesterified ricinoleic acid (emulsifier)
477	Propylene glycol mono- and di-esters or Propylene glycol esters of fatty acids (emulsifier)
480	Dioctyl sodium sulphosuccinate (emulsifier)
481	Sodium lactylate or Sodium oleyl lactylate or Sodium stearoyl lactylate (emulsifier, stabiliser)
482	Calcium lactylate or Calcium oleyl lactylate or Calcium stearoyl lactylate (emulsifier, stabiliser)
491	Sorbitan monostearate (emulsifier)
492	Sorbitan tristearate (emulsifier)
500	Sodium carbonate or Sodium bicarbonate (acidity regulator, raising agent, anti-caking agent)
501	Potassium carbonates (acidity regulator, stabiliser)
503	Ammonium bicarbonate or Ammonium hydrogen carbonate (acidity regulator, raising agent)
504	Magnesium carbonate (acidity regulator, anti-caking agent)
507	Hydrochloric acid (acidity regulator)
508	Potassium chloride (gelling agent)
509	Calcium chloride (firming agent)
510	Ammonium chloride (bulking agent)
511	Magnesium chloride (firming agent)
512	Stannous chloride (antioxidant)
514	Sodium sulfate (acidity regulator)
515	Potassium sulfate (acidity regulator)
516	Calcium sulfate (firming agent)
518	Magnesium sulfate (firming agent)
519	Cupric sulfate (mineral salt)
526	Calcium hydroxide (acidity regulator, firming agent)
529	Calcium oxide (acidity regulator)
530	Magnesium oxide (anti-caking agent)
535	Sodium ferrocyanide (anti-caking agent)
536	Potassium ferrocyanide (anti-caking agent)
541	Sodium aluminium phosphate (acidity regulator, emulsifier)
542	Bone phosphate (anti-caking agent, emulsifier)
551	Silicon dioxide, amorphous (anti-caking agent)
552	Calcium silicate (anti-caking agent)
553	Magnesium silicate or Talc (anti-caking agent)
554	Sodium aluminosilicate (anti-caking agent)
555	Potassium aluminium silicate
556	Calcium aluminium silicate (anti-caking agent)
558	Bentonite (anti-caking agent)
559	Aluminium silicate

Table F.5 List of food additives (continued)

Code number	Prescribed name
560	Potassium silicate (anti-caking agent)
570	Stearic acid or fatty acid (glazing agent, foaming agent)
575	Glucono d -lactone or Glucono delta-lactone (acidity regulator, raising agent)
577	Potassium gluconate (sequestrant)
578	Calcium gluconate (acidity regulator, firming agent)
579	Ferrous gluconate (colour retention agent)
580	Magnesium gluconate (acidity regulatory, firming agent)
586	4-Hexylresorcinol (antioxidant)
620	L-Glutamic acid (flavour enhancer)
621	Monosodium L-glutamate or MSG (flavour enhancer)
622	Monopotassium L-glutamate (flavour enhancer)
623	Calcium glutamate (flavour enhancer)
624	Monoammonium L-glutamate (flavour enhancer)
625	Magnesium glutamate (flavour enhancer)
627	Disodium 5'-guanylate (flavour enhancer)
631	Disodium 5'-inosinate (flavour enhancer)
635	Disodium 5'-ribonucleotides (flavour enhancer)
636	Maltol (flavour enhancer)
637	Ethyl maltol (flavour enhancer)
640	Glycine (flavour enhancer)
641	L-Leucine (flavour enhancer)
900a	Polydimethylsiloxane or Dimethylpolysiloxane (anti-caking agent, emulsifier)
901	Beeswax, white and yellow (glazing agent)
903	Carnauba wax (glazing agent)
904	Shellac (glazing agent)
905b	Petrolatum or Petroleum jelly (glazing agent)
914	Oxidised polyethylene (humectant)
920	L-Cysteine monohydrochloride (raising agent)
941	Nitrogen (propellant)
942	Nitrous oxide (propellant)
943a	Butane (propellant)
943b	Isobutane (propellant)
944	Propane (propellant)
946	Octafluorocyclobutane (propellant)
950	Acesulphame potassium (sweetener)
951	Aspartame (sweetener)
952	Calcium cyclamate or Sodium cyclamate or Cyclamate (sweetener)
953	Isomalt (humectant, sweetener, bulking agent, anti-caking agent)
954	Saccharin or Calcium saccharin or Sodium saccharin or Potassium saccharin (sweetener)
955	Sucralose (sweetener)
956	Alitame (sweetener)
957	Thaumatin (flavour enhancer, sweetener)
961	Neotame (sweetener)
965	Maltitol and Maltitol syrup or Hydrogenated glucose syrup (sweetener, stabiliser, emulsifier, humectant)
966	Lactitol (sweetener, humectant)
967	Xylitol (sweetener, humectant, stabiliser)
968	Erythritol (humectant, sweetener)
1001	Choline salts (emulsifier)
1100	a-amylase (enzyme)
1101	Proteases (papain, bromelain, ficin) (stabiliser, enzyme)
1102	Glucose oxidase (antioxidant)
1104	Lipases (enzyme)
1105	Lysozyme (enzyme, preservative)
1200	Polydextrose (humectant, bulking agent, stabiliser, thickener)
1201	Polyvinylpyrrolidone (stabiliser)
1400	Dextrin roasted starch (thickener, stabiliser)
1401	Acid treated starch (thickener, stabiliser)
1402	Alkaline treated starch (thickener, stabiliser)
1403	Bleached starch (thickener, stabiliser)
1404	Oxidised starch (thickener, stabiliser)
1405	Enzyme treated starches (thickener, stabiliser)
1410	Monostarch phosphate (thickener, stabiliser)
1412	Distarch phosphate (thickener, stabiliser)
1413	Phosphated distarch phosphate (thickener, stabiliser)
1414	Acetylated distarch phosphate (thickener, stabiliser)
1420	Starch acetate esterified with acetic anhydride (thickener, stabiliser)
1422	Acetylated distarch adipate (thickener, stabiliser)
1440	Hydroxypropyl starch (thickener, stabiliser)
1442	Hydroxypropyl distarch phosphate (thickener, stabiliser)
1450	Starch sodium octenylsuccinate (thickener, stabiliser)
1505	Triethyl citrate (antifoaming agent)
1518	Triacetin (humectant)
1520	Propylene glycol (humectant)
1521	Polyethylene glycol 8000 (antifoaming agent)

References

1. Food Standards Australia New Zealand. Food additives. At: www.foodstandards.gov.au.
2. Royal Prince Alfred Hospital, Allergy Unit. Food allergies & intolerances. At: www.cs.nsw.gov.au/rpa/allergy/resources/foodintol/ffintro.cfm.

Section G

Physicochemical data

Millimoles

A millimole (mmol) amount of a species (whether ionic or molecular) is one thousandth the amount of that species and contains as many elementary units as there are carbon atoms in 12 g of carbon 12.

The weight in grams of 1 mmol of a substance is one thousandth of its gram molecular weight. The use of millimoles is preferred to that of milliequivalents and use of equivalents should be discouraged.

The following table provides data on ions and salts commonly used in parenteral infusions.[1]

Table G.1 Millimoles for ions and salts

Ion	mg per mmol	Salt	mg of salt containing 1 mmol of ion
Na^+	23.0	Sodium acid phosphate ($NaH_2PO_4.2H_2O$)	156
		Sodium bicarbonate	84
		Sodium chloride	58.5
		Sodium citrate ($C_6H_5Na_3O_7.2H_2O$)	98
		Sodium hydroxide	40
		Sodium lactate	112
		Sodium phosphate ($Na_2HPO_4.12H_2O$)	179
K^+	39.1	Potassium acid phosphate (KH_2PO_4)	136
		Potassium bicarbonate	100
		Potassium chloride	74.6
		Potassium citrate ($C_6H_5K_3O_7.H_20$)	108.1
		Potassium phosphate (K_2HPO_4)	87.1
Ca^{2+}	40.0	Calcium chloride ($CaCl_2.2H_2O$)	147
		Calcium gluconate	448
Mg^{2+}	24.3	Magnesium chloride ($MgCl_2.6H_2O$)	203.3
		Magnesium sulfate ($MgSO_4.7H_2O$)	246
NH_4^+	18.0	Ammonium chloride	53.5
Cl^-	35.5	Ammonium chloride	53.5
		Calcium chloride ($CaCl_2.2H_2O$)	73.5
		Magnesium chloride ($MgCl_2.6H_2O$)	101.7
		Potassium chloride	74.6
		Sodium chloride	58.5
HCO_3^-	61.0	Potassium bicarbonate	100
		Sodium bicarbonate	84
		Sodium lactate[a]	112
HPO_4^{2-}	96.0	Potassium phosphate (K_2HPO_4)	174.2
		Sodium phosphate ($Na_2HPO_4.12H_2O$)	358
$H_2PO_4^-$	97.0	Potassium acid phosphate (KH_2PO_4)	136
		Sodium acid phosphate ($NaH_2PO_4.2H_2O$	156
Lactate	89.1	Sodium lactate[a]	112

a. Sodium lactate is sometimes required in terms of bicarbonate because lactate is metabolised to bicarbonate.

References

1. Lund W, ed. The pharmaceutical codex. 12th edn. London: The Pharmaceutical Press, 1994;46–50.

Isosmotic and isotonic solutions

Aqueous solutions are considered isosmotic with body fluids such as blood serum and lachrymal secretions when they have a freezing point depression of 0.52 °C or contain about 300 milliosmoles of solute.

The number (n) of osmoles per litre of solution is given by:

$$n = \text{molarity} \times P$$

where P is the number of osmotically active particles formed upon the effective dissociation of a molecule of solute.

Solutions which are isosmotic with body fluids are only considered to be isotonic if they satisfy the following criteria:

- Membranes in contact with the solution are impermeable to the solute.
- The solute does not alter the permeability of membranes to any other substance present.
- No chemical reaction leads to a change in the total concentration of dissolved ions or molecules.

Problems are often encountered with solutions of some substances, such as boric acid, urea, ethanol and certain other monohydric or polyhydric alcohols, as well as some local anaesthetics. These solutions cause haemolysis of red blood cells in isosmotic concentrations and hence are not isotonic with red blood cells.

When these conditions are satisfied, the isotonic concentration (per cent) of a substance is:

$$C_{iso} = \frac{0.52}{FD_{1\%}}$$

where $FD_{1\%}$ is the freezing point depression of a 1% solution.

Solutions which are hypotonic to blood and lachrymal secretions may be adjusted to isotonic behaviour by the addition of a suitable substance—usually sodium chloride or glucose.

To calculate the amount of adjusting material to be added, the following formula may be used:

$$w = \frac{0.52 - a}{b}$$

where:

w = the percentage w/v of the adjusting material;

a = the freezing point depression of the unadjusted solution (i.e. the freezing point depression of the solution of drug(s) and other substances); and

b = the $FD_{1\%}$ of the adjusting material.

Three points should be noted:

- The method assumes that freezing point depression (FD) is directly proportional to concentration for dilute solutions. In other words, a 2% solution of a drug will have twice the FD of a 1% solution of that drug, while a 0.25% solution will have one-quarter of the FD of a 1% solution. This is a close approximation for most drugs in dilute solution.
- The value 'a' is obtained by multiplying the $FD_{1\%}$ of the substance to be adjusted (i.e. the drug, sometimes referred to as the 'unadjusted substance') by the percentage strength of this substance. In other words, 'a' could be considered as equal to XY, where X = $FD_{1\%}$ of the substance to be adjusted and Y = percentage strength of that substance.
- Where two or more ingredients are present and the solution requires adjustment to isotonicity, the above expression could be considered in the following expanded form:

$$w = \frac{0.52 - (X_1Y_1 + X_2Y_2 + X_3Y_3 + \ldots)}{b}$$

Sodium chloride equivalence

Alternatively, the sodium chloride equivalence (SCE) method may be used to calculate isotonicity values. The SCE is the weight in grams of sodium chloride which is osmotically equivalent to 1 gram of the substance. The SCE of a substance can be calculated from the $FD_{1\%}$ by the relationship:

$$SCE = \frac{0.9}{0.52} \times F_{1\%} \text{ grams}$$

where 0.9 is the percentage strength of an isotonic solution of sodium chloride.

These values are obtained from Table G.2 and are used as follows:

- to calculate the isotonicity value of a single substance—e.g. glucose:

$$= \frac{0.9\%}{SCE_{glucose}}$$

- to calculate the amount of adjusting substance needed to make a solution isotonic—e.g. to adjust an 0.5% solution of methoxamine hydrochloride to isotonicity using sodium chloride. The percentage of sodium chloride to be added is:

$$= 0.9 - \left(\frac{\text{SCE methoxamine hydrochloride} \times \%}{\text{methoxamine hydrochloride}}\right)$$
$$= 0.9 - (0.26 \times 0.5)$$
$$= 0.9 - 0.13$$
$$= 0.77\%$$

If more than one substance is present, the percentage is determined similarly for each in turn and the total subtracted from 0.9%.

If glucose is being used as the adjusting substance, first calculate the amount of sodium chloride required and divide this figure by the SCE of glucose, 0.16.[1]

Table G.2 Isosmotic concentration, freezing point depression and sodium chloride equivalence for a range of substances

	C_{iso} (%)	$FD_{1\%}$ (°C)	SCE (g)
Acetazolamide sodium	3.85	0.135	0.23
Acetic acid		0.31	0.54
Adrenaline acid tartrate	5.7	0.098	0.18
Aminocaproic acid		0.148	0.26
Aminophylline		0.098	0.17
Amitriptyline hydrochloride		0.10	0.17
Ampicillin sodium	5.78	0.09	0.16
Amylobarbitone sodium	3.6	0.143	0.25
Antazoline hydrochloride		0.132	0.23
Apomorphine hydrochloride		0.08	0.14
Ascorbic acid	5.04	0.105	0.18
Atropine methonitrate	6.52	0.10	0.17
Atropine sulfate	8.85	0.074	0.13
Benzalkonium chloride		0.09	0.16
Benztropine mesylate		0.115	0.21
Benzyl alcohol		0.094	0.15
Benzylpenicillin (potassium)	5.48	0.102	0.18
Benzylpenicillin (sodium)	5.54	0.10	0.17
Bethanechol chloride	3.05	0.225	0.39
Borax	2.6	0.241	0.42
Boric acid[a]	1.9	0.288	0.5
Calcium chloride ($2H_2O$)	1.7	0.298	0.52
Calcium gluconate		0.091	0.16
Calcium lactate	4.5	0.14	0.23
Carbachol	2.82	0.205	0.36
Carbenicillin sodium	4.4	0.118	0.2
Cephaloridine		0.041	0.07
Cephalothin sodium	6.8	0.095	0.17
Cephazolin sodium		0.074	0.13
Cetrimide		0.05	0.09
Chloramphenicol sodium succinate	6.83	0.078	0.14
Chlorbutol		0.14 (calc)	0.24
Chlorpheniramine maleate		0.085	0.15
Chlorpromazine hydrochloride		0.058	0.10
Citric acid monohydrate	5.52	0.098	0.18
Cloxacillin sodium		0.08	
Cocaine hydrochloride	6.3	0.09	0.16
Codeine phosphate	7.3	0.08	0.14
Cyclopentolate hydrochloride	5.30	0.117	0.20
Cytarabine	8.92	0.066	0.11
Dimethyl sulfoxide		0.245	0.42
Dexamethasone sodium phosphate	6.75	0.095	0.17
Diphenhydramine hydrochloride		0.161	0.28
Disodium edetate		0.132	0.23
Ecothiopate iodide		0.090	0.16
Edrophonium chloride	3.36	0.179	0.31
Ephedrine hydrochloride	3.2	0.165	0.29
Ergometrine maleate		0.089	0.15
Erythromycin lactobionate		0.04	0.07
Ethanol (dehydrated alcohol)[a]	1.28	0.41	0.7
Fluorescein sodium	3.34	0.181	0.31
Gentamicin sulfate		0.030	0.05
Glucose (anhydrous)	5.05	0.101	0.17
Glucose	5.55	0.091	0.16
Glycerol[a]	2.6	0.203	0.35
Heparin sodium	12.2	0.042	0.07
Histamine acid phosphate	4.1	0.149	0.26
Homatropine hydrobromide	5.67	0.097	0.17
Hyoscine hydrobromide	7.85	0.068	0.12
Imipramine hydrochloride		0.110	0.20
Isoniazid	4.35	0.144	0.25
Kanamycin sulfate		0.041	0.07
Lactose	9.75	0.04	0.07
Lignocaine hydrochloride	4.42	0.13	0.22
Lincomycin hydrochloride	6.6	0.09	0.16
Magnesium chloride	2.02	0.26	0.45
Magnesium sulfate	6.3	0.094	0.16
Mannitol	5.07	0.098	0.17
Methadone hydrochloride		0.101	0.17
Methicillin sodium	6.0	0.099	0.18
Methoxamine hydrochloride	3.82	0.150	0.26

Table G.2 Isosmotic concentration, freezing point depression and sodium chloride equivalence for a range of substances

	C_{iso} (%)	$FD_{1\%}$ (°C)	SCE (g)
Metoclopramide hydrochloride		0.084	0.15
Morphine hydrochloride		0.086	0.15
Morphine sulfate		0.079	0.14
Naloxone hydrochloride	8.07	0.083	0.14
Naphazoline hydrochloride	4.0	0.156	0.27
Neomycin sulfate		0.063	0.11
Neostigmine bromide		0.127	0.22
Neostigmine methylsulfate	5.2	0.115	0.20
Nicotinamide	4.5	0.148	0.26
Nicotinic acid		0.144	0.25
Nikethamide[a]	5.94	0.10	0.17
Papaverine hydrochloride		0.061	0.11
Pentolinium tartrate		0.098	0.17
Pethidine hydrochloride	4.8	0.125	0.22
Phenobarbitone sodium	3.95	0.135	0.23
Phenol	2.8	0.20	0.35
Phenylephrine hydrochloride	3.0	0.185	0.32
Phenylethyl alcohol		0.141	0.25
Physostigmine salicylate		0.09	0.16
Physostigmine sulfate	7.74	0.074	0.13
Pilocarpine hydrochloride	4.08	0.138	0.24
Pilocarpine nitrate		0.132	0.23
Polymyxin B sulfate		0.052	0.09
Potassium acid phosphate (anhydrous)	2.18	0.254	0.44
Potassium chloride	1.19	0.439	0.76
Potassium iodide	2.6	0.196	0.34
Potassium nitrate	1.6	0.324	0.56
Pralidoxime chloride	2.87	0.183	0.32
Procainamide hydrochloride		0.127	0.22
Procaine hydrochloride[a]	5.05	0.122	0.21
Prochlorperazine edisylate		0.033	0.06
Promethazine hydrochloride		0.104	0.18
Propranolol		0.122	0.20
Propylene glycol[a]	2.0	0.262	0.45
Pyridostigmine bromide	4.13	0.125	0.22
Pyridoxine hydrochloride		0.213	0.37
Silver nitrate	2.74	0.19	0.33
Sodium acetate ($3H_2O$)		0.163	
Sodium acid phosphate ($2H_2O$)	2.8	0.207	0.36
Sodium benzoate	2.25	0.23	0.40
Sodium bicarbonate	1.4	0.38	0.66
Sodium chloride	0.9	0.576	1.00
Sodium citrate	3.02	0.178	0.31
Sodium iodide	2.37	0.222	0.39
Sodium lactate	1.72	0.315	0.55
Sodium metabisulfite	1.38	0.386	0.67
Sodium nitrite	1.08	0.48	0.84
Sodium phosphate ($12H_2O$)	4.45	0.127	0.22
Sodium salicylate	2.53	0.21	0.36
Sodium sulfate	3.95	0.148	0.26
Sodium thiosulfate	3.0	0.181	0.31
Spectinomycin hydrochloride	5.66	0.092	0.16
Streptomycin sulfate		0.036	0.06
Sucrose	9.25	0.047	0.08
Sulfacetamide sodium	3.8	0.132	0.23
Sulfadiazine sodium	4.2	0.138	0.24
Suxamethonium chloride		0.115	0.20
Tetracycline hydrochloride		0.081	0.14
Thiamine hydrochloride	4.2	0.139	0.24
Thiethylperazine maleate		0.050	0.09
Thiopentone sodium	3.5	0.155	0.27
Thiotepa	5.67	0.090	0.16
Timolol maleate		0.077	0.13
Tobramycin		0.038	0.07
Tolazoline hydrochloride	3.05	0.196	0.34
Tubocurarine chloride		0.076	0.13
Zinc chloride		0.35	0.59
Zinc sulfate	7.65	0.086	0.15

a. May cause haemolysis of red blood cells.

References

1. Lund W, ed. The pharmaceutical codex. 12th edn. London: The Pharmaceutical Press, 1994;50–66.

Buffer solutions

Buffer solutions are used to minimise changes in pH value if small amounts of acid or alkali are added. Those mostly used in pharmacy are solutions of weak acids with their salts of strong bases. The pH of pharmaceutical preparations is controlled so that solubility can be increased, chemical instability minimised, product colour standardised and to protect the preparation from microbial contamination.

Phosphate buffers are generally used for adjustment of parenteral preparations, provided they are compatible with the substance to be injected. Phosphates react with calcium to form an insoluble precipitate of calcium phosphate. They exert their maximum buffer capacity at a pH value of about 6.8. For ophthalmic preparations, either phosphate or borate buffers may be used, depending on the pH value required and compatibility with the substances present. Borate buffers should not be used for injections or on abraded skin, where systemic absorption may occur.[1]

Buffer solutions may be adjusted to be isotonic with blood and lachrymal fluids by the addition of sodium chloride. Examples of buffers are given in Tables G.3 to G.8.[1]

Table G.3 Sorensen's phosphate buffer (0.067 M)

0.067 M disodium hydrogen phosphate: 2.39% $Na_2HPO_4.12H_2O$ in aqueous solution ($FD_{1\%}$ = 0.127 °C).
0.067 M potassium dihydrogen phosphate: 0.908% KH_2PO_4 in aqueous solution ($FD_{1\%}$ = 0.254 °C).
To obtain a solution with a particular pH value, these solutions are mixed in the following proportions.

0.067 M KH_2PO_4 (mL)	0.067 M $Na_2HPO_4.12H_2O$ (mL)	pH value at 25 °C
90.0	10.0	5.9
80.0	20.0	6.3
70.0	30.0	6.5
60.0	40.0	6.6
50.0	50.0	6.8
40.0	60.0	7.0
30.0	70.0	7.1
20.0	80.0	7.4
10.0	90.0	7.8
5.0	95.0	8.1

Table G.4 Walpole's acetate buffer (0.1 M)

0.1 M acetic acid: 0.6% w/v CH_3COOH in aqueous solution ($FD_{1\%}$ = 0.31 °C).

0.1 M sodium acetate: 1.36% $CH_3COONa.3H_2O$ in aqueous solution ($FD_{1\%}$ = 0.163 °C).

To obtain a solution with a particular pH value, these solutions are mixed in the following proportions.

0.1 M CH_3COOH (mL)	0.1 M $CH_3COONa.3H_2O$ (mL)	pH value at 25 °C
92.6	7.4	3.6
88.0	12.0	3.8
82.0	18.0	4.0
73.6	26.4	4.2
61.0	39.0	4.4
51.0	49.0	4.6
40.0	60.0	4.8
29.6	70.4	5.0
21.0	79.0	5.2
17.6	82.4	5.4
9.6	90.4	5.6

Table G.5 Isotonic phosphate buffer

0.067 M sodium acid phosphate: 1.04% $NaH_2PO_4.2H_2O$ in aqueous solution ($FD_{1\%}$ = 0.207 °C).

0.067 M disodium hydrogen phosphate (sodium phosphate BP): 2.39% $Na_2HPO_4.12H_2O$ in aqueous solution ($FD_{1\%}$ = 0.127 °C).

To obtain a solution with a particular pH value, these solutions are mixed in the proportions shown below, and to make the solution isotonic the specified amount of sodium chloride is added, as shown. Note that if a drug is to be dissolved in the buffer system, the amount of sodium chloride should be reduced appropriately. For pH calculations involving phosphoric acid, pKa2 is better expressed as the practical value of 6.8 at isotonic ionic strength, rather than the thermodynamic value of 7.1.

0.067 M $NaH_2PO_4.2H_2O$ (mL)	0.067 M $Na_2HPO_4.12H_2O$ (mL)	NaCl (g)	pH value at 25 °C	pH value at 37 °C
90	10	0.52	5.8	5.7
80	20	0.51	6.1	6.1
70	30	0.50	6.4	6.3
60	40	0.49	6.5	6.5
50	50	0.48	6.7	6.7
40	60	0.46	6.9	6.9
30	70	0.45	7.1	7.1
20	80	0.44	7.3	7.3
10	90	0.43	7.7	7.7
5	95	0.42	8.1	8.1

Table G.6 Isotonic borate buffer

0.2 M boric acid: 1.24% boric acid in aqueous solution ($FD_{1\%}$ = 0.288 °C).

0.05 M borax: 1.91% borax in aqueous solution ($FD_{1\%}$ = 0.241 °C).

To obtain a solution with a particular pH value, these solutions are mixed in the proportions shown below, and to make the solution isotonic the specified amount of sodium chloride is added, as shown.

0.2 M boric acid (mL)	0.05 M borax (mL)	NaCl (g)	pH value at 25 °C	pH value at 37 °C
97	3	0.27	6.8	6.8
94	6	0.27	7.1	7.1
90	10	0.27	7.4	7.4
85	15	0.26	7.6	7.6
80	20	0.26	7.9	7.8
70	30	0.24	8.1	8.1
65	35	0.23	8.2	8.2
55	45	0.21	8.4	8.4
45	55	0.19	8.6	8.5
40	60	0.18	8.7	8.6
30	70	0.14	8.8	8.7
20	80	0.11	9.0	8.9
10	90	0.07	9.1	9.0

Table G.7 Isotonic citrate buffer

1.1% citric acid monohydrate in aqueous solution ($FD_{1\%}$ = 0.098 °C).

1.5% sodium citrate in aqueous solution ($FD_{1\%}$ = 0.178 °C).

To obtain a solution with a particular pH value, these solutions are mixed in the proportions shown below, and to make the solution isotonic the specified amount of sodium chloride is added, as shown.

1.1% citric acid monohydrate (mL)	1.5% sodium citrate (mL)	NaCl (g)	pH value at 37 °C
32.1	67.9	0.54	5.0
29.7	70.3	0.53	5.1
24.5	75.5	0.51	5.3
17.8	82.2	0.49	5.6
10.7	89.3	0.48	5.9
6.2	93.8	0.47	6.2
3.2	96.8	0.46	6.5

Table G.8 McIlvaine universal citrate–phosphate buffer

'Universal' buffers contain two or more buffer systems and give a buffering action over a relatively wide range of pH values. Their buffering capacity is lower than that of the general buffers at the same concentration. The citrate–phosphate buffer system (McIlvaine) covers the range from pH 2.2 to pH 8.0.

To obtain a solution with a particular pH value, the following amounts of sodium phosphate ($Na_2HPO_4.12H_2O$) and citric acid ($C_6H_8O_7.H_2O$) are added to 1 litre of water.

pH	$Na_2HPO_4.1\ 2H_2O$ (g/L)	$C_6H_80_7.H_2O$ (g/L)
2.2	1.4	20.6
2.4	4.4	19.7
2.6	7.8	18.7
2.8	11.4	17.7
3.0	14.7	16.7
3.2	17.7	15.8
3.4	20.4	15.0
3.6	23.1	14.2
3.8	25.4	13.6
4.0	27.6	12.9
4.2	29.7	12.3
4.4	31.6	11.7
4.6	33.5	11.2
4.8	35.3	10.7
5.0	36.9	10.2
5.2	38.4	9.7
5.4	39.9	9.3
5.6	41.5	8.8
5.8	43.3	8.3
6.0	45.2	7.7
6.2	47.3	7.1
6.4	49.6	6.5
6.6	52.1	5.7
6.8	55.3	4.8
7.0	59.0	3.7
7.2	62.3	2.7
7.4	65.1	1.9
7.6	67.1	1.3
7.8	68.6	0.9
8.0	69.7	0.58

References

1. Lund W, ed. The pharmaceutical codex. 12th edn. London: The Pharmaceutical Press, 1994;67–9.

pKa values

Table G.9 lists the pKa values of some compounds of pharmaceutical interest. A compound that dissociates by releasing a proton is termed an acid, and the dissociation constant is given in the left-hand column of the table. If the compound is a base, the pKa of the corresponding protonated form is listed in the right-hand column. A low value in the left-hand column indicates a strong acid. A low value in the right-hand column indicates a weak base.

The values are taken from published data and should be regarded as approximate only. Unless otherwise indicated, the values given are at 25 °C and represent the thermodynamic values.

If the compound is a weak acid, it will demonstrate increasing aqueous solubility at pH values above its pKa. Solubility will be essentially unchanged as a function of pH when solutions are at low pH values—i.e. up to one or two pH units below its pKa. The converse is true if the compound is a base. Compounds that are zwitterions normally have at least one acid group and one basic group. Such compounds normally have a U- or V-shaped curve when solubility is plotted as a function of pH, depending on how different the pKa values are from each other.

The curves for partition coefficient will be the inverse of those observed for solubility. For example, a plot of partition coefficient as a function of pH for a zwitterion will appear as an inverted U or V.

For some drugs, passive reabsorption in renal tubules, and therefore renal clearance, may be influenced by physicochemical properties such as polarity, as well as the degree of ionisation. The pKa values of ionisable groups will influence the degree of ionisation and hence polarity of drugs at any specific pH. Reabsorption also depends on physiological variables such as urine flow rate and pH.

Urine pH may vary in the range of 4.5 to 7.5 under forced acidification and alkalinisation respectively. Dietary changes, drugs and the clinical state of a patient can alter urine pH within this range.

Variation in urinary pH or flow rate can cause marked variation of renal clearance of acidic drugs with pKa values of about 3.0 to 7.5. Increasing urinary pH will increase renal clearance of susceptible acidic drugs by reducing tubular reabsorption. Basic drugs which have pKas of their conjugate acids in the range of about 7.5 to 10.5 can have highly variable renal clearance. Increasing urinary pH will cause a decrease of renal clearance for susceptible basic drugs. Such drugs may have a highly variable fraction of drug excreted in urine and total body clearance. Hence, half-life, area under the plasma drug concentration versus time curve, efficacy and toxic effects may also be highly variable.

Conversely, drugs which are highly polar in their non-ionised state or whose total body clearance is not highly dependent on renal clearance are unlikely to demonstrate significant changes in elimination when urinary pH or flow rate are altered.[1]

Table G.9 pKa values[2–6]

	Acid	Base
Acebutolol		9.4
Acetazolamide	7.2	
Acetic acid	4.8	
Acetylcysteine	3.2	
Acitretin	5.0	
Adefovir dipivoxil		4.6
Adrenaline	10.2; 12.0 (20 °C)	8.7
Alclofenac	4.6	
Alfentanil		6.5
Allopurinol		9.4
Alprazolam		2.4
Alprenolol		9.5 (20 °C)
Amantadine		10.4
Amiloride		8.7
Aminacrine		9.5
Aminocaproic acid	4.4	10.8
Aminophylline		5.0
Aminosalicylic acid	3.6	1.8
Amiodarone		6.6
Amitriptyline		9.4
Ammonia		9.3
Amoxycillin	2.4; 9.6	7.4
Amphetamine		9.9 (20 °C)
Amphotericin B	5.5	10.0
Ampicillin	2.7	7.2
Amylobarbitone	7.9	
Antazoline		2.5; 10.1
Aprepitant		4.2
Ascorbic acid	4.2; 11.6	
Aspirin	3.5	
Atazanavir	11.1	4.8
Atenolol		9.6 (24 °C)

Table G.9 pKa values[2–6] (continued)

	Acid	Base
Atomoxetine		10.1
Atropine		9.9 (20 °C)
Azathioprine	8.2	
Baclofen	3.9	9.6
Bendrofluazide	8.5	
Benzoic acid	4.2	
Benzylpenicillin	2.8	
Boric acid	9.2	
Bromazepam		2.9; 11.0
Bromocriptine		4.9
Brompheniramine		3.9; 9.2
Bupivacaine		8.1
Buprenorphine	10.0	8.5
Butobarbitone	8.0	
Caffeine	14.0	0.6
Captopril	3.7, 9.8	
Carbenicillin	2.6; 2.7	
Carbonic acid	6.4; 10.4	
Cefoperazone	2.6	
Cefotaxime	3.3	
Cefuroxime	2.5	
Cephacetrile	2.0	
Cephalexin	5.2	2.5; 7.3
Cephaloridine	3.4	
Cephalothin	2.2 (35 °C)	
Cephamandole	2.5	
Cephazolin	4.71	
Cephradine	2.5	7.3 (35 °C)
Chloral hydrate	10.5	
Chlorambucil	5.8	
Chloramphenicol	5.5	
Chlordiazepoxide		4.6 (20 °C)
Chlormethiazole		3.2
Chloroquine		8.4; 10.8
Chlorothiazide	6.8; 9.4	
Chlorpheniramine		9.1
Chlorphentermine		9.6
Chlorpromazine		9.3 (20 °C)
Chlorpropamide	5.0	
Chlortetracycline	3.3; 7.4	9.3
Chlorthalidone	9.4	
Cimetidine		6.8
Citric acid	3.1; 4.6; 6.4	
Clindamycin		7.7
Clofibric acid	3.0	
Clonazepam	10.5	1.5
Clonidine		8.2
Cloxacillin	2.7	
Codeine		8.2
Colchicine		1.7 (20 °C)
Cyclobarbitone	7.6	
Cycloserine	4.5	7.4
Cytarabine		4.3
Dacarbazine		4.4
Dantrolene	7.5	
Dapsone		1.3; 2.5
Dasatinib	10.8	3.1; 6.8
Debrisoquine		11.9
Deferiprone	9.4	3.0
Demeclocycline	3.3; 7.2	9.4
Desipramine		10.2 (24 °C)
Desloratadine		9.4
Dextropropoxyphene		6.3
Diazepam		3.3
Diazoxide	8.5	
Diclofenac	4.0	
Dihydrocodeine		8.8
Dihydroergotamine		6.8 (24 °C)
Diltiazem		7.7
Dinoprostone	4.8	
Diphenhydramine		9.0
Diphenoxylate		7.1
Disopyramide	10.2	8.4
Dobutamine		9.5
Dopamine	10.6	8.8
Doxepin		8.3
Doxorubicin		8.2; 10.2
Doxycyline	3.4; 7.7	9.3
Droperidol		7.6
Ephedrine		9.6
Ergometrine		7.2
Ergotamine		6.4 (24 °C)
Erlotinib		5.42
Erythromycin		8.91[a]
Ethacrynic acid	3.5 (20 °C)	
Ethambutol		6.3; 9.5
Ethanolamine		9.4
Ethosuximide	9.5	

Table G.9 pKa values[2–6] (continued)

	Acid	Base
Ethylnoradrenaline		8.4
Etidocaine		7.7
Etomidate		4.2
Famotidine		7.1
Fenfluramine		9.1
Fenoprofen	4.5	
Fenoterol	10.0	8.5
Fentanyl		8.4
Flecainide		9.3
Flucloxacillin	2.7	
Flucytosine	10.7	2.9
Flufenamic acid	3.9	
Flunitrazepam		1.8
Fluorouracil	8.0; 13.0	
Fluphenazine		3.9; 8.1
Fluvastatin	5.5	
Folic acid	4.7; 6.8; 9.0	
Fosamprenavir calcium	1.8	1.8
Frusemide	3.9	
Fusidic acid	5.4	
Galantamine		7.9
Gentamicin		8.0
Glibenclamide	5.3	
Gliclazide	5.8	
Glycine	2.3	9.8
Glutethimide	4.5	
Granisetron		10.5
Guanethidine		8.3, 11.4
Haloperidol		8.3
Hexobarbitone	8.3	
Homatropine		9.7 (23 °C)
Hydralazine		0.5; 7.1
Hydrochlorothiazide	7.0; 9.2	
Hydrocortisone sodium succinate	5.1	
Hydromorphone		8.2
Hydroxyzine		2.1; 7.1
Hyoscine		7.6 (23 °C)
Hyoscyamine		9.3
Ibuprofen	4.4; 5.2	
Idoxuridine	8.3	
Imipramine		9.5 (24 °C)
Indapamide	8.3	
Indomethacin	4.5	

	Acid	Base
Isocarboxazid		10.4
Isoniazid		2.0; 3.9
Isoprenaline	10.1; 12.0 (20 °C)	8.6 (20 °C)
Isoxsuprine	9.8	8.0
Kanamycin		7.2
Ketamine		7.5
Ketoconazole		2.9; 6.5
Ketorolac	3.5	
Ketoprofen	4.8	
Labetalol	7.4	8.7
Lactic acid	3.9	
Lamotrigine		5.7
Lansoprazole	8.8	
Levamisole	8.0	
Levodopa	2.3; 9.7; 13.4	8.7
Lignocaine		7.9
Lincomycin		7.5
Liothyronine	8.5	
Loperamide		8.7
Lorazepam	11.5	1.3
Maprotiline		10.5
Mazindol		8.6
Mebhydrolin		6.7
Mecillinam	3.4	8.9
Meclozine		6.2; 3.1
Mefenamic acid	4.2	
Mepacrine		7.7; 10.3
Mepivacaine		7.7
Mercaptopurine	7.8	
Mesalazine	1.9	5.4
Metaraminol		8.6
Metformin		2.8; 11.5 (32 °C)
Methacycline	3.5; 7.6	9.2
Methadone		8.3
Methaqualone		2.5
Methdilazine		7.5
Methicillin	2.8	
Methohexitone	8.3	
Methotrexate	3.8; 4.8	5.6
Methyclothiazide	9.4	
Methyldopa	2.3; 10.4; 12.6	9.0
Methylhydroxybenzoate	8.4 (22 °C)	
Methylphenobarbitone	7.8	
Methysergide		6.6

Table G.9 pKa values[2–6] (continued)

	Acid	Base
Metoclopramide		0.6; 9.0
Metolazone	9.7	
Metoprolol		9.7
Metronidazole		2.5
Mexiletine		9.0
Mianserin		7.1
Miconazole		6.7
Midazolam		6.2
Minocycline	2.8; 7.8	5.0; 9.5
Minoxidil		4.6
Morphine	9.9	7.9
Mustine		6.4
Nalidixic acid	6.0	
Nalorphine		7.8
Naloxone		7.9
Naproxen	4.2	
Naphazoline		10.9
Neostigmine		12.0
Nicotinamide		0.5; 3.3
Nicotinic acid	4.8	2.0
Nitrazepam	10.8	3.2
Nitrofurantoin	7.2	
Noradrenaline	9.8; 12.0	8.6
Nortriptyline		9.7
Orciprenaline	9.0; 11.4	10.1
Orphenadrine		8.4
Oxazepam	11.6	1.7
Oxprenolol		9.5
Oxycodone		8.9
Paracetamol	9.5	
Penicillamine	1.8; 10.5	7.9
Pentazocine		8.8
Pentobarbitone	8.1	
Perphenazine		3.7; 7.8
Pethidine		8.7
Phenacetin		2.2
Phenethicillin	2.7	
Phenformin		2.7; 11.8
Phenindione	4.1	
Pheniramine		4.2; 9.3
Phenobarbitone	7.4	
Phenol	10.0	
Phenoxymethylpenicillin	2.7	
Phentermine		10.1
Phentolamine		7.7
Phenylbutazone	4.4	
Phenylephrine	9.8	8.8
Phenytoin	8.3	
Pholcodine		9.3; 8.0
Phosphoric acid	2.1; 7.12[b]; 12.3	
Physostigmine		7.9; 1.8
Pilocarpine		1.6; 7.0
Pimozide		7.3
Pindolol		8.8
Piroxicam	5.1	1.5
Practolol		9.5
Pralidoxime		8.0
Prazosin		6.5
Pregabalin	4.2	11.3
Probenecid	3.4	
Procainamide		9.2
Procaine		9.0
Procarbazine		6.8
Prochlorperazine		3.7; 8.1
Promazine		9.4
Promethazine		9.1
Propranolol		9.5
Propyl hydroxybenzoate	8.4 (22 °C)	
Propylthiouracil	7.8	
Pseudoephedrine		9.8
Pyridoxine	9.0	5.0
Quinalbarbitone	7.9	
Quinethazone	9.3; 10.7	
Quinidine		4.2; 8.8
Quinine		4.2; 8.8
Ranitidine		2.3; 8.2
Reserpine		6.6
Riboflavin	10.2	
Rifampicin	1.7	7.9
Rimiterol	10.3	8.7
Rolitetracycline	7.4	
Ropinirole		9.5
Saccharin	1.6	
Salbutamol	9.4	10.0
Salicylic acid	3.0; 13.4	
Sotalol	8.3	9.8
Spectinomycin		7.0; 8.7
Sucralfate	0.43–1.19	

Table G.9 pKa values[2–6] (continued)

	Acid	Base
Sulfamethoxazole	5.9	
Sulindac	4.5	
Sulfacetamide	5.4	1.8
Sulfadiazine	6.5	2.0
Sulfadimidine	7.4	
Sulfafurazole	5.0	
Sulfamethizole	5.3	2.0
Sulfasalazine	2.4; 8.3; 11.0	0.6
Sulfathiazole	7.1	2.4
Sulfinpyrazone	2.8	
Sunitinib		8.95
Tartaric acid	3.0; 4.2	
Temazepam		1.8
Terbutaline	10.1; 11.2	8.8
Tetracycline	3.3; 7.7	9.7
Theophylline	8.6	3.5
Thiamine		4.8; 9.0
Thiopentone	7.6	
Thioridazine		9.5
Thyroxine	2.2; 6.7	10.1
Ticarcillin	2.5; 3.4	
Timolol		8.8
Tobramycin		6.2; 7.4; 7.6; 8.6
Tocainide		7.8
Tolazamide	3.1	5.7
Tolbutamide	5.3	
Tranylcypromine		8.2
Triamterene		6.2
Trifluoperazine		8.1
Trimethoprim		7.2
Tubocurarine		8.1; 9.1
Urea		0.2
Valproic acid	4.8	
Varenicline	9.2	
Venlafaxine		9.4
Vinblastine		5.4; 7.4
Vincristine		5.0; 7.4
Vindesine		5.4; 7.4
Warfarin	5.0	

a. Determined in 66% dimethyl formamide.

b. A more practical value of pKa2 of phosphoric acid at isotonic ionic strength is 6.8.

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Section H

Standards and guidelines

Standards and guidelines

Because the development of standards and guidelines is a dynamic process and in order to maintain the currency of this handbook, this section has been revised in an effort to have the most up to date version of the standards and guidelines more readily available. Therefore a general overview of standards and guidelines is provided here followed by a list of selected documents produced by PSA. The documents can be accessed at PSA's website, from the 'Policy' page (www.psa.org.au/policy).

What are standards and guidelines?

As the professional organisation for pharmacists in Australia, PSA develops many standards and guidelines relevant to professional pharmacy practice. Various other bodies may also produce 'standards' and 'guidelines' for different purposes. These include:

- guidelines developed by state or territory pharmacy registering authorities (pharmacy boards) which advise pharmacists on acceptable practice and how they may best fulfil their professional duties and responsibilities
- standards contained in the Pharmacy Guild of Australia's Quality Care Pharmacy Program, which is a quality assurance program covering all operational aspects of community pharmacy. For more information go to www.guild.org.au/qcpp
- standards of practice developed by the Society of Hospital Pharmacists of Australia which outline practice levels and standards primarily for hospital pharmacy services. For more information go to www.shpa.org.au
- standards and guidelines issued by bodies such as the Therapeutic Goods Administration or state health authorities—e.g. on infection control or labelling of medicines.

The terms 'standards' and 'guidelines' are often used interchangeably, possibly leading to confusion among pharmacists. It is important that pharmacists understand the difference between the two types of documents and are aware that they should be considered side by side. For clarity, PSA refers to these two types of documents as 'professional practice standards' and 'professional guidelines'.

Professional practice standards relate to the systems, procedures and information used by a pharmacist in providing a professional service or activity. The standards consist of objective statements of minimum requirements necessary to ensure consistency and uniformity in performance. They can be used as a benchmark against which performance may be assessed since compliance with the standards is intended to promote the delivery of a quality professional service to consumers.

Professional guidelines are designed to provide advice or guidance to pharmacists on process issues, desired behaviour for good practice, and how duties and responsibilities may best be fulfilled. They are not definitive statements of correct procedure.

These definitions are intended to inform pharmacists of the consistent approach adopted by PSA. By having a better understanding of the purpose of these documents, pharmacists should find them less daunting and easier to use in practice.

In addition, if you are familiar with PSA's Continuing Professional Development and Practice Improvement (CPD&PI) program (www.psa.org.au/cpdpi), you will be aware that there are two types of 'standards': the 'competency standards' (which are relevant to the CPD component of the program) and the professional practice standards (which relate to the PI component).

Competency standards describe the skills, attitudes and attributes (including values and beliefs) of an individual based on knowledge (gained through study) and experience (gained through practice) which together are considered sufficient to enable the individual to practice as a pharmacist.

There is an inherent assumption that pharmacists using and meeting the professional standards are also competent as pharmacists. Delivery of professional services requires personal competence as well as quality procedures if the service is to be delivered to a standard that is acceptable to both consumers and professional peers, has credibility in a professional sense, and meets all regulatory requirements.

Generally, legislative requirements are not addressed in the professional practice standards. In the event of conflict or overlap between the standards and legislation, the requirements of the applicable legislation will prevail to the extent of the conflict or overlap.

Selected list of PSA's standards and guidelines

The following list of standards and guidelines is not exhaustive; it is intended to provide an overview of documents produced by PSA.

As noted, the documents can be accessed at PSA's website from the 'Policy' page (www.psa.org.au/policy). Pharmacists are encouraged to refer regularly to this website page: additional resources produced by PSA (and other organisations, where appropriate) are often made available together with the relevant documents. New standards and guidelines are also posted on the website, often in advance of (and sometimes in place of) publication of a hard-copy version.

Note that access to some documents is restricted to PSA members.

Standards

- *Competency Standards for Pharmacists in Australia 2003*
- *Professional Practice Standards*
- Individual standards contained in the *Professional Practice Standards* publication
  - Fundamental Pharmacy Practice
  - Comprehensive Pharmacy Care
  - Comprehensive Medication Review
  - Home Medicines Review (Domiciliary medication management review)
  - Dispensing
  - Distance Supply
  - Counselling
  - Dose Administration Aids Service
  - Opioid Substitution Program
  - Compounding (Extemporaneous dispensing)
  - Preparation of Cytotoxic Drug Products
  - Smoking Cessation Service
  - Needle and Syringe Program
  - Monitoring and Case Detection
  - Health Promotion
  - Drug Information Service
  - Services to Residential Care Facilities
  - Organisation of Pharmacy Practice
- *Standards for the provision of Pharmacy Medicines and Pharmacist-Only Medicines in Community Pharmacy*

Guidelines

This section lists guideline documents as well as consolidated guidelines and standards publications.

Protocols for Pharmacist Only Medicines (levonorgestrel, oral fluconazole, orlistat and pantoprazole) can be found in the 'OTC Counselling guides', in section E.

- *Code of Practice—pseudoephedrine*
- *Code of Professional Conduct*
- *Consumer Medicine Information and the Pharmacist*
- *Diabetes Medication Assistance Service* [Guidelines and Standards]
- *Dispensing Practice Guidelines*
- *Domiciliary Medication Management Review* (Home medicines review)
- *Dose Administration Aids Service* [guidelines and standards]
- *Employment of Other Health Practitioners in Pharmacy*
- *Guidelines and Standards for the Collaborative and Pharmacist Residential Medication Management Review (RMMR) Program and Associated Quality Use of Medicines (QUM) Services*
- *Guidelines for Managing Pharmacy Systems for Quality and Safety*
- *Guidelines for Pharmacists for Concordance Assessments*
- *Guidelines for Pharmacists in Providing Services to People with Impaired Vision*
- *Guidelines for Pharmacists on PBS Brand Substitution*
- *Guidelines for Pharmacists on Providing Medicines Information to Patients*
- *Guidelines for Pharmacists Providing Opioid Pharmacotherapy Services*
- *Guidelines for Pharmacists' Relationship With The Pharmaceutical Industry*
- *Medication Profiling Service* [guidelines and standards]
- *Professional Practice and the Privacy Act*
- *PSA/PGoA Joint Guidelines for Pharmacists Issuing Medical Certificates*
- *The Provision of Pharmacy Services to Aboriginal and Islander Health Services* [guidelines and standards]
- *The Provision of Pharmacy Services to Residential Aged Care Facilities*

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