HIS MAJESTY SULTAN QABOOS BIN SAID
Foreword

It is my great pleasure to introduce the Omani National Formulary (ONF) in its third edition to all health providers in the Sultanate. There have been several changes and additional material which readers are encouraged to study. The formulary contains detailed and updated monographs of all of the drugs approved by the Central Drug Committee (CDC) for use in Ministry of Health facilities today. Deleted preparations are listed at the front.

This formulary is the effort of the Directorate of Rational Use of Medicine and I thank them for the high standard of their efficient work. The new edition is smaller for easier carriage and ready reference. The nature of therapeutics today means that the ONF is a dynamic work and will be subject to regular revision as and when significant changes in policy occur and therapies are added or deleted. I hope that the use of this formulary will have the desired benefit for all health workers and ultimately for our patients.

Dr. Ahmed bin Mohammed bin Obaid Al-Saidi
Minister of Health

Acknowledgements

Ph. Batool Jaffer Suleiman, BSc, MSc
Director, Rational Use of Medicine Directorate

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Preface

The Omani National Formulary (ONF) is a publication of the Ministry of Health (MOH) for all medicines/indications approved by the Central Drug Committee (CDC). It is a joint effort between the Directorate of Rational Use of Medicine and different reviewers from consultants at hospitals and senior pharmacists. It is intended as a guide to the medicines approved for use in public health facilities; it does not cover all the items available in the private sector. The information stated in the ONF is meant to provide prescribers, dispensers and drug administrators with guidance to make a rational selection and ultimately achieve rational use of medicines. Kindly note that not all indications for drug use internationally are listed in this edition.

Layout of the ONF

The first part of the ONF contains guidance on how to write appropriate prescription, and how to effectively prescribe drugs in special conditions and cases such as paediatric, pregnant, breast-feeding and geriatric patients, and in the presence of renal or hepatic impairments. Notes on adverse drug reactions and how to report important clinical observation resulting from such interactions are also detailed.

The second part of the ONF contains the main text where major therapeutic categories are listed with drug information for each individual drug. The notes preceding each therapeutic subcategory or group are meant to help the reader in making rational drug selection for individual patients. Drug entries are arranged in the sequence of: generic drug name, indications, contra-indications, cautions, side-effects and doses. The approved dosage forms, strengths and pack sizes (if known) are stated under preparations. Sometimes indications, contra-indications and cautions are stated in the introductory notes for the main therapeutic category or group, and referred to when individual drug are discussed.

The third part of the ONF includes 8 appendices; appendix 1 includes an introduction to drug interactions and an alphabetical list of most of the clinically important drug interactions for the drugs discussed in the ONF. Appendix 2 and appendix 3 give information about the different mechanisms of injury to liver and kidney caused by hepatotoxic and nephrotoxic drugs respectively in addition to some formulas for creatinine clearance calculation. Appendix 4 highlights the drugs that should be stopped for some days prior to blood donation according to the Central Blood Bank in Oman. Appendix 5 involves a list of drugs that should be avoided in patients with...
G6PD deficiency. Appendix 6 contains child-BSA-nomogram. Appendix 7 concerns therapeutic drug monitoring, the reference ranges are from the Royal Hospital. Finally, appendix 8 explains and illustrates the different methods for drugs administration.

The fourth part of the ONF is the index. The ONF is meant to be an easy and rapid reference; it does not contain all possible information for prescribing. For more detailed information, other references should be consulted.

Aims and objectives

The abundance of the drugs available in the pharmaceutical world is beyond full comprehension nowadays. Health authorities are encouraged all over the world to establish national drug policies to avoid confusion created by the diversity of resources and to cost-effectively manage their drug supplies. The Central Drug Committee (CDC) is the concerned body that observes drug policies and maintains vigilance on current development. The CDC had successfully produced a national drug list that covers the national need for drugs to tackle major health problems. This third edition of the ONF is supplementary and complementary to the national list where necessary information and policy issues are discussed and advocated. One of the fundamental objectives of the ONF is to unify the prescribing patterns in the Sultanate; as a good proportion of the service providers have various degrees of experience and backgrounds. The ONF will also be of particular value to medical and pharmaceutical teaching to promote the rational use of the approved drugs. To achieve such goals, the formulary is set for regular review and updating.

A great deal of time and effort was spent in preparing the ONF and a large number of references and experts were consulted. The Formulary Committee will be pleased to receive any recommendations, suggestions or corrections that would enrich any future editions. Please bear in mind that this guide is meant to be a quick reference for users. The editorial body has tried to include most of the reviewers’ suggestions and an apology is extended if some of these suggestions do not appear in this edition.

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| **Section 1**  
Gastrointestinal | • Atropine sulphate 1mg /10ml prefilled disposable injection  
• Esomeprazole granules, 10 mg/sachet  
• Sodium acid phosphate enema, 5 mL enema | • Antispasmodic drop |
| **Section 2**  
Cardiovascular | • Argatroban injection, 100 mg/ mL, 2.5 mL vial  
• Atorvastatin tablet,40 mg tab.  
• Bisoprolol tablet, 5mg tab.  
• Captopril suspension, 1 mg/ml  
• Fondaparinux sodium injection, 5 mg/ mL, 0.3 mL prefilled syringe  
• Fondaparinux sodium injection, 5 mg/ mL, 0.5 mL prefilled syringe  
• Glyceryl trinitrate 0.4mg /dose 200 dose spray  
• Ivabradine tablets, 5 mg tab.  
• Metoprolol 1mg/ml  
• Micronized fenofibrate tablet,145mg – 200mg tabs  
• Nifedipine suspension  
• Phytomenadione injection, 2 mg/0.2 mL ampoule  
• Rivaroxaban tablet, 15 mg tab.  
• Rivaroxaban tablet, 20 mg tab.  
• Spironolactone syrup, 2.5 mg/ mL  
• Valsartan tablet,160 mg tab. | • Cilazapril tablets,2.5mg tab.  
• Fenofibrate capsules,300 mg cap.  
• Furosemide tablets, 500 mg tab.  
• Phytomenadione tablets, 10 mg tab.  
• Terazosin capsules, 5 mg cap. |
| **Section 3**  
Respiratory | • Budesonide/ Formoterol powder for inhalation, 160/4.5 micrograms/ blister  
• Fluticasone/Salmeterol powder for inhalation, 500/50 micrograms/ blister  
• Montelukast sachets, 4 mg/ sachet  
• Omalizumab 150mg/ml  
• Pirfenidone capsules, 200 mg cap. | • Beclometasone dipropionate metered aerosol inhaler, 250 microgram/ metered inhalation  
• Beclometasone dipropionate metered aerosol inhaler, 50 microgram/metered inhalation  
• Salbutamol syrup 2mg/5ml  
• Salbutamol tablet, 4 mg tab. |
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<th>Section 4</th>
<th>Additions and Deletions</th>
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| CNS       | • Aprepitant capsules, 125 mg cap.  
• Aprepitant capsules, 80 mg cap.  
• Carbidopa with Entacapone and Levodopa tablets, 100/25/200 mg tab.  
• Carbidopa with Entacapone and Levodopa tablets, 150/37.5/200 mg tab.  
• Donepezil tablets, 5 mg tab.  
• Duloxetine tablets, 120 mg tab.  
• Duloxetine tablets, 30 mg tab.  
• Ethosuximide syrup, 250 mg/5 mL  
• Fentanyl transdermal patches, 12.5 micrograms/hour for 72 hours  
• Galantamine tablets, 8 mg tab.  
• Levetiracetam tablets, 1 g tab.  
• Methylphenidate tablets, 10 mg tab.  
• Methylphenidate tablets, 20 mg tab.  
• Methylphenidate tablets, 5 mg tab.  
• Midazolam syrup  
• Morphine sulphate slow-release tablets, 40 mg S.R. tab.  
• Risperidone depot injection, 25 mg inj.  
• Risperidone depot injection, 50 mg inj.  
• Rivastigmine capsules, 3 mg cap.  
• Rivastigmine capsules, 6 mg cap.  
| Deletions | • Ergotamine tartrate + caffeine tablets, 1 mg + 100 mg tab.  
• Lorazepam Injection, 4 mg/ml |

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<th>Section 5</th>
<th>Additions and Deletions</th>
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</table>
| Infections | • Anidulafungin injection, powder for reconstitution, 100 mg vial  
|            | • Ketoconazole tablets, 200 mg tab. |
Additions and Deletions

- Artemether/ lumefantrine tablets, 20 mg/ 120 mg tab.
- Artesunate injection, 60 mg inj.
- Caspofungin injection, powder for reconstitution, 50 mg vial
- Clarithromycin injection, powder for reconstitution, 500 mg vial
- Clarithromycin suspension, 250 mg/ 5 mL
- Clindamycin suspension, 75 mg/ 5 ml
- Cloxacillin injection, powder for reconstitution, 500 mg vial
- Darunavir tablets, 300 mg tab.
- Efavirenz capsules, 200 mg cap.
- Efavirenz capsules, 50 mg cap.
- Efavirenz 600mg + Emtricitabine 200mg + Tenofovir disoproxil 300mg
- Ertapenem injection, powder for reconstitution, 1 g vial
- Lamivudine solution, 10 mg/mL
- Linezolid injection, 600 mg inj.
- Linezolid suspension, 100 mg/ 5 ml susp.
- Linezolid tablets, 600 mg tab.
- Lopinavir / Ritonavir oral solution, 80 mg/ 20 mg/ mL
- Lopinavir / Ritonavir tablets, 100 mg/ 25 mg tab.
- Lopinavir / Ritonavir tablets, 200 mg/ 50 mg tab.
- Meropenem trihydrate injection, powder for reconstitution, 1 g vial
- Nevirapine suspension, 10 mg/mL sus.
- Pentamidine isethionate, solution for inhalation, 300 mg vial
- Rifabutin tablets, 150 mg tab.
- Sodium Fusidate injection, powder for reconstitution, 500 mg vial
- Tetracycline hydrochloride tablets/ capsule, 250 mg tab/cap.
### Additions and Deletions

- Tigecycline injection, 50 mg inj.
- Voriconazole injection, powder for reconstitution, 200 mg vial
- Voriconazole tablets, 200 mg tab.
- Zidovudine syrup, 10 mg/mL

### Section 6. Endocrine

- Cabergoline tablets, 500 microgram tab.
- Carbimazole tablets, 20 mg tab.
- Denosumab injection, 60 mg/mL, 1mL prefilled syringe
- Denosumab injection, 70 mg/mL, 1.7mL (120-mg) vial
- Estradiol pessary, 10 microgram
- Estradiol pump, 750 microgram pack
- Exenatide Injection, 5 microgram/dose (60 doses) in prefilled pen
- Insulin Aspart injection, 100 units/mL, prefilled pen
- Insulin Detemir injection, 100 units/mL, prefilled pen
- Insulin Glargine injection, 100 units/mL, prefilled pen
- Insulin Lispro injection, 100 units/mL, prefilled pen
- Levothyroxine oral solution, 100 microgram/5 mL
- Levothyroxine sodium tablets, 100 micrograms tab.
- Octreotide acetate injection, powder and solvent, 20 mg vial
- Sitagliptin phosphate tablets, 100 mg tab.
- Thyrotropin Alfa injection, 1.1 mg inj.
- Triptorelin injection, powder for reconstitution, 11.25 mg vial

- Glipizide tablets, 5 mg tab.
- Strontium ranelate granules, 2 g/sachet
### Additions and Deletions

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<td>- Vildagliptin tablets, 50 mg tab.</td>
<td>- Indometacin neonatal injection, powder for reconstitution, 1 mg vial</td>
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<td>- Etonogestrel 68 mg intradermal implant</td>
<td>- Oxybutynin hydrochloride tablets, 5 mg tab.</td>
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<tr>
<td>- Hydroxyprogesterone hexanoate injection, 250 mg inj.</td>
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<td>- Solifenacin succinate tablets, 5 mg tab</td>
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<th>Section 8. Malignant diseases &amp; immunosuppressant</th>
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<tr>
<td>- Azacitidine injection, powder for reconstitution, 100 mg/vial</td>
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<td>- Bendamustine injection, powder for reconstitution, 100 mg vial</td>
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<td>- Bendamustine injection, powder for reconstitution, 25 mg vial</td>
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<td>- Bicalutamide tablets, 150 mg tab.</td>
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<td>- Clofarabine injection, 20 mg vial</td>
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<td>- Dasatinib tablets, 50 mg tab.</td>
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<tr>
<td>- Everolimus tablets, 0.75 mg tab.</td>
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<tr>
<td>- Everolimus tablets, 10 mg tab.</td>
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<tr>
<td>- Everolimus tablets, 5 mg tab.</td>
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<tr>
<td>- Fingolimod hydrochloride capsules, 500 microgram caps.</td>
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<tr>
<td>- Fulvestrant injection, 250-mg prefilled syringe</td>
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<tr>
<td>- Gefitinib tablets, 250 mg tab.</td>
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<tr>
<td>- Imatinib tablets, 400 mg tab.</td>
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<td>- Lapatinib tablets, 250 mg tab.</td>
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<td>- Lenalidomide capsules, 10 mg &amp; 25 mg cap.</td>
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<tr>
<td>- Methotrexate sodium injection, 20 mg in pre-filled syringe</td>
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<td>- Mycophenolate Sodium tablets, 360 mg tab.</td>
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<td>- Oxaliplatin injection, 100 mg vial</td>
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<td>- Panitumumab injection, 100 mg vial</td>
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<td>- Sorafenib tablets, 200 mg tab.</td>
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<td>- Sunitinib capsules, 12.5 mg cap.</td>
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<tr>
<td>- Sunitinib capsules, 50 mg cap.</td>
<td></td>
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<tr>
<td>Additions and Deletions</td>
<td></td>
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<td>-------------------------</td>
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<tr>
<td>- Tacrolimus sachets, 1 mg per sachet.</td>
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<tr>
<td>- Tacrolimus sachets, 200 micrograms per sachet</td>
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<tr>
<td>- Thalidomide tablets, 100 mg &amp; 200 mg tab.</td>
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<tr>
<td>- Calcium syrup, 100 mg/ 5 mL</td>
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<td>- Cinacalcet tablets, 30 mg tab.</td>
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<td>- Colecalciferol capsules, 50,000 units cap.</td>
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<tr>
<td>- Colecalciferol drops 10,000 IU / ml</td>
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<td>- Colecalciferol drops 400 IU / ml</td>
</tr>
<tr>
<td>- Darbepoetin Alfa injection, 10 micrograms prefilled syringe</td>
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<td>- Deferasirox tablets, 125 mg, 250 mg &amp; 500 mg tab.</td>
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<td>- Glutamine injection, 200 mg inj.</td>
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<td>- Nitisinone capsules, 2 mg cap.</td>
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<td>- Plerixafor injection, 24 mg in 1.2 mL vial</td>
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<td>- Romiplostim injection, powder for reconstitution, 250 microgram vial</td>
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<td>- Sevelamer powder, 800 mg per sachet</td>
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<td>- Sodium bicarbonate tablets, 500 mg tab.</td>
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<td>- Sodium Phenylacetate and Sodium Benzoate 100 mg/mL (of sodium phenylacetate) and 100 mg/mL (of sodium benzoate) in a concentration for injection</td>
</tr>
<tr>
<td>- Sodium phenylbutyrate tablets, 500 mg tab.</td>
</tr>
<tr>
<td>- Vitamine D3 drops, 10,000 IU</td>
</tr>
<tr>
<td>- Zinc syrup, 20 mg/ 5 mL, 50-75 mL</td>
</tr>
</tbody>
</table>
## Additions and Deletions

| Section 10. MSK | • Celecoxib tablets, 200 mg tab.  
• Diclofenac sodium suppositories, 25 mg tab.  
• Etanercept injection, 50 mg prefilled syringe  
• Etoricoxib tablets, 120 mg tab.  
• Etoricoxib tablets, 90 mg tab.  
• Ibuprofen injection, 10 mg / mL  
• Leflunomide tablets, 20 mg tab.  
• Naproxen tablets, 250 mg tab  
• Rasburicase injection, powder for reconstitution, 1.5 mg vial  
• Rasburicase injection, powder for reconstitution, 7.5 mg vial  
• Tocilizumab Injection, 20 mg/ mL, 4 or 10 mL vial |
|---|---|
| Section 11. Eye | • Apraclonidine eye drops, 0.5%  
• Apraclonidine eye drops, 1.0%  
• Cyclopentolate eye drops, 0.5% ; 5 mL/bottle  
• Cyclopentolate eye drops, 1% ; 5 mL/bottle  
• Latanoprost with Timolol eye drops, 50 microgram latanoprost and 5 mg timolol per mL  
• Moxifloxacin eye drops, 0.5%  
• Ranibizumab injection, 10 mg/ 1 mL in prefilled syringe |
| Section 12. ENT | • Budesonide nasal spray, 64 micrograms/metered spray, 120 doses/ metered spray |
| Section 13. skin | • Calcipotriol/ betamethasone dipropionate cream  
• Calcipotriol/ Betamethasone gel  
• Heparinoid cream, 0.3%  
• Heparinoid gel, 0.3% |
| | • Calcipotriol cream, 50 microgram/ g cream, 30 g tube |
### Additions and Deletions

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<th>• Tetanus antitoxins injection, 1,500 units injection in 1mL ampoule</th>
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<td>Section 15. Anaesthesia</td>
<td>• Dexmedetomidine injection, 100 micrograms/mL</td>
<td>• Ketamine hydrochloride injection, 10 mg (preservative free injection)</td>
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<td></td>
<td>• Ketorolac Injection, 30 mg/mL. 1 mL ampoule</td>
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<td></td>
<td>• Levobupivacaine injection, 25 mg / 10 mL ampoule</td>
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<td></td>
<td>• Levobupivacaine injection, 50 mg / 10 mL ampoule</td>
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<tr>
<td>Section 16. Contrast media</td>
<td>• Barium sulfate suspension, 0.1%, 750 mL</td>
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</table>
Prescribing Guidance

Guidance on appropriate prescribing

General remarks

Medicines should be prescribed only when improvement of the clinical condition is possibly achieved with the minimum risk to the patient. Drug therapy sometimes is unnecessary, unsuitable or ineffective. It is the prescriber’s duty to explain to the patient in a simple, convincing way that some ailments are self limiting and drugs are not always necessary.

Great care should be practiced when prescribing during pregnancy to avoid any harmful drug effect to either the mother or the foetus. Cautious prescribing is retained for paediatric and geriatric patients, in patients with renal or hepatic impairment or in the immunocompromised and also for breast feeding mothers.

Rational use of medicines (RUM) as defined by WHO is “All patients should receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to themselves and their community.” RUM should be highly encouraged and promoted at all levels of the health services. The concept of RUM should not be mistaken as only rationing medication or reducing cost. RUM aims to:

- Avoid over prescribing
- Minimise adverse drug effects
- Select the right drug for the right clinical condition
- Increase awareness about drug costs
- Establish national drug policies

Irrational or non-rational use is the use of medicines in a way that is not compliant with the definition above. Worldwide more than 50% of all medicines are prescribed, dispensed or sold inappropriately, while 50% of patients fail to take them correctly.

Drugs in Oman are categorized for administrative purposes into the following:

- Restricted drugs: to be prescribed by consultants and specialists or to be used by specialized units.
Prescribing Guidance

- **Controlled drugs**: to be prescribed on a special prescription and these include three classes: a- *Narcotics* as classified according to International Narcotic Control Board (INCB) to be prescribed using *red prescription*; b- *Psychotropics* to be prescribed using *green prescription*; c- *Other drugs* that may pose a special threat of misuse as decided by local health authority, e.g., tramadol, these agents are prescribed using the green prescription.

- **Complementary drugs as per complementary drug list (CDL)** for rare disorders or in exceptional circumstances to be made available on demand by specialists

- **General drugs**: are prescribed by doctors without any specific limitation.

Primary health doctors are permitted to prescribe a limited number of the general drugs (see Primary Health Care Formulary, circular MH/DGMS/DGO/4/C/5/472 of 31 July 2002) and these are noted in separate formulary published by the Directorate General of Medical Supplies.

**Prescription writing**

A prescription is a medico-legal document, which should be legibly written in ink. The Doctor’s name and professional title should clearly appear with the signature on the prescription. The prescription should contain full information about the patient such as, patient’s name, registration number, sex, age or the date of birth, and body weight (if appropriate). Drug related information must carefully be written and these include the following:

- **Drug name**: drugs should be prescribed in their generic names wherever possible. This will minimise the confusion caused by the many trade names given to one single generic molecule. When a combined preparation is prescribed, it is advisable that acceptable terminology is used to describe such a preparation; e.g., *cough syrup*, for cough mixture; *oral decongestants* for antihistamine and sympathomimetics etc. Never invent a drug name or use non standard abbreviations.

- **Strengths or volumes** should be stated using the metric system (see table below). Doses less than 1 g should be stated in mg.
Prescribing Guidance

(e.g. 250 mg or 500 mg and not as 0.25 g or 0.5 g). Doses less than 1 mg should be stated in micrograms (e.g. 250 or 500 micrograms and not as 0.25 mg or 0.5 mg). When decimals are unavoidable, a zero should appear before the decimal point where there is no other figure, e.g. 0.5 mL and not .5 mL

<table>
<thead>
<tr>
<th>Measure Unit</th>
<th>Symbol</th>
<th>Incorrect symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram</td>
<td>g</td>
<td>G or gm</td>
</tr>
<tr>
<td>Milligram</td>
<td>mg</td>
<td>mgm</td>
</tr>
<tr>
<td>Microgram</td>
<td>microgram</td>
<td>mcg</td>
</tr>
<tr>
<td>Millilitre</td>
<td>mL or ml</td>
<td>cc or cm³</td>
</tr>
<tr>
<td>Litre</td>
<td>l</td>
<td>L, lr or lt</td>
</tr>
</tbody>
</table>

- **Dose regimen**: always state dose strength, dose frequency, duration of treatment, and quantity to be dispensed. Avoid using abbreviations as they may cause confusion. However, it may be convenient to use some internationally recognized Latin abbreviations such as bid, tid and qid for 2, 3 and 4 times daily respectively. Preferably, time intervals should be mentioned for example, every 6 hours, every 8 hours etc. Avoid using abbreviations as PRN or SOS alone or phrases such as “as directed, as required or on need”; frequency of dosing should be clearly mentioned, such as “PRN, one tablet three times daily” or “as required, 3 times daily”.

Prescribing at the two extremes of age

Most drugs are developed and tested in young to middle aged adults. At the two ends of the age spectrum, individuals differ both in their pharmacodynamic and pharmacokinetic characteristics. These differences may impose critical adjustments in the dose or dose regimen to produce the desired effect with the minimum of harmful or unwanted effects.

Paediatric prescribing

Drug clearance pathways are limited in the newly born, and develop variably in the first year and keep showing variations until puberty. Apart from immaturity of physiological processes, the reaction of infants and young children to drugs is influenced indirectly through complications such as fever, dehydration, and acid-base disturbances. Pharmacodynamic differences between children and adults have led to unexpected outcomes of therapy.
and adverse effects. For example, while antihistamine and barbiturates generally sedate adults, these drugs cause many children to become hyperactive. It remains very difficult to work out a reliable method to determine the dose in children based on adult dose. Many formulas have been suggested using body weight, surface area or age as indicators to convert adult doses of drugs into a safe and effective dose in children. In the ONF children’s doses are mentioned in the drug entries unless the drug is not recommended for pediatric use. The following table is an approximate guide to paediatric doses. The doctor should make a rational assessment to decide on the dose regimen that is suitable for each individual patient.

### Age/weight table

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight (kg)</th>
<th>Surface area (m²)</th>
<th>% of adult dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate (term)</td>
<td>3.5</td>
<td>0.23</td>
<td>12.5</td>
</tr>
<tr>
<td>1 month</td>
<td>4</td>
<td>0.25 - 0.26</td>
<td>14 - 14.4</td>
</tr>
<tr>
<td>3 months</td>
<td>6</td>
<td>0.32 - 0.34</td>
<td>15 - 18</td>
</tr>
<tr>
<td>6 months</td>
<td>8</td>
<td>0.38 - 0.40</td>
<td>20 - 22</td>
</tr>
<tr>
<td>1 year</td>
<td>10</td>
<td>0.46 - 0.49</td>
<td>25 - 27</td>
</tr>
<tr>
<td>2 years</td>
<td>12</td>
<td>0.54 - 0.58</td>
<td>30 - 32</td>
</tr>
<tr>
<td>3 years</td>
<td>14</td>
<td>0.61 - 0.64</td>
<td>33 - 35</td>
</tr>
<tr>
<td>4 years</td>
<td>16</td>
<td>0.67 - 0.71</td>
<td>36 - 39</td>
</tr>
<tr>
<td>5 years</td>
<td>18</td>
<td>0.72 - 0.77</td>
<td>40 - 43</td>
</tr>
<tr>
<td>7 years</td>
<td>22</td>
<td>0.86 - 0.90</td>
<td>47 - 50</td>
</tr>
<tr>
<td>10 years</td>
<td>30 - 32</td>
<td>1.04 - 1.11</td>
<td>58 - 62</td>
</tr>
<tr>
<td>12 years</td>
<td>38 - 40</td>
<td>1.21 - 1.30</td>
<td>70 - 75*</td>
</tr>
<tr>
<td>14 years</td>
<td>48 - 50</td>
<td>1.46 - 1.50</td>
<td>80 - 87*</td>
</tr>
</tbody>
</table>

* Doses might be 100% of adult dose dependent on individual and drug

To calculate Body surface area (BSA) by using child-BSA-nomogram see appendix 6

### Geriatric prescribing

In the general population, functional capacity of most of the major organ systems shows a decline with advancing age. This may be reflected in absorption, distribution, metabolism and elimination of drugs. In addition, it is believed that geriatric patients are more “sensitive” to the action of many drugs, implying a change in the pharmacodynamic interaction of drugs
Prescribing Guidance

with their sites of action. Such changes could also be attributed to diminished homeostatic responses. Drug usage patterns in the elderly also change due to an increasing incidence of disease with age. Among other changes are, the increasing incidence of multiple diseases, nutritional problems, reduced financial resources, and decreased compliance for a variety of reasons. Because of an increasing risk of adverse effects when prescribing in the elderly, the following precautionary measures are recommended:

- Drugs are prescribed only when highly indicated
- Start low and go slow every time a new drug is prescribed
- Avoid polypharmacy
- It is advisable some times to use paediatric formulations (such as liquids, suppositories or effervescent tablets) instead of oral tablets or capsules; the former preparations offer a better dose adjustment and improve compliance.
- Do not rush to treat a new symptom or complaint; it could be attributed to an adverse effect of an already used drug.

Drugs with greater risk in the elderly include, sedatives and hypnotics, analgesics, antipsychotics, antidepressant drugs, cardiovascular drugs, antimicrobials, long acting antidiabetic drugs and anti-inflammatory drugs. For individual drugs see drug entries in the ONF.

Prescribing in renal impairment

Drugs that are entirely or partially eliminated by the renal system may produce toxicity in the presence of renal impairment. Such toxicity is more serious with drugs that have a narrow safety margin. Problems arising from use of drugs in renal impairment can be avoided by reducing the dose, or the use of alternative drugs, or by increasing the dosing time interval. Dose reduction depends on whether the drug is entirely or partially eliminated by the renal system and on how toxic it is. For many drugs with only minor dose-related toxicity very strict modification of the dose regimen is unnecessary and a simple scheme for dose reduction is sufficient.

For drugs with toxic dose-related side-effects, the dose reduction is dependent on the glomerular filtration rate. However, glomerular filtration rate (GFR) is only used to initiate the dose regimen, but for maintenance, the judgement is based on clinical response and the drug-plasma concentration. The practical way of determining glomerular filtration rate is by measuring creatinine clearance. For creatinine clearance calculations, see appendix 3
Prescribing Guidance

Nephrotoxic drugs should be avoided in patients with renal disease because the consequences of nephrotoxicity are likely to be more severe when the renal reserve is already reduced. See appendix 3 for lists of common drugs associated with nephrotoxicity. The state of renal function must be determined not only before but also during the treatment, since some drugs may cause further deterioration of renal function. Caution should be taken in elderly patients as renal function might be reduced even in the presence of normal serum urea or creatinine. For dosing reduction regimen, consult drug literature. In the ONF, relevant cautionary notes about individual drug and renal impairment are mentioned in the drug entries.

Prescribing in hepatic impairment

Reduced liver function may alter responses and lead to adverse drug reactions. This depends mainly on the severity of liver disease and on the extent of drug hepatic metabolism. Drugs that are entirely metabolised are more affected than those partially subjected to liver metabolism or excreted unchanged by the renal system.

It is not simple to determine the degree of liver impairment, and hence it is difficult to come out with a standard dose reduction regimen. The liver has a great reserve capacity and only very severe impairment will effectively decrease the rate of metabolism of some drugs leading to adverse effects. This is more frequent with drugs of low margin of safety. Drugs may induce hepatotoxicity, which aggravates existing liver impairment. Therefore, hepatotoxic drugs should be avoided in the presence of hepatic impairment and should only be used after assessing their benefit versus their risks. For more information about drug-induced hepatotoxicity, see appendix 2.

As a general rule, to avoid drug adverse reactions in the presence of hepatic impairment, avoid drugs that are extensively metabolised in the liver, or reduce the dose and closely observe the clinical response and the development of adverse effect. In the ONF, relevant cautionary notes about individual drug and hepatic impairment are mentioned in the drug entries.

Prescribing during pregnancy

Most drugs taken by pregnant women can cross the blood-placental barrier and expose the developing embryo and foetus to their detrimental effects. Many factors contribute to the occurrence of congenital malformation (teratogenesis), such as the genetic susceptibility of the embryo, pathological...
Prescribing Guidance

and nutritional status of the mother, as well as exogenous factors; drugs are one of the exogenous factors involved. The occurrence is also dependent on the following drug related factors:

- The physicochemical properties of the drug
- The rate at which the drug crosses the placenta and the amount reaching the foetus
- The duration of exposure
- Distribution characteristics in foetal tissues
- The stage of foetal development at the time of exposure

During the first 2 weeks following conception (pre-implantation period), the embryo is probably resistant to drugs because there is no direct circulatory link between the mother and the embryo. The period of greatest risk is from the 3rd to the 11th week of pregnancy. During this period cellular division and differentiation is most sensitive to harmful drug effects. All drugs should be avoided as much as possible during this period (1st trimester). After the first trimester most organs are formed, although the genital apparatus, teeth, and the nervous system continue to mature. Thus drugs administered during the second and third trimesters may affect growth and functional development of the foetus. Drugs given towards the end of pregnancy or during labour may have adverse effects on the neonate.

As a general rule, drugs should be avoided during pregnancy and especially during the first trimester, unless there is a clear indication and the expected benefit is greater to the mother than the risk to the foetus. If medication is a necessity, drugs of well tested safety should be used in the smallest effective dose and for the shortest possible therapeutic duration.

Doctors should always consider (1) the possibility of pregnancy when prescribing for women of childbearing age, (2) Pregnancy results in profound physiological changes, which may alter the pharmacokinetics of many drugs. In the ONF, relevant cautionary notes about individual drug use during pregnancy are mentioned in the drug entries.

Prescribing during breast-feeding

Drugs taken by lactating mother may be passed to the breast-fed infant through the milk. Some drugs appear in the milk in a pharmacologically significant concentration to cause adverse effect in the breast-fed infants. However, some drugs have inhibitory or stimulatory action on lactation such as bromocriptine or phenothiazines.
Breast-feeding should be maintained in women who need drug therapy provided that the infant is closely observed for possible adverse effects. However, some times it becomes necessary to avoid some drugs and occasionally to stop breast-feeding when:

- a drug is harmful to the infant even when it appears in small concentration in the milk
- a drug is liable to accumulate in the nursing mother circulation due to the presence of renal or hepatic impairment.

In the ONF, relevant cautionary notes about individual drug use during breast-feeding are mentioned in the drug entries.

**Adverse drug reactions (ADR)**

The use of drugs is often associated with the risk of adverse reactions: Severe adverse reaction to marketed drugs are uncommon as most of such reactions are noted during the various phases of clinical trials and upon their occurrence usually the manufacture is deterred from marketing the drug.

The mechanisms of adverse reactions fall into two main categories. Those in the first group are often extension of the pharmacological effects and thus are predictable by researchers and clinicians. In the second group, which may be immunological or of unknown mechanisms, are unexpected and may not be encountered unless the drug is put for use for many years; clinicians usually discover these toxicities. It is therefore of utmost importance, that an adverse reaction reporting system is actively brought up by practicing clinicians. A drug reaction may occur as early as the first dose, such as anaphylaxis or haemolytic anaemia. Serious toxic effects may occur during prolonged treatment as with corticosteroids. Other reactions may well occur long after cessation of treatment. The incidence of adverse effects increases with the number of drugs used by the patient. Some of these adverse reactions may be due to drug interactions. In the elderly, particular vigilance is required. Confusion, falls or severe constipation may be signs of adverse reactions. All drugs taken during pregnancy should be reported when an infant is born with congenital abnormalities or there is a malformed aborted foetus, as an adverse drug reaction might have been the cause. Adverse reactions may be prevented as follows:
Prescribing Guidance

- Drugs should only be used when evidently indicated.
- Great caution should be experienced in prescribing to pregnant or breast-feeding women.
- Ask your patient about any previous allergy or other adverse reactions.
- Be aware of any other drugs taken by the patient before prescribing new one. Make sure to ask about over the counter (OTC or self-purchased) medicines.
- Prescribe as few drugs as possible and clearly instruct the patient in their appropriate use.
- More attention is given to newly introduced drugs. Caution the patient to report any undesirable effect.

Reporting of adverse drug reactions

Medical staff are requested to report any adverse reaction encountered with new drugs. However, unusual, unexpected or serious reactions to established drugs or biological products should also be reported. In case of congenital abnormalities or deformities in aborted foetus, all drugs taken by the mother during pregnancy should be reported. The reported information is processed with a high degree of confidentiality. The attached format (see the yellow forms at the back of this publication) should be used for reporting purposes.

Report ADR to:
Directorate General of Pharmaceutical Affairs and Drug Control
Muscat
How to use the ONF

How the material is organised
There are 17 main sections, 8 appendixes. Each main section represents a particular body system or an aspect of medical care. Within each section there are introductory notes about each group of drugs. These notes are intended for the use of doctors, dentists, nurses, pharmacists and other health care providers to assist in the selection of suitable treatments. The notes are followed by details of the available drugs and preparations (as per template below).

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRUG NAME – approved generic name</td>
<td></td>
</tr>
<tr>
<td>Indications:</td>
<td></td>
</tr>
<tr>
<td>Contraindications:</td>
<td></td>
</tr>
<tr>
<td>Cautions:</td>
<td></td>
</tr>
<tr>
<td>Side effects:</td>
<td></td>
</tr>
<tr>
<td>Dose:</td>
<td></td>
</tr>
<tr>
<td>Preparations</td>
<td></td>
</tr>
</tbody>
</table>

Guidance on Prescribing
There are notes on appropriate prescribing including the principles of rational prescribing and drug use; prescription writing; controlled drugs including psychotropics and narcotics; restricted drugs; prescribing at the extremes of age; prescribing in renal failure and hepatic impairment. There are additional notes on prescribing in pregnancy and breast feeding and reporting of adverse drugs reactions (ADRs). In the text are examples of the different prescription forms found in Oman and the ADR reporting forms.

Appendixes
There are total of 8 appendixes. For more details, see under the preface/layout of the ONF

Emergency Treatment of Poisoning
Section 17 is devoted to the management of acute poisoning both accidental and self-administered. General aspects of management are included as well as details of specific antidotes where appropriate.

Index
The general index is placed at the back of the book and is often the first point of contact for most practitioners Major key words have also been included to allow searches based on a particular condition or disease.
<table>
<thead>
<tr>
<th>Department</th>
<th>Date</th>
<th>Name</th>
<th>اسم</th>
<th>Age</th>
<th>عمر</th>
<th>Weight</th>
<th>الوزن</th>
<th>Sex</th>
<th>جنس</th>
<th>رقم التسجيل</th>
<th>Name of Prescriber</th>
</tr>
</thead>
</table>

**FOR PHARMACY USE ONLY (PACK & QTY. ENDORSEMENT)**

Dispensed by

Checked by

Signature

Name of Prescriber

Ministry of Health Out-Patient Prescription

SPECIMEN
Example Prescriptions

Ministry of Health
Directorate General of Pharmaceutical Affairs and Drug Control

Hospital Name: ________________________________  No. 0608

Out Patient Prescription for Oral Narcotics

Patient’s Detailed Residence Location  Patient’s Label

Diagnosis: ________________________________

Rx

<table>
<thead>
<tr>
<th>Name of Drug &amp; strength</th>
<th>Dose &amp; Frequency</th>
<th>Duration</th>
<th>Quantity In Hand</th>
<th>Quantity Dispensed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Date & quantity of last oral dose: ________________________________

Doctor’s Sign. : ________________________________  Dispensed by: ________________________________
& Stamp/Name : ________________________________  (name & sign.)

Date: ________________________________  Checked by: ________________________________

Date: ________________________________

*Please write in Capital Letters.

Patient’s Copy  Hospital Stamp
Example Prescriptions
1: Gastro-intestinal system

- Antacids
- Antispasmodics
- Ulcer healing drugs
- Antidiarrhoeal drugs
- Laxatives
- Ano-rectal preparations
- Drugs affecting gastrointestinal secretion

Antacids neutralise the acid secreted by the gastric parietal cells. They help relieve symptoms of ulcer dyspepsia. Antacids should be used upon occurrence of symptoms, usually taken between meals and at bedtime 4 or more times daily. Healing of an ulcer might be achieved with additional doses up to one every hour, however healing of an ulcer is better achieved with antisecretory drugs (e.g. H2-receptor blockers).

Aluminium hydroxide alone or in combination with magnesium salts (hydroxide or trisilicate) is commonly used. Antiflatulants, such as dimeticone are sometimes added to antacid preparations. Aluminium hydroxide tends to cause constipation while magnesium salts are laxative. Compound antacids have no advantage over single preparations in their neutralising capacity. Liquid preparations are more effective than tablets.

**Dried aluminium hydroxide gel**
- **Indications**: dyspepsia, hyperphosphataemia.
- **Contraindications**: hypophosphataemia.
- **Cautions**: renal failure, porphyria, congestive heart failure, recent gastrointestinal haemorrhage.
- **Side-effects**: constipation, faecal impaction, chalky taste, stomach cramps, nausea, vomiting.
- **Dose**: One tab/cap 4 times daily and at bedtime. Child not recommended for antacid therapy.
- **Preparations**: Aluminium Hydroxide capsules, 475 mg cap.

**Magnesium trisilicate or hydroxide with aluminium hydroxide**
- **Indications**: dyspepsia, gastritis, gastric and duodenal ulceration, reflux oesophagitis.
- **Contraindications**: hypophosphataemia.
- **Cautions**: patients with gastrointestinal haemorrhage, patient with CHF, oedema, hypertension, renal failure, cirrhosis.
- **Side-effects**: constipation; large doses may cause osteomalacia, encephalopathy.

xxviii
Section 1: Gastro-Intestinal System

- Antacids
- Antispasmodics
- Ulcer healing drugs
- Antidiarrhoeal drugs
- Laxatives
- Ano-rectal preparations
- Drugs affecting gastrointestinal secretion

1 A: Antacids

Antacids neutralise the acid secreted by the gastric parietal cells. They help relieve symptoms of ulcer dyspepsia. Antacids should be used upon occurrence of symptoms, usually taken between meals and at bedtime 4 or more times daily. Healing of an ulcer might be achieved with additional doses up to one every hour, however healing of an ulcer is better achieved with antisecretory drugs (e.g. H2-receptor blockers).

Aluminium hydroxide alone or in combination with magnesium salts (hydroxide or trisilicate) is commonly used. Antiflatulants, such as dimeticone are sometimes added to antacid preparations. Aluminium hydroxide tends to cause constipation while magnesium salts are laxative. Compound antacids have no advantage over single preparations in their neutralising capacity. Liquid preparations are more effective than tablets.

1 A.1: Aluminium Hydroxide

*Dried aluminium hydroxide gel*

**Indications:** dyspepsia, hyperphosphataemia.

**Contraindications:** hypophosphataemia.

**Cautions:** renal failure, porphyria, congestive heart failure, recent gastrointestinal haemorrhage.

**Side-effects:** constipation, faecal impaction, chalky taste, stomach cramps, nausea, vomiting.

**Dose:** One tab/cap 4 times daily and at bed time. Child not recommended for antacid therapy.

**Preparations**

Aluminium Hydroxide capsules, 475 mg cap.

1 A.2: Compound Antacid Preparations

*Magnesium trisilicate or hydroxide with aluminium hydroxide*

**Indications:** dyspepsia, gastritis, gastric and duodenal ulceration, reflux oesophagitis.

**Contraindications:** hypophosphataemia.

**Cautions:** patients with gastrointestinal haemorrhage, patient with CHF, oedema, hypertension, renal failure, cirrhosis.

**Side-effects:** constipation; large doses may cause osteomalacia, encephalopathy.
1: Gastro-intestinal system

Dose: 1-2 tablets or 10-20 mL suspension 4 times daily. Child under 12 years, not recommended.

Preparations
Compound antacid tablets, 505 mg tab
Compound antacid suspension, 100-200 mL/bottle

1 B: Antispasmodics

1 B.1: Antimuscarinics

Antimuscarinics reduce intestinal motility and gastric secretion. They can be useful in dyspepsia, irritable bowel syndrome and diverticular disease. Other indications include asthma, motion sickness, Parkinsonism, urinary incontinence and as an antidote for organophosphorus poisoning. Atropine sulphate, hyoscine n-butylbromide, hyoscine hydrobromide, and homatropine are useful in gastrointestinal spasm. Atropine is more lipid soluble and hence is more likely to cross the blood-brain barrier and induce central effects such as confusion. These side-effects are less likely with hyoscine and homatropine.

Cautions: Due to the diversity of their actions, antimuscarinics should be used with caution in Down’s syndrome, in children and in the elderly, in reflux oesophagitis, diarrhoea and ulcerative colitis. Greater caution should be taken when used in patients with acute myocardial infarction, hypertension and in conditions characterized by tachycardia.

Contra-indications: Antimuscarinics are contraindicated in angle-closure glaucoma, myasthenia gravis, paralytic ileus, and prostate enlargement.

Side-effects: Constipation, dilatation of the pupil with loss of accommodation, photophobia, dry mouth, flushing and dryness of the skin, urinary retention and tachycardia. In the elderly, confusion may occasionally occur.

Atropine Sulphate

Indications: symptomatic relief of gastrointestinal disorders associated with smooth muscle spasm. In pre-medication, to prevent excessive salivation and bronchial secretion.

Contra-indications, cautions and side-effects: see notes above.

Dose: adult 400-600 micrograms every 4-6 hours. Child, with great caution, 10 micrograms/kg every 4-6 hours.

Preparations
Atropine sulphate injection, 600 micrograms/mL, 1 mL injection Atropine sulphate disposable syringe, 1 mg / 10 mL injection (Restricted)

Hyoscine n-Butylbromide

Indications: symptomatic relief of gastrointestinal or genito-urinary disorders characterized by smooth muscle spasm.
Contra-indications, cautions and side-effects: see notes above.
Dose: orally, adult 10-20 mg 3-4 times daily. Child, 6-12 years, 10 mg 3 times daily.
Intramuscular or intravenous, 20 mg repeated as necessary (daily maximum dose 80 mg).

Preparations
Hyoscine n-buty1bromide tablets, 10 mg tab
Hyoscine n-buty1bromide injection, 20 mg/mL ampoule

1 B.2: Other antispasmodics and motility stimulants

Mebeverine is an antispasmodic which may be useful in irritable bowel syndrome. It should be avoided in paralytic ileus. Metoclopramide and domperidone are motility stimulants with dopamine antagonist actions. Motility stimulants stimulate gastric emptying, intestinal transit, and increase the strength of oesophageal sphincter contraction. They are of use in short term management of non-ulcer dyspepsia. Metoclopramide and domperidone are also used to control vomiting and nausea of non-specific nature or drug-induced (see section 4).

Mebeverine hydrochloride
Indications: adjunct in gastrointestinal disorders characterized by smooth muscle spasm. Pain associated with irritable bowel syndrome and diverticular disease.
Cautions: Avoid in paralytic ileus, pregnancy, breast-feeding, porphyria.
Dose: orally, 135 mg tablet 3 times daily preferably before meal.

Preparations
Mebeverine hydrochloride tablets, 100 mg -135mg tab

Metoclopramide
Indications: gastro-oesophageal reflux disease, diabetic gastroparesis, nausea and vomiting, hic-cups.(see section 4)
Cautions: hepatic and renal failure; elderly and young children.
Note: Metoclopramide should be reserved only for severe, intractable vomiting of known cause in persons younger than 20 years of age.
Side-effects: extrapyramidal effects especially in children and young adults; tardive dyskinesia may develop on chronic use.
Dose: Orally, adults over 15 years, 10 mg tablet 3 times daily; young adults 12-14 years; 5 mg (half a tablet) 3 times daily.

Preparations
Metoclopramide tablets, 10 mg tab
Metoclopramide injection, 10 mg/2 mL ampoule

1 C: Ulcer healing drugs
Peptic ulceration is a self-limiting disorder of the digestive tract. It might involve the stomach (gastric ulcer), the duodenum (duodenal ulcer) or the oesophagus. Healing can be promoted by general measures such as stopping smoking, avoiding alcohol, spicy food or stressful life style. Healing can also be promoted by antacids or antisecretary drugs. *Helicobacter pylori* is the causative factor in all duodenal ulcers and most gastric ulcers that are not associated with NSAID use. Eradication of *H. pylori* infection can result in long term healing of duodenal and gastric ulcers.

Acid inhibition combined with antibacterial treatment is highly effective in the eradication of *H. pylori*; reinfection is rare. For initial treatment, a one-week triple therapy regimen that comprises a proton pump inhibitor, clarithromycin and either amoxicillin or metronidazole can be used. This regimen will eradicate *H. pylori* in about 85% of cases. Only if the ulcer is large or has complications does the proton pump inhibitor need to be continued. Two-week triple therapy regimens have a higher eradication rate compared to the one-week regimen, but adverse effects are common and poor compliance reduces the beneficial effects of the two-week treatment option. Two example dosing regimens are shown below:

### Triple therapy example 1:

- Esomeprazole 20 mg twice daily;
- Amoxicillin 1 g twice daily; Clarithromycin 500 mg twice daily.

### Triple therapy example 2:

- Esomeprazole 20 mg twice daily;
- Clarithromycin 250 mg twice daily;
- Metronidazole 400 mg twice daily.

## 1 C.1: H2-receptor antagonists

The H2-receptor antagonists reduce gastric acid secretion by virtue of their competitive inhibition of the H2-receptors in the parietal cells. Ranitidine and nizatidine are used to heal gastric and duodenal ulcers and to relieve peptic oesophagitis. Although superseded by a new class of antisecretory drugs, H2-receptor antagonists are still used to promote healing of NSAID induced ulcers and in Zollinger-Ellison syndrome. The long treatment course and the cost are disfavouring these compounds against the new short treatment regimen with proton pump inhibitors. (PPI).

**Cautions:** should be used with caution in renal impairment, pregnancy and breast-feeding. They may mask symptoms of gastric cancer. Should be avoided in patients on warfarin, theophylline and phenytoin.

**Side-effects:** Gastrointestinal disturbances, headache, dizziness and tiredness. In the elderly, mental confusion and hallucination are more frequent. Cimetidine has

## 1: Gastro-intestinal system

Peptic ulceration is a self-limiting disorder of the digestive tract. It might involve the stomach (gastric ulcer), the duodenum (duodenal ulcer) or the oesophagus. Healing can be promoted by general measures such as stopping smoking, avoiding alcohol, spicy food or stressful life style. Healing can also be promoted by antacids or antisecretory drugs. *Helicobacter pylori* is the causative factor in all duodenal ulcers and most gastric ulcers that are not associated with NSAID use. Eradication of *H. pylori* infection can result in long term healing of duodenal and gastric ulcers.

Acid inhibition combined with antibacterial treatment is highly effective in the eradication of *H. pylori*; reinfection is rare. For initial treatment, a one-week triple therapy regimen that comprises a proton pump inhibitor, clarithromycin and either amoxicillin or metronidazole can be used. This regimen will eradicate *H. pylori* in about 85% of cases. Only if the ulcer is large or has complications does the proton pump inhibitor need to be continued. Two-week triple therapy regimens have a higher eradication rate compared to the one-week regimen, but adverse effects are common and poor compliance reduces the beneficial effects of the two-week treatment option. Two example dosing regimens are shown below:

### Triple therapy example 1:

- Esomeprazole 20 mg twice daily;
- Amoxicillin 1 g twice daily; Clarithromycin 500 mg twice daily.

### Triple therapy example 2:

- Esomeprazole 20 mg twice daily;
- Clarithromycin 250 mg twice daily;
- Metronidazole 400 mg twice daily.

## 1 C.1: H2-receptor antagonists

The H2-receptor antagonists reduce gastric acid secretion by virtue of their competitive inhibition of the H2-receptors in the parietal cells. Ranitidine and nizatidine are used to heal gastric and duodenal ulcers and to relieve peptic oesophagitis. Although superseded by a new class of antisecretory drugs, H2-receptor antagonists are still used to promote healing of NSAID induced ulcers and in Zollinger-Ellison syndrome. The long treatment course and the cost are disfavouring these compounds against the new short treatment regimen with proton pump inhibitors. (PPI).

**Cautions:** should be used with caution in renal impairment, pregnancy and breast-feeding. They may mask symptoms of gastric cancer. Should be avoided in patients on warfarin, theophylline and phenytoin.

**Side-effects:** Gastrointestinal disturbances, headache, dizziness and tiredness. In the elderly, mental confusion and hallucination are more frequent. Cimetidine has

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**Side-effects:** Gastrointestinal disturbances, headache, dizziness and tiredness. In the elderly, mental confusion and hallucination are more frequent. Cimetidine has
been associated with gynaecomastia and impotence; such effects are less frequent in the new generation members of H₂-receptor antagonists.

**Ranitidine**

**Indications:** benign gastric, duodenal and NSAID induced ulcers, oesophageal reflux disease, Zollinger-Ellison syndrome and where reduction of gastric acidity is desirable.

**Cautions:** see notes above

**Side-effects:** see notes above; rarely tachycardia, agitation, visual disturbances, alopecia.

**Dose:** orally, for benign gastric, duodenal or NSAID induced ulcers treatment, 300 mg once at night, or 150 mg twice daily for 4-8 weeks. Maintenance, 150 mg once at night. Orally, for gastro-oesophageal reflux disease, 150 mg twice daily or 300 mg at night for 12 weeks. In moderate or severe cases, 150 mg 4 times daily or 300 mg twice daily for 8-12 weeks. Maintenance, 150 mg twice daily.

Orally, in Zollinger-Ellison syndrome, 150 mg 3 times daily. Doses can be increased according to patients’ response up to 6g daily in divided doses.

Intramuscular injection or slow intravenous infusion, in surgical procedures 50 mg 45-50 minutes before induction of anaesthesia, may be repeated every 6-8 hours.

**Preparations**

Ranitidine tablets, 150 mg tab.
Ranitidine injection, 50 mg/2 mL ampoule
Ranitidine syrup, 75 mg/5 mL, 300 mL bottle (for paediatric gastroenterology only)

**1.C.2: Proton pump inhibitors (PPI)**

The hydrogen-potassium adenosine triphosphate enzyme system (proton—pump) is unique to the parietal cells. Inhibiting this system contributes to a reduction in gastric acid secretion. Proton pump inhibitors (PPI), such as omeprazole, can inhibit the acid secretion to any desirable limit. They are of particular benefit in patients with hypergastrinaemia, severe erosive oesophagitis and those not responding well to treatment with H₂-receptor antagonists. Eradication of *H. pylori* infection has been successfully achieved with omeprazole in combination with antibiotics.

**Cautions:** To be used with caution in presence of liver diseases, in pregnancy, breast-feeding. Gastric malignancy should be excluded before initiation of treatment. Can increase the risk of fractures particularly in the elderly

**Side-effects:** PPI can cause a number of side-effects including headache, diarrhoea, rashes, dizziness, nausea and vomiting, constipation, abdominal pain, flatulence, bronchospasm, blurred vision and dry
1: Gastro-intestinal system

mouth. Intensive decrease in gastric acidity increases the risk of gastro-intestinal infections.

**Esomeprazole (Restricted)**

**Indications**: NSAID induced ulcers, prophylaxis of NSAID-associated gastric ulcer in patients with an increase chance of gastro-duodenal complications, prophylaxis of stress ulceration, gastro-oesophageal reflux disease, duodenal ulcer associated with *H. pylori* infection, Zollinger-Ellison syndrome.

**Cautions**: see notes above

**Side-effects**: see notes above and Omeprazole below.

**Dose**: NSAID induced ulcer treatment, 20 mg once daily for 4-8 weeks.

Gastro-oesophageal reflux disease, 20 mg daily for up to 4 weeks then 20 mg when needed. Child 12–17 years, 20 mg once daily for up to 4 weeks. In the presence of erosive reflux oesophagitis, 40 mg for 4 weeks then maintenance of 20 mg daily. Child 12–17 years. Initially 40 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed or symptoms persist; maintenance 20 mg daily.

Ulcers associated with *H. pylori* infection, 20 mg twice daily.

Zollinger-Ellison syndrome, initial dose 40 mg twice daily adjusted to 80-160 mg daily

Gastric acid reduction during general surgical manipulation, 40 mg the night before surgery and then 40 mg 2-6 hours before surgery.

**Preparations**

- Esomeprazole granules, 10 mg/sachet.

**Omeprazole (Restricted)**

**Indications**: benign gastric, duodenal and NSAID induced ulcers, oesophageal reflux disease, ulcers associated with *H. pylori* infection, Zollinger-Ellison syndrome, gastric acid reduction during surgical manipulations.

**Cautions**: see notes above

**Side-effects**: see notes above. Increased sweating, hallucination, insomnia, gynaecomastia, taste disturbance, paraesthesia

**Dose**: orally for benign gastric, duodenal or NSAID induced ulcers treatment, 20 mg once daily for 4-8 weeks. The dose can be increased to 40 mg in severe cases. Ulcers associated with *H. pylori* infection, see treatment regimen above.

Zollinger-Ellison syndrome, initial dose 60 mg once daily, up to 120 divided into 2 daily doses.

Gastric acid reduction during general surgical manipulation, 40 mg the night before and then 40 mg 2-6 hours before surgery.

**Preparations**

- Omeprazole capsules, 20 mg cap.
- Omeprazole injection, powder for reconstitution, 40 mg vial (Restricted)
Gastro-oesophageal reflux disease, 20 mg when needed. Child 12–17 years, 20 mg once daily for up to 4 weeks then maintenance, 20 mg once daily for 4–8 weeks. The dose can be increased to 40 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed or symptoms persist; extended to 12 weeks in resistant cases.

Sucralfate (Restricted)
Indications: benign gastric and duodenal ulcer and chronic gastritis.
Cautions: Renal impairment, pregnancy and breast-feeding.
Side-effects: constipation, dry mouth, skin rash.
Dose: Benign duodenal and gastric ulcer, 2 g twice daily (on rising and at bed time) or 1 g four times daily (1 hour before meal and at bed time) for 4–6 weeks and can be extended to 12 weeks in resistant cases.

Preparations
Sucralfate tablets, 1 g tab.

1 C.3: Chelates and complexes

Tripotassium dicitratobismuthate is a bismuth chelate that promotes healing of gastric and duodenal ulcer by selectively chelating with protein in the ulcer base, thus protecting it from the effects of acid and pepsin. It also stimulates the secretion of bicarbonate. It has antibacterial activity against H. pylori and this effect gives it a place in eradication therapy as mentioned above. Sucralfate is a basic aluminium salt of sulphated sucrose. It is viscous at acid pH and forms a protective paste that adheres to the ulcerated area. This paste protects the ulcer from the effects of acid, pepsin and bile salts. It is useful in gastric and duodenal ulcers and chronic gastritis.

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Side-effects: constipation, dry mouth, skin rash.
Dose: Benign duodenal and gastric ulcer, 2 g twice daily (on rising and at bed time) or 1 g four times daily (1 hour before meal and at bed time) for 4–6 weeks and can be extended to 12 weeks in resistant cases.

Preparations
Sucralfate tablets, 1 g tab.

1 D: Antidiarrhoeal drugs

Acute diarrhoea is defined as passing of 3 or more watery stools in any 24 hours, or any watery stool if accompanied by fever, abdominal pain and/or vomiting. Acute diarrhoea contributes significantly to the problem of malnutrition in infants and children and is more responsible for mortality than any other cause. The first line of treatment is the replacement of the lost water and electrolytes and prevention of dehydration. Oral rehydration therapy (ORT) can prevent and correct dehydration and prevent many diarrhoea-associated deaths. About 90–95% of all patients with watery diarrhoea can be treated with oral rehydration salt (ORS). No antibiotics are needed even in bacterial diarrhoea as in simple gastro-enteritis, as the condition will mostly resolve with oral rehydration. Not all acute diarrhoea is infectious. Toxins, anxiety, diet, drugs or microorganisms could cause diarrhoea. Viruses are the most important causative agent in children under the age of 5 years, especially during the drier, cooler months, whereas bacterial diarrhoea tends to peak during the warm rainy season in Oman. (For the management and prevention of diarrhoea and dehydration in children under five years, see MOH guidelines).
# 1: Gastro-intestinal system

## 1 D.1: Oral rehydration therapy (ORT)

**Oral rehydration salt (ORS)**

**Indication:** oral replacement of water and electrolyte in acute diarrhoea.

**Cautions and Contraindications:** ORS should be used with caution in patients with heart failure, hypertension and diabetes.

**Side-effects:** rarely hypernatraemia, which is very brief and clinically not very important. If puffiness of the eyes occurs, ORS should be stopped until it disappears.

**Dose and content:** ORS comes in sachets that are ready to be reconstructed, each in 200 mL of drinking water. Each sachet contains, anhydrous dextrose 2.70 g, sodium chloride 0.52 g, trisodium citrate dihydrate 0.58 g and potassium chloride 0.30 g.

The volume of the ORS to be taken is determined by the patient’s body weight and degree of dehydration. The objectives are to replace lost fluids and salts and to compensate for subsequent losses. Mild to moderate dehydration requires the following ORT.

**Rehydration phase**

Mild dehydration: 50 mL/kg administered within 4-6 hr.

Moderate dehydration: 100 mL/kg administered within 4-6 hr.

**Maintenance phase**

Mild diarrhoea: 100 mL/kg/day until diarrhoea stops.

Severe diarrhoea: Replace stool losses volume for volume, or give 10-15 mL/kg/hr.

**Preparations**

ORS sachets, 4.1 g/ sachet

## 1 D.2: Agents that reduce motility

Opioid derivatives and loperamide are drugs used to reduce intestinal motility and hence help in reducing the frequency of diarrhoea. These drugs have no place in the management of diarrhoea in children under 5 years.

Though they reduce stool frequency, these drugs do not prevent dehydration; in fact they obscure the size and seriousness of dehydration.

**Loperamide hydrochloride**

**Indications:** adjunct to rehydration in acute and chronic diarrhoea in adults and in acute diarrhoea in over 5 yrs. children.

**Contraindications:** hypersensitivity to loperamide products, in conditions such as active ulcerative colitis or antibiotic-associated colitis.

**Side-effects:** abdominal cramp, skin rash, drowsiness, dry mouth.

**Dose:** acute diarrhoea, adult 4 mg followed by 2 mg after each loose stool, do not exceed 16 mg daily; Child over 5 years only (6-8 yrs) 2 mg bid, (8-12 yrs) 2 mg 3 times daily.
Chronic diarrhoea, 4-8 mg daily in 2 divided doses. Maintenance according response.

Preparations
Loperamide capsules, 2 mg cap

1 D.3: Treatment of chronic diarrhoea

Tumours should be excluded before managing chronic diarrhoea. Management includes appropriate diet or exclusion of certain foods, maintenance of adequate fluid intake and drug therapy. Conditions associated with chronic diarrhoea are among others, irritable bowel syndrome, ulcerative colitis, Crohn’s disease, diverticular disease, mal-absorption syndrome, and Pseudo-membranous colitis. Aminosalicylate compounds, corticosteroids and cholestyramine are drugs of use in chronic diarrhoea management.

1 D.3.1: Aminosalicylate compounds.

Mesalazine
Indications: treatment of mild to moderate ulcerative colitis and maintenance of remission.
Contra-indications: severe renal and hepatic impairment, salicylates hypersensitivity.
Cautions: elderly, pregnancy, breast-feeding, check blood count (risk of blood dyscrasias), check renal function regularly.
Side-effects: headache, flatulence, abdominal pain, diarrhoea, nausea, alopecia, rash, blood disorders.
Dose: orally, dose is up to 4g in divided doses to control an acute attack. Maintenance dose is usually 1.5g daily in divided doses. By enema, 1g at bedtime.

Preparations
Mesalazine tablets, 500 mg tab. Mesalazine enema, 1 g/100 mL pack

Olsalazine sodium (Restricted)
Indications: induction and maintenance of remission in ulcerative colitis.
Contraindications: salicylates hypersensitivity.
Cautions: avoid during pregnancy, breast-feeding. Blood should be regularly checked as blood disorders may occur.
Side-effects: diarrhoea, headache, nausea, exacerbation of colitis, hematological disorders.
Dose: 1g daily in divided doses after meals. Increase, after one week, to a maximum of 3 g daily in divided doses (max single dose = 1 g).
Maintenance dose: 500 mg twice daily after meals.

Preparations
Olsalazine sodium capsules, 250 mg cap.
**1: Gastro-intestinal system**

*Sulfasalazine (Sulphasalazine)*

**Indications:** mild to moderate ulcerative colitis and maintenance of remission; colonic Crohn’s disease.

**Contraindications:** Sulphonamide hypersensitivity, blood disorders.

**Cautions:** hepatic and renal failures; G6PD deficiency. There is a risk of haematological disorders, which necessitate a regular blood examination.

**Side-effects:** diarrhoea, headache, nausea, exacerbation of colitis, haematological disorders, tinnitus, rash, ocular complications, vertigo.

**Dose:** 1-2 g 4 times/day, maintenance dose 500 mg 4 times/day.

**Preparations**

Sulfasalazine tablets, 500 mg tab.

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**1 D.3.2: Corticosteroids**

Local corticosteroids are applied in diarrhoea due to acute ulcerative colitis in the forms of enemas, suppositories or foam preparations.

*Prednisolone sodium metasulphobenzoate*

**Indications:** ulcerative colitis, Crohn’s disease.

**Contra-indications, cautions, and side-effects:** (see hydrocortisone sec. 6)

**Dose:** rectal, one rectal enema daily at bed time for 2-4 weeks.

**Preparations**

Prednisolone sodium metasulphobenzoate retention enema, 20 mg/100 mL enema

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**1 E: Laxatives**

Constipation is a condition in which the passage of hard stool is less frequently than the patients’ own normal pattern. Constipation should be investigated to exclude being secondary to an underlying undiagnosed complaint. It can be prevented and treated with a combination of adequate exercise, a high fibre diet, and occasionally by appropriate laxative.

Laxatives are indicated when straining may be dangerous (as in angina), in painful anal conditions, in drug induced constipation, prior to GI surgery or radiology and other conditions. The abuse of laxatives could lead to atonic colon and dependence; dependence on laxatives is a common cause of constipation. Bowel movement habit varies among people and constipation should be considered when a patient’s bowel movement deviate from normal.

Laxatives are classified, depending on their mechanism of actions, into:

- Bulk forming laxatives
- Stimulant laxatives
- Osmotic laxatives
- Faecal softeners
1 E.1: Bulk forming laxatives

Bulk forming laxatives increase the faecal mass and hence stimulate peristalsis. They consist of hydrophilic colloids or indigestible vegetable fibres that promote large soft stool by holding water in the bowel lumen. Bran, methylcellulose, sterculia and ispaghula husk are bulk laxative preparations.

**Indications:** constipation due to inadequate dietary intake of fibre, in patients with colostomy, ileostomy, haemorrhoids. They are also of use in patients with chronic diarrhoea associated with irritable bowel syndrome (IBS), diverticular disease and ulcerative colitis.

**Cautions:** patients should be instructed to take adequate amount of fluids.

**Contra-indications:** in patients with intestinal obstructions, atony of the colon or faecal impaction.

**Ispaghula husk**

**Indications:** see notes above; hypercholesterolaemia.

**Contraindications, cautions:** see notes above.

**Side-effects:** flatulence, abdominal distension, GI obstruction or impaction. Hypersensitivity has been reported.

**Dose:** 3.5 g powder of 90% ispaghula husk once or twice daily with water preferably after meal. For children above 6 years, one or half a 5 mL spoonful daily.

1 E.2: Stimulant laxatives

This group of laxatives increases motility by stimulating the sensory nerves of the colon and promote the accumulation of water and electrolytes in the colonic lumen. Their main use is for constipation and for the evacuation of the bowel prior to surgery, X-ray and endoscopy. Bisacodyl, glycerol and sodium picosulphate are used in different dosage formulations. They should be avoided in intestinal obstruction. Chronic use may lead to atonic non-functional colon and hypokalaemia.

**Bisacodyl**

**Indication:** constipation, colonic evacuation.

**Contra-indications:** abdominal pain, appendicitis, intestinal obstruction.

**Side-effects:** abdominal discomfort.

**Dose:** 5-10 mg at night. Avoid taking with milk or antacids. Tablets take 10-12 hours to act. Suppositories act within 30-60 min.

**Preparations:**

- Bisacodyl tablets, 5 mg tab

**Glycerin suppositories**

**Indications:** constipation.
## 1: Gastro-intestinal system

**Contra-indications:** hypersensitivity to glycerin, severe dehydration.

**Cautions:** hypovolemic and elderly patients.

**Side-effects:** local irritation, abdominal pain.

**Dose:** suppositories are moulded for use in infants, children and adults. The suppository should be moistened with water before use. They contain 0.9-2.5 g of glycerin.

**Preparations**
- Glycerin child suppository, 0.9-2 g supp.
- Glycerin adult suppository, 1.8-2.5 g supp.

### Sodium picosulfate (Sodium picosulphate) + Magnesium citrate (Restricted)

This laxative preparation contains sodium picosulphate, which is a stimulant laxative and magnesium citrate, which is an osmotic laxative that traps water and electrolytes to provide a wash-out effect.

**Indications:** constipation; bowel evacuation before surgery or endoscopy.

**Contra-indications:** GI obstruction; renal impairment.

**Side-effects:** headache, tiredness, nausea, gripping and anal pain.

**Dose:** adult and child over 9 years, one sachet dissolved in water before breakfast one day prior to examination, repeat 6-8 hours later.

**Preparations**
- Sodium picosulfate and magnesium citrate powder

## 1 E.3: Osmotic laxatives

Osmotic laxatives trap water in the bowel by osmosis. A phosphate enema is useful in bowel evacuation. Lactulose, a semi-synthetic disaccharide, is not absorbed from the gastro-intestinal tract. It causes osmotic diarrhoea with low pH due to lactic acid production, and inhibits the proliferation of ammonia-producing organisms. It is useful in hepatic encephalopathy.

### Lactulose

**Indications:** constipation (it takes 2 days to show effect), hepatic encephalopathy.

**Contra-indications:** intestinal obstruction, galactosaemia.

**Side-effects:** flatulence, abdominal pain, bloating.

**Dose:** lactulose preparations contain 3.2-3.7 g/5 mL.

For constipation in adults, 15 mL twice daily adjusted according to patient’s need. Child, 5-10 yrs. 10 mL twice daily. For hepatic encephalopathy, 30-50 mL, 3 times daily, adjust to produce 2-3 soft stools daily.

**Preparations**
- Lactulose syrup, 3.35 g/5 mL syrup

### Sodium acid phosphate enema (Restricted)
**1: Gastro-intestinal system**

**Indications:** constipation; bowel evacuation before surgery or endoscopy.

**Contra-indications:** acute GI conditions; renal failure, congestive heart failure.

**Side-effects:** local irritation, oedema, hypotension.

**Dose:** sodium acid phosphate enema is prepared by dissolving 12.8 g sodium acid phosphate and 10.24 g sodium phosphate in 128 mL water.

Adult: 128 mL enema as needed
Child: 5 mL enema as needed

**Preparations**

Sodium acid phosphate enema, 128 - 133 mL enema
Sodium acid phosphate enema, 5 mL enema

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**PEG 3350 + sodium chloride + sodium bicarbonate + potassium chloride + anhydrous sodium sulphate (Restricted)**

PEG=polyethylene glycol

**Indications:** see notes above.

**Contra-indications:** GI obstruction, GI ulceration, perforated bowel, congestive cardiac failure.

**Cautions:** Pregnancy; heart diseases; ulcerative colitis, diabetes mellitus; reflex oesophagitis; in the presence of a possibility of regurgitation or aspiration.

**Side-effects:** nausea and vomiting; bloating.

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**Liquid Paraffin**

**Indications:** constipation.

**Caution:** avoid prolong use.

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**1 E.4: Faecal softeners**

Mineral oils such as liquid paraffin are indigestible and absorbed to a limited extent. They penetrate and soften the stool and may interfere with water absorption.

Adverse effects: leakage of oil past the anal sphincter leading to irritation, chronic use may lead to mal-absorption of fat-soluble vitamins and drugs, lipid pneumonia consequent to aspiration of oil droplets can result after oral use.

**Preparations**

Sodium acid phosphate enema, 128 - 133 mL enema
Sodium acid phosphate enema, 5 mL enema

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**1 E.5: Bowel cleansing solutions**

Bowel cleansing solutions should not be routinely used as a laxative for constipation. They are used before colonic surgery, colonoscopy or radiological examination to ensure the bowel is free of solid contents.
1: Gastro-intestinal system

Dose: each powder sachet contains: PEG 3350 59 g, anhydrous sodium sulphate 5.68 g, sodium bicarbonate 1.685 g, sodium chloride 1.46 g, potassium chloride 743 mg. Each sachet is dissolved in water to one litre.

Adult, 250 mL of reconstituted solution every 10-15min. or by nasogastric tube 20-30 mL/min.

Child, not recommended.

Preparations
PEG 3350 59 g + anhydrous sodium sulphate 5.68 g + sodium bicarbonate 1.685 g + sodium chloride 1.46 g + potassium chloride 743 mg oral powder sachet

1 F: Ano-rectal preparations

Patients with haemorrhoids, fistula or proctitis may suffer from anal and perianal pruritis. These symptoms are best treated with plain ointment that contains astringents, local anaesthetics, lubricants, mild antiseptics or heparinoids. Local anaesthetics are useful in relieving pain but should not be used chronically as they may sensitize the anal skin. Diets with bulky residues are also helpful.

In proctitis, the above measures may supplement treatment with corticosteroids or aminosalicylates. Corticosteroid-containing ointments or creams are useful for the treatment of perianal regions provided that infections are excluded.

Corticosteroid suppositories are used to relieve inflammation of proctitis.

1 F.1: Local anaesthetic containing preparations

Lidocaine (lignocaine) 5% (Restricted)

Indications: to relieve pain associated with haemorrhoids and pruritus ani. It should be used before defaecation to relieve pain associated with anal fissure.

Cautions: excessive use should be avoided, as absorption is possible from rectal mucosa. In infants and children the use should be for a short (2-3 days) period.

Application: locally once or twice daily.

Preparations
Lidocaine ointment, 5%; 15-35 g/tube

1 F.2: Rectal Sclerosants

Oily phenol injection is administered into the tissue around internal haemorrhoids as an analgesic sclerosing agent.

Phenol 5% in almond oil (Restricted)

Indications: haemorrhoids.

Side-effects: irritation and tissue necrosis.
Preparations
Oily phenol injection, 5%, 5 mL ampoule

1F.3: Miscellaneous combinations

A variety of combinations made of corticosteroids, local anaesthetics and soothing agents are available for use in the treatment of haemorrhoids. They are suitable for occasional short-term use after exclusion of infections. Haemorrhoids in children are rare.

Anti-haemorrhoidal cream/ointment and suppositories

Preparations
Anti-haemorrhoidal ointments and suppositories
Contents: benzyl benzoate, bismuth oxide, bismuth subgalate, Peru balsam, zinc oxide
Or
Contents: Cinchocaine HCl and hydrocortisone

1 G: Drugs affecting gastrointestinal secretion

1 G.1: Digestive enzyme preparations

Pancreatin is orally supplemented to patients with total or partial absence of exocrine secretion in cystic fibrosis and following pancreatetomy, total gastrectomy or chronic pancreatitis. Pancreatin assists in the digestion of fat, protein and starch. Pancreatin is inactivated by gastric acidity. Enteric-coated preparations are therefore used, or the drug can be taken alongside with antacids or immediately before meals. Pancreatin preparations should be protected from heat as they tend to be destroyed. Pancreatin has irritating effects on the buccal mucus, and should not be retained in the mouth for long. The most frequent side-effects are GI irritation including nausea, vomiting and abdominal discomfort.

Pancreatin (C.D.L)
It is a mixture of digestive enzymes, such as amylase, protease, and lipase. The preparations are of porcine origin.

Indication, cautions and side-effects: see notes above

Preparations
Pancreatin capsules containing, protease 430 unit, lipase 8000 unit, amylase 9000 unit in a capsule
Pancreatin capsules, 25,000 units cap. containing, protease 1000 unit, lipase 25000 unit, amylase 18000 unit in a capsule
pancreatin micro granules, providing: protease 200 units, lipase 5000 units, amylase 3600 units per 100 mg/20 g container
1: Gastro-intestinal system

1 G.2: Drugs affecting biliary composition and flow

_Ursodeoxycholic acid_

**Indications:** dissolution of the gallstones, primary biliary cirrhosis.

**Contra-indications:** radio-opaque stones, pregnancy, non-functioning gall bladder, inflammatory diseases and other conditions of the small intestine, colon and liver which interfere with entero-hepatic circulation of bile salts.

**Cautions:** liver disease.

**Side-effects:** nausea, vomiting, diarrhoea; gallstone calcification; pruritus.

**Dose:** Dissolution of gallstones, 8–12 mg/kg daily as a single dose at bedtime or in two divided doses, for up to 2 years; treatment is continued for 3–4 months after stones dissolve.

Primary biliary cirrhosis, 10–15 mg/kg daily in 2–4 divided doses.

**Preparations**

_Ursodeoxycholic acid capsules,_ 250 mg cap.

_Ursodeoxycholic acid suspension,_ 250 mg/5 mL, 250 mL bottle.
Section 2: Cardiovascular system

- Positive inotropic drugs
- Diuretics
- Anti-arrhythmic drugs
- Beta-adrenoceptor blocking agents
- Antihypertensive therapy
- Nitrates and vasodilators
- Calcium channel blocking agents
- Sympathomimetics
- Coagulants
- Anticoagulants and protamine
- Anti-platelet drugs
- Fibrinolytic drugs
- Anti-fibrinolytics
- Lipid lowering drugs
- Local sclerosants
- Blood products

down heart rate and atrio-ventricular conduction, decrease ventricular response in atrial fibrillation, and potentiate vagal effect on the heart. Therapeutically, they are useful in heart failure to improve ventricular filling and increase cardiac output. Other uses include, slowing of the ventricular rate in AF (atrial fibrillation) and flutter, increasing vagal tone in PSVT (paroxysmal supraventricular tachycardia).

Digoxin is the most commonly used cardiac glycoside. It can be given orally and intravenously. Orally, it is well absorbed and mainly excreted unchanged. Renal impairment will prolong its plasma availability and hence its effect and toxicity. Most cases of heart failure do not require a loading dose; oral therapy is usually sufficient with a daily dose of 0.25 - 0.5 mg to reach a therapeutic plasma level within 1-2 weeks. When a rapid response is needed, digoxin may be given by intravenous infusion in a digitalizing dose of 0.5-1 mg, preferably in 50 mL over a period of 2 hours. Maintenance doses need to be administered once daily since the digoxin half-life is long (36-48 hr). The plasma concentration of digoxin alone is not enough to predict toxicity, as the sensitivity of the myocardium and conducting system to digoxin varies among patients. A good knowledge of toxicity signs and careful monitoring are essential. In the elderly, care
2: Cardiovascular system

should be practiced in using digoxin since the susceptibility to digoxin toxicity is increased. Treatment of heart failure has been geared toward the use of vasodilators and in particular the ACE-inhibitors, and/or diuretics. Digoxin still has a role to play but its chronic inotropic effect in the presence of sinus rhythm has been debated.

**Digoxin**

**Indications**: heart failure and supraventricular arrhythmias especially atrial fibrillation.

**Contra-indications**: intermittent complete heart block, second degree AV block, supra ventricular arrhythmias caused by Wolff-Parkinson-White syndrome, hypertrophic obstructive cardiomyopathy.

**Cautions**: in hypokalaemia; recent infarction; thyroid dysfunction; elderly and renal impairment; avoid rapid IV administration; pregnancy.

**Side-effects**: are frequent and may be serious; mainly associated with over dosage; fatigue; visual disturbances; anorexia; nausea and vomiting; headache; arrhythmias; heart block.

**Dose**: oral, rapid digitalization, 1 - 1.5 mg over 24 hours in divided doses.

Slow digitalization, 250 - 500 microgram daily for 1-2 weeks.

Maintenance, 62.5-500 microgram daily according to renal function and, in atrial fibrillation, on heart-rate response.

**Preparations**

Digoxin tablets, 250 micrograms tab.

Digoxin tablets, 62.5 micrograms tab.

Digoxin paediatric elixir, 50 micrograms/mL elixir; 60 mL bottle

Digoxin injection, 250 micrograms/mL ; 2 mL ampoule

2 A.2: Phosphodiesterase Inhibitor

**Milrinone (CDL)**

**Indications**: treatment of patients with acute decompensated heart failure after failure of conventional maintenance therapy.

**Contra-indications**: hypersensitivity to the drug.

**Cautions**: obstructive valvular heart disease, monitor ECG, heart rate, blood pressure, central venous pressure, electrolytes and renal status, pregnancy, breastfeeding.

**Side-effects**: arrhythmias, hypotension, chest pain, tremor, bronchospasm and anaphylactic shock.

**Dose**: by intravenous injection, 50 microgram/kg over 10 minutes followed by intravenous infusion at rate of 375-750 nanogram/kg/minute. Dosage should not exceed 1.13 mg/kg/day and duration of therapy depends on patient responsiveness.

**Preparations**

Milrinone injection, 1 mg/mL, 10 mL ampoule
2 B: Diuretics

Diuretics are drugs employed to increase the output of water and sodium. They are useful in relieving oedema caused by cardiac, renal or hepatic diseases. They are also useful in treatment of hypertension either alone or in combination with other antihypertensive drugs. They are classified in this section into:

- Thiazide and related diuretics
- Potassium sparing diuretics
- Osmotic diuretics
- Carbonic anhydrase inhibitors

2 B.1: Thiazide and related diuretics

These are moderately potent diuretics that increase sodium excretion in urine due to inhibition of sodium re-absorption at the cortical part of the ascending loop of Henlé near the distal convoluted tubule. Their chronic use may cause hypokalaemia and patients may show sign of glucose intolerance and hyperglycaemia. They interfere with urate excretion and may cause hyperuricaemia. Thiazide diuretics have an antidiuretic effect in patients with nephrogenic diabetes insipidus through an as yet unknown mechanism.

**Indications:** Thiazides and related compounds are indicated in the treatment of hypertension, mild cardiac failure, mild oedema due to renal or hepatic disease, and in some cases of nephrogenic diabetes insipidus.

**Contra-indications:** Renal and hepatic impairment, pregnancy, hyperuricaemia, severe hypokalaemia

**Cautions:** May aggravate hypokalaemia, diabetes and gout. Pregnancy, breast-feeding, elderly, hepatic or renal impairment

**Side-effects:** The most important side effect of thiazides is hypokalaemia which can be prevented or minimized by intermittent use of the drug, increasing dietary intake of potassium, simultaneous use of potassium sparing diuretic. Other effects include, hyperuricaemia, aggravation of diabetes, allergic rashes, disturbances of plasma lipid levels, thrombocytopenia, postural hypotension, impotence (reversible).

**Hydrochlorothiazide**

**Indications:** oedema, hypertension

Contra-indications, cautions and side-effects: see notes above.

**Dose:** oedema: Initial dose 50-100 mg once daily, reduce for maintenance.

Hypertension: 25-50 mg daily. 12.5 mg in mild or moderate hypertension

**Preparations**

Hydrochlorothiazide tablets, 25 mg tab.
## 2: Cardiovascular system

### Metolazone (Restricted)

**Indication:** oedema, hypertension  
**Contraindications and side-effects:** see notes above.  
**Cautions:** Excessive diuresis when combined with loop diuretics.  
**Dose:** Orally for oedema: 5-10 mg daily, increase according to patients need. Maximum; 80 mg daily.  
Orally for hypertension: Initially, 5 mg daily. Maintenance, 5 mg every other day.

**Preparations**  
Metolazone tablets, 5 mg tab.

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### Furosemide (Frusemide)

**Indications:** Oedema associated with left ventricular failure, congestive heart failure, cirrhosis of the liver and renal disease including nephrotic syndrome, oliguria due to renal failure.  
**Contra-indications:** hypovolaemia, anuria, liver cirrhosis coma, renal failure due to nephrotoxic drugs.  
**Cautions:** Hypotension; dehydration; pregnancy; breast-feeding; prostatic enlargement.  
**Side-effects:** hyponatraemia, hypokalaemia, and hypomagnesae mia; hypotension; GI disturbances. It causes an increased excretion of calcium. Tinnitus and deafness may result from chronic use or with rapid parenteral administration.  
**Dose:** orally, oedema, initially 40 mg daily, reduce to 20 mg daily or 40 mg every other day. Child, 1-3 mg/kg/day, maximum, 40 mg daily. Oliguria, initially 250 mg daily, increase gradually in steps of 250 mg; 250 mg 3-4 times daily, maximum 2 g daily.  
By intramuscular or slow intravenous injection, initially 20-50 mg. Child, 0.5-1 mg/kg, maximum daily dose 20 mg.  
By intravenous infusion in oliguria, 250 mg–1g at a rate not exceeding 4 mg/min.

**Preparations**  
Furosemide tablets, 40 mg tab.  
Furosemide sugar free paediatric liquid, 1 mg/mL, 100 - 150 mL bottle

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### 2 B.2: Loop diuretics

These are highly potent diuretics that increase sodium and water output in urine due to inhibition of sodium and chloride re-absorption at the medullary part of the ascending loop of Henlé. They are effective with as low glomerular filtration rate as 10 mL/min. Hypokalaemia, hypotension and severe dehydration may result from the unguarded use of loop diuretics. An effect will be seen after 1 hr with an oral dose and after 10 minutes with IV administration. Hearing loss may occur with prolonged use or during concomitant use with aminoglycosides. Due to its high potency and large volume of urine produced, frusemide should be administered during the day to avoid disturbing the patient’s sleep.
Furosemide injection, 10 mg/mL, 2 mL ampoule (Restricted)
Furosemide injection, 10 mg/mL, 25 mL ampoule (Restricted)

2 B.3: Potassium sparing diuretics

These are weak diuretics that cause retention of potassium by interfering with the exchange of potassium with sodium at the distal convoluted tubule. Their action is in part aldosterone dependent.

Spironolactone, which is an aldosterone antagonist, and amiloride, which does not possess this action but acts directly on the tubules, are potassium sparing diuretics. They are used in combination with thiazides or loop diuretics to overcome hypokalaemia and as substitute for a potassium supplement regimen. Potassium sparing diuretics should not be used with ACE-inhibitors because of the danger of severe hypokalaemia. Spironolactone is useful in hyper-aldosteronism (Conn’s syndrome).

Spironolactone
Indications: Oedema and ascites in liver cirrhosis, nephrotic syndrome, primary hyper-aldosteronism
Contra-indications: Elderly; hepatic impairment; renal impairment;

Cautions: pregnancy; breast-feeding; hyperkalaemia; Addison’s disease
Side-effects: GI disturbances; impotence; gynaecomastia; menstrual disturbances; headache; confusion; hyperkalaemia; blood disorders.
Dose: In ascites, hyperaldosteronism, and nephritic syndrome, 100-200 mg daily increased to 400 mg as required.
In hypokalaemia or hypertension, 25-100 twice daily

Preparations
Spironolactone tablets, 25 mg tab.
Spironolactone tablets, 100 mg tab.
Spironolactone syrup, 2.5 mg/mL (CDL)

Amiloride (Restricted)
Indications: oedema, in combination with thiazides or loop diuretics to avoid hypokalaemia.
Contra-indications: hyperkalaemia; renal impairment;
Cautions: pregnancy; breast-feeding; hyperkalaemia; elderly, diabetes mellitus
Side-effects: GI disturbances, dry mouth, rash, hyperkalaemia, hypotension.
Dose: If used alone: 5 mg twice daily or 10 mg once daily, adjust according to response, maximum 20 mg daily.
For combined diuretic therapy: 5-10 mg daily.

Preparations
Amiloride tablets, 5 mg tab.
2: Cardiovascular system

2 B.4: Osmotic Diuretics

These agents are freely filtered by the glomeruli with limited reabsorption by the renal tubules. The resultant increase of solute in the renal tubule will lead to an increase in urine volume. Mannitol is a widely used osmotic diuretic. Therapeutically, it is used to reduce intracranial or intraocular pressure. It is also used to promote diuresis in acute drug poisoning.

Mannitol

Indications: intracranial / intraocular hypertension, cerebral oedema, to induce diuresis in acute poisoning.

Contra-indications: pulmonary oedema, congestive heart failure.

Cautions: renal impairment; avoid extravasation (causes inflammation thrombophlebitis). Monitor urine output and electrolyte balance

Side-effects: chills, fever

Dose: Cerebral oedema, intracranial / intraocular hypertension: 1-2 g/kg intravenous infusion over 30-60 min.

Other uses: 1-2 g/kg IV infusion over 24 hr.

Preparations

Mannitol intravenous Infusion, 20% solution, 500 mL bottle

2 B.5: Carbonic anhydride inhibitors

These are weak diuretics that are mainly used for the treatment of glaucoma and not used for their diuretic effect. They reduce the aqueous humor production through inhibition of the carbonic anhydrase enzyme. Acetazolamide, the main drug in this group, is administered orally or by injection. It is a sulphonamide derivative.

Acetazolamide

Indications: reduction of intraocular pressure in open-angle glaucoma, secondary glaucoma, and peri-operatively in angle-closure glaucoma.

Contra-indications: Electrolyte disturbances; severe hepatic impairment; renal impairment; sulphonamide sensitivity

Cautions: Avoid prolonged use; elderly; pregnancy; breast feeding, avoid extravasation at injection site (danger of necrosis), pulmonary obstruction

Side-effects: taste disturbances, nausea, vomiting, diarrhoea, parasthesia, flushing, headache, fatigue, depression, metabolic acidosis and electrolyte disturbances, blood disorders, skin disorders

Dose: 0.25-1 g daily in divided doses, oral or by intravenous injection

Preparations
2 C: Anti-arrhythmic Drugs

Arrhythmias are abnormalities in the cardiac rate, rhythm, or site of origin and conduction of cardiac impulse. Management of an arrhythmia requires precise diagnosis of the type of arrhythmia, and electrocardiography is essential. Drugs that modify the cardiac electrophysiology have a narrow margin between the dose for a desired effect and those associated with the adverse effects. More over, the adverse effects from anti-arrhythmic drugs may include the induction of new arrhythmias with possibly fatal consequences. Non pharmacological treatments, such as cardiac pacing and electrical defibrillation are indicated for some arrhythmias; for other cases no therapy is required though an arrhythmia is detected (see below). Treatment depends on the rate of arrhythmia and the underlying cause.

2 C.1: Drugs used for supra-ventricular and ventricular arrhythmia

a) Supraventricular premature contractions (Ectopic beats) are frequently benign. If spontaneous with normal heart, no treatment is required. Reassurance and abstinence from tobacco, caffeine, and alcohol is often all that is needed. If the condition is troublesome, small doses of beta-blockers can be used.

b) Paroxysmal supraventricular tachycardia (PSVT) is a common arrhythmia and may occur in the absence of any detectable cardiac disease. The fast heart rate tends to start and stop suddenly and may last anywhere from a few minutes to many hours. Sedation, vagotonic manoeuvres or Valsalva manoeuvre can treat attacks. If these manoeuvres do not work, intravenous digoxin, verapamil, adenosine or beta-blockers may be used. If drug therapy fails, cardioversion (delivery of an electrical shock) can be tried. Prevention is more difficult than treatment and drugs such as beta–blockers, verapamil or digoxin are useful alone or in combination.

c) Atrial flutter and fibrillation are very fast electrical discharge patterns that the atria contract extremely rapidly, thus causing the ventricles to contract faster and less efficiently than normal. Atrial flutter is usually caused by organic heart disease. Conversion to normal sinus rhythm is best achieved by low energy cardioversion. Alternatively, amiodarone may be used to restore, and amiodarone and sotalol to maintain sinus rhythm. Anticoagulant therapy should be considered if the condition is long–standing.
2: Cardiovascular system

Atrial fibrillation usually occurs in association with organic heart disease. It may be caused by thyrotoxicosis. The ventricular rate can be controlled with digoxin. If adequate control cannot be achieved readily a beta-blocker or verapamil can be added. Anticoagulants are indicated for patients at risk. Aspirin is less effective than warfarin at preventing emboli but may be appropriate if there are no other risk factors for stroke.

**Adenosine (Restricted)**

**Indications:** paroxysmal supraventricular tachycardia  
**Contra-indications:** second and third degree AV block and sick sinus syndrome, asthma  
**Cautions:** atrial fibrillation or flutter; heart transplant  
**Side-effects:** arrhythmias, facial flush, dyspnoea, and bronchospasm, choking sensation  
**Dose:** By rapid intravenous injection, 3 mg over 2 seconds with cardiac monitoring; if necessary followed by 6 mg after 1-2 minutes, and then by 12 mg after a further 1-2 minutes.

**Preparations**

Adenosine injection, 3 mg/mL, 2 mL ampoule.

**Amiodarone hydrochloride (Restricted)**

**Indications:** resistant cases of supraventricular and ventricular arrhythmias; Wolff-Parkinson-White syndrome. Treatment should be initiated in hospital under specialist observation.  
**Contra-indications:** sinus bradycardia, sino-atrial heart block, thyroid dysfunction; pregnancy and breast feeding; iodine sensitivity; Avoid intravenous injection in severe respiratory failure, circulatory collapse, severe arterial hypotension.  
**Cautions:** heart failure; regular tests of liver and thyroid functions; renal impairment, elderly. Regular check of the eye during long-term therapy.  
**Side-effects:** reversible corneal microdeposits, peripheral neuropathy and myopathy, photosensitivity, hypotension, bradycardia, thyroid dysfunction, hepatitis, nausea and vomiting, metallic taste, tremor, vertigo, impotence, insomnia, fatigue  
**Dose:** orally: 200 mg 3 times daily for one week reduce to 200 mg twice daily for further 1-2 weeks. Maintenance, 200 mg daily or titrated as needed to control arrhythmia. Intravenous infusion via caval catheter 5 mg/kg over 20-120 minutes with ECG monitoring, maximum daily 1.2g.

**Preparations**

Amiodarone HCl injection, 50 mg/mL, 3 mL ampoule  
Amiodarone HCl tablets, 200 mg tab.

**Flecainide acetate (Restricted)**
2: Cardiovascular system

**Indications:** supra ventricular and ventricular arrhythmias.

**Contra-indications:** heart failure; history of myocardial infarction; long standing atrial fibrillation.

**Cautions:** patients with pacemakers; avoid in sinus node dysfunction; elderly; hepatic and renal dysfunction.

**Side-effects:** Arrhythmia, dizziness, visual disturbances, dyspnoea, headache

**Dose:** orally, 50-100 mg twice daily
Intravenous injection, 2 mg/kg over 10-30 minutes with ECG monitoring

**Preparations**
Flecainide acetate tablets, 100 mg tab.
Flecainide acetate injection, 10 mg/mL, 15 mL ampoule

---

**2 C.2: Drugs used for ventricular arrhythmias**

*a) Ventricular premature contraction (ventricular ectopic beats)* is an extra heartbeat caused by electrical activation of the ventricles before the normal heartbeat. It does not indicate danger in people who do not have heart disease. On the other hand, if they frequently occur in a patient with heart failure or aortic stenosis, they may be followed by more dangerous arrhythmias such as ventricular fibrillation. Treatment can be a carried out with lignocaine or procainamide. Other drugs include disopyramide or beta-blockers.

**B) Ventricular tachycardia (VT)** is almost always associated with organic heart disease and is particularly common in acute myocardial infarction (MI). It requires urgent treatment with cardioversion followed by IV infusion of lignocaine. In less urgent cases, lignocaine alone in IV bolus dose of 50-100 mg which can be repeated if arrhythmia is not converted to sinus rhythm.

**Lidocaine hydrochloride**

**Indications:** ventricular arrhythmias especially after myocardial infarction.

**Contra-indications:** sino-atrial disorders, all grades of atrioventricular block.

**Cautions:** hypersensitivity, lower doses in hepatic impairment.

**Side-effects:** dizziness, hypotension, mental confusion.

**Dose:** IV injection: 50-100 mg as bolus dose, repeated after 10 minutes if necessary. Maintenance, intravenous infusion 2-4 mg/minute.

**Preparations**
Lidocaine hydrochloride injection, 2% prefilled 5 mL syringe (100 mg/syringe).
Lidocaine hydrochloride injection, 2% (20 mg/mL), 50 mL vial.
2: Cardiovascular system

2 D: Beta-adrenoceptor blocking agents (beta-blockers)

Beta-blockers have good efficacy in the treatment of hypertension, ischaemic heart disease, and certain types of arrhythmias. They are also useful in the management of thyrotoxicosis, phaeochromocytoma, somatic symptoms of anxiety and intraocular hypertension. Their main action is through the blockade of beta -receptors in various tissues. Many beta-blockers are available for therapeutic use; they are all equally effective. There are, however, differences between them which may affect choice in treating particular disease or individual patients. Beta blockers can be classified into non-selective and β1–selective blockers. Non-selective β-blockers antagonize the sympathomimetic effects of both β1 and β2 receptors in many tissues. Blockade of β2 receptors in the bronchial smooth muscles results in bronchospasm, especially in patients with bronchial asthma. It is worth mentioning that β1-selective blockers are cardioselective but not cardiospecific, and they do not show absolute safety in asthmatic patients. Furthermore, Beta-blockers can also be classified according to their membrane stabilizing effects, presence or absence of intrinsic sympathomimetic activity and the extent of their lipid solubility (see table below).

**Indications:**

- **Hypertension:** Beta-blockers are widely used and effective antihypertensives, but mechanism of action is not fully understood. They reduce cardiac output; alter baroceptor reflex sensitivity and block peripheral adrenoceptors. It is possible that central effects may also be involved. Beta-blockers have the advantage of causing less postural and exercise induced hypotension.

Beta-blockers may be used in combination with thiazide diuretics to achieve better control of hypertension. This combination should not be initiated unless hypertension is not reasonably controlled by beta-blockers or thiazide alone. In phaeochromocytoma, beta–blockers are used to control heart rate. However, they should never be used alone since beta blockade without concomitant use of alpha-adrenoceptor blockers may lead to hypertensive crises.

- **Ischaemic heart disease:** Beta-blockers cause a reduction in cardiac work, activity and oxygen consumption at rest and during exercise or stress. Thus beta-blockers improve exercise tolerance in angina pectoris and reduce the severity and frequency of attacks. The dose required depends on the agent used and the severity of disease. Therapy should always be initiated with small doses and increase it gradually until symptoms are controlled. Abrupt withdrawal could be dangerous as it may lead to exacerbation of angina. Beta-blockers have
also been applied in preventing re-
infarction in patients who have suf-
fered an acute myocardial infarct-
ion.

**Arrhythmias:** Beta–blockers are
valuable agents in the management
of cardiac arrhythmias principally
by attenuating the sympathetic ef-
facts on conductivity and auto-
maticity of the heart. These drugs are
useful in slowing the ventricular rate in patients with paroxysmal su-
praventricular tachycardia (PSVT),
atrial fibrillation and atrial flutter.
They are also effective in treating
digitalis induced arrhythmias and
those occurring during general
anaesthesia. Esmolol, a cardioselec-
tive, and sotalol, a nonselective,
beta-blocker are mostly used for
treatment of arrhythmias.

**Thyrotoxicosis:** Beta-blockers are
used in pre-operative preparation
for thyroidectomy. Propranolol can
reverse clinical symptoms of thyro-
toxicosis without altering the thy-
roid function.

**Other uses:** Beta-blockers have
been used to reduce somatic symp-
toms of anxiety such as tremor, pal-
pitation and tachycardia. In mi-
gain, beta-blockers are used for
prophylaxis. Topical application of
some beta-blockers is effective in
reducing raised intra-ocular pres-
sure.

**Contra-indications:**
Beta-blockers should be avoided in
patients with bronchial asthma, hy-
potension, sinus bradycardia, cardi-
ogenic shock, congestive heart fail-
ure (unless it is due to tachyarrhyth-
mania treatable with beta-blockers),
intermittent claudication, metabolic
acidosis and allergic rhinitis.

**Cautions:**
Abrupt withdrawal should be
avoided. When treatment is to be
discontinued, it should be gradually
done and the patient should be care-
fully monitored.

In patients with diabetes, cardiose-
lective agents are preferred, as beta-
blockers might mask the warning
signs of hypoglycemia.

In the presence of renal or hepatic
impairment, selection of a beta-
blocker depends on the pharmaco-
kINETICS of the individual agent (see
table above).

**Side-effects:**
GI disturbances, dizziness, fatigue,
cold extremities, hypotension, bradycardia, congestive heart fail-
ure, bronchospasm, sleep disturb-
ances, depression, hallucination
and skin rash. Side-effects can be
minimised by proper selection of
patient, drug and the initiation of
therapy with small doses.
In this group, which is a large group, only four beta-blockers are approved for therapeutic use in government institutions in Oman. These are Propranolol, labetalol, carvedilol and sotalol.

### Carvedilol (Restricted)

**Indications**: hypertension; angina; adjunct to diuretics, ACE-inhibitors or digoxin in symptomatic chronic heart failure.

**Contraindications and cautions**: see notes above. Closely monitor at beginning of therapy or a new dose increase.

**Side-effects**: see note above. Occasional diminished peripheral circulation, peripheral oedema, dry mouth, dry eye, impotence.

**Dose**: orally, for hypertension, 12.5 mg once daily increase after 2 days to 25 mg daily, maximum 50 mg in single or divided doses.

- Angina: 12.5 mg twice daily, increase to 25 mg twice daily.
- Heart failure, start with a very low dose of 3.125 mg twice daily, increase to 6.25 mg twice daily within two weeks; further increase gradually if necessary to reach a maximum of 25 -50 mg twice daily according to patient’s body weight.

**Maximum**: 25 mg twice daily body weight <85kg; 50 mg twice daily body weight >85kg

### Labetalol (Restricted)

**Indications**: hypertension (including hypertension in pregnancy); hypertensive crises; phaeochromocytoma

**Contraindications and cautions**: see notes above.

**Side-effects**: postural hypotension, tiredness, headache

**Dose**: Orally, initially 50 -100 mg twice daily, increase to 200 mg twice daily or further at 14 days interval for each step increment. Max. 2.4 g daily.

- Intravenous injection: 50 mg over 1 minute, repeated if necessary after 5 minutes. Max. 200 mg.
- Intravenous infusion: 2 mg/minute, maximum 200 mg, higher doses could be used in phaeochromocytoma.

### Propranolol hydrochloride

**Indications**: hypertension; angina; arrhythmias, thyrotoxicosis, prevention of re-infarction, migraine prophylaxis

**Contraindications and cautions**: see notes above. With caution in pregnancy, breast feeding, in renal

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### Pharmacological properties of beta-blockers

<table>
<thead>
<tr>
<th>Compound</th>
<th>Daily dose frequency</th>
<th>Gut absorption</th>
<th>Liver metabolism</th>
<th>Relative Lipid solubility</th>
<th>MSA**</th>
<th>ISA*</th>
<th>CNS effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-selective beta-blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>2-4</td>
<td>100%</td>
<td>100%</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Labetalol</td>
<td>1-2</td>
<td>100%</td>
<td>80%</td>
<td>_</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Sotalol</td>
<td>1-2</td>
<td>100%</td>
<td>1%</td>
<td>_</td>
<td>0</td>
<td>0</td>
<td>±</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>1-2</td>
<td>100%</td>
<td>100%</td>
<td>++</td>
<td>±</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

| **Selective beta-blockers**                |                      |                |                  |                            |       |      |             |
| Atenolol      | 1                    | 50%            | _                | _                          | 0     | 0    | ±           |
| Esmolol       | IV only              | _              | _                | _                          | 0     | 0    | _           |

* ISA = Intrinsic sympathomimetic activity

** MSA= Membrane stabilizing activity

*** Act as α and β- receptor antagonist
2 D.1: Non-selective beta-blockers

In this group, which is a large group, only four beta-blockers are approved for therapeutic use in government institutions in Oman. These are, Propranolol, labetalol, carvedilol and sotalol.

**Carvedilol (Restricted)**

**Indications**: hypertension; angina; adjunct to diuretics, ACE-inhibitors or digoxin in symptomatic chronic heart failure.

**Contraindications and cautions**: see notes above. Closely monitor at beginning of therapy or a new dose increase.

**Side-effects**: see note above. Occasionally diminished peripheral circulation, peripheral oedema, dry mouth, dry eye, impotence.

**Dose**: orally, for hypertension, 12.5 mg once daily increase after 2 days to 25 mg daily, maximum 50 mg in single or divided doses.

Angina: 12.5 mg twice daily, increase to 25 mg twice daily.

Heart failure, start with a very low dose of 3.125 mg twice daily. Increase to 6.25 mg twice daily within two weeks; further increase gradually if necessary to reach a maximum of 25-50 mg twice daily according to patient’s body weight. Maximum 25 mg twice daily body weight <85kg; 50 mg twice daily body weight >85kg

**Preparations**
Carvedilol tablets, 6.25 mg tab.
Carvedilol tablets, 25 mg tab.

**Labetalol hydrochloride (Restricted)**

**Indications**: hypertension (including hypertension in pregnancy); hypertensive crises; phaeochromocytoma

**Contraindications and cautions**: see notes above.

**Side-effects**: postural hypotension, tiredness, headache

**Dose**: Orally, initially 50-100 mg twice daily. Increase to 200 mg twice daily or further at 14 days interval for each step increment. Max. 2.4g daily.

Intravenous injection: 50 mg over 1 minute, repeated if necessary after 5 minutes. Max. 200 mg

Intravenous infusion: 2 mg/minute, maximum 200 mg, higher doses could be used in phaeochromocytoma.

**Preparations**
Labetalol tablets, 100 mg tab
Labetalol injection, 5 mg/mL, 20 mL ampoule.

**Propranolol hydrochloride**

**Indications**: hypertension; angina; arrhythmias, thyrotoxicosis, prevention of re-infarction, migraine prophylaxis

**Contraindications and cautions**: see notes above. With caution in pregnancy, breast feeding, in renal
2: Cardiovascular system

and hepatic impairment. In phaeochromocytoma, not to be used alone but with an alpha-blocker

**Side-effects:** see note above

**Dose:** orally, for hypertension, initially 80 mg twice daily, increase as necessary at weekly interval; maintenance 160-320 mg daily.

Angina, initially 40 mg 2-3 times daily; maintenance 120-240 mg daily

Arrhythmias, anxiety tachycardia and thyrotoxicosis, 10-40 mg 3-4 times daily

Anxiety with symptoms of palpitation, sweating, tremor, 40 mg once daily increased if necessary to 3 times daily.

Prophylaxis after myocardial infarction, 40 mg 4 times daily for 2-3 days, then 80 mg twice daily, beginning 5-21 days after infarction

Intravenous injection: In arrhythmias and thyrotoxic crises, 1 mg over a minute, repeat at 2 min. interval. Max 10 mg.

**Preparations**

Propranolol tablets, 10 mg tab.
Propranolol tablets, 40 mg tab.
Propranolol injection, 1 mg/mL, 1 mL ampoule

*Sotalol hydrochloride (Restricted)*

**Indications:** life threatening ventricular arrhythmias

**Contra-indications and cautions:** see notes above. Correct electrolyte imbalance.

**Side-effects:** See notes above

**Dose:** orally, for arrhythmias, 80 mg daily in 1-2 divided doses. Increase at 2-3 days interval to 160-320 mg daily in 2 divided doses.

**Preparations**

Sotalol tablets, 80 mg tab.

2 D.2: Selective beta-blockers

**Atenolol**

**Indications:** hypertension, angina and arrhythmias.

**Contra-indications and cautions:** see notes above. Reduce dose in renal impairment

**Side-effects:** see notes above.

**Dose:** orally, for hypertension, 25-50 mg daily (100 mg daily is no more considered necessary)

Angina, 100 mg daily in 1 or 2 divided doses

Arrhythmias, 50-100 mg daily

**Preparations**

Atenolol tablets, 25 mg tab (Restricted)
Atenolol tablets, 50 mg tab.
Atenolol tablets, 100 mg tab.

**Bisoprolol (Restricted)**

**Indications:** Hypertension. Angina. Adjunct in heart failure

**Contra-indications:** Acute or decompensated heart failure requiring intravenous inotropes; sino-atrial block; beta-blockers, including those considered to be cardioselective, should usually be avoided in patients with a history of asthma,
bronchospasm or a history of obstructive airways disease. However, when there is no alternative, a cardioselective beta-blocker can be given to these patients with caution and under specialist supervision. In such cases the risk of inducing bronchospasm should be appreciated and appropriate precautions taken.

**Cautions:** Ensure heart failure not worsening before increasing dose; Diabetes; first-degree AV block; history of obstructive airways disease (introduce cautiously); myasthenia gravis; portal hypertension (risk of deterioration in liver function); psoriasis; symptoms of hypoglycaemia may be masked; symptoms of thyrotoxicosis may be masked.

**Side-effects:** Cramp; depression; muscle weakness; alopecia; bradycardia; bronchospasm; coldness of the extremities; conduction disorders; dizziness; dyspnoea; exacerbation of intermittent claudication; exacerbation of psoriasis; exacerbation of Raynaud’s phenomenon; fatigue; gastro-intestinal disturbances; headache; heart failure; hyperglycaemia (in patients with or without diabetes); hypoglycaemia (in patients with or without diabetes); hypotension; paraesthesia; peripheral vasoconstriction; psychoses; purpura; sexual dysfunction; sleep disturbances (with nightmares); symptoms of hypoglycaemia masked; thrombocytopenia; vertigo; visual disturbances

**Dose:** Hypertension. Angina 5–10 mg once daily; maximum 20 mg per day.

Adjunct in heart failure. Initially 1.25 mg once daily for 1 week, dose to be taken in the morning, then increased if tolerated to 2.5 mg once daily for 1 week, then increased if tolerated to 3.75 mg once daily for 1 week, then increased if tolerated to 5 mg once daily for 4 weeks, then increased if tolerated to 7.5 mg once daily for 4 weeks, then increased if tolerated to 10 mg once daily; maximum 10 mg per day.

**Preparations**
Bisoprolol fumarate tablets, 5 mg tab

**Metoprolol (Restricted)**

**Indications:** Hypertension, angina, arrhythmias, migraine prophylaxis, hyperthyroidism (adjunct), surgery, early intervention within 12 hours of infarction

**Contra-indications:** Asthma; cardiogenic shock; hypotension; marked bradycardia; metabolic acidosis; phaeochromocytoma (apart from specific use with alpha-blockers); Prinzmetal’s angina; second-degree AV block; severe peripheral arterial disease; sick sinus syndrome; third-degree AV block; uncontrolled heart failure.

**Cautions:** Diabetes; first-degree AV block; history of obstructive airways disease (introduce cautiously); myasthenia gravis; portal hypertension (risk of deterioration
in liver function); psoriasis; symptoms of hypoglycaemia may be masked; symptoms of thyrotoxicosis may be masked.

**Side-effects**: Dry eyes (reversible on withdrawal); rashes (reversible on withdrawal); Alopecia; bradycardia; bronchospasm; coldness of the extremities; conduction disorders; dizziness; dyspnoea; exacerbation of intermittent claudication; exacerbation of Raynaud’s phenomenon; fatigue; gastro-intestinal disturbances; headache; heart failure; hyperglycaemia (in patients with or without diabetes); hypoglycaemia (in patients with or without diabetes); hypotension; paraesthesia; peripheral vasoconstriction; psychosis; purpura; sexual dysfunction; sleep disturbances (with nightmares); symptoms of hypoglycaemia masked; thrombocytopenia; vertigo; visual disturbances.

**Dose**: Hypertension, orally with immediate-release medicines, initially 100 mg daily, increased if necessary to 200 mg daily in 1–2 divided doses, high doses are rarely required; maximum 400 mg per day. Orally with modified-release medicines, 200 mg once daily.

Angina, orally with immediate-release medicines, 50–100 mg 2–3 times a day. Orally with modified-release medicines, 200–400 mg daily.

Arrhythmias, orally with immediate-release medicines, usual dose 50 mg 2–3 times a day, then increased if necessary up to 300 mg daily in divided doses. By intravenous injection, up to 5 mg, dose to be given at a rate of 1–2 mg/minute, then up to 5 mg after 5 minutes if required, total dose of 10–15 mg.

Migraine prophylaxis, orally with immediate-release medicines, 100–200 mg daily in divided doses. Orally with modified-release medicines, 200 mg daily.

Hyperthyroidism (adjunct), orally with immediate-release medicines 50 mg 4 times a day.

In surgery, by slow intravenous injection, initially 2–4 mg, given at induction to control arrhythmias developing during anaesthesia, then 2 mg, repeated if necessary; maximum 10 mg per course.

Early intervention within 12 hours of infarction, initially by intravenous injection, 5 mg every 2 minutes, to a max. of 15 mg, followed by oral doses of 50 mg every 6 hours for 48 hours. The first oral dose is to be taken 15 minutes after intravenous injection; oral maintenance dose is 200 mg daily in divided doses.

**Preparations**

Metoprolol tartrate 1 mg per 1 ml solution for injection, 5 mg ampoule

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2 E: Antihypertensive therapy

Antihypertensive therapy has reduced the frequency of cardiovascular events associated with hypertension. In Oman, cardiovascular
2: Cardiovascular system

diseases are responsible for 30-40% of all deaths. High blood pressure is a major cause of stroke and significantly contributes to coronary disease. The risk of death increases in proportion to the height of the blood pressure (B.P.) with no clear demarcation when lethal hypertension begins. It follows that early diagnosis and treatment of symptomatic and symptomless hypertension will reduce mortality and help prevent serious health consequences. Most of the hypertension cases are of no identifiable cause (essential hypertension) and therefore require a life-long treatment regimen. A small percentage of cases can be correlated with a defined cause (secondary hypertension), treating the cause will bring the B.P. back to normal in most conditions. Non-pharmacological intervention in hypertension should be considered in all cases and may be all that is needed in mild cases. These interventions include:

- weight reduction
- dietary salt restrictions,
- avoiding stress
- no smoking and alcohol
- regular mild exercise

The treatment objectives are to bring B.P. to normal and tolerable level and to reduce associated risk factors. Treatment objectives might be achieved with a single drug or combination of drugs when necessary with minimal adverse effects. Antihypertensive drugs include:

- Diuretics
- Beta-blockers
- Centrally acting drugs
- Alpha-adrenoceptor blockers
- Angiotensin converting enzyme inhibitors (ACE-Inhibitors)
- Calcium channel blockers
- Vasodilator antihypertensives
- Angiotensin-II receptor antagonists (Angiotensin-II receptor blockers, ARB)

If a drug from the above major classes is ineffective in lowering blood pressure in a given patient, it is advisable to substitute a drug from a different class. If therapy with a single drug is only partly effective, it may be preferable to add a small dose of a second drug from another class rather than increase the dose. Contraindications and cautions to the use of the above drugs should be considered and a proper choice is made (see table on the next page).

2 E.1: Vasodilator antihypertensive Drugs

This group includes potent drugs. They are rarely used alone in the chronic management of hypertension. They are mainly used in cases of hypertensive emergencies where
they are administered intrave-
nously. Orally they are used as ad-
junct drugs with other antihyperten-
sives in cases of severe or resistant hypertension. Drugs such as hy-
dralazine, sodium nitroprusside and
tolazoline are directly acting vaso-
dilators. They cause reduction in
peripheral resistance, increase in
heart rate and cardiac output.

**Hydralazine**

**Indications**: hypertension, adjunct with other antihypertensive drugs;
chronic heart failure, adjunct to
long acting nitrates; hypertensive
crises

**Contra-indications**: hypersensi-
tivity to hydralazine, dissecting aor-
tic aneurysm, severe tachycardia

**Cautions**: hepatic impairment; cer-
ebrovascular disease, check for
acetylator status before increasing
the dose.

**Side-effects**: tachycardia, flushing,
palpitation, hypotension, fluid re-
tention

**Dose**: orally, for hypertension, 25
mg twice daily, increase if neces-
sary to 50 mg twice daily For heart
failure, initial dose 25 mg 3-4 times
daily, increase gradually to usual
dose of 50-75 mg –4 times daily.
Intravenous injection, in hyperten-
sive crises with renal complica-
tions, 5-10 mg diluted with 10 mL
saline, repeated after 20-30minutes.

**Preparations**

Hydralazine tablets, 25 mg tab.
Hydralazine powder for injection,
20 mg ampoule
### Guidelines for selecting first line drugs for hypertension

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<tr>
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<tr>
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<td>Alpha blockers</td>
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<td>Afro-Caribbean patients, elderly, aortic or mitral valve stenosis, Hypertrophic cardiomyopathy, Pregnancy, Breast feeding.</td>
</tr>
</tbody>
</table>
2: Cardiovascular system

**Sodium nitroprusside**

**Indications:** hypertensive crises  
**Contra-indications:** severe hepatic impairment; severe vitamin B₁₂ deficiency.  
**Cautions:** hypothyroidism, renal failure, excessive hypotension, methaemoglobinaemia  
**Side-effects:** mainly related to the rapid effect on reducing B.P.; Dizziness, headache, nausea, palpitation  
**Dose:** in hypertensive crises by IV infusion, 0.5-1.5 microgram/kg/minute, adjust by gradual increment of 0.5 microgram/kg/minute every 5 minutes within a range of 0.5-8 micrograms/kg/minute.

**Preparations**  
Sodium nitroprusside injection, 50 mg ampoule

2 E.2: Diuretics

*See* section 2 B.

2 E.3: Beta-blockers

*See* section 2 D.

2 E.4: Centrally acting antihypertensives

Methyldopa is a prototype of this group of antihypertensives. It acts centrally through inhibition of sympathetic outflow. It lowers B.P. and peripheral resistance and no effect on reflex vasoconstriction. It has the advantage of being safe in asthmatics, heart failure and pregnancy.

**Methyldopa**

**Indications:** hypertension; hypertension in asthmatics and during pregnancy.  
**Contra-indications:** depression, active liver disease, phaeochromocytoma  
**Cautions:** positive direct Coomb’s test in 20% of patients; reduce initial dose in renal dysfunction; regular blood count and liver function test advised  
**Side-effects:** sedation, dry mouth, postural hypotension, systemic lupus erythematous-like syndrome, haemolytic anaemia  
**Dose:** oral 125-250 mg 2-3 times daily. Gradually increase if necessary to a maximum of 3 g daily in divided doses.

**Preparations**  
Methyldopa tablets, 250 mg tab.

2 E.5: Alpha-adrenoceptor blocking drugs

Alpha adrenoceptor blocking drugs antagonize the sympathomimetic effects on both alpha 1 and 2 receptors. The resulting effects, which are mainly on the cardiovascular system, vary among the different members of the group. Prazosin and related compounds such as alfuzosin, terazosin, doxazosin and tamsulosin have postsynaptic alpha
blocking and vasodilator properties and rarely cause tachycardia. They cause rapid reduction in B.P after the first dose (“the first dose effect”) and should therefore be introduced with caution. Phentolamine and phenoxybenzamine cause peripheral vasodilatation and lowering of B.P. Reflex tachycardia and postural hypotension are limiting factors for their use in the treatment of hypertension. Phenoxybenzamine is used in the treatment of benign prostatic hyperplasia and in the long duration management of hypertension caused by phaeochromocytoma.

**Prazosin (Restricted)**
**Indications:** hypertension, benign prostatic hyperplasia
**Contra-indications:** congestive heart failure due to mechanical obstruction
**Cautions:** first dose effect may cause serious postural hypotension (advisable to take first dose upon retiring to bed); renal impairment; elderly; pregnancy
**Side-effects:** drowsiness, headache, lack of energy
**Dose:** for hypertension, 500 micrograms 2-3 times daily, initial dose at bedtime. Increase after 3-7 days to 1 mg 2-3 times daily, maximum 20 mg daily
Benign prostatic hyperplasia, 500 micrograms twice daily for a week, adjust dose according to response

**Preparations**
Prazosin hydrochloride tablets, 1 mg tab.
Prazosin hydrochloride tablets, 5 mg tab.

**Doxazosin (Restricted)**
**Indications:** see Prazocin
**Contra-indications and cautions:** see Prazocin.
**Side-effects:** postural hypotension, vertigo, asthenia, oedema, somnolence
**Dose:** for hypertension, 1 mg once daily, increase after 1 week to 2 mg once daily and then to 4 mg once daily, if necessary

**Preparations**
Doxazosin tablets, 1 mg tab.
Doxazosin tablets, 4 mg tab.

**Tamsulosin (Restricted)**
**Indications:** See Prazocin Above.
**Contra-indications and cautions:** see Prazocin.
**Side-effects:** peripheral oedema, asthenia, dizziness

**Preparations**
Tamsulosin capsules, 400 micrograms cap.

**Terazosin (Restricted)**
**Indications:** see Prazocin
**Contra-indications and cautions:** see Prazosin
**Side-effects:** peripheral oedema, asthenia, dizziness
## 2: Cardiovascular system

**Dose:** for hypertension, 1 mg daily at bedtime, increase after 7 days to 2 mg daily, increase if necessary; do not exceed 10 mg daily  
**Preparations**  
Terazosin capsules, 2 mg cap.  

### Alfuzosin

**Indications:** see Prazosin  
**Contra-indications:** see Prazosin; severe liver impairment.  
**Side-effects:** flushes, chest pain  
**Dose:** 2.5 mg three times daily, max 10 mg daily; Elderly initially 2.5 mg twice daily.  
**Preparations**  
Alfuzosin hydrochloride tablets; 2.5 mg tab  

- **Note:** MoH policy is that only one of the above alpha blockers will be purchased and supplied for use based on its cost effectiveness

### Phenolamine mesylate  
*(Restricted)*

**Indications:** hypertension; hypertension crises due to phaeochromocytoma; diagnosis of phaeochromocytoma  
**Contra-indications:** hypotension, history of myocardial infarction, angina  
**Cautions:** blood pressure and heart rate to be monitored during use; renal impairment; peptic ulcer

**Dose:** by intravenous injection, 2-5 mg repeated if necessary  
**Preparations**  
Phentolamine mesylate injection, 10 mg/mL ampoule

## 2 E.6.1: Angiotensin converting enzyme inhibitors

The essential effect of angiotensin converting enzyme inhibitors (ACE inhibitors) on the renin-angiotensin system is to inhibit the conversion of the relatively inactive angiotensin I to the active angiotensin II. They are highly selective in this regard and do not interfere with other component of the rennin-angiotensin system.  
There are a good number of ACE inhibitors for use that have similar therapeutic effects. There is no compelling reason to favor one ACE inhibitor over another; since all ACE inhibitors effectively inhibit the conversion of angiotensin I to angiotensin II and all have similar therapeutic indications, adverse effects profiles and contra-indications. With few exceptions, the majority of ACE inhibitors are predominantly cleared by the kidneys. Captopril is a short acting while lisinopril and enalapril are long acting ACE inhibitors approved for use in Oman.
2: Cardiovascular system

**Indications:** hypertension, heart failure, myocardial infarction, diabetic nephropathy

**Contra-indications:** ACE inhibitors are contraindicated in patients with hypersensitivity to ACE inhibitors, and in known or suspected renovascular disease, aortic stenosis or outflow tract obstruction. **ACE inhibitors should not be used in pregnancy.**

**Cautions:** ACE inhibitors should be used with great caution in patients receiving diuretics. The first doses may cause hypotension especially in patients taking diuretics, on a low-sodium diet, on dialysis, dehydrated or with heart failure. Renal function should be monitored before and during treatment. ACE inhibitors have to be avoided in patients with a history of idiopathic or hereditary angioedema. Use with caution in breast-feeding. Avoid using ACE inhibitors with antacids, as they may tend to reduce their bioavailability.

**Adverse effects:** ACE inhibitors can cause profound hypotension, angioedema; rash, persistent dry cough, upper respiratory symptoms such as sinusitis, sore throat and rhinitis. Hyperkalaemia, acute renal failure and blood disorders have also been reported.

**Captopril**

**Indications:** see notes above

**Contra-indications and cautions:** see notes above

**Side-effects:** see notes above; tachycardia; weight loss; photosensitivity

**Dose:** in hypertension, used alone, initial 12.5 mg twice daily (first dose at bedtime). Reduce to 6.25 mg twice daily in elderly or patients receiving diuretics. Maintenance, 25-50 mg twice daily

In heart failure as an adjunct therapy, initially 6.25-12.5 mg, maintenance, 25 mg 2-3 times daily

For prophylaxis after infarction, initially 6.25 mg starting as early as 3 days after infarction, increase as needed over several weeks to 150 mg daily in divided doses.

**Preparations**

Captopril tablets, 25 mg tab.

Captopril suspension 1 mg/ml (CDL)

**Enalapril**

**Indications:** see notes above

**Contra-indications and cautions:** see notes above

**Side-effects:** see notes above; tachycardia; cerebrovascular accidents; angina; chest pain; anorexia; confusion; mood changes; impotence; skin disorders; blood disorders

**Dose:** in hypertension, used alone, initial 5 mg once daily. Reduce to 2.5 mg daily in elderly or patients receiving diuretics. Maintenance, 10-20 mg once daily

**Preparations**

Enalapril maleate tablets, 5 mg tab.
2: Cardiovascular system

Enalapril maleate tablets, 20 mg tab.

**Lisinopril**

**Indications:** see notes above  
**Contra-indications and cautions:** see notes above  
**Side-effects:** see notes above; tachycardia; cerebrovascular accidents; dry mouth; confusion; mood changes; impotence  
**Dose:** for hypertension, used alone, initial 10 mg daily. Maintenance, 10–20 mg daily. Maximum, 40 mg daily. Reduce the dose if used in addition to diuretic  
In heart failure as an adjunct therapy, initially 2.5 mg. Maintenance, 5–20 mg daily  
For prophylaxis after infarction, the B.P. is a determining factor for the dose regimen. Systolic B.P. over 120mmHg, 5 mg daily for 3 days and then 10 mg daily. Systolic B.P. 100–120 mmHg, 2.5 mg daily increased to 5 mg daily  

**Preparation**  
Lisinopril tablets, 5 mg tab.  
Lisinopril tablets, 10 mg tab.

Note: MoH policy is that only one of the above ACE I inhibitors, enalapril or lisinopril, will be purchased and supplied for use based on its cost effectiveness

2: Nitrates and other vasodilators

**2 F.1: Nitrates**

Nitrates are vasodilators that are useful in the management of angina. They induce vasodilatation of coronary arteries leading to increased coronary blood flow. In addition, they induce venodilatation that leads to reduced venous return which consequently reduces ventricular filling pressure, myocardial

**2 E.6.2: Angiotensin II receptor antagonists ( Angiotensin II Receptor Blockers {ARB} )**

Therapeutically, angiotensin II receptor antagonists are as effective as ACE inhibitors. They do not cause the persistent dry cough or dry mouth, which are common with ACE inhibitors.

**Valsartan (Restricted)**

**Indication:** hypertension  
**Contra-indications:** hepatic impairment; biliary obstruction  
**Cautions:** renal artery stenosis, renal impairment, pregnancy, breastfeeding  
**Side-effects:** hypotension; fatigue  
**Dose:** usually 80 mg once daily. Reduce in elderly, renal and hepatic impairment or intravascular volume depletion to 40 mg once daily. Increase if necessary after 3–4 weeks to 160 mg daily (80 mg daily in hepatic impairment)  

**Preparations**  
Valsartan capsules, 80 mg caps  
Valsartan capsules, 160 mg caps
work and oxygen consumption. Arteriolar dilatation reduces vascular resistance and myocardial work. Sublingual glyceryl trinitrate (GTN) tablets are no longer used in Oman. They are replaced by isosorbide dinitrate 5 mg tablets. Transdermal GTN preparations are used for a prolonged effect. Isosorbide dinitrate is a more stable nitrate for oral use. It has a slower onset and a longer duration that could last up to 12 hours in modified release preparations.

**Tolerance.**

*Tolerance may develop to the effects of nitrates with the continuous use of long-acting preparations such as the transdermal patches.*

If tolerance is suspected then patients should leave patches off for several hours in a 24 hour period or if on a modified release preparation of isosorbide dinitrate tablets patients should take the second of their two daily doses after about 8 hours rather than 12 hours.

**Glyceryl trinitrate**

**Indications:** prophylaxis and treatment of angina

**Contra-indications:** hypersensitivity to nitrates; hypotension; severe anaemia

**Cautions:** severe hepatic or renal impairment; malnutrition and hypothermia; recent history of myocardial infarction

**Side-effects:** postural hypotension, throbbing headache, flushing

**Dose:** intravenous infusion, 10 – 200 microgram / minute.

Patches, Apply one patch to lateral chest wall or upper arm. Replace after 24 hours on a different area.

**Preparations**

Glyceryl trinitrate injection, 5 mg/mL, 10 mL ampoule

Glyceryl trinitrate injection, 1 mg/mL, 50 mL ampoule

Glyceryl trinitrate transdermal patch, 25 mg patch

Glyceryl trinitrate spray, 0.4 mg / dose, 200 dose spray

**Isosorbide dinitrate**

**Indications:** prophylaxis and treatment of angina; left ventricular failure

**Contra-indications, cautions and side-effects:** see notes under glyceryl trinitrate

**Dose:** Oral in divided doses: for angina, 30-120 mg daily; for left ventricular failure, 40-160 mg up to 240 mg if necessary.

**Preparations**

Isosorbide dinitrate tablets, 5 mg sublingual tab.

Isosorbide dinitrate tablets, 10 mg tab.

Isosorbide dinitrate tablets, 40 mg S.R. tab.

---

2 F.2: Other vasodilators
2: Cardiovascular system

**Papaverine (Restricted)**

**Indications**: vasodilator, erectile dysfunction (see sec. 7D.4)

**Side-effects**: hypotension

**Preparations**

Papaverine injection, 30 mg/mL; 2 mL ampoule

**Ivabradine (Restricted)**

**Indications**: Treatment of angina in patients in normal sinus rhythm. Mild to severe chronic heart failure

**Contra-indications**: Acute myocardial infarction; cardiogenic shock; congenital QT syndrome; do not initiate for angina if heart rate below 70 beats per minute; do not initiate for chronic heart failure if heart rate below 75 beats per minute; immediately after cerebrovascular accident; patients dependent on pacemaker; second- and third-degree heart block; severe hypotension; sick-sinus syndrome; sino-atrial block; unstable angina; unstable or acute heart failure.

**Cautions**: Atrial fibrillation or other arrhythmias (treatment ineffective); elderly; in angina, consider stopping if there is no or limited symptom improvement after 3 months; intraventricular conduction defects; mild to moderate hypotension (avoid if severe); retinitis pigmentosa

**Side-effects**: Atrial fibrillation; blurred vision; bradycardia; dizziness; first-degree heart block; headache; phosphenes; ventricular extrasystoles; visual disturbance

**Dose**: Treatment of angina in patients in normal sinus rhythm. Initially 5 mg twice daily for 3–4 weeks, then increased if necessary to 7.5 mg twice daily; reduced if not tolerated to 2.5–5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute. Elderly initially 2.5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute.

**Preparations**

Ivabradine tablets, 5 mg tab

2 G: Calcium channel blocking agents

Calcium channel blocking agents inhibit membrane transport of calcium. They affect the myocardial cells, the cells within the conducting system of the heart and the smooth muscle cells of the vasculature. Thus, resulting in depression of the myocardium and diminishing the coronary and systemic vascular tone. They should be avoided in heart failure because of a possible further depression of the cardiac function.
Calcium channel blocking agents come from different chemical groups. They can be classified as dihydropyridine, phenylalkylamine or benzothiazepine types. Nifedipine and nimodipine are members of the dihydropyridine group. Nifedipine is a vasodilator with antianginal and antihypertensive effects. It has little or no depressant effect at the S-A or A-V node. It is also a more potent peripheral vasodilator with moderate antiplatelet activity. In clinically practical doses, nifedipine has no antiarrhythmic properties. Nimodipine has a preferential cerebrovascular vasodilatory action. It is indicated for prevention of neurological defects secondary to cerebral artery spasm. Nimodipine also appears to be effective in the prevention of migraine headaches.

Verapamil is a calcium channel-blocking agent of phenylalkylamine group with vasodilatory and antiarrhythmic effects. Verapamil increases myocardial oxygen supply and reduces myocardial oxygen demand secondary to decreasing heart rate and afterload. Its efficacy in variant angina is secondary to its ability to increase myocardial oxygen supply, whereas in exertion angina, beneficial effects are secondary to reduced myocardial oxygen demand.

Diltiazem is a benzothiazepine derivative calcium channel blocker. Its mechanism of action is similar to that of verapamil with less effect on AV node in equal doses and preferential vasodilatation of coronary vasculature. Diltiazem possesses less negative inotropic activity than Verapamil and only one-tenth the vasodilator potency of nifedipine.

Calcium channel blocking agents are mainly indicated in the treatment of angina, hypertension and arrhythmias (for other uses see individual agents). Sudden withdrawal of calcium channel blocking agents in patients with angina may exacerbate angina.

**Amlodipinebesilate (Restricted)**

**Indications:** prophylaxis of angina; hypertension

**Contra-indications:** cardiogenic shock, unstable angina; pregnancy and breast feeding

**Cautions:** hepatic impairment

**Side-effects:** headache, oedema, fatigue, gum hyperplasia, rashes, dizziness

**Dose:** 5 mg daily, maximum 10 mg daily

**Preparations**
Amlodipine besilate tablets, 5 mg tab.

**Diltiazem hydrochloride (Restricted)**

**Indications:** prophylaxis and treatment of angina; hypertension

**Contra-indications:** severe brady-cardia, left ventricular failure, heart block; pregnancy and breast feeding
### 2: Cardiovascular system

**Nimodipine (Restricted)**

**Indications:** prevention and treatment of neurological deficit following subarachnoid haemorrhage

**Cautions:** cerebral oedema, avoid concomitant administration of other calcium channel blocking agents or beta-blockers; reduce dose in renal impairment

**Side-effects:** hypotension, variation in heart rate, flushing, headache

**Dose:** prevention, orally, 60 mg every 4 hours, maximum 360 mg. Treatment, intravenous infusion, 1 mg/hour initially, then 2 mg/hour. Reduce dose in elderly or in patients with less than 70kg body weight

**Preparations**

- Nimodipine tablets, 30 mg tab.
- Nimodipine injection, 200 mcg/mL, 50 mL vial

**Verapamil hydrochloride**

**Indications:** supraventricular arrhythmias, hypertension, angina pectoris

**Contra-indications:** hypotension, heart block, bradycardia, heart failure

**Cautions:** not to be used in patients taking beta-blockers; acute phase of myocardial infarction; hepatic impairment; pregnancy and breast feeding

**Side-effects:** constipation; hypotension, bradycardia and asystole may follow an IV administration

**Dose:** orally, supraventricular arrhythmias 40-120 mg 3 times daily
2: Cardiovascular system

Angina, 80-120 mg 3 times daily
Hypertension, 240-480 mg daily in 2-3 divided doses.
Slow intravenous injection, 5-10 mg over 2-3 minutes, repeated after 5-10 minutes if required.

Preparations
Verapamil tablets, 40 mg tab.
Verapamil 240 mg S.R tab.
Verapamil HCl injection, 2.5 mg/mL, 2 mL ampoule (Restricted)

2 H: Sympathomemtics

Drugs such as adrenaline, isoprenaline, and dobutamine are agonists for alpha and/or beta-receptors.

2 H.1: Direct sympathomemtics

In cardiac arrest, adrenaline in a concentration of 1 in 10,000 is recommended in a dose of 10 mL. Isoprenaline is used during cardiac surgery to resuscitate the heart. Anaphylactic shock necessitates a prompt action to treat laryngeal oedema, bronchospasm and hypotension. The first line treatment includes securing the airway, restoration of blood pressure and administration of adrenaline intramuscularly.

Adrenaline (Epinephrine)

Indications: anaphylactic shock; cardiopulmonary resuscitations, acute bronchial asthma.
Cautions: angle closure glaucoma, anaesthesia with cyclopropane or halothane, thyrotoxicosis, diabetes, pregnancy with maternal BP above 130/80, HTN or other cardiovascular disorders.
Side-effects: anxiety, tachycardia, tremor, headache, in high doses arrhythmias
Dose: cardiac arrest, intravenous injection of 10 mL of 1 in 10,000 (1 mg/10 mL)
Anaphylactic shock, intramuscular injection of 1 in 1,000 (0.5 mg/0.5 mL or 1 mg/mL) solution

Preparations
Adrenaline injection, 1 in 10000 (1 mg/10 mL) ampoule
Adrenaline injection, 1 in 1000 (0.5 mg/0.5 mL) ampoule

Isoprenaline Hydrochloride
Indications: heart block; severe bradycardia
Cautions: ischemic heart diseases, diabetes mellitus, hyperthyroidism
Side-effects: tachycardia, tremor, arrhythmias, hypotension
Dose: by intravenous infusion, 0.5-10 micrograms/minute

Preparations
Isoprenaline hydrochloride injection, 1 mg/mL, 2 mL ampoule
Isoprenaline hydrochloride injection, 0.2 mg/mL, 1 mL ampoule
2: Cardiovascular system

2 H.2: Vasoconstrictor sympathomimetics

These are vasoconstrictor drugs that act on the alpha-receptors in peripheral blood vessels resulting in a transient rise in blood pressure. They should only be used to raise blood pressure in cases of emergencies when other measures have failed.

**Noradrenaline acid tartrate**

*Indications*: acute severe hypotension,

*Contra-indications*: hypertension

*Cautions*: vascular thrombosis, hyperthyroidism, diabetes mellitus; extravasation may cause necrosis at site of injection

*Side-effects*: hypertension, arrhythmias, headache

*Dose*: acute hypotension, by intravenous infusion, of a solution containing 80 micrograms/mL at an initial rate of 0.16-0.33 mL / minute, adjusted according to response

*Preparations*

Noradrenaline acid tartrate injection, 2 mg / mL; 2 mL ampoule (equivalent to noradrenaline base 1 mg/mL)

**Phenylephrine hydrochloride**

*Indications*: acute hypotension

*Contra-indications*: cautions and side-effects: see noradrenaline above; phenylephrine has a longer duration of action than noradrenaline, which may cause an excessive and prolonged rise in blood pressure

*Dose*: by subcutaneous or intramuscular injection, 2.2-5 mg

By slow intravenous injection, 1 mg/mL solution, 100-500 micrograms repeated after 15 minutes if necessary

By intravenous infusion, initial rate of 180 micrograms/minute, reduce according to response

*Preparations*

Phenylephrine injection, 1% (10 mg/mL); 1 mL ampoule

2 H.3: Positive inotropics

Dobutamine and dopamine stimulate the heart and increase contractility with little effect on the rate. They act through stimulating the beta1-receptors in the heart. Their main indication is in cardiogenic shock.

**Dobutamine hydrochloride**

*Indications*: inotropic support in infarction and cardiac surgery

*Cautions*: severe hypotension complicating cardiogenic shock

*Side-effects*: tachycardia and marked increase in systolic blood pressure indicate overdosage

*Dose*: by intravenous infusion, 2.5-10 micrograms/kg/minute, adjusted according to response

*Preparations*


2: Cardiovascular system

**Dobutamine hydrochloride**

**Indications:** cardiogenic shock in infarction or cardiac surgery  
**Contra-indications:** tachyarrhythmia, phaeochromocytoma  
**Cautions:** correct hypovolaemia; low dose in shock due to acute myocardial infarction  
**Side-effects:** tachycardia, hypotension, hypertension peripheral vasoconstriction,  
**Dose:** by intravenous infusion, 2-5 micrograms/kg/minute initially

**Preparations**  
Dobutamine injection, 12.5 mg/mL, 20 mL vial for dilution and use as intravenous infusion

check the product literature for details.

**Phytomenadione**

**Indications:** haemorrhagic disorders of newborns, antagonist to the effect of oral coumarin anticoagulants  
**Cautions:** intravenous injections should be given very slowly  
**Dose:** see product literature

**Preparations**  
Phytomenadione injection, 1 mg/0.5 mL ampoule,  
Phytomenadione injection, 2 mg / 0.2 mL ampoule,  
Phytomenadione injection, 10 mg/1 mL ampoule

2 J: Anticoagulants and protamine

This group of drugs includes:  
- Parenteral anticoagulants  
- Oral anticoagulants  
- Protamine sulphate

2 J.1: Parenteral Anticoagulants

Heparin is a directly acting anticoagulant with an immediate effect when injected intravenously. It activates plasma antithrombin III, which in turn inhibits several clotting factors particularly factor X and thrombin. Inhibition of factor X requires low doses of heparin. This explains the need for small
doses in the prophylaxis of thrombosis versus high doses for the treatment of pre-existing thrombosis. Heparin is not absorbed through the gastrointestinal mucosa and therefore is given parenterally. It is administered by intravenous infusion, intermittent intravenous injection or subcutaneous injection.

The most important adverse effect of heparins is bleeding from various sites. Protamine sulphate antagonizes the action of heparin and is used by slow intravenous injection. *(The table on the subsequent page shows a comparison between unfractionated heparin and low molecular heparin)*

Argatroban is a thrombin inhibitor. An oral anticoagulant can be given with argatroban, but it should be started once thrombocytopenia has been substantially resolved. Consult the product literature for the dosing regime details.

Fondaparinux is a synthetic pentasaccharide that inhibits activated factor X.

**Heparin**

**Indications**: treatment of deep-vein thrombosis, pulmonary embolism, prophylaxis in orthopaedic and general surgery, used in the management of coronary artery diseases and in the maintenance of extracorporeal circuits in cardiopulmonary bypass and haemodialysis.

**Contra-indications**: haemophilia and other haemorrhagic disorders, peptic ulcer, recent cerebral haemorrhage.

**Cautions**: hepatic and renal impairment; pregnancy; hypersensitivity to heparin; thrombocytopenia; hyperkalaemia.

**Side-effects**: haemorrhage, skin necrosis, hyperkalaemia, thrombocytopenia.

**Dose**: prophylaxis in general surgery, by subcutaneous injection, 5,000 units 2 hours before surgery, then every 8-12 hours for 7 days or until patient is ambulant. Treatment of deep-vein thrombosis and pulmonary embolism, by intravenous injection, loading dose of 5,000 units, followed by continuous infusion of 1,000-2,000 unit/hour, or subcutaneous injection of 15,000 units every 12 hours.

**Preparations**

Heparin injection, 1,000 IU/mL, 5 mL vial  
Heparin injection, 5,000 IU/mL, 5 mL vial.  
Heparin injection, 25,000 IU/mL, 5 mL vials  
Low molecular weight heparin injection of the type Dalteparin, Enoxaparin or Tinzaparin 15,000 - 20,000 IU multidose vial  
Enoxaparin 4,000 and 8,000 IU vials  
Dalteparin 5,000 and 10,000 IU vials
### Cardiovascular system

#### Unfractionated heparin

- **Average molecular weight**: 20,000 Dalton
- **APTT monitoring**: APTT monitoring is required
- **Route of administration**: Intravenous, so hospitalization is required
- **Frequency of administration**: Continuous infusion of unfractionated heparin is needed
- **Cost**: Low
- **Side-effects**: Higher likelihood of bleeding, thrombo-cytopenia or osteoporosis.

#### Low molecular weight heparin

- **Average molecular weight**: 3,000 Dalton
- **APTT monitoring**: APTT monitoring not required but monitoring of anti-Factor Xa activity may be necessary in patients at increased risk of bleeding (e.g. in renal impairment and those who are underweight or overweight).
- **Route of administration**: Subcutaneous, so possible to permit outpatient treatment
- **Frequency of administration**: Has long duration of action so once-daily dosing might be enough
- **Cost**: High
- **Side-effects**: Lower likelihood of bleeding, thrombo-cytopenia or osteoporosis.

---

Heparin

- **Indications**: Treatment of deep-vein thrombosis, pulmonary embolism, prophylaxis in orthopaedic and general surgery, used in the management of coronary artery diseases and in the maintenance of extracorporeal circuits in cardiopulmonary bypass and haemodialysis.
- **Contra-indications**: Haemophilia and other haemorrhagic disorders, peptic ulcer, recent cerebral haemorrhage.
- **Cautions**: Hepatic and renal impairment; pregnancy; hypersensitivity to heparin; thrombocytopenia; hypokalaemia.
- **Side-effects**: Haemorrhage, skin necrosis, hyperkalaemia, thrombocytopenia.

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<th>Average molecular weight</th>
<th>Unfractionated heparin</th>
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<th>Cost</th>
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| Side-effects | Higher likelihood of bleeding, thrombo-cytopenia or osteoporosis. | Lower likelihood of bleeding, thrombo-cytopenia or osteoporosis. |
2: Cardiovascular system

Argatroban

**Indications:** Anticoagulation in patients with heparin-induced thrombocytopenia type II who require parenteral antithrombotic treatment.

**Cautions:** Bleeding disorders; diabetic retinopathy; gastro-intestinal ulceration; immediately after lumbar puncture; major surgery (especially of brain, spinal cord, or eye); risk of bleeding; severe hypertension; spinal anaesthesia.

**Side-effects:** Haemorrhage; nausea; purpura.

**Dose:** Initially 2 micrograms/kg/minute, dose to be adjusted according to activated partial thromboplastin time, (by intravenous infusion) increased to up to 10 micrograms/kg/minute maximum duration of treatment 14 days.

An oral anticoagulant can be given with argatroban, consult the product literature for the dosing regime details.

**Preparations**
Argatroban injection, 100 mg/ml, 2.5 ml

Fondaparinux

**Indications:** See dose information below

**Contra-indications:** Active bleeding; bacterial endocarditis

**Cautions:** Active gastro-intestinal ulcer disease; bleeding disorders; brain surgery; elderly patients; low body-weight; ophthalmic surgery; recent intracranial haemorrhage; risk of catheter thrombus during percutaneous coronary intervention; spinal or epidural anaesthesia (risk of spinal haematoma—avoid if using treatment doses); spinal surgery

**Side-effects:** Anaemia; bleeding; purpura

**Dose:** Prophylaxis of venous thromboembolism in patients after undergoing major orthopaedic surgery of the hip or leg, or abdominal surgery. Initially 2.5 mg by subcutaneous injection, dose to be given 6 hours after surgery, then 2.5 mg once daily.

Prophylaxis of venous thromboembolism in medical patients immobilised because of acute illness, 2.5 mg by subcutaneous injection once daily.

Treatment of superficial-vein thrombosis. Adult (body-weight 50 kg and above) 2.5 mg once daily by subcutaneous injection for at least 30 days (max. 45 days if high risk of thromboembolic complications), treatment should be stopped 24 hours before surgery and restarted at least 6 hours post operatively.

Treatment of unstable angina and non-ST-segment elevation myocardial infarction 2.5 mg once daily by subcutaneous injection for up to 8 days (or until hospital discharge if sooner), treatment should be stopped 24 hours before coronary artery bypass graft surgery (where possible) and restarted 48 hours post operatively.

Treatment of ST-segment elevation myocardial infarction. Initially 2.5
mg by intravenous injection or intravenous infusion daily for the first day, then (by subcutaneous injection) 2.5 mg once daily for up to 8 days (or until hospital discharge if sooner), treatment should be stopped 24 hours before coronary artery bypass graft surgery (where possible) and restarted 48 hours post operatively.

Treatment of deep-vein thrombosis and pulmonary embolism. Adult (body-weight up to 50 kg) 5 mg by subcutaneous injection every 24 hours, an oral anticoagulant (usually warfarin) is started at the same time as fondaparinux (fondaparinux should be continued for at least 5 days and until INR ≥ 2 for at least 24 hours). Adult (body-weight 50–100 kg) 7.5 mg every 24 hours, an oral anticoagulant (usually warfarin) is started at the same time as fondaparinux (fondaparinux should be continued for at least 5 days and until INR ≥ 2 for at least 24 hours). Adult (body-weight 101 kg and above) 10 mg every 24 hours, an oral anticoagulant (usually warfarin) is started at the same time as fondaparinux (fondaparinux should be continued for at least 5 days and until INR ≥ 2 for at least 24 hours).

2 J.2: Oral anticoagulants

Warfarin is the most commonly used oral anticoagulant. It inhibits the hepatic synthesis of vitamin K-dependent clotting factors: II, VI, VII, IX and X. Warfarin is well absorbed orally and extensively bound to plasma proteins and metabolized by the liver. The full anticoagulant effect of warfarin is delayed for a few days. If an immediate effect is required, heparin can be used concomitantly.

It is essential that the INR (international normalised ratio) be determined daily or on alternate days in early days of treatment with Warfarin, then at longer intervals. Haemorrhage is the main adverse effect of oral anticoagulants. They are also teratogenic and should not be used during the first trimester of pregnancy. Warfarin passes the blood-placental barrier and may cause placental and foetal bleeding, especially towards the end of pregnancy and at delivery.

Rivaroxaban is a direct inhibitor of activated factor X (factor Xa)

**Rivaroxaban (Restricted)**

**Indications:** Prophylaxis of venous thromboembolism following knee replacement surgery. Prophylaxis of venous thromboembolism following hip replacement surgery. Initial treatment of deep-vein throm-
2: Cardiovascular system

bosis. Initial treatment of pulmonary embolism. Continued treatment of deep-vein thrombosis (following initial treatment). Continued treatment of pulmonary embolism (following initial treatment). Prophylaxis of recurrent deep-vein thrombosis. Prophylaxis of recurrent pulmonary embolism. Prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation and with at least one of the following risk factors: congestive heart failure, hypertension, previous stroke or transient ischaemic attack, age ≥ 75. Prophylaxis of atherothrombotic events in acute coronary syndrome (with aspirin alone or aspirin and clopidogrel)

Contra-indications: Active bleeding; in acute coronary syndrome—previous stroke; in acute coronary syndrome—transient ischaemic attack; malignant neoplasms; oesophageal varices; recent brain surgery; recent gastro-intestinal ulcer; recent intracranial haemorrhage; recent ophthalmic surgery; recent spine surgery; significant risk of major bleeding; vascular aneurysm

Cautions: Anaesthesia with postoperative indwelling epidural catheter (risk of paralysis—monitor neurological signs and wait at least 18 hours after rivaroxaban dose before removing catheter and do not give next dose until at least 6 hours after catheter removal); bronchicc-
20 mg once daily, to be taken with food.
Prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation and with at least one of the following risk factors: congestive heart failure, hypertension, previous stroke or transient ischaemic attack, age ≥ 75 years, or diabetes mellitus 20 mg once daily, to be taken with food.
Prophylaxis of atherothrombotic events in acute coronary syndrome (with aspirin alone or aspirin and clopidogrel) 2.5 mg twice daily usual duration 12 months.

Preparations
Rivaroxaban tablets 15 mg tab
Rivaroxaban tablets 20 mg tab

Warfarin Sodium (Restricted)
Indications: prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation; prophylaxis after introduction of prosthetic heart valve; prophylaxis and treatment of venous thrombosis and pulmonary embolism; transient ischaemic attacks
Contra-indications: haemorrhagic tendencies, pregnancy, blood dyscrasias, hypersensitivity to warfarin products, hypertension
Cautions: hepatic or renal disease, breast feeding, recent surgery, concomitant use of antiplatelet or ulcerogenic agents
Side-effects: haemorrhage, skin rash, alopecia, nausea and vomiting

Dose: initially, 10 mg daily for 3 days; reduce dose in elderly, liver disease and cardiac failure. Maintenance dose depends on prothrombin time, usually 3-9 mg daily taken at the same time each day.

Preparations
Warfarin tablets, 1 mg tab.
Warfarin tablets, 2 mg tab.
Warfarin tablets, 5 mg tab.

2 J.3: Protamine Sulphate

Protamines are low molecular weight, polycationic, strongly basic proteins used to neutralize the anticoagulant effects of heparin.

Protamine sulphate
Indications: Overdosage of heparin
Cautions: allergy to protamine
Side-effects: hypotension, bradycardia, hypersensitivity reactions, flushing
Dose: by intravenous injection, over about 10 minutes, 1 mg neutralizes 80-100 units of heparin when given immediately after heparin administration, maximum 50 mg.

Preparations
Protamine sulphate injection, 10 mg/mL, 5 mL ampoule

2 K: Antiplatelet drugs
2: Cardiovascular system

Antiplatelet drugs are used to prevent arterial thrombus formation where thrombi are formed by platelet aggregation and anticoagulants have little effect. Injury to the wall of an artery initiates processes in which platelets play an essential role: (a) adhesion of platelets to exposed subendothelium followed by platelet aggregation, leading to the formation of a primary haemostatic plug. (b) enhancement of several reactions in the coagulation pathway leading to the formation of fibrin. The fibrin network reinforces the platelet aggregates to form a stable thrombus.

Aspirin 75-300 mg has been shown to reduce mortality after myocardial infarction, and as prophylaxis to prevent thrombus formation following bypass surgery, atrial fibrillation, stable angina or intermittent claudication.

Other drugs such as dipyridamole, anagrelide and ticlopidine have also been used to prevent platelet aggregation. Their mechanisms of action, somehow, differ from that of aspirin.

**Aspirin**

**Indications:** prophylaxis of cerebrovascular disease or myocardial infarction. *(see also section 4. D 1)*

**Contra-indications, cautions and side-effects:** see section 4. D 1

**Dose:** a controversy over the proper dose for the antiplatelet effect of aspirin has arisen from different studies conducted. A dose between 70-300 mg has been suggested for secondary prevention.

**Preparations**

Aspirin tablets, 75-100 mg tab.
Aspirin tablets, 300 mg tab.

**Anagrelide hydrochloride (C.D.L)**

**Indications:** reduction of platelets in essential thrombocythemia

**Cautions:** renal and hepatic impairment; cardiovascular disease may be worsened

**Side-effects:** headache, palpitations, thrombocytopenia, orthostatic hypotension

**Dose:** initially, 0.5-1 mg twice daily for a weak, maintenance dose is kept at minimum to maintain platelets below 600,000/mL, maximum 10 mg daily in 4 divided doses.

**Preparations**

Anagrelide tablets, 0.5 mg tab.
Anagrelide tablets, 1 mg tab.

**Clopidogrel (Restricted)**

**Indications:** thrombotic disorders prophylaxis in acute myocardial infarction, peripheral arterial disease, cerebrovascular accident.

**Contra-indications:** active bleeding (such as peptic ulcer or intracranial haemorrhage), breast-feeding.

**Cautions:** discontinue use 7 days prior to elective surgery if antiplatelet effect is not desired, patients at risk of increased bleeding from trauma, surgery, or other pathological condition, renal impairment, hepatic impairment, pregnancy,
concomitant use with drugs that increase risk of bleeding e.g. aspirin. **Side-effects:** abdominal pain, constipation, diarrhoea, gastritis, bleeding disorders (including gastrointestinal and intracranial), headache, rash, leucopenia, thrombocytopenia, duodenal ulcer, hypertension, hypercholesterolaemia. **Dose:** acute coronary syndrome (with or without ST segment elevation), initially 300 mg then 75 mg daily (with aspirin). Prevention of atherosclerotic events in peripheral arterial disease or after myocardial infarction or ischaemic stroke, 75 mg once daily.

**Preparations**
Clopidogrel tablets, 75 mg tab.
Clopidogrel tablets, 300 mg tab.

**Dipyridamole (Restricted)**
**Indications:** prophylaxis in cardiac valve replacement, platelet aggregation prophylaxis
**Cautions:** hypotension, rapidly worsening angina
**Side-effects:** GIT disturbances, dizziness, headache, hypotension
**Dose:** 300-600 mg daily in 3-4 divided doses before meals

**Preparations**
Dipyridamole tablets, 75 mg tab.

**Ticlopidine (Restricted)**
**Indications:** prophylaxis during angioplasty

**Contra-indications:** active bleeding disorders, neutropenia / thrombocytopenia, severe liver impairment
**Cautions:** hepatic and renal impairment; monitor blood count
**Side-effects:** bleeding manifestation, blood disorders, diarrhoea, nausea and vomiting, myelosuppression, cholestatic jaundice
**Dose:** 250 mg twice daily

**Preparations**
Ticlopidine tablets, 250 mg tab.

**Tirofiban**
**Indications:** unstable angina and non–ST-segment elevation MI in high risk patients. Contra-indications: severe uncontrolled hypertension (systolic BP >180 or diastolic BP >110 mm Hg), active internal bleeding, recent significant GI or genitourinary bleeding (within 6 weeks), bleeding disorders; e.g. thrombocytopenia, haemophilia, Von Willebrand's disease, history of intracranial disease (neoplasm, arteriovenous malformation, aneurysm), history of haemorrhagic stroke, INR >2.0.
**Cautions:** concomitant drugs that may increase the risk of bleeding, pregnancy, breastfeeding, renal or hepatic impairment, anaemia, severe heart failure, major surgery or trauma (within 3 months), monitor platelet count, haemoglobin and haematocrit before treatment;
2: Cardiovascular system

within 6 hours after start of treatment and at least once daily thereafter.

**Side-effects:** bleeding, thrombocytopenia.

**Dose:** Intravenous infusion, 400 nanogram/kg/minute for 30 minutes, followed by 100 nanogram/kg/minute for 48–108 hours.

**Preparations**

Tirofiban injection, 250 micrograms/mL, 50 mL vial

#### 2 L: Fibrinolytic drugs

Fibrinolytic drugs help dissolve clots that have already formed. Dissolving clots quickly may prevent the death of heart tissue deprived of its blood supply because of blocked blood vessels.

Fibrinolytic drugs such as streptokinase and plasminogen activators (e.g. alteplase or reteplase) have been shown to reduced mortality due to myocardial infarction.

**Cautions:** risk of bleeding is very high. Risk of allergic reaction

**Contra-indications:** recent haemorrhage, trauma or surgery, recent cerebrovascular events, recent symptoms of peptic ulcer, heavy vaginal bleeding, previous allergic reaction to streptokinase. Also, streptokinase should not be used again beyond 4 days of first administration.

**Side-effects:** haemorrhage, which can be treated with antifibrinolytic agents; fever, liver enzyme abnormalities; hypotension and arrhythmias may occur as a result of reperfusion.

**Human tissue type plasminogen activator (Restricted)**

**Alteplase or reteplase**

**Indications:** acute myocardial infarction; pulmonary embolism

**Cautions, contra-indications and side-effects:** see notes above

**Dose:** as for alteplase:

- Myocardial infarction, accelerated regimen initiated within 6 hours; patients over 65kg total dose 100 mg intravenously, give 15 mg bolus, 50 mg over 30 minutes, then 35 mg over 60 minutes
- Patients under 65kg intravenously, 15 mg bolus, then 0.75 mg/kg over 30 minutes, then 0.50 mg/kg over 60 minutes
- Myocardial infarction initiated within 6-12 hours, intravenously 10 mg as bolus dose, 50 mg over 60 minutes, then four infusions each of 10 mg over 30 minutes, in patients over 65kg. Reduce dose in patients less than 65 kg.
- Pulmonary embolism intravenously, 10 mg as bolus dose over 1-2 minutes, followed by 90 mg over 2 hours for patients over 65 kg.

**Preparations**

- Alteplase injection, powder for reconstitution, 50 mg (29 mega units) vial
- Reteplase injection, powder for reconstitution, 10 units vial
2: Cardiovascular system

Streptokinase (Restricted)
Indications: acute myocardial infarction, deep vein thrombosis, pulmonary embolism, central retinal venous or arterial thrombosis
Contra-indications, cautions and side-effects: see notes above
Dose: Myocardial infarction, by intravenous infusion, 1,500,000 units over 60 minutes
For other indications, by intravenous infusion, 250,000 units over 30 minutes then 100,000 units every hour for up to 12-72 hours depending on the patients response
Preparations
Streptokinase injection, powder for reconstitution, 750,000 unit vials

2 M: Antifibrinolytics

Tranexamic acid inhibits plasminogen activation and impairs fibrin dissolution. It is used when haemorrhage cannot be controlled as in prostatectomy, dental extraction in haemophilic patient and menorrhagia; it can also be used in streptokinase overdose.

Tranexamic acid (Restricted)
Indications: see notes above
Contra-indications: thromboembolic disease
Cautions: reduce dose in renal impairment; massive haematuria; concomitant oestrogen therapy
Side-effects: nausea, vomiting, diarrhoea

Dose: oral, local fibrinolysis, 15 - 25 mg/kg 2 - 3 times daily
Menorrhagia, 1 - 1.5 g 3 - 4 times daily for 3 - 4 days
By intravenous injection, 0.5-1 g 3 times daily
Preparations
Tranexamic acid injection, 100 mg/mL, 5 mL ampoule
Tranexamic acid syrup, 500 mg/5 mL, 300 mL sugar free syrup

2 N: Lipid-regulating drugs

High lipid level has been associated with increased risk of coronary atherosclerosis. There is evidence that lowering LDL-cholesterol by 25-35% is effective in both the primary and secondary prevention of the clinical manifestation of coronary heart disease.
Patients with coronary heart disease, and those at high risk of having it because of multiple risk factors, are candidates for treatment with lipid-regulating drugs.
Presently, treatment with statins has proved to be effective in reducing myocardial infarction, coronary deaths and overall mortality.
Statins are the drugs of choice for treatment of hypercholesterolaemia or hyperlipidaemia in patients with high risk of coronary heart disease. Fibrates can be used for hyper-triglyceridaemia.
2: Cardiovascular system

Nonpharmacological measures should go parallel with drug therapy such as strict dietary habits, stopping smoking and keeping near ideal body weight.

Lipid-regulating drugs include:
- Fibrates
- Bile acids binding resins
- Statins

2 N.1: Fibrates

Fibrates are broad-spectrum lipid-regulating drugs. Though they tend to reduce serum triglycerides they also tend to reduce LDL-cholesterol and to raise HDL-cholesterol.

**Bezafibrate**

**Indications**: hyperlipidaemias  
**Contra-indications**: severe renal or hepatic impairment, gall bladder disease  
**Cautions**: myotoxicity, renal and hepatic impairment  
**Side-effects**: GI disturbances; skin disorders; impotence; headache; hepatotoxicity  
**Dose**: 200 mg 3 times daily after food. Slowly released preparations, 400 mg once daily after food.

Preparations  
Bezafibrate retard tablets, 400 mg tab.

**Fenofibrate**

**Indications**: hyperlipidaemias  
**Contra-indications**: severe renal or hepatic impairment, gall bladder disease  
**Cautions**: myotoxicity, renal and hepatic impairment, pregnancy and breast-feeding  
**Side-effects**: GIT disturbances; skin disorders; impotence; headache; hepatotoxicity  
**Dose**: Micronized preparations, 145-200 mg 1-2 times daily

Preparations  
Fenofibrate (Micronized) tablets 145-200 mg tab.

Note: MoH policy is that only one of the above fibrates bezafibrate or fenofibrate, will be purchased and supplied for use based on its cost effectiveness.

2 N.2: Bile acid binding resin

Colestyramine is a synthetic polyanionic resin, which lowers plasma cholesterol by binding bile acids in the intestine and inhibiting their reabsorption and enterohepatic cycling and increasing their faecal excretion.  
Its main side-effects are GIT disturbances. It should be avoided in complete biliary obstruction and during pregnancy. Fat-soluble vitamins absorption might be affected and supplementary vitamin A, D and K may be needed in patients taking high doses.
**2: Cardiovascular system**

*Colestyramine (Cholestyramine) (Restricted)*

**Indications:**
hypercholesterolaemia, pruritus associated with partial biliary obstruction

**Contra-indications:** complete biliary obstruction

**Cautions:** check for fat-soluble vitamin deficiency, pregnancy and breast-feeding

**Side-effects:** constipation, abdominal discomfort/pain, flatulence, nausea, vomiting, bleeding tendencies due to hypoprothrombinaemia associated with vitamin K deficiency

**Dose:** oral for lipid reduction, 12-24 g daily in single or divided doses, max. 36 g daily.

For pruritus, 4-8 g daily

N.B: other drugs should be taken at least 1 hour before or 4-6 hours after colestyramine to reduce possible interference with absorption

**Preparations**
Colestyramine sachets, 4 g sachet

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**2 N.3: Statins**

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a crucial enzyme in the synthesis of cholesterol by the liver. These compounds are more effective than the polyamine binding resins in lowering LDL-cholesterol, but less effective than the fibrates in reducing triglycerides and raising HDL-cholesterol.

Lowering cholesterol levels produces an important reduction in coronary events, in all cardiovascular events, and in total mortality in patients aged up to 75 years with coronary heart disease and with total serum cholesterol concentration of 5 mmol/litre or greater.

**Cautions:** Statins should be used with caution in patients with liver diseases or with high alcohol intake. Liver function tests should be carried out before starting treatment with statins and regularly thereafter.

**Contra-indications:** active liver disease; pregnancy and breast-feeding

**Side-effects:** myositis, myopathy

*Atorvastatin (Restricted)*

**Indications:** primary hypercholesterolaemia or combined hyperlipidaemia in patients who have not responded to dietary restrictions and other measures

**Contra-indications:** see notes above

**Cautions:** see notes above

**Side-effects:** see notes above; also insomnia, angioedema, anorexia, asthenia, paraesthesia, peripheral neuropathy, pruritus, alopecia, impotence

**Dose:** primary hypercholesterolaemia and combined hyperlipidaemia, usually 10 mg once daily.
2: Cardiovascular system

Familial hypercholesterolaemia, initially 10 mg, increased at 4 weeks interval to 40 mg once daily

Preparations
Atorvastatin tablets, 10 mg tab.
Atorvastatin tablets, 40 mg tab.

**Fluvastatin (Restricted)**
**Indications**: primary hypercholesterolaemia, in patients with total cholesterol concentration of 6.5 mmol/litre or higher; adjunct to diet as preventive measure to retard the progression of coronary atherosclerosis.

**Contra-indications**: see notes above

**Cautions**: see notes above

**Side-effects**: see notes above; insomnia

**Dose**: initial 20-40 mg daily in the evening. Adjust up to 40 mg twice daily if necessary.

Preparations
Fluvastatin capsule, 40 mg cap
Fluvastatin capsule, 80 mg cap.

**Pravastatin (Restricted)**
**Indications**: primary hypercholesterolaemia, in patients not responding to diet restriction; adjunct to diet as preventive measure to retard the progression of coronary atherosclerosis; adjunct to diet in hypercholesterolaemia without clinically evident coronary heart disease

**Contra-indications**: see notes above

**Cautions**: see notes above

**Side-effects**: see notes above; rash, chest pain, fatigue

**Dose**: 10-40 mg daily in the evening. Adjust as necessary

Preparations
Pravastatin tablets, 20 mg tab.

**Simvastatin (Restricted)**
**Indications**: primary hypercholesterolaemia or combined hyperlipidaemia in patients who have not responded to dietary restrictions and other measures; adjunct to diet as preventive measure to retard the progression of coronary atherosclerosis.

**Contra-indications**: see notes above

**Cautions**: see notes above

**Side-effects**: see notes above; also rash, alopecia, dizziness, depression

**Dose**: 10 mg daily in the evening. Adjust up to 40 mg once daily if necessary.

Preparations
Simvastatin tablets, 20 mg tab

Note: MoH policy is that only one of the above statins will be purchased and supplied for use based on their cost effectiveness

2 O: Local sclerosants

**Sodium tetradecyl sulphate**
**Indications**: sclerotherapy of varicose veins.
**Contra-indications**: inability to walk, acute phlebitis, oral contraceptive use, obese legs.
2: Cardiovascular system

Cautions: extravasation may cause necrosis of tissues.
Side-effects: allergic reaction.
Dose: slow intravenous injection, 0.1-1 mL of 3% solution into empty isolated segment of the vein.

Preparations
Sodium tetradecyl sulphate injection, 3% solution, 5 mL ampoule

2 P: Blood products

Drotrecogin Alfa (Restricted)
(Recombinant Human Activated Protein C)
Indications: for adult patients with severe sepsis associated with acute multiple organ dysfunction who have a high risk of death.
Contra-indications: internal bleeding, intracranial neoplasm, low platelets count, not for children below 18 years, chronic severe liver disease.
Cautions: pregnancy, breastfeeding, concomitant use with drugs that increase risk of bleeding.
Side-effects: bleeding, ecchymosis.

Preparations
Drotrecogin Alfa injection, powder for reconstitution, 5 mg vial

Human fibrinogen factor IX (C.D.L)
Indications: congenital factor IX deficiency (haemophilia B).
Cautions: risk of thrombosis.
Side-effects: allergic reactions.

Preparations
Factor IX injection, 500-600 IU vial

Human coagulating factor VIII (Restricted)
Indications: control of haemorrhage in haemophilia A.
Section 3: Respiratory system

- Bronchodilators
- Corticosteroids
- Leukotriene receptor antagonists
- Allergic disorders
- Respiratory stimulants and pulmonary surfactants
- Aromatic inhalation
- Cough preparations
- Mucolytics

3 A: Bronchodilators

Various drugs including adrenoceptor stimulants, antimuscarinics and theophylline can produce bronchodilation.

3 A.1: Adrenoceptor stimulants

Adrenoceptor stimulants are either selective beta2-adrenoceptor stimulants such as salbutamol and salmeterol, or nonselective adrenoceptor stimulants such as adrenaline and ephedrine.

3 A.1.1: Selective beta2-adrenoceptor stimulants

Selective beta2-adrenoceptor stimulants are available in various pharmaceutical formulations and can be effectively used in the management of mild to moderate types of asthma. Rapid response can be achieved with pressurized aerosol inhalers. Oral preparations are reserved for children and patients who cannot tolerate inhalation; they have slower onset but longer duration of action than inhalers. It is more likely that side-effects such as tremor and headache are experienced more frequently with oral than inhalational preparations. Intravenous or subcutaneous injections are reserved for severe acute attacks when intense bronchospasm prevents the proper delivery of aerosol to the airways.

Use of inhalational preparations:

Administration by inhalation delivers the drug directly to the bronchi and is therefore required only in small doses.

Aerosols or pressurized inhalation is a convenient method for administration and drugs delivered can last for 3-5 hours for recommended doses of salbutamol and 12 hours for salmeterol or eformoterol. Patients should clearly be instructed and trained in the proper use of inhalers. Inadequate use should not be mistaken for drug ineffectiveness.

Respirator or nebuliser solutions are administered over a period of 5-15 minutes usually driven from an oxygen cylinder or a special electrical compressor. For recommended management of different types of asthma see below.
3. Respiratory system

**Salbutamol sulphate**

**Indications:** asthma; premature labour

**Contra-indications:** hypersensitivity to salbutamol.

**Cautions:** hyperthyroidism, hypertension, serious cardiovascular diseases, diabetes mellitus; labour and delivery may be complicated; hypokalaemia may be exacerbated by high doses of salbutamol.

**Side-effects:** fine tremor, nervous tension, headache, muscle cramp.

**Dose:** oral (but use by inhalation preferred), 4 mg (maximum 8 mg) 3–4 times daily, reduce in elderly. Child, under 2 years 100 micrograms/kg 4 times daily (2–5 years 1-2 mg 3–4 times daily, 6–12 years 2 mg 3–4 times daily. Subcutaneous or intramuscular, 500 microgram every 4 hours if necessary. Slow intravenous injection, 250 microgram repeated if necessary. Slow intravenous infusion, initially 5 microgram/minute adjusted to 3–20 microgram/minute according to response. Aerosol inhalation, 100–200 microgram (1–2 puffs) 3–4 times daily, repeated every 4 hours when necessary for persistent symptoms. Child, 1 puff increased to 2 puffs if necessary, 3–4 times daily. Inhalation of powder (salbutamol rotacap) 200 microgram 3–4 times daily. Inhalation of nebulised solutions 2.5–5 mg up to 4 times daily when necessary. Child, 2.5 mg repeated if necessary up to 4 times daily.

**Preparations**

- Salbutamol sulphate rotacap, 200 microgram/rotacap (Restricted)
- Salbutamol sulphate inhaler, 100 microgram/metered inhalation
- Salbutamol sulphate nebules, 1 mg/mL, 2.5 ml nebules (Restricted)
- Salbutamol sulphate nebuliser solution, 5 mg/mL solution, 15 – 30 mL (Restricted)

**Salmeterol (Restricted)**

**Indications:** asthma when long-term therapy is required.

**Contra-indications Cautions and side-effects:** see under salbutamol.

**Dose:** aerosol inhalation, 50 microgram (2 puff) twice daily, could be increased to 100 microgram twice daily. Child, above 4 years 50 micrograms twice daily.

**Preparations**

- Salmeterol aerosol inhaler, 25 microgram/ metered inhalation

**Formoterol fumarate (Efor-moterol fumarate) (Restricted)**

**Indications:** asthma when long-term therapy is required.

**Contra-indications Cautions and side-effects:** see under salbutamol.

**Dose:** Powder inhalation, adult and child over 5 years, 12 microgram twice daily.

**Preparations**
3: Respiratory system

Formoterol powder for inhalation, 12 microgram/capsule

3 A.1.2: Other adrenoceptor stimulants

Ephedrine and adrenaline are non-selective adrenoceptor stimulants, which should be avoided in asthma since they are liable to cause cardiac irregularities. Adrenaline injection (see section 2) is used in the emergency treatment of acute allergic and anaphylactic reactions.

**Ephedrine hydrochloride**

**Indications:** asthma

**Contra-indications:** thyrotoxicosis; diabetes; pregnancy with maternal blood pressure above 130/80 mmHg; hypertension or other cardiovascular disorders.

**Cautions:** elderly, prostatic hypertrophy

**Side-effects:** tachycardia, anxiety restlessness.

**Dose:** subcutaneous injection, 25-50 mg.

Intravenous injection, 5-25 mg/dose slowly, maximum 150 mg/day.

**Preparations**

Ephedrine SO₄ or HCl injection, 30-50 mg/mL, 1 mL ampoule

3 A.2: Antimuscarinics

Antimuscarinics, such as ipratropium, block acetylcholine from inducing bronchospasm or increasing the viscosity of mucous secretion.

Bronchodilation can be further induced by these drugs in patients already receiving beta2-adrenoceptor stimulants.

Ipratropium is more effective in relieving bronchoconstriction associated with chronic obstructive pulmonary diseases (COPD) than in relieving asthma.

**Ipratropium bromide (Restricted)**

**Indications:** bronchospasm, particularly in chronic bronchitis.

**Contra-indications and Cautions:** prostatic hypertrophy, glaucoma, pregnancy.

**Side-effects:** dry mouth; rarely urinary retention, constipation.

**Dose:** aerosol inhalation, 20-40 microgram, up to 80 microgram at a time, 3-4 times daily; child up to 6 years 20 microgram 2-3 times daily; 6-12 years 20-40 microgram 2-3 times daily.

Inhalation of nebulised solution, 250-500 microgram up to 4 times daily; child under 5 years 125-250 micrograms max. 1 mg daily; 6-12 years 250 micrograms, max. 1 mg daily.

**Preparations**

Ipratropium bromide aerosol inhaler, 20 microgram/metered inhalation

Ipratropium bromide nebuliser solution, 250 micrograms/mL vial

Ipratropium bromide nebuliser solution, 500 micrograms/2 mL vial
**3. Respiratory system**

**Tiotropium**

**Indications**: Maintenance treatment in COPD.

**Contra-indications, cautions and side-effects**: see under ipratropium bromide

**Dose**: 18 micrograms inhaled once daily.

**Preparations**

Tiotropium inhaler powder, hard capsules, 18 micrograms/cap.

Note: each 18 micrograms capsule delivers 10 micrograms of tiotropium.

**3 A.3: Theophylline**

Theophylline and related compounds induce bronchodilatation by inhibiting phosphodiesterase enzyme and leading to increased intracellular cAMP which acts as a mediator for relaxation of smooth muscle and inhibition of histamine release from mast cells. Theophylline derivatives are orally effective in less severe and more chronic asthma. Sustained release preparations are preferred to simple rapid release preparations.

Plasma concentration of theophylline can vary with serious consequences. There is a narrow margin between the therapeutic and toxic dose and therefore, the differences in half-life are very important. Theophylline is metabolized in the liver; there is considerable variation in its half-life particularly in smokers, alcoholics, hepatic failure and when other drugs are used concomitantly.

The use of injectable theophylline should be avoided in patients already receiving oral preparations; plasma level should be considered before administration in severe cases of asthma.

Intravenous aminophylline should be administered very slowly over a 20-30 minutes; intramuscular injection is painful.

**Aminophylline**

Note: aminophylline is a stable mixture of theophylline and ethylenediamine.

**Indications**: acute severe asthma.

**Contra-indications**: sensitivity to the drug.

**Cautions**: cardiac diseases, hypertension, epilepsy, hepatic impairment, slow administration (see notes above).

**Side-effects**: anxiety, confusion, nausea, insomnia, tachycardia; rapid intravenous injection may cause severe hypotension and sudden death if given too rapidly.

**Dose**: slow intravenous injection (over 20-30 minutes), 250-500 mg. Intravenous infusion, young patients, 750 mg /24 hours; adults, 1500 mg /24 hours.

**Preparations**

Aminophylline intravenous injection, 25 mg/mL, 10 mL ampoule
3: Respiratory system

**Theophylline**

**Indications:** chronic asthma.
**Contra-indications:** sensitivity to the drug.
**Cautions:** cardiac diseases, hypertension, epilepsy, hyperthyroidism, hepatic impairment, peptic ulcer.
**Side-effects:** anxiety, confusion, nausea, insomnia, tachycardia.
**Dose:** sustained release oral preparation, 200-300 mg twice daily. Children over 6 years, 125-250 mg twice daily.

**Preparations**
Theophylline sustained release tablets, 300 mg tab.
Theophylline syrup, 60 mg/5 mL

In patients with chronic continuing asthma, long-term therapy with oral steroids is used when other drugs fail to produce a response or patient relapses repeatedly into status asthmaticus. Concomitant use of inhalational steroids reduces the need for large oral doses. Oral steroids should be given as single morning dose to reduce interference with circadian secretion. Inhalational corticosteroids are better administered using large-volume spacer devises. These devices help by increasing airway deposition and reducing oropharyngeal deposition, which will contribute to a lesser incidence of oral candidiasis (thrush).

3 B : Corticosteroids

Inhalational corticosteroids are widely used for the treatment of less severe and more chronic asthma. Their use is associated with less frequent side-effects than systemic corticosteroids. The use of inhalational corticosteroids must be regularly maintained to achieve a therapeutic effect; 3-7 days are needed to get a maximum benefit. Patients are also advised to use salbutamol inhalation prior to the steroid inhalation for a better penetration of the steroid.

A short course of oral steroid such as prednisolone, or an injection of hydrocortisone is still used in the treatment of acute attacks of asthma (see treatment charts and sec.6 C.1).

**Budesonide**

**Indications:** prophylaxis of asthma.
**Cautions:** untreated severe respiratory infection; tuberculosis.
**Side-effects:** paradoxical bronchospasm; adrenal crisis (with prolonged high doses); adrenal suppression (with prolonged high doses); aggression (particularly in children); anxiety; behavioural changes (particularly in children); bruising; candidiasis of the mouth; candidiasis of the throat; cataracts; coma (with prolonged high doses); Cushing’s syndrome (with moon face, striae and acne); depression; dysphonia; glaucoma (with prolonged high doses); hoarseness; hyperactivity (particularly in children); hyperglycaemia (usually only with high doses); irritability.
(particularly in children); lower respiratory tract infections in older patients with chronic obstructive pulmonary disease (with high doses); pneumonia in older patients with chronic obstructive pulmonary disease (with high doses); reduced mineral bone density (with long-term treatment of high doses); side-effects applicable to systemic corticosteroids may also apply if absorption occurs following inhaled use; sleep disturbances; throat irritation

**Dose:** inhalation of nebulised solutions, 1-2 mg twice daily, child 3 months-12 years, half the above doses.

**Preparations**

Budesonide nebuliser solution (Respules), 250 micrograms/mL, 2 mL ampoule

Budesonide nebuliser solution (Respules), 500 micrograms/mL, 2 mL ampoule

**Budesonide/ Formoterol (Restricted)**

**For Indications, cautions and side-effects:** see under individual drugs

**Preparations**

Budesonide / Formoterol powder for inhalation, 160/4.5 micrograms/blister

**Fluticasone (Restricted)**

Indications, cautions and side-effects: see under budesonide.

**Dose:** aerosol inhalation, adult, 125-250 microgram (1-2 puffs) twice daily, child 4-16 years, 50-100 microgram (1-2puffs) twice daily. Dose can be adjusted according to severity of asthma.

**Preparations**

Fluticasone aerosol inhaler, 50 microgram/metered inhalation

Fluticasone aerosol inhaler, 100 microgram/metered inhalation

**Fluticasone/ Salmeterol (Restricted)**

For indications, cautions and side-effects: see under individual drugs

**Preparations**

Fluticasone/Salmeterol powder for inhalation, 100/50 micrograms/blister

Fluticasone/Salmeterol powder for inhalation, 125/50 microgram/blister

Fluticasone/Salmeterol powder for inhalation, 250/50 micrograms/blister

Fluticasone/Salmeterol powder for inhalation, 500/50 micrograms/blister

**3 C: Leukotriene receptor antagonists**

The leukotriene receptor antagonists including montelukast, block the effects of cysteinyi leukotrienes in the airways. They are effective in asthma when used alone or with
Montelukast

Indications: see notes above, prophylaxis of asthma, chronic asthma, symptomatic relief of seasonal allergic rhinitis in patients with asthma.

Cautions: pregnancy, breast-feeding.

Side-effects: abdominal pain, thirst; hyperkinesia (in young children), headache, dry mouth, diarrhoea, dyspepsia, nausea, vomiting, hepatic disorders, palpitation, oedema, increased bleeding, depression, tremor, asthenia, dizziness, hallucinations, paraesthesia, hypoaesthesia, sleep disturbances, abnormal dreams, agitation, aggression, seizures, arthralgia, myalgia, pruritus, Churg-Strauss syndrome (medium and small vessel autoimmune vasculitis, leading to necrosis. It has occurred very rarely in association with the use of leukotriene receptor antagonists; in many of the reported cases the reaction followed the reduction or withdrawal of oral corticosteroid therapy. The prescribers should be alert to the development of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropathy).

Dose: prophylaxis of asthma, adult and child over 15 years, 10 mg once daily in the evening; child 6 months–6 years 4 mg once daily in the evening; 6–15 years 5 mg once daily in the evening; seasonal allergic rhinitis, adult and child over 15 years, 10 mg once daily in the evening.

Preparations
- Montelukast chewable tablets, 5 mg tab.
- Montelukast chewable tablets, 10 mg tab.
- Montelukast sachet, 4 mg / sachet.

3 D: Monoclonal Antibodies

Omalizumab (Restricted)

Indications: Prophylaxis of severe persistent allergic asthma. Add-on therapy for chronic spontaneous urticaria in patients who have had an inadequate response to H1 antihistamine treatment

Cautions: Autoimmune disease; susceptibility to helminth infection—discontinue if infection does not respond to anthelmintic

Side-effects: Abdominal pain; arthralgia; headache; injection-site reactions; pyrexia; sinusitis; upper respiratory tract infection; bronchospasm; cough; diarrhoea; dizziness; drowsiness; dyspepsia; flushing; influenza-like illness; malaise;
3. Respiratory system

Antihistamines have been classified according to their potential to induce sedation into sedating and non-sedating antihistamines. Antihistamines differ in their duration of action, incidence of drowsiness and anticholinergic effects while no difference can be drawn on efficacy. Most of the non-sedating antihistamines have a long duration of action compared to the sedating agents. Promethazine may act for a long duration (10-12 hours).

3 E.1: Antihistamines

These are H₁-receptor antagonists used for symptomatic relief of rhinorrhea and sneezing associated with hay fever; they are less effective in relieving nasal congestion. Antihistamines are also used in prevention of urticaria, treatment of skin allergic reactions, insect bites, and drug-induced allergies.

Preparations

Omalizumab solution injection, 150 mg/ml prefilled syringe

3 E: Allergic disorders

Drugs affecting allergic disorders of the upper respiratory tract, particularly antihistamines, are discussed in this section.

3 E.1.1: Sedating antihistamines

3 E.1.1.1: Alkylamines

Chlorphenamine maleate (Chlorpheniramime)

Indications: allergic disorders; emergency treatment of anaphylactic reactions.

Contra-indications and cautions: antihistamines should be used with caution in patients with glaucoma, prostatic hypertrophy, urinary retention and hepatic diseases. Elderly and children are more susceptible to side-effects.

Side-effects: drowsiness, headache, antimuscarinics effects; hypotension may be induced with injection.

Dose: oral, 4 mg 3-4 times daily; Child under 1 year not recommended, 1-2 years, 1 mg twice daily, 2-5 years 1 mg 3-4 times daily.
3: Respiratory system

daily, 6-12 years  2 mg 3-4 times daily.
Subcutaneous, intramuscular or slow intravenous injection, 10-20 mg; Child 1-6 years, 2.5-5 mg, 6-12 years 5-10 mg (for all dose can be repeated up to four times in 24 hours).

Preparations
Chlorphenamine maleate tablets, 4 mg tab.
Chlorphenamine syrup, 2 mg/5 mL; 100 mL/bottle
Chlorphenamine maleate injection, 10 mg/mL ampoule

3 E.1.1.2 Phenothiazines

Promethazine hydrochloride
Indications: symptomatic relief of allergy; emergency treatment of anaphylactic reactions; sedation; motion sickness
Contra-indications, cautions and side-effects: as for chlorpheniramine
Dose: oral, 10-20 mg 2-3 times daily, or 25 mg at bed time, increased to 2 times daily; Child, under 2 years not recommended; 2-5 years 5-10 mg daily in 1-2 divided doses, 5-10 years 10-25 mg daily in 1-2 divided doses.
Deep intramuscular injection, 25-50 mg, maximum 100 mg; Child 5-10 years 6.25-12.5 mg
Slow intravenous injection in emergencies, 25-50 mg as a solution containing 2.5 mg/mL in water for injection, maximum 100 mg

Preparations
Promethazine hydrochloride tablets, 10 mg tab.
Promethazine hydrochloride tablets, 25 mg tab.
Promethazine hydrochloride syrup, 5-6 mg/5 mL; 100-125 mL/bottle
Promethazine hydrochloride injection, 25 mg/mL ampoule

3 E.2: Non-sedating antihistamines

Loratidine (Restricted)
Indications: symptomatic relief of allergy
Contra-indications and cautions: as for other antihistamines.
Side-effects: less antimuscarinics and sedative effects than other antihistamines; for other effects see chlorpheniramine.
Dose: orally, adult and child over 5 years 10 mg daily; Child 2-5 years 5 mg daily

Preparations
Loratidine tablets, 10 mg tab.
Loratidine syrup, 5 mg/5 mL; 75-100 mL/bottle

Cetirizine hydrochloride (Restricted)
Indications: symptomatic relief of allergy
Contra-indications and cautions: as for other antihistamines; reduce dose in renal impairment
3. Respiratory system

**Side-effects:** less antimuscarinic and sedative effects than other antihistamines; for other effects see chlorpheniramine.

**Dose:** 10 mg daily or 5 mg twice daily; Child 2-6 years 5 mg daily or 2.5 mg twice daily

**Preparations**
- Cetirizine hydrochloride tablets, 10 mg tab.
- Cetirizine hydrochloride syrup, 5 mg/5 mL; 75-100 mL/bottle

**Note:** MoH policy is that only one of the above non-sedating antihistamines, loratidine or cetirizine, will be purchased and supplied for use based on its cost effectiveness.

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3 E.3: Antihistamines and decongestants combinations

Oral antihistamines and sympathomimetic decongestants may be combined in one preparation to be used for the symptomatic relief of hay fever or vasomotor rhinitis. The decongestants may counter some of the sedative effects of antihistamine.

**Antihistamine and decongestant preparations**

**Indications:** symptomatic relief of allergy; hay fever and vasomotor rhinitis.

**Contra-indications and cautions:** see under antihistamines and sympathomimetics (see sec 2)

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3 F: Respiratory stimulants and pulmonary surfactants

Respiratory stimulants (analectics) such as doxapram are of doubtful value in treating respiratory failure induced by barbiturates or other CNS depressants. They are ineffective and may be harmful in asthma or in respiratory failure due to neurological or muscular disorders and in drug toxicity. However, analeptics are useful in acute ventricular failure in patients with chronic lung disease. These drugs have a narrow safety margin and can readily induce convulsion. Their use should be confined to inpatients under strict expert supervision. The use of analeptics has largely been replaced by ventilatory support. Surfactants have been used in the management...
3: Respiratory system

of respiratory distress syndrome in preterm infants

**Caffeine Citrate**

**Indications:** neonatal apnoea; adjunct to extubation in preterm infants.

**Cautions:** necrotizing enterocolitis may occur, infants with cardiovascular disorders, hepatic or renal impairment and seizure disorders, other causes of apnoea should be eliminated before use, safety and efficacy in long-term treatment not established.

**Side-effects:** physical signs of withdrawal including irritability, lethargy; headache, tachycardia, raised serum glucose concentration.

**Dose:** orally or by intravenous injection, initially 20 mg/kg, then 5 mg/kg once daily starting 24 hours after initial dose (some neonates may require 10 mg/kg).

**Preparations**
- Caffeine citrate oral solution injection, 20 mg/mL, 3 mL (single dose vial)
- Caffeine citrate injection, 20 mg/mL, 3 mL vial

**Doxapram hydrochloride**

**Indications:** respiratory depression; acute respiratory failure

**Contra-indications:** severe hypertension, status asthmaticus, epilepsy.

**Cautions:** give with oxygen in severe irreversible airway obstruction; hyperthyroidism, hepatic impairment, pregnancy.

**Side-effects:** arrhythmias, nausea & vomiting, flushing, pruritus, tremors.

**Dose:** postoperative respiratory depression, intravenous injection 1-1.5 mg/kg or by intravenous infusion, 2-3 mg/minute adjusted according to response.

Acute respiratory failure, intravenous infusion 1.5-4 mg/minute adjusted according to response.

**Preparations**
- Doxapram injection, 20 mg/mL; 5 mL ampoule

**Beractant**

**Indications:** prevention and treatment of neonatal respiratory distress syndrome.

**Cautions:** continuous monitoring of blood gases.

**Side-effects:** pulmonary haemorrhage reported especially in more premature infants.

**Dose:** by endotracheal tube, 100 mg/kg equivalent to a volume of 4 mL/kg within 8 hours of birth, may be repeated within 48 hours at 6 hours interval.

**Preparations**
- Beractant suspension, 25 mg/mL phospholipid suspension, 8 mL vial

**Colfosceril**

**Indications:** treatment and prophylaxis of respiratory distress syndrome.

**Cautions:** as beractant

**Side-effects:** as beractant
3. Respiratory system

**Dose:** by endotracheal tube, treatment, 67.5 mg/kg; if still intubated, may be repeated after 12 hours; prophylaxis, first dose soon after birth, if still intubated may be repeated 12 and 24 hours later.

**Preparations**
Colfosceril palmitate suspension 108 mg for reconstitution with 8 mL water for injections (when reconstituted contains 67.5 mg/5 mL) with endotracheal tube connectors

**Note:** Ministry of Health policy is that only one of the above pulmonary surfactants beractant or colfosceril will be purchased and made available for use

**3 G: Oxygen**

Oxygen should be considered as a drug. It is prescribed to hypoxaemic patients to increase alveolar oxygen tension and decrease the work effort of breathing to maintain a given arterial oxygen tension $P_aO_2$. The concentration depends on the condition being treated; an incorrect concentration could have serious or lethal effects. **High concentration therapy** up to 60% is safe in conditions like pneumonia, pulmonary thromboembolism and fibrosing alveolitis. In acute severe asthma the arterial carbon dioxide $P_aCO_2$ is subnormal but as asthma deteriorates it may rise steeply (especially in children).

These patients usually require high concentrations of oxygen and if the $P_aCO_2$ remains high in spite of other treatment, intermittent positive pressure ventilation needs to be urgently considered. Where blood gas measurements are not readily available a concentration of 35% to 50% oxygen delivered through a conventional mask is recommended. Exceptionally, asthma is diagnosed in patients with a long history of chronic bronchitis and probable respiratory failure; in these patients a lower concentration (24 to 28%) may be needed to limit oxygen-induced reduction of respiratory drive. **Low concentration oxygen therapy** (controlled oxygen therapy) is reserved for patients with ventilatory failure due to chronic obstructive pulmonary disease (COPD) or other causes. The concentration should not exceed 28% and in some patients a concentration greater than 24% may be excessive. The aim is to provide just enough oxygen to correct the hypoxaemia without worsening pre-existing CO$_2$ retention and respiratory acidosis. Treatment should be carried out in hospital where facilities for blood gas measurements are available.

**Oxygen gas**

Re-fillable cylinders of 6, 12, 24, 48, 100 and 200 cubic feet (CF) are available.
3: Respiratory system

3 H: Aromatic inhalation

Inhalation of aromatic substances such as benzoin tincture compound or menthol added to warm water will facilitate the inhalation of moist warm air, which is useful and comforting in bronchitis. It can also help relieve nasal congestion in rhinitis or sinusitis.

Benzoin tincture compound, 4.5% solution.

Direction for use: add 5ml of tincture benzoin to 500 mL hot water (not boiling) and inhale the vapour.

3 I: Cough preparations

Cough preparations are generally of two classes; cough suppressants that help by ridding the patients of the distress of dry coughing, and cough expectorants, which help maintaining easy cough to expel mucous exudates.

3 I.1: Cough expectorants

These preparations have no advantage over warm steam inhalation to facilitate the expulsion of bronchial secretion; they may have some placebo effect. These are compound preparation that may contain a number of ingredients often in sub-therapeutic doses of expectorant materials such as iodide, cough suppressants, antihistamines, sympathomimetics and sedatives.

Preparations
Cough expectorant for Children; 100-125 mL/bottle
Cough expectorant for Adults; 100-120 mL/bottle

3 I.2: Cough suppressants

Cough suppressants are used to stop unproductive cough and when cough is distressing. They may cause sputum retention and this may be harmful in patients with chronic bronchitis and bronchiectasis.

Codeine and dextromethorphan are commonly included in commercial cough preparations. Long-term use may lead to abuse and dependence problems. Sedating antihistamines are also found in many cough suppressant preparations and they tend to induce sedation and drowsiness. Codeine containing cough preparations are not recommended for use in children and are totally avoided in those under 1 year of age.

Preparations
Cough Suppressant (e.g. Butamir- ate citrate 15 mg/10 mL; 200 mL/bottle

3 J: Mucolytics

Bromhexine

Indications: for ICU patients to facilitate thin mucous secretion in bronchial obstruction caused by thick mucus.

Side-effects: nausea, diarrhoea
3. Respiratory system

**Dose**: with nebuliser, 2 mg/mL, 5 mL solution.

**Preparations**
Bromhexine nebulised solution, 2 mg/mL solution; 40 mL bottle

**Dornase alfa (Restricted)**
(Phosphorylated glycosylated recombinant human deoxyribonuclease 1 (rhDNase))

**Indications**: management of cystic fibrosis patients with a forced vital capacity (FVC) of greater than 40% of predicted to improve pulmonary function.

**Cautions**: pregnancy, breast-feeding.

**Side-effects**: pharyngitis, voice changes, chest pain, laryngitis, rashes, urticaria, conjunctivitis.

**Dose**: adult and child over 5 years, by inhalation of nebulised solution (by jet nebuliser), 2.5 mg (2500 units) once daily (patients over 21 years may benefit from twice daily dosage).

**Preparations**
Dornase alfa nebuliser solution, 1 mg/mL (1000 units) solution, 2.5 mL vial

3 K: Antifibrotics

The exact mechanism of action of pirfenidone is not yet understood, but it is believed to slow down the progression of idiopathic pulmonary fibrosis by exerting both anti-fibrotic and anti-inflammatory properties.

**Pirfenidone (Restricted)**

**Indications**: Treatment of mild to moderate idiopathic pulmonary fibrosis

**Contra-indications**: Cigarette smoking

**Cautions**: Avoid exposure to direct sunlight—if photosensitivity reaction or rash occurs, dose adjustment or treatment interruption may be required (consult product literature).

If treatment is interrupted for 14 consecutive days or more, the initial 2 week titration regimen should be repeated; if treatment is interrupted for less than 14 consecutive days, the dose can be resumed at the previous daily dose without titration.

**Side-effects**: Abdominal discomfort; anorexia; arthralgia; constipation; diarrhoea; dizziness; dry skin; dysgeusia; dyspepsia; erythema; flatulence; gastritis; gastro-oesophageal reflux disease; headache; hot flush; insomnia; malaise; myalgia; nausea; non-cardiac chest pain; photosensitivity reaction; pruritus; raised hepatic enzymes; rash; somnolence; upper respiratory tract infection; urinary tract infection; vomiting; weight loss

**Dose**: Initially 267 mg 3 times a day for 7 days, then increased to 534 mg 3 times a day for 7 days, then increased to 801 mg 3 times a day.
Insomnia should be considered an underlying symptom that has many causes including emotional and physical disorders or as a drug unwanted effect. Difficulty in falling asleep is common in the young and the elderly. It often occurs with emotional disturbances such as anxiety, nervousness, depression or fear. Sometimes people find it difficult to fall asleep simply because their body and brain are not tired. Insomnia may be transient, of short term or chronic.

Tolerance to the hypnotic effect may develop within 3-14 days of continued use. Prolonged use may cause rebound insomnia and precipitate a withdrawal syndrome when treatment is discontinued. Hypnotics should be avoided in children and in the elderly who may become ataxic and confused. Caution should be observed when using the higher range of dose, which should only be used in the short term.

Midazolam (Controlled/restricted)
Indications: anaesthesia induction; conscious sedation.
Contra-indications: acute angle glaucoma.
Cautions: avoid intra-arterial injection, avoid extravasation; concomitant use of ketoconazole or itraconazole (syrup).
Side-effects: amnesia, respiratory depression.
Dose: intravenously, as induction agent, 0.15–0.35 mg/kg. For conscious sedation, 0.05–0.1 mg/kg.
Preparations
Midazolam injection, 5 mg/mL, 3 mL ampoule
Midazolam tablets, 7.5 mg tab.
Midazolam syrup 2 mg/ml

3: Respiratory system

Preparations
Pirfenidone capsules, 200 mg cap
4. Central nervous system

Section 4: Central nervous system
- Hypnotics and anxiolytics
- Drugs used in psychosis and related disorders
- Antidepressants
- Analgesics
- Antiepileptics
- Drugs used in Parkinsonism and related disorders
- Drugs used in nausea, vomiting and vertigo
- Drug used in substance dependence
- Drugs used for attention deficit hyperactivity disorder
- Dementia

4 A: Hypnotics and anxiolytics

4 A.1: Hypnotics

Insomnia should be considered an underlying symptom that has many causes including emotional and physical disorders or as a drug unwanted effect. Difficulty in falling asleep is common in the young and the elderly. It often occurs with emotional disturbances such as anxiety, nervousness, depression or fear. Sometimes people find it difficult to fall asleep simply because their body and brain are not tired. Insomnia may be transient, of short term or chronic. Tolerance to the hypnotic effect may develop within 3-14 days of continued use. Prolonged use may cause rebound insomnia and precipitate a withdrawal syndrome when treatment is discontinued. Hypnotics should be avoided in children and in the elderly who may become ataxic and confused. Caution should be observed when using the higher range of dose, which should only be used in the short term.

4 A.1.1: Hypnotic benzodiazepine derivatives

Midazolam (Controlled/restricted)
Indications: anaesthesia induction; conscious sedation.
Contra-indications: acute angle glaucoma.
Cautions: avoid intra-arterial injection, avoid extravasation; concomitant use of ketoconazole or itraconazole (syrup).
Side-effects: amnesia, respiratory depression.
Dose: intravenously, as induction agent, 0.15 - 0.35 mg / kg.
For conscious sedation, 0.05 - 0.1 mg / kg.
Preparations
Midazolam injection, 5 mg/mL, 3 mL ampoule
Midazolam tablets, 7.5 mg tab.
Midazolam syrup 2 mg/ml

4 A.1.2: Chloral and derivatives

Chloral hydrate
Indications: insomnia in children and the elderly (short-term use).
4. Central nervous system

Contra-indications: cardiac disease; gastritis; hepatic and renal impairment; pregnancy and breastfeeding.
Cautions: respiratory diseases; avoid contact with skin and mucous membrane.
Side-effects: gastrointestinal disturbances, ataxia, nightmares, skin rush.

Dose: 0.5 - 1 g with plenty of water (30 minutes before bed time) maximum 2 g. Child 30-50 mg / kg, maximum 1 g.

Preparations
Chloral hydrate syrup, 500 mg/5 mL, 500 mL bottle

4 A.2: Anxiolytics

4 A.2.1: Benzodiazepine anxiolytics

Benzodiazepines are the most commonly used anxiolytics. They have replaced older generations of drugs such as barbiturates and meprobamate that used to have more adverse effects and interactions than benzodiazepines. Benzodiazepine may show paradoxical effects such as increased aggression and hostility, increased anxiety and perceptual disorders. Patients on benzodiazepine should be advised not to drive or operate machinery that requires a high degree of attention as benzodiazepines impair psychomotor performance.

Both emotional and physical dependence may develop to benzodiazepines. Abrupt cessation may precipitate confusion, toxic psychosis, delirium or convulsion. Long-term use of benzodiazepines should be avoided. Withdrawal of benzodiazepine should be gradual to avoid withdrawal syndrome.

a) Long-acting benzodiazepine

Diazepam (Controlled)
Indications: anxiety or insomnia (short-term use); status epilepticus, febrile convulsion (see Sec 4 E.4), muscle spasm, perioperatively.
Contra-indications: respiratory depression; severe hepatic impairment, neuromuscular respiratory weakness, sleep apnoea syndrome.
Cautions: respiratory disease, muscle weakness and myasthenia gravis, simultaneous use of alcohol, pregnancy and breastfeeding, renal and hepatic impairment, avoid prolonged use and abrupt withdrawal.
Side-effects: drowsiness, light-headedness, confusion and ataxia, amnesia may occur.

Dose: oral, 2 mg 3 times daily for anxiety, increase to 5-10 mg 3 times daily when necessary. Insomnia, 5-10 mg at bedtime.

Intramuscular or slow intravenous in acute panic state, 10 mg repeated after 4 hours if necessary. By rectum, as rectal solution, acute anxiety 500 microgram/ kg repeated af-
ter 12 hours if required. As suppos-
itories, when oral route is not ap-
propriate, 10-30 mg.
For use in status epilepticus, see sec. 4.E.2

Preparations
Diazepam tablets, 5 mg tab.
Diazepam injection, 5 mg/mL, 2 mL ampoule
Diazepam suppository, 10 mg supp.
Diazepam rectal tube (rectal solution), 2.5-10 mg tube

b) Short-acting benzodiazepines

Bromazepam (Controlled /re-
stricted)
Indications: anxiety (short-term use).
Contra-indications, cautions and side-effects: see diazepam.
Dose: 1.5 - 3 mg up to 3 times daily. Elderly and child, half the daily adult doses.

Preparations
Bromazepam tablets, 1.5 mg tab.

Lorazepam
Indications: anxiety or insomnia (short-term use). Also, in compari-
sion to diazepam, it has less hang over effect.
Contra-indications, cautions and side-effects: see diazepam. Also, it carries greater risk of withdrawal syndrome than diazepam.
Dose: orally, 1-4 mg daily in di-
vided doses for anxiety, 1-2 mg at bedtime for insomnia. Elderly, half the daily adult doses.
Preparations
Lorazepam tablets, 1 mg tab.

4 A.2.2: Miscellaneous anxiolytics

Buspirone Hydrochloride (Con-
trolled/restricted)
Indications: generalized anxiety disorders.
Contra-indications: epilepsy; se-
vere hepatic or renal impairment, pregnancy and breast feeding.
Cautions: does not alleviate benzodiazepine withdrawal syndrome (a patients on benzodiazepine should still be gradually withdrawn). The dependence and abuse liability of buspirone has not yet been estab-
lished.
Side-effects: dizziness, light-head-
edness, nausea.
Dose: 5 mg 2-3 times daily increase gradually. Usual maintenance dose 15-30 mg daily in divided doses. Long-term use may be indicated.

Preparations
Buspirone tablets, 5 mg tab.
Buspirone tablets, 10 mg tab.

Hydroxyzine hydrochloride
Indications: anxiety (short term), pruritus.
Contra-indications, cautions and side-effects: see notes under sedat-
ing antihistamines (sec.3.D.1.1)
Dose: anxiety, adult only 50-100 mg 4 times daily.
4. Central nervous system

Pruritus, 25 mg at night, increase as needed to 3-4 times daily. Child over 6 years, 15-25 mg daily, increase to 50 mg daily in divided doses.

Preparations
Hydroxyzine tablets, 10 mg tab.

4 B: Drugs used in psychosis and related disorders

Drugs used for the treatment of psychosis and manic conditions will be reviewed in this section.

4 B.1: Antipsychotics

Antipsychotics are of various chemical groups. Phenothiazines, butyro-phenones, thioxanthene derivatives and the newly introduced atypical antipsychotics are effectively applied in the management of psychotic disorders. They share the capability of blocking dopamine receptors in the brain. The new generation of atypical antipsychotics block both dopamine and serotonin brain receptors.

Antipsychotics improve mood and behaviour in schizophrenia. However, they treat delusion, hallucination, agitation and thought disorders in schizophrenia mania, dementia or acute intoxication with substances such as amphetamines. The typical antipsychotics produce emotional quieting, psychomotor slowing and indifference and may seriously impair consciousness/alertness. They do not produce excessive sedation nor do they induce physical dependence. Antipsychotics are more effective in acute schizophrenia than in treating chronic symptoms.

Atypical antipsychotics reduce negative as well as positive symptoms of psychosis and do not seriously impair alertness and consciousness. Treatment with antipsychotics should continue for quite a long time after the first episode. Withdrawal requires careful supervision since acute relapse may follow cessation of therapy in some patients. Relapse, in others, appear after several weeks of stopping therapy.

The blockade of dopamine receptors in the brain is so widely distributed that the antipsychotic effects are hardly achieved without unwanted extrapyramidal (EP) effects.

EP effects are easily recognized but difficult to predict because they depend partly on the dose, type and duration of the antipsychotics; and partly on the susceptibility of the patient. Atypical antipsychotics rarely produce EP effects.

EP effects can be manifested as: Acute dystonia, which is characterized by spasm of tongue, face, neck and back leading to abnormal movements. This could occur at a very early stage of treatment. It can be treated with antiparkinsonian drugs.

Akathesia (restlessness), which may resemble an exacerbation of
the condition being treated. This may appear after 5-60 days of therapy. It can be treated by reducing the dose or changing the drug. **Parkinsonian symptoms**, which may develop gradually and can be treated with antiparkinsonian drugs of good anticholinergic effects. **Tardive dyskinesia**, which develops as a delayed sequela of long-term antipsychotic use. It is difficult to treat but can be avoided by allowing the antipsychotic treatment course to be interrupted intermittently.

Other adverse effects associated with the use of antipsychotics include:

**Hypotension and interference with temperature regulation** which are dose related and could cause serious falls and hypothermia in the elderly.

**Neuroleptic malignant syndrome** manifested by hyperthermia, akinesia, muscle rigidity, autonomic imbalance and altered consciousness is a rare but lethal reaction to antipsychotics.

**Hyperprolactinaemia** has been associated with chronic use of antipsychotics. Effects such as galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported.

Choice of therapy from the available wide range of antipsychotics is a matter of suitability to a particular patient, the degree of sedation required and susceptibility to EP effects. The atypical antipsychotics are better tolerated and show less serious EP effects.

### 4 B.1.1: Phenothiazines

**Chlorpromazine hydrochloride**

**Indications**: psychosis; antiemetic in palliative care; intractable hiccup.

**Contra-indications**: coma due to CNS depressants; bone marrow depression.

**Cautions**: epilepsy, parkinsonism, respiratory disease, pregnancy and breast-feeding.

**Side-effects**: dry mouth, constipation, EP effects, galactorrhoea, hypotension, sedation and drowsiness, headache, hypothermia.

**Dose**: For nausea, vomiting and agitation; 10-25 mg once or twice daily for a short period of time. Intramuscular injection 25-50 mg may be preferred in serious acute cases of agitation. For excitement, restlessness, and violent behaviour control, 50-100 mg orally or deep intramuscularly. May be repeated every 3-4 hours up to 400 mg daily. In elderly one third or half the above dose. Child 6-12 years, half the adult dose (maximum 75 mg daily). Intractable hiccup, 25-50 mg 3-4 times daily.
4. Central nervous system

**Preparations**
Chlorpromazine tablets, 25 mg tab.
Chlorpromazine tablets, 100 mg tab.
Chlorpromazine HCl injection, 25 mg/mL, 2 mL ampoule *(Restricted)*

**Fluphenazine decanoate**
**Indications:** maintenance in schizophrenia and other psychosis.
**Contra-indications:** see under chlorpromazine above. Do not use in children and in severely depressed.
**Cautions:** see under chlorpromazine. When transferring from oral to depot preparations, dosage by mouth should be gradually phased out.
**Side-effects:** EP effects may appear few hours after administration by injection and continue for two days and may be delayed. Others: see under chlorpromazine
**Dose:** deep intramuscular injection into the gluteal muscle, 12.5-25 mg at intervals of 2-5 weeks adjust according to response.

Preparations
Fluphenazine decanoate injection, 25 mg/mL, 1 mL vial

**Trifluoperazine**
**Indications:** Psychosis.
**Contra-indications, cautions and side-effects:** see under chlorpromazine; less sedation and hypotension. EP effects are more frequent and may occur with low doses but more often with doses exceeding 6 mg daily.
**Dose:** schizophrenia and other psychotic disorders, adjunctive management of agitation, excitement and violent impulsive behaviour, 5 mg twice daily, or 10 mg modified release preparations. Increase as necessary. Child up to 12 years, 5 mg daily.

Preparations
Trifluoperazine tablets, 1 mg tab.
Trifluoperazine tablets, 5 mg tab.
Trifluoperazine retard capsules, 10 mg cap.

4 B.1.2 :Atypical antipsychotics

**Clozapine (CDL)**
**Indication:** is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia.
**Contraindications:** in patients with myeloproliferative disorders, uncontrolled epilepsy, paralytic ileus, history of agranulocytosis or neutropenia, severe cardiovascular disorders, severe renal impairment, depression or comatose states from any cause.
**Cautions:** avoid abrupt withdrawal, monitor leucocytes and differential blood count, hepatic impairment, pregnancy, prostatic hypertrophy, susceptibility to angle closure glaucoma.
**Side-effects:** tachycardia, vomiting, constipation, nausea, headache, tremor, drowsiness, sweating, leukopenia, leucocytosis.
4. Central nervous system

**Dose:** by mouth; initially, 12.5 mg once or twice on first day. If well tolerated, can be increased gradually, usual dose is 200-450 mg daily. Maximum dose 900 mg daily.

**Preparations**
Clozapine tablets, 25 mg tab.

**Olanzapine (Restricted)**
**Indications:** psychosis.
**Contra-indications:** angle closure glaucoma, breast feeding.
**Cautions:** cardiovascular disease, epilepsy Parkinson’s disease, prostatic hypertrophy, pregnancy, blood disease. Serum level may be slightly lowered by concomitant smoking or the use of carbamazepine.
**Side-effects:** weight gain, postural hypotension, mild EP effects, blood dyscrasias, hyperglycaemia.
**Dose:** initial, 10 mg daily, adjusted to 5-20 mg daily after assessment.

**Preparations**
Olanzapine tablets, 5 mg tab.
Olanzapine tablets, 10 mg tab.

**Quetiapine**
**Indications:** schizophrenia, treatment of episodes of mania either alone or with mood stabilisers.
**Contraindications:** breast-feeding.
**Cautions:** pregnancy, hepatic impairment, renal impairment, cerebrovascular disease, diabetes mellitus.

**Side-effects:** orthostatic hypotension, increased liver enzymes, agitation, drowsiness, dyspepsia, constipation, dry mouth, mild asthenia, rhinitis, tachycardia, leucopenia, neutropenia, eosinophilia, elevated plasma-triglyceride and cholesterol concentrations, reduced plasma-thyroid hormone concentrations, possible QT interval prolongation, oedema, priapism.
**Dose:** orally; Schizophrenia, 25 mg twice daily on day one, 50 mg twice daily on day two, 100 mg twice daily on day three, 150 mg twice daily on day four, then adjusted according to response, usual range 300–450 mg daily in 2 divided doses; max. 750 mg daily; elderly initially 25 mg daily as a single dose, increased in steps of 25–50 mg daily in 2 divided doses. Mania, 50 mg twice daily on day one, 100 mg twice daily on day two, 150 mg twice daily on day three, 200 mg twice daily on day four, then adjusted according to response in steps of up to 200 mg daily to max. 800 mg daily; usual range 400–800 mg daily in 2 divided doses; elderly initially 25 mg daily as a single dose, increased in steps of 25–50 mg daily in 2 divided doses.

**Preparations**
Quetiapine tablets, 25 mg tab.
Quetiapine tablets, 100 mg tab.
Quetiapine tablets, 200 mg tab.
4. Central nervous system

**Risperidone (Restricted)**

**Indications:** psychosis in which both negative and positive symptoms are prominent.

**Contra-indications:** breast-feeding.

**Cautions:** cardiovascular disease, pregnancy, renal and hepatic impairment.

**Side-effects:** insomnia, agitation, impaired concentration, constipation, blurred vision, dry mouth, hyperprolactinaemia, sexual dysfunction, blood disorders.

**Dose:** initial dose 2 mg daily in divided doses, titrate gradually, usual dose range 4-6 mg daily in divided doses.

**Preparations**
- Risperidone tablets, 2 mg tab.
- Risperidone tablets, 4 mg tab.
- Risperidone depot injection, 25 mg injection
- Risperidone depot injection, 50 mg injection

**Flupentixol decanoate (Flupenthixol decanoate)**

**Indications:** maintenance in schizophrenia and other psychosis.

**Contra-indications:** see notes above, and under chlorpromazine

**Cautions:** see under chlorpromazine. When transferring from oral to depot preparation, dosage by mouth should be gradually phased out. It may have a mood elevating effect.

**Side-effects:** EP effects may appear 1-3 days after administration by injection and continue for 5-10 days and may be delayed. Others, see under chlorpromazine.

**Dose:** by deep intramuscular depot injection into the gluteal muscle, 20-40 mg at interval of 2-4 weeks. Adjust dose according to response; max. 400 mg weekly.

**Preparations**
- Flupentixol decanoate oily injection, 40 mg/mL ampoule
- Flupentixol decanoate oily injection, 100 mg/mL ampoule

**Zuclopenthixol acetate**

**Indications:** maintenance in schizophrenia and other psychosis, particularly with aggression and agitation.

**Contra-indications:** see notes above

**Cautions:** see notes above

**Side-effects:** see notes above. Less sedation.

**Dose:** by deep intramuscular injection in the gluteal muscle, 50-100 mg at intervals of 2-3 days, adjusted according to response.

**Preparations**
- Zuclopenthixol acetate injection, 50 mg/mL ampoule
4. Central nervous system

4 B.1.4: Butyrophenones

**Haloperidol**

**Indications:** schizophrenia and other psychosis, aggressive behaviour.

**Contra-indications, cautions and side-effects:** see under chlorpromazine; less sedation and fewer antimuscarinics or hypotensive effects. EP effects are more frequent in thyrotoxic patients.

**Dose:** oral, 1.5-3 mg 2-3 times daily, or 3-5 mg 2-3 times daily in severe cases. Higher doses might be used in resistant cases. Child, initially 25-50 microgram/kg daily in 2 divided doses; increase as necessary.

By intramuscular injection, 2-10 mg, repeated every 4-8 hours according to response.

For use in nausea and vomiting, intractable hiccup, orally 0.5-1.5 mg 3 times daily, adjusted according to response.

**Preparations**

Haloperidol tablets/capsules, 1.5 mg tab./cap.
Haloperidol tablets/capsules, 5 mg tab./cap.
Haloperidol tablets/capsules, 10 mg tab./cap.
Haloperidol liquid, 2 mg/mL, 100 mL bottle
Haloperidol liquid, 2 mg/mL, 15 mL drops
Haloperidol injection, 5 mg/mL ampoule

4 B.2: Anti-manic drugs

**Lithium carbonate**

**Indications:** prophylaxis and treatment of mania; prophylaxis of bipolar disorders; prophylaxis of recurrent depression.

**Contra-indications:** renal disease; cardiac disease, parkinsonism, potent sodium depleting diuretics, pregnancy, breast feeding.

**Cautions:** because of the narrow margin of safety, regularly monitor serum level; thyroid function test should be regularly performed; advise patient on adequate sodium and water intake; treatment to be discontinued when signs of toxicity appear such as ataxia, coarse tremor, dysarthria, blurred vision; severe toxicity is characterized by hyperextension of limbs, convolution, circulatory failure and coma.

**Side-effects:** GI disturbances, nausea, diarrhoea, oedema, polyuria, polydipsia; hypothyroidism; hypokalaemia.

**Dose:** initially, 0.25-2g daily in divided doses; dose should be adjusted to give serum level 0.6-1.2mmol/litre in samples taken on empty stomach 12 hours after the last dose.

**Preparations**

Lithium carbonate tablets, 400 mg tab.
4. Central nervous system

4 C: Antidepressants

Older antidepressants such as the MAO inhibitors are presently of secondary role in the management of depression. Tricyclic and non-tricyclic compound are widely used with the non-tricyclic compounds showing less incidence of adverse effects. However, a new group of selective serotonin re-uptake inhibitors (SSRIs) are progressively used which show fewer antimuscarinic side-effects than tricyclic compounds and also less cardiotoxic effects in high doses. Some neuroleptics in small doses may also have antidepressant effects though they do not fit into the above classification (e.g. flupenthixol which is used for the treatment of psychosis but has an antidepressant effect when used in small doses).

Patients with depression should be frequently assessed, especially in the early weeks of treatment, to detect any suicidal tendencies. Limited quantities of antidepressant drugs should be dispensed and made available to patients as antidepressants are highly toxic in overdosage. Newer drugs tend to be safer than tricyclic compounds. Treatment cannot be assessed before two weeks and thereafter should be maintained for about 6 months after the depression has resolved. In cases of relapses, patients may be in need for longer-term treatment.

The dose of antidepressants should be adjusted to obtain optimum response; optimum doses vary between individuals. Premature or sudden withdrawal of treatment may lead to recurrence of symptoms and increase risk of suicide.

4 C.1: Tricyclic and related antidepressant drugs

These drugs are effectively used for the treatment of moderate to severe depression. Psychomotor and physiological changes associated with depression are also affected; sleep normalization is the first benefit to be noticed. In most patients, due to the long half-life of tricyclic antidepressants, a single daily dose is sufficient, usually at night.

Tricyclic and related antidepressants can roughly be divided into sedative and less sedative. Agitated and anxious patients can be treated with sedative antidepressants such as, amitriptyline, maprotiline and clomipramine. Apathetic and withdrawn patients will benefit more from the less sedating antidepressants. The choice of antidepressant is governed by patient response and clinical assessment.

4 C.1.1: Tricyclic antidepressants

Amitriptyline hydrochloride

Indications: depression when sedative effect is particularly required; nocturnal enuresis in children.
Contra-indications: recent myocardial infarction, severe liver disease; arrhythmia.
Cautions: cardiac disease, epilepsy, pregnancy, breast feeding, thyroid dysfunction, urinary retention, angle closure glaucoma.
Side-effects: sedation, dry mouth, constipation, blurred vision, cardiovascular side-effects, behavioural changes, interference with sexual functions, weight gain and increased appetite.
Dose: depression, 75 mg daily in divided doses (reduce in elderly and young adult, 30-75 mg) or as a single dose at bed time. Increase gradually, if necessary, to maximum of 150 mg daily. Nocturnal enuresis, child 7-10 years 10-20 mg, 11-16 years 25-50 mg at night, for 3 months (gradual withdrawal).

Preparations
Amitriptyline HCl tablets, 25 mg tab.

Clomipramine hydrochloride
Indications: depression; obsessive-compulsive disorders.
Contra-indications, cautions and side-effects: see under amitriptyline
Dose: depression, 10 mg daily, increase as necessary to 30-150 mg daily in divided doses or as a single daily dose at bedtime. Reduce dose in elderly. Obsessive compulsive disorders, 25 mg daily, increase over 2 weeks to 100-150 mg daily.

Preparations
Clomipramine HCl tablets, 10 mg tab.
Clomipramine HCl tablets, 25 mg tab.

Imipramine Hydrochloride
Indications: depression when less sedative effects than amitriptyline are required; nocturnal enuresis in children.
Contra-indications, cautions and side-effects: see under amitriptyline but less sedation.
Dose: depression, initially up to 75 mg daily in divided doses increased gradually when necessary to 150-200 mg, reduced dose in elderly Nocturnal enuresis in children, 7 years 25 mg, 8-11 years 25-50 mg, over 11 years 50-75 mg at bedtime for three months, (gradual withdrawal).

Preparations
Imipramine HCl tablets, 25 mg tab.

4 C.1.2: Related antidepressants

Maprotiline hydrochloride
Indications: depression, particularly when sedative effect is required
Contra-indications, cautions and side-effects: see under amitriptyline; antimuscarinics effects less frequent; skin rashes are common; risk of convulsions with higher dosage.
4. Central nervous system

**Dose**: initially 25-75 mg daily in divided doses or as a single dose at bedtime, increase gradually as necessary to maximum of 150 mg daily.

**Preparations**
Maprotiline HCl tablets, 25 mg tab.
Maprotiline HCl tablets, 50 mg tab.

### 4 C.2: Selective serotonin re-uptake inhibitors (SSRIs)

SSRIs are found effective in depression with less antimuscarinic, sedative and cardiovascular effects than tricyclic compounds. They are of particular advantage in obsessive-compulsive disorders. Side-effects of their own such as anorexia and weight loss, abdominal pain, dyspepsia, constipation, diarrhoea, vomiting are also reported. Other side-effects include, nervousness, headache, anxiety, insomnia, tremor, sexual dysfunction, sweating and movement disorders. SSRIs are contraindicated in epilepsy and in a patient entering a manic phase.

**Citalopram (Restricted)**

**Indications**: depression, panic disorder.

**Contra-indications**: see notes above

**Cautions**: concurrent electro-convulsive therapy, history of mania, history of bleeding disorders, hepatic and renal impairment, pregnancy and breast feeding.

**Dose**: initially 20 mg daily, increase gradually when response after 2 months; review treatment at least every 3 months, maximum dose to be given in divided doses; maximum 120 mg per day.

**Side-effects**: see notes above, palpitation, tachycardia, postural hypotension, coughing, amnesia, migraine.

**Dose**: depression, 20 mg daily as a single dose, increase as necessary, maximum 60 mg daily.

Panic disorder, initially 10 mg daily gradually increased to 20 mg daily.

**Preparations**
Citalopram tablets, 20 mg tab.

**Fluoxetine hydrochloride (Restricted)**

**Indications**: depression, bulimia nervosa, obsessive-compulsive disorder.

**Contra-indications**: see notes above

**Cautions**: see notes above

**Side-effects**: see notes above; hypersensitivity reactions; insomnia, asthenia, tremor, headache, lupus-like syndrome, abnormal bleeding.

**Dose**: depression, 20 mg daily.

Bulimia nervosa, 60 mg daily.

Obsessive-compulsive disorder, initially 20 mg daily.

**Preparations**
Fluoxetine HCl capsules, 20 mg cap.

**Paroxetine (Restricted)**

**Indications**: depression, obsessive-compulsive disorder, social phobia, panic disorder.

**Contra-indications**: see notes above

**Cautions**: see notes above
**Side-effects:** see notes above; extrapyramidal side-effects have been reported; postural hypotension.

**Dose:** depression, 20 mg daily at morning, increase gradually when necessary to maximum of 50 mg daily.

Compulsive obsessive disorder, initially 20 mg at morning, increase gradually to a maximum of 60 mg daily.

Social phobia, 20 mg in the morning, increase gradually if response is not adequate after 2 weeks.

**Preparations**

Paroxetine tablets, 20 mg tab.

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**4 C. 3: Other antidepressant drugs**

**Duloxetine (Restricted)**

**Indications:** Major depressive disorder. Generalised anxiety disorder. Diabetic neuropathy. Moderate to severe stress urinary incontinence

**Cautions:** Bleeding disorders; cardiac disease; elderly; history of mania; history of seizures; hypertension (avoid if uncontrolled); raised intra-ocular pressure; susceptibility to angle-closure glaucoma.

**Side-effects:** Abdominal pain; abnormal dreams; anorexia; anxiety; constipation; decreased appetite; diarrhoea; dizziness; drowsiness; dry mouth; dyspepsia; fatigue; flatulence; headache; hot flush; insomnia; nausea; nervousness; palpitation; paraesthesia; pruritus; sexual dysfunction; sweating; tremor; visual disturbances; vomiting; weakness; weight changes; Bruxism; cold extremities; dysphagia; gastritis; halitosis; hepatitis; hypertension; hypothyroidism; impaired attention; impaired temperature regulation; movement disorders; muscle twitching; musculoskeletal pain; photosensitivity; postural hypotension; raised cholesterol; stomatitis; syncope; tachycardia; taste disturbance; thirst; urinary disorders; vertigo.

**Dose:** Major depressive disorder 60 mg once daily.

Generalised anxiety disorder. Initially 30 mg once daily, increased if necessary to 60 mg once daily; maximum 120 mg per day.

Diabetic neuropathy 60 mg once daily, discontinue if inadequate response after 2 months; review treatment at least every 3 months, maximum dose to be given in divided doses; maximum 120 mg per day.

Moderate to severe stress urinary incontinence 40 mg twice daily, patient should be assessed for benefit and tolerability after 2–4 weeks, alternatively initially 20 mg twice daily for 2 weeks, this can minimise side-effects, then increased to 40 mg twice daily, the patient should be assessed for benefit and tolerability after 2–4 weeks.

**Preparations**

Duloxetine tablets, 30 mg tabs

Duloxetine tablets, 120 mg tabs
4. Central nervous system

Flupentixol dihydrochloride (Flupenthixol dihydrochloride)

Indications: short term management of depression; psychosis (see section 4. B.1.3)

Contra-indications and cautions: cardiovascular disease, senile confusional state, parkinsonian disorders.

Side-effects: restlessness, insomnia, extrapyramidal effects.

Dose: initially 1 mg in the morning increased after 7 days to 2 mg when necessary, discontinue if no adequate response after one week of maximum dose (3 mg daily).

Preparations
Flupentixol dihydrochloride tablets, 1 mg tab.
Flupentixol dihydrochloride tablets, 3 mg tab.

4 D: Analgesics

4 D.1: Non-opioid analgesics

Mild to moderate pain can be treated with non-opioid analgesics such as aspirin or paracetamol. Headache, mild musculoskeletal pain or dysmenorrhoea can be managed with paracetamol or aspirin. Aspirin is contraindicated in children less than 12 years of age and in breast-feeding unless specifically indicated because of the possibility of developing Rye’s syndrome. It is also contraindicated in patients with peptic ulceration and in patients with a history of hypersensitivity to aspirin or other NSAIDs.

Paracetamol

Indications: pyrexia, mild to moderate pain.

Contra-indications: hepatic and renal impairment, alcohol dependence.

Cautions: high doses may cause hepatic damage, which might not be apparent for 4-6 days.

Acetyl salicylic acid (Aspirin)

Indications: pyrexia, mild to moderate pain, antplatelet (sec. 2.K.) and rheumatoid arthritis (sec. 10)

Contra-indications: children under 12 years and in breast feeding, GI ulceration, haemophilia.

Cautions: asthma, allergic disease, pregnancy.

Side-effects: generally highly tolerated, but high incidence of GI irritation. Asthma and skin rash in hypersensitive patients.

Dose: orally 300-900 mg every 4-6 hours when necessary. Maximum 4g daily.

By intravenous or intramuscular injection, 500-1000 mg repeated every 4-6 hours when needed.

Preparations
Aspirin tablets, 75-100 mg tab.
Aspirin tablets, 300 mg soluble tab.
Side-effects: rare when used for short period within recommended dosage ranges; rash and blood disorder.

Dose: adult, 0.75-1g 3-4 times daily, maximum 4 g daily in divided doses.
Child, 2 months old 60 mg for post immunization fever.
Under 3 months 10 mg / kg, 3-4 times daily.
3-12 months 60-120 mg, 3-4 times daily.
1-5 years 120-250 mg, 3-4 times daily.
6-12 years 250-500 mg, 3-4 times daily.

Preparations
Paracetamol tablets, 500 mg tab.
Paracetamol syrup, 120 mg/5 mL syrup, 50 - 75 mL/ bottle
Paracetamol paediatric drop, 100 mg/mL 15 mL drop
Paracetamol suppositories, 125-150 mg/supp.(for infants)
Paracetamol suppositories, 200-300 mg /supp (for children)
Paracetamol injection, 10 mg/mL, 100 mL vial (Restricted) Caution to be used in children under 11 years old, consult product literature for further information

4 D.2: Opioid analgesics

Opioid analgesics are used for moderate to severe pain that is mainly of visceral origin. The main concern over the use of opioids is the tendency of developing tolerance and dependence over repeated use. However this is not a deterrent from using them during terminal illnesses. Opioids dispensing is strictly controlled and restricted. The control measures require the writing of a special prescription by authorized doctors. All responsible staff must maintain proper records. Opioids, in addition to analgesia and to some extent euphoria, may induce sedation, constipation respiratory depression; cough suppression, urinary retention, nausea and vomiting. They produce these effects with some qualitative and quantitative variations. Opioids are contraindicated in patients with asthma (avoid during attack), hypotension, head injury, intestinal obstruction, in patients with a history of drug abuse, raised intracranial pressure, during pregnancy or breast-feeding. Morphine remains the most commonly used drug of this group for severe pain and it is the standard against which other opioid analgesics are compared. Morphine is the drug of choice for oral therapy of severe pain in palliative care. Phenothiazines in addition to their antiemetic effect, can be used concomitantly with morphine to improve the analgesic, sedative and euphoric effects. Pethidine produces rapid but short lasting and less potent analgesic ef-
4. Central nervous system

Effects than morphine. It has been applied during labour and pre-medication due to its weaker respiratory depressant effect. Alfentanil and other related compounds are used by injection for intra-operative analgesia. Methadone has a longer duration than morphine and has the advantage of being orally administered and less sedative. Tramadol has fewer of the opioid side-effects and is thought to act by two different mechanisms; as an opioid and as enhancer of the serotonergic and adrenergic pathways.

Morphine (Narcotic)

Indications: moderate to severe pain of visceral origin; euphoria in terminal illnesses; pre-medication. Contra-indications: see notes above Cautions: hepatic and renal impairment, reduce dose in elderly, convulsive disorders, urinary retention. Side-effects: nausea and vomiting (keeping patient at rest reduce side-effects) constipation, large doses produce respiratory depression, urinary retention, biliary spasm, headache, sweating, some patients may experience dysphoria and mood changes. Dose: Acute pain, intramuscular or subcutaneous injection 10-15 mg every 4-6 hours if necessary. Child, 1-5 years 2.5-5 mg, 6-12 years 5-10 mg. Slow intravenous injection, quarter to half corresponding intramuscular dose. Premedication, by intramuscular or subcutaneous injection, up to 10 mg 60-90 minutes before operation. Post-operative pain by intramuscular or subcutaneous injection, 10 mg every 2-4 hours. Chronic pain, by mouth or subcutaneous or intramuscular injection 5-20 mg regularly every 4 hours, dose may be increased according to need.

Preparations
Morphine sulphate injection, 10 mg/mL ampoule Morphine sulphate preservative free injection, 10 mg/mL ampoule Morphine sulphate oral solution, 10 mg/5 mL vial or 100 mg/5 mL vial Morphine sulphate slow release tablets, 10 mg S.R. tab. Morphine sulphate slow release tablets, 30 mg S.R. tab. Morphine sulphate slow release tablets, 40 mg S.R. tab. Morphine sulphate slow release tablets, 60 mg S.R. tab. Morphine sulphate regular release tablets, 10 mg tab. Morphine sulphate regular release tablets, 30 mg tab. Morphine sulphate regular release tablets, 60 mg tab.

Codeine Phosphate (Controlled)

Indications: mild to moderate pain. Contra-indications, cautions and side-effects: see under morphine and notes above
4. Central nervous system

**Dose:** 30-60 mg every 4-6 hours when necessary max, 240 mg daily in divided doses. Child, 1-12 years, 3 mg / kg daily in divided doses.

Preparations
- Codeine phosphate tablets, 30 mg tab.

**Fentanyl (Narcotic)**

**Indications:** adjunct analgesic in anaesthesia; severe pain in cancer cases.

**Contra-indications, cautions and side-effects:** see under morphine and notes above; local reactions such as rash, and itching have been reported; rapid injection may produce muscular stiffness, bradycardia. Monitor patients using patches for increased side-effects if fever present (increased absorption possible).

**Dose:** by intravenous injection with spontaneous respiration, 50-200 micrograms then 50 micrograms as required. Child, 3-5 microgram/ kg and then 1 microgram/ kg as required.

With assisted ventilation larger doses are used, 300-3500 micrograms (0.3-3.5 mg) then 100-200 micrograms as required. Child, 15 micrograms/ kg, then 1-3 micrograms/ kg as required.

Preparations
- Fentanyl citrate injection, 50 microgram/mL, 2 mL ampoule
- Fentanyl citrate injection, 50 microgram/mL, 10 mL ampoule

Fentanyl transdermal patches, 12.5 micrograms/hour for 72 hours
Fentanyl transdermal patches, 25 micrograms/hour for 72 hours
Fentanyl transdermal patches, 50 micrograms/hour for 72 hours

**Hydromorphone hydrochloride**

**Indications:** severe pain in cancer.

**Contra-indications:** see notes above; also acute abdomen

**Cautions:** see under morphine; also pancreatitis; toxic psychosis

**Side-effects:** see under morphine; also paralytic ileus, seizures, asthenia, agitation, and myoclonus

**Dose:** orally, 1.3 mg every 4 hours, increased if necessary according to severity of pain; child under 12 years not recommended.

Preparations
- Hydromorphone hydrochloride capsules, 1.3 mg cap.
- Hydromorphone hydrochloride capsules, 2.6 mg cap.

**Pethidine hydrochloride (Narcotic)**

**Indications:** moderate to severe pain, obstetric analgesia, peri-operative analgesia.

**Contra-indications:** see under morphine and notes above

**Cautions:** see under morphine and notes above; avoid with enzyme inhibitors.
4. Central nervous system

**Side-effects:** see under morphine and notes above; convulsions reported with over-dosage.
**Dose:** acute pain, intramuscular injection, 50-100 mg (1-1.5 mg / kg) repeated after 4 hours. Child 0.5-2 mg / kg.
Slow intravenous injection 25-50 mg (0.5-1 mg / kg) repeated after 4 hours.
Obstetric analgesia, by intramuscular injection 50-100 mg (1-1.5 mg / kg), repeated after 1-3 hours.
Premedication, by intramuscular injection 50-100 mg (1-1.5 mg / kg) one hour before operation.

**Preparations**
Pethidine HCl injection, 50 mg/mL ampoule
Pethidine HCl injection, 50 mg/mL 2 mL ampoule
Remifentanil (Narcotic)

**Indications:** supplementation of general anaesthesia during induction and maintenance.
**Contra-indications cautions and side-effects:** see under morphine and notes above; bradycardia.
**Dose:** induction, intravenous infusion of 0.5-1 microgram/ kg/minute.
Maintenance in ventilated patient, intravenous infusion 0.05-2 microgram/ kg/minute.
Maintenance in spontaneous ventilation, 40nanograms/ kg/minute.

**Preparations**
Remifentanil injection, 1 mg vial
Remifentanil injection, 5 mg vial

**Tramadol hydrochloride (Controlled)**

**Indications:** moderate to severe pain.
**Contra-indications cautions and side-effects:** see under morphine and notes above; also hypertension may occur, hallucination and convulsions, not useful for patient as substitute for opioid dependence.
**Dose:** oral, 50-100 mg, every 4-6 hours, maximum 400 mg daily. Not recommended in children.
By intramuscular or intravenous injections, or intravenous infusion 50-100 mg every 4-6 hours.

**Preparations**
Tramadol HCl capsules, 50 mg cap.
Tramadol HCl injection, 50 mg/mL, 2 mL ampoule
Tramadol drop, 100 mg/mL solution, 10 mL/bottle (C.D.L)

4 D.3: Anti-migraine drugs

Migraine headache is a common disorder that is characterized by throbbing sensation and association with nausea and vomiting, photophobia, and a positive family history. Acute attack may well respond to simple measures such as bed rest and simple analgesics such as aspirin and paracetamol.
Metoclopramide is of particular benefit when acute attack is associated with gastric stasis, as it will stimulate the absorption of analgesics and exerts an antiemetic effect.
Prophylactic therapy is not necessary in patients having one attack a month or less. If attacks occur more frequently, a prophylactic measure needs to be taken. A wide variety of drugs have been used including antidepressants, antihistamines or beta-blockers. A selective 5HT1 agonist such as sumatriptan has been found considerably effective in the management of acute attacks.

**Flunarizine hydrochloride (Restricted)**

**Indications:** prophylaxis of migraine.

**Contra-indications:** hypersensitivity to flunarizine or cinnarizine.

**Side-effects:** sedation and drowsiness.

**Dose:** doses of 10 mg daily as a single dose and doses up to 20 mg 3 times daily have been used.

**Preparations**

Flunarizine hydrochloride capsules, 5 mg cap.

**Naratriptan**

**Indications:** treatment of acute attack of migraine.

**Contra-indications:** peripheral vascular diseases, ischaemic heart diseases, previous history of stroke, uncontrolled hypertension.

**Cautions:** hepatic and renal impairment, pregnancy and breast-feeding, sensitivity to sulphonamides.

**Driving:** May cause drowsiness and affect performance of skilled tasks

**Side-effects:** vision changes, tingling sensations, tiredness or weakness, nausea, vomiting, dizziness.

**Dose:** by mouth, 2.5 mg as soon as possible after onset. Can be repeated after four hours. However, if there is no benefit from the first dose a second dose should not be given. Maximum dose 5 mg in 24 hours.

**Preparations**

Naratriptan tablets, 2.5 mg tab.

**Rizatriptan**

**Indication:** treatment of acute attack of migraine.

**Contra-indications:** ischemic heart disease, uncontrolled hypertension, Concurrent administration of MAO inhibitors, another 5-HT1 agonist, or an ergotamine-containing medication.

**Cautions:** renal impairment, hepatic impairment, elderly and children, patients taking propranolol, pregnancy.

**Side-effects:** palpitation, diarrhoea and vomiting, paraesthesia, decreased mental acuity, euphoria and tremor, dyspnea, hot flushes.

**Driving:** May cause drowsiness and affect performance of skilled tasks.

**Dose:** single dose of 10 mg tablet, can be repeated after at least 2 hours; no more than 20 mg in 24-hour period.
4. Central nervous system

Preparations
Rizatriptan tablets, 10 mg tab.
Similar drugs:
Almotriptan tablets, 12.5 mg tab.
Frovatriptan tablets, 2.5 mg tab.

Sumatriptan succinate (Restricted)
Indications: treatment of acute attack of migraine.
Contra-indications: ischaemic heart disease, uncontrolled hypertension.
Cautions: should not be used for prophylaxis; hepatic impairment; pregnancy and breast-feeding; not to be used with other migraine therapy.
Side-effects: sensation of tingling, heat, and heaviness, tightness that may be due to coronary vasoconstriction or anaphylaxis.
Dose: 50 mg up to 100 mg immediately after an attack, maximum daily dose is 300 mg.

Preparations
Sumatriptan succinate tablets, 100 mg tab.

Zolmitriptan
Indications: treatment of acute attack of migraine.
Contra-indications: peripheral vascular diseases, ischaemic heart diseases, previous history of stroke, uncontrolled hypertension, Wolff-Parkinson-White syndrome or arrhythmias associated with accessory cardiac conduction pathways.

Cautions: hepatic and renal impairment, pregnancy and breast-feeding, should not be taken concurrently with other therapies for acute migraine.
Driving: May cause drowsiness and affect performance of skilled tasks.
Side-effects: see under Naratriptan; dry mouth, drowsiness.
Dose: orally, 2.5 mg as soon as possible after onset. If migraine persists, can be repeated after at least two hours. Maximum dose 10 mg in 24 hours.

Preparations
Zolmitriptan tablets, 2.5 mg tab.

4 D.4: Other analgesics

Clonidine
Note: This drug is only used in Oman for its analgesic property
Indications: adjunct in pain management, postoperative analgesia, essential hypertension.
Contraindication: anticoagulant therapy, bleeding diathesis, epidural administration above the C4 dermatome, injection site infection.
Cautions: cardiovascular disease, depressive illness, concurrent antihypertensive therapy, pain management for obstetrical, post-partum, or perioperative (risk of haemodynamic instability).
Side-effects: hypotension, dry mouth, sedation, dizziness, nausea, nocturnal restlessness, bradycardia, rashes.
4. Central nervous system

4 E: Antiepileptics

Epilepsy is a disorder of the electrical activity in the brain (cerebral dysrhythmia) characterized clinically by recurrent transient fits or disturbance of consciousness or abnormal motor activity or autonomic functioning. The aim of therapy is to control fits without producing a serious impairment so that the patient can lead a normal life with minimal restrictions. Therapy usually starts with the minimal dose and gradually increases until fits are controlled or side-effects dominate. Low frequency of administration should be maintained to ensure patient compliance. Most antiepileptics are given twice daily except for some long acting drugs such as Phenobarbital or phenytoin that might be given once daily. Treatment should be initiated with a single drug. Drug combinations should not be tried unless alternating with single drugs is no more effective in spite of administering maximum doses. Drug plasma concentration may need to be monitored to avoid fluctuation in response. Most antiepileptics have a narrow therapeutic index. Interactions with other drugs are a main cause of fluctuation in response.

Once treatment has started and control of fits is achieved, it should be maintained for at least 2 years. Abrupt withdrawal may aggravate the condition and precipitate status epilepticus. There is an increasing risk of teratogenicity associated with the use of antiepileptics during pregnancy. Women on antiepileptics who wish to be pregnant should be advised on the possible consequences. Adequate folate administration before and during pregnancy may lower the possibility of neural tube defects. Withdrawal of the treatment during pregnancy involves greater danger to the mother and the foetus. Choice of therapy depends on the type of epilepsy. Generalized tonic-clonic seizure is better treated with carbamazepine, phenytoin and sodium valproate. Phenobarbital is an alternative but is more sedating. For absence seizure (petit mal) ethosuximide and sodium valproate are the drugs of choice. Myoclonic seizures are well treated with sodium valproate. Clonazepam, ethosuximide or lamotrigine may also be used.

4 E.1: Control of grand mal and partial seizures
4. Central nervous system

Carbamazepine

**Indications:** partial and generalized tonic-clonic seizures; trigeminal neuralgia.

**Contra-indications:** AV conduction abnormality; bone marrow depression.

**Cautions:** hepatic or renal impairment; blood disorders; pregnancy and breast feeding.

**Side-effects:** nausea and vomiting, dizziness, drowsiness, ataxia, blood disorders, skin rashes.

**Dose:** oral, 100-200 mg 1-2 times daily, increase gradually to maintenance dose of 0.8-1.2g daily in divided doses. Child up to 1 year 100-200 mg, 1-5 years 200-400 mg, 6-10 year 400-600 mg, 10-15 year 600 mg-1g, daily in divided doses.

**Preparations**
- Carbamazepine tablets, 100 mg tab.
- Carbamazepine tablets, 200 mg tab.
- Carbamazepine tablets, 200 mg controlled release tab.
- Carbamazepine syrup, 100 mg/5 mL (2%) syrup; 100 mL/bottle

Clonazepam (Controlled/restricted)

**Indications:** adjunct in all forms of epilepsy.

**Contra-indications:** severe liver disease, respiratory insufficiency.

**Cautions:** avoid abrupt withdrawal, reduce dose in elderly, renal and hepatic impairment, as benzodiazepine derivatives see under diazepam.

**Side-effects:** drowsiness, fatigue, muscle hypotonia, and hypersalivation in infants.

**Dose:** 1 mg initially at night for 4 nights, increased gradually to 4-8 mg daily in divided doses if necessary. Child up to 1-year 250 microgram increased gradually to 0.5-1 mg, 1-5 years 250 microgram increased gradually to 1-3 mg, 6-12 years 0.5 mg increased gradually to 3-6 mg, daily in divided doses.

**Preparations**
- Clonazepam tablets, 0.5 mg tab.
- Clonazepam tablets, 2 mg tab.
- Clonazepam oral drops, 2.5 mg/mL; 10 ml drops

Ethosuximide (Restricted)

**Indications:** Absence seizure.

**Cautions:** hepatic and renal impairment; regular blood counts for possible blood disorders.

**Side-effects:** nausea, abdominal pain, headache, fatigue, ataxia, hiccup, psychosis, and depression.

**Dose:** initially 500 mg daily increased gradually to patient’s needs, maximum 2 g daily. Child up to 6 year 250 mg daily, over 6 year 500 mg increased slowly to a maximum 1 g daily.

**Preparations**
- Ethosuximide capsules, 250 mg cap.
- Ethosuximide syrup 250 mg / 5 ml

Gabapentin (Restricted)
4. Central nervous system

**Indications:** monotherapy and adjunctive treatment of partial seizures with or without secondary generalisation, peripheral neuropathic pain, trigeminal neuralgia.

**Cautions:** avoid abrupt withdrawal, elderly; renal impairment, diabetes mellitus, false positive readings with some urinary protein tests, pregnancy, breast-feeding.

**Side-effects:** diarrhoea, dry mouth, dyspepsia, nausea, vomiting, constipation, abdominal pain, flatulence, appetite changes, gingivitis, weight gain; hypertension, vasodilation, oedema; dyspnoea, cough, rhinitis; confusion, depression, hostility, sleep disturbances, headache, dizziness, anxiety, amnesia, ataxia, dysarthria, nystagmus, tremor, asthenia, paraesthesia, hyperkinesia; influenza-like symptoms; impotence, urinary incontinence; leucopenia; myalgia, arthralgia; diplopia, amblyopia; rash, purpura, pruritus, acne, pancreatitis, hepatitis, jaundice, palpitation, hallucinations, movement disorders, thrombocytopenia, blood-glucose fluctuations in patients with diabetes, tinnitus, acute renal failure, Stevens-Johnson syndrome, and alopecia.

**Dose:** epilepsy and neuropathic pain, orally, 300 mg on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times daily on day 3 or initially 300 mg 3 times daily on day 1; then increased according to response in steps of 300 mg daily (in 3 divided doses) every 2–3 days; usual dose 900 to 3600 mg/day in 3 divided doses.

**Preparations**
Gabapentin tablets, 300 mg tab.

**Levetiracetam (Restricted)**

**Indication:** monotherapy treatment mainly for partial seizures with or without secondary generalisation or as an adjuvant. **Cautions:** renal impairment and hepatic impairment; pregnancy; breastfeeding. Avoid sudden withdrawal.

**Side-effects:** dizziness, ataxia, convulsion, depression, weight changes, insomnia, tremor, visual disturbances, dyspepsia, nausea.

**Dose:** for monotherapy, initially 250 mg twice daily increased according to response; maximum 1.5 g twice daily. For adjuvant therapy 500 mg twice daily up to 1.5 g at same frequency. Child and adolescent (4-18 years), 10 mg/kg twice daily up to 30 mg/kg at same frequency.

**Preparations**
Levetiracetam tablets, 250 mg tab.
Levetiracetam tablets, 500 mg tab.
Levetiracetam tablets, 1 g tab.
Levetiracetam syrup, 100 mg/mL, 300 mL bottle

**Phenobarbital (Phenobarbitone) (Controlled/restricted)**

**Indications:** all forms of epilepsy except absence seizure; status epilepticus.
4. Central nervous system

**Cautions:** elderly, children, impaired hepatic or renal function, respiratory depression, pregnancy and breast feeding, potentiate other CNS depressants.

**Side-effects:** sedation, lethargy mental depression, ataxia, and allergic skin reactions.

**Dose:** oral, 60-180 mg at night. Child 5-8 mg / kg daily.

Intramuscular injection, 200 mg repeated after 6 hours if necessary.

Status epilepticus, by intravenous injection (dilute injection 1 in 10 mL of water for injection) 10 mg / kg at a rate not exceeding 100 mg /minute, maximum 1g.

**Preparations**
Phenobarbital tablets, 30 mg tab.
Phenobarbital elixir, 15 mg/5 mL elixir; 500 mL/bottle
Phenobarbital injection, 200 mg/mL, 1 mL ampoule

**Phenytoin**

**Indications:** all forms of epilepsy except absence seizure.

**Cautions:** hepatic impairment; pregnancy and breast feeding; avoid sudden withdrawal; blood count to be carried out regularly.

**Side-effects:** nausea and vomiting, mental confusion, headache, insomnia, and tremor occur commonly. Skin rash, coarse facies, acne and hirsutism, fever and hepatitis; epidermal necrolysis, lupus erythematosus, Stevens-Johnson syndrome, polyarteritis nodosa; gingival hypertrophy, and tenderness; rarely haematological disorders including megaloblastic anaemia which responds to folic acid therapy; plasma calcium concentration may be lowered leading to rickets and osteomalacia.

Intravenous (rapid) administration may lead to heart block and cardiac arrhythmias particularly in patients with cardiac disease and the elderly; it may also cause hypotension and CNS depression.

Sign of overdose include slurred speech, nystagmus, blurred vision and ataxia.

**Dose:** orally 150-300 mg daily, gradually increased to 400 mg if necessary, as a single dose or 2 divided doses. Child 1 month-12 years, 1.5-2.5mg/kg twice daily adjusted to between 2.5-5mg / kg twice daily for maintenance.

Intravenous (see section 4 E.2)

**Preparations**
Phenytoin sodium capsule, 50 mg cap.
Phenytoin sodium capsule, 100 mg cap.
Phenytoin sodium suspension, 30 mg/5 mL susp.; 500 mL/bottle

**Sodium valproate**

**Indications:** all forms of epilepsy.

**Contra-indications:** active liver disease, porphyria.

**Cautions:** monitor liver function; renal impairment; check for bleeding tendencies.

**Side-effects:** nausea, gastric irritation, reversible hair loss; oedema;
inhibition of platelet aggregation; weight gain and increased appetite. **Dose:** orally, 600 mg daily in 2 divided doses after meal, increase at 3 days intervals by 200 mg to a maximum of 2.5g daily in divided doses if necessary, usual maintenance dose 1-2g daily.

Child under 20 kg, initially 20 mg / kg daily in divided doses. Child over 20kg, 400 mg daily in divided doses.

**Preparations**
Sodium valproate tablets, 200 mg tab.
Sodium valproate tablets, 500 mg tab. Sodium valproate syrup, 200 mg/5 mL syrup 100 – 150 mL /bottle
Sodium valproate injection, 400 mg vial

**Topiramate (Restricted)**

**Indications:** partial and generalized tonic-clonic seizures; adjunctive treatment of seizures in Lennox–Gastaut syndrome; prevention of migraine in adults.

**Contra-indications:** breast-feeding.

**Cautions:** history of psychiatric disorders, ensure adequate hydration (especially if history of nephrolithiasis and hypercalciuria), renal impairment and hepatic impairment.

**Side-effects:** headache, confusion, amnesia, impaired concentration, depression, nervousness, agitation, hallucinations, paraesthesia, dizziness, fatigue, speech disorder, reduced serum bicarbonate (Metabolic acidosis), nephrolithiasis, weight loss, leucopenia. Also, has been associated with acute myopia with secondary angle-closure glaucoma.

**Dose:** In epilepsy: if used alone, initially, 25 mg once daily at bedtime; then increase daily dose at intervals of at least a week by 25–50 mg. Maintenance, 50 mg twice daily. Maximum dose is 400 mg daily, child 6-16, initially 0.5-1 mg/kg daily. Maintenance, 3–6 mg/kg daily in 2 divided doses. Maximum 15mg/kg daily. In adjunctive treatment, initially, 25 mg once daily as a single dose at bedtime then increase gradually. Usual dose, 100–200 mg twice daily. Maximum, 800 mg daily. Child 2-16, initially, 1–3 mg/kg daily (up to 25) mg daily as a single dose at bedtime; increase daily dose at intervals of at least a week by 1–3 mg/kg. Maintenance, 5–9 mg/kg daily in 2 divided doses. Maximum, 15 mg/ kg daily. Migraine prophylaxis: Initially, 25 mg daily as a single dose at bedtime; then increase daily dose at intervals of at least a week by 25 mg, according to response. Maintenance, 25–50 mg twice daily.

**Preparations**
Topiramate tablets, 25 mg tab.
Topiramate tablets, 50 mg tab.
Topiramate tablets, 100 mg tab.
4. Central nervous system

Topiramate sprinkle capsules, 15 mg cap.

4 E.2: Drugs for status epilepticus

The drug of first choice in the treatment of status epilepticus is intravenous diazepam. The possibility of respiratory depression should be kept in mind and resuscitation facilities should be available. Absorption from intramuscular injection is too slow to cater for the emergency situation. If status epilepticus continues or returns in short period then other drugs are tried.

Phenytoin is given by slow intravenous injection to prevent recurrence.

Clomethiazole (Chlormethiazole) is given by intravenous infusion and because of its short half life, the rate of infusion can be monitored to meet the patient’s clinical condition.

Diazepam (Controlled/restricted)
Indications: status epilepticus, convulsion (see sec.4 A.2.1 for other indications)
Contra-indications, cautions and side-effects: see under diazepam; hypotension and apnoea may occur with intravenous administration.
Dose: intravenous injection, 10-20 mg at a rate of 5 mg / minute, repeated if necessary after 30-60 minutes.
Child 200-300 microgram / kg or 1 mg per year of age.

Preparations
Diazepam injection, 5 mg/mL, 2 mL ampoule

Phenytoin Injection (Restricted)
Indications: status epilepticus, seizure in neurosurgery (others see sec. 4E.1)
Contra-indications: heart block.
Cautions: hypotension, heart failure, resuscitation facilities should be available.
Side-effects: intravenous injection may cause cardiovascular and CNS depression.
Dose: intravenous infusion or slow injection, loading dose 10-15 mg / kg at a rate not greater than 50 mg / minute, followed by maintenance oral or intravenous dose of 100 mg every 6-8 hours.
Child, a loading dose of 15-20 mg / kg at a rate not greater than 1-3 mg / kg / minute.

Preparations
Phenytoin injection, 50 mg/mL, 5 mL ampoule

4 E.3: Adjunct therapy of epilepsy

Lamotrigine (Restricted)
Indications: monotherapy and adjunctive treatment of partial seizure and primary and secondary generalized tonic-clonic seizure.
Contra-indications: hepatic impairment.
Cautions: closely monitor for blood disorder, hepatic and renal
functions; skin rash, influenza like symptoms might call for early withdrawal. Avoid abrupt withdrawal; withdraw gradually over 1-2 weeks. **Side-effects:** rash, fatigue, dizziness, headache, Steven’s Johnson Syndrome, toxic epidermal necrolysis, hypersensitivity reactions. **Dose:** monotherapy, 25-50 mg 4 times daily, increase as necessary to maximum 500 mg daily. Adjunct therapy with other antiepileptics, adjust dose according to response.

**Preparations**
- Lamotrigine tablets, 5 mg tab.
- Lamotrigine tablets, 25 mg tab.
- Lamotrigine tablets, 50 mg tab.

**Vigabatrin (Restricted)**

**Indications:** epilepsy not satisfactorily controlled by other antiepileptics, monotherapy for the management of infantile spasms.

**Contra-indications:** pregnancy, visual field defects.

**Cautions:** renal impairment; elderly; close monitoring of the neurological functions; history of psychosis and behavioural problems.

**Side-effects:** drowsiness, dizziness, behaviour changes, anxiety, weight gain.

**Dose:** 2-3 g daily in divided doses. Child 1-2 g daily in divided doses.

**Preparations**
- Vigabatrin tablets, 500 mg tab.

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**4 E.4: Febrile Convulsions**

Brief febrile convulsions need only simple treatment such as antipyretics e.g. paracetamol. Prolonged febrile convulsions (15 minutes or more), recurrent febrile convulsions or those occurring in a child at risk need more active treatment as there is a possibility of brain damage. Diazepam is the drug of choice given either by slow intravenous injection or preferably, rectally in solution.

The rectal route is the preferred route in febrile convulsions using the rectal solution. Suppositories are not suitable for febrile convulsions as absorption is too slow. For preparations see under Diazepam Sec 4 A.2.1

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**4 F: Drugs used in Parkinsonism and related disorders**

Parkinson’s disease is a slowly progressing, degenerative disorder of the nervous system. It has several distinguished characteristics; tremor at rest, sluggish initiation of movement and muscle rigidity. The basal ganglia nerve cells help smooth movement and coordinate changes in posture through a balance between the cholinergic and dopaminergic systems. Degeneration of nerve cells in the basal ganglia will lead to a reduction in dopamine, the dopaminergic neuro-
transmitter. There is no clear reason for this degeneration. Parkinson’s disease can be of known cause as in case of late complications of viral encephalitis, or drug induced as in the case with antipsychotic drugs. Treatment of Parkinson’s disease centred on replenishing the depleted dopamine stores in the basal ganglia. Inhibiting the cholinergic activities can also help in treatment by using centrally acting antimuscarinic drugs.

Peripheral metabolism of levodopa will reduce the centrally available drug. It is therefore recommended that peripheral decarboxylase inhibitors be administered with levodopa. This, in addition to inhibiting peripheral metabolism, will lower the peripheral effects such as cardiovascular side-effects. Levodopa may some times lose its effectiveness after several months of therapy and the patient experiences marked change from mobility to immobility (known as on-off effect). These fluctuating disabilities may last from minutes to hours. The cause of this fluctuation could be attributed to plasma level variation.

### Levodopa + Carbidopa (Co-Careldopa)

**Indications:** parkinsonism (but not drug-induced).

**Contra-indications:** closed angle glaucoma.

**Cautions:** peptic ulcer, cardiovascular diseases, diabetes mellitus, open angle glaucoma, avoid abrupt withdrawal.

**Side-effects:** anorexia, nausea and vomiting; insomnia, agitation, postural hypotension reddish discoloration of urine and other body fluids, psychotic disorders.

**Dose:** levodopa 100 mg + carbidopa 25 mg, one tablet thrice daily increased according to response. Maximum 8 tablets daily in divided doses.

Levodopa 250 mg + carbidopa 25 mg one tablet twice daily increased according to response. Maintenance dose 3-6 tablets in divided doses.

**Preparations**

- Levodopa + carbidopa tablets, 100 + 25 mg tab.
- Levodopa + carbidopa tablets, 250 + 25 mg tab.

### Carbidopa with Entacapone and Levodopa (Restricted)

**Indications:** Parkinson's disease

**Contra-indications:** History of neuroleptic malignant syndrome;
history of non-traumatic rhabdomyolysis, phaeochromocytoma; also see co-careldopa.

**Cautions:** Excessive daytime sleepiness and sudden onset of sleep can occur with carbidopa with entacapone and levodopa. ischemic heart disease; also see co-careldopa.

**Side-effects:** Abdominal pain; abnormal dream; confusion; constipation; diarrhoea; dizziness; dry mouth; dyskinesia; dystonia; fatigue; hallucinations; insomnia; ischemic heart disease; nausea, sweating, reddish-brown urine, vomiting; myocardial infarction; also see co-careldopa.

**Dose:** See product literature.

**Preparations**
- Carbidopa with Entacapone and Levodopa tablet 100/25/200 mg tabs
- Carbidopa with Entacapone and Levodopa tablet 150/37.5/200 mg tabs

**Amantadine hydrochloride**

**Indications:** Parkinson’s disease, antiviral.

**Contraindication:** epilepsy, history of gastric ulceration, pregnancy, breast-feeding.

**Cautions:** hepatic impairment; renal impairment, congestive heart disease, confused or hallucinatory states, elderly, avoid abrupt withdrawal in Parkinson’s disease.

**Driving:** May cause drowsiness and affect performance of skilled tasks

**Side-effects:** anorexia, nausea, nervousness, inability to concentrate, insomnia, dizziness, convulsions, hallucinations or feelings of detachment, blurred vision, gastrointestinal disturbances, livedo reticularis, peripheral oedema, leucopenia, rashes.

**Dose:** Parkinson’s disease, 100 mg daily increased after one week to 100 mg twice daily, max. 400 mg daily; elderly 65 years and over, 100 mg daily adjusted according to response.

**Preparations**
- Amantadine hydrochloride capsules, 100 mg cap.

**Selegiline hydrochloride**

**Indications:** Parkinson’s disease, used alone or as adjunct to levodopa with dopa-decarboxylase inhibitor.

**Contraindications:** pregnancy, breast-feeding.

**Cautions:** avoid abrupt withdrawal; gastric and duodenal ulceration (avoid in active ulceration), uncontrolled hypertension, arrhythmias, angina, psychosis, side-effects of levodopa may be increased, concurrent levodopa dosage can be reduced by 10–20%.

**Side-effects:** nausea, constipation, diarrhoea, dry mouth; postural hypotension; dyskinesia, vertigo,
sleeping disorders, confusion, hallucinations; arthralgia, myalgia; mouth ulcers with oral lyophilisate; arrhythmias, agitation, headache, micturition difficulties, skin reactions; chest pain. **Dose:** 10 mg in the morning, or 5 mg at breakfast and midday, elderly; start treatment with a dose of 2.5 mg daily.

**Preparations**
Selegiline hydrochloride tablets, 5 mg tab.

### 4 F.2: Antimuscarinic drugs

Antimuscarinic drugs are less effective than levodopa in the treatment of parkinsonism although they may supplement its effects. They are more effective in reducing rigidity and tremor but do not affect hypokinesia. Mild cases of Parkinsonism can be managed with antimuscarinic drugs alone and in severe cases can be combined with levodopa or other drugs. They have a value in post-encephalitic parkinsonism.

Antimuscarinic drugs also reduce the symptoms of drug-induced Parkinsonism, but there is no justification on using them with antipsychotics unless parkinsonian side-effects appear. There is no place for antimuscarinic drugs in the therapy of tardive dyskinesia, they may even exacerbate the condition.

**Procyclidine hydrochloride**

**Indications:** parkinsonism; drug induced extrapyramidal symptoms (see notes above)

**Contra-indications:** untreated urinary retention, angle-closure glaucoma, GI obstruction.

**Cautions:** cardiovascular disease, hepatic and renal impairment.

**Side-effects:** dry mouth, dizziness, confusion, blurred vision, and lightheadedness.

**Dose:** orally 2.5 mg 3 times daily gradually increase if necessary, maximum daily dose is 30 mg in divided doses. Intramuscularly in acute dystonia, 5-10 mg repeated if necessary after 20 minutes. Intravenously, 5 mg, which usually acts within 5 minutes.

**Preparations**
Procyclidine HCl tablets, 5 mg tab. Procyclidine HCl injection, 5 mg/mL, 2 mL ampoule

### 4 F.3: Drugs used in essential tremor, chorea, tics, and related disorders

**Botulinum Toxin Type A**

**Indications:** blepharospasm, hemifacial spasm.

**Contra-indications:** generalized disorders of muscle activity like myasthenia gravis.

**Cautions:** pregnancy, breast-feeding, history of aspiration or dysphagia, specific cautions related to above indications; angle closure glaucoma, avoid injection in lower lid area to avoid ectropion.
Side-effects: excessive doses may paralyse distant muscles, influenza like symptoms, hypersensitivity reactions, specific side-effects related to above indications; keratitis, eye dryness, ptosis, facial oedema, photophobia.

Preparations
Botulinum Toxin Type A injection, 100 unit vial

4 G: Drugs used in nausea, vomiting and vertigo

Anti-emetic drugs should only be prescribed when the underlying cause of vomiting is well identified; otherwise symptomatic treatment may delay the diagnosis and therapy of the underlying disease. Knowing and treating the underlying cause, as with vomiting in diabetic acidosis, overdosage of digitalis or acute bacterial infection will mitigate the need for antiemetics. The possibility of drug-induced vomiting should be excluded; otherwise either the dose is reduced or the drug is changed. Antiemetics are more useful for prophylaxis than for treatment. Drugs such as hyoscine and antihistamines can prevent motion sickness. The adverse effects of hyoscine may limit its use in motion sickness in spite of being the most effective. Although drowsiness is common with most antihistamines, sedation may contribute to their effectiveness.

Vertigo and nausea associated with Ménière’s disease and middle-ear surgery can be reduced by betahistine, a histamine analogue that is claimed to improve the microcirculation. Drug therapy is not always effective.

Vomiting of pregnancy during the first trimester dose not require drug therapy. If vomiting is very severe, antihistamines or phenothiazines may be used for a short period. If symptoms have not settled within 24-48 hours, a specialist opinion should be sought.

4 G.1: Antiemetics

Prochlorperazine
Indications: severe nausea and vomiting, vertigo.
Contra-indications and cautions: see under chlorpromazine (sec. 4.B1.1)
Side-effects: see under chlorpromazine.
Extrapyramidal effects may occur more frequently in children, elderly and debilitated.
Dose: orally, acute attack of nausea and vomiting, 20 mg initially followed by 10 mg after 2 hours. Prophylaxis, 5-10 mg 2-3 times daily.
Child over 10kg, 250 microgram / kg 2-3 times daily oral route only.

Preparations
4. Central nervous system

Prochlorperazine tablets, 5 mg tab.

**Metoclopramide**

**Indications:** nausea and vomiting in adults, particularly in gastrointestinal disorders, and treatment with cytotoxic or radiotherapy; prophylaxis of migraine. *In patients under 20 years the use is restricted for intractable vomiting of known cause, vomiting of radiotherapy and cytotoxics, or for premedication.*

**Cautions:** hepatic and renal impairment, elderly, young adults and children; pregnancy and breast feeding.

**Side-effects:** Extrapyramidal effects, especially in children/young adults, restlessness, depression.

**Dose:** orally, 10 mg 3 times daily reduce to 5 mg in young adults 15-19 years.

Intramuscular and slow intravenous injections 10 mg 3 times daily if necessary, maximum 500 microgram/ kg daily.

Restricted use in children. Titrate dose very carefully.

**Preparations**

Metoclopramide tablets, 10 mg tab.

Metoclopramide HCl injection, 10 mg ampoule

**Domperidone hydrochloride**

**Indications:** nausea and vomiting.

**Cautions:** renal impairment; pregnancy and breast feeding; not recommended for prolonged use, use cautiously in children.

**Side-effects:** dystonia, arrhythmia, galactorrhoea, sexual dysfunction, rashes.

**Dose:** orally for acute nausea and vomiting, 10-20 mg every 4-8 hours.

Child 200-400 microgram/kg every 4-8 hours.

By rectum in suppositories, 30-60 mg every 4-8 hours, not recommended for child under 15 kg.

Child over 2 years for severe nausea and vomiting induced by cytotoxic drugs or radiotherapy, according to body weight:

- 10-15 kg 15 mg twice daily
- 15.5-25 kg 30 mg twice daily
- 25.5-35 kg 30 mg three times daily

**Preparations**

Domperidone oral suspension, 0.1% suspension (5 mg/5 mL); 150-200 mL/bottle (Restricted)

Domperidone tablets, 10 mg tab.

Domperidone suppositories, 10 mg supp.

Domperidone suppositories, 30 mg supp.

4 G.2: Anti-vertigo drugs

**Betahistine dihydrochloride**

**Indications:** vertigo, Méniere’s disease.

**Contra-indications:** phaeochromocytoma.

**Cautions:** asthma, history of peptic ulcer, pregnancy and breast-feeding.

**Side-effects:** GI disturbances, headache, pruritus, rashes.
4. Central nervous system

Dose: 8-16 mg 3 times daily. Maintenance 24-48 mg daily.

Preparations
Betahistine dihydrochloride tablets, 16 mg tab.

4 G.3: Specific serotonin receptor antagonist (5HT3 antagonists)

**Ondansetron** *(Restricted)*

**Indications:** nausea and vomiting induced by chemotherapy or radiotherapy; prevention and treatment of postoperative nausea and vomiting.

**Cautions:** pregnancy and breast feeding, hepatic impairment.

**Side-effects:** constipation, headache, sensation of warmth or flushing; transient alteration of liver enzymes.

**Dose:** for moderate vomiting due to chemotherapy or radiotherapy, orally 8 mg 1-2 hours before treatment, 8 mg immediately before treatment. Intramuscular or slow intravenous injections, 8 mg immediately before treatment, then by mouth 8 mg every 12 hours for up to 5 days.

For severe nausea and vomiting due to chemotherapy and radiotherapy, 8 mg immediately before treatment followed by 8 mg at intervals of 2-4 hours when necessary for further two doses, then by mouth 8 mg every 12 hours for up to 5 days.

Child, by slow intravenous injection, 5 mg / m² immediately before chemotherapy then 4 mg by mouth every 12 hours for up to 5 days.

For prevention of postoperative nausea and vomiting, orally 8-16 mg 1 hour before anaesthesia which may be followed by 8 mg at 8 hours intervals for further 2 doses, alternatively, intramuscular or slow intravenous injection 4 mg at induction of anaesthesia. Child, over 2 years, 100 microgram/ kg intravenously before, during or after induction.

Treatment of postoperative nausea and vomiting, intramuscular or slow intravenous injection 4 mg. Child over 2 years, 100 micrograms/ kg by slow intravenous injection.

**Preparations**

Ondansetron injection, 2 mg/mL, 2 mL ampoule
Ondansetron injection, 2 mg/mL, 4 mL ampoule
Ondansetron tablets, 4 mg tab.
Ondansetron tablets, 8 mg tab.

4 G4: Neurokinin-receptor antagonists

**Aprepitant** *(Restricted)*

**Indications:** Adjunct to dexamethasone and a 5HT3-receptor antagonist in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy

**Contra-indications:** Acute porphyrias
4. Central nervous system

**Side-effects:** Anorexia; asthenia; constipation; diarrhoea; dizziness; dyspepsia; headache; hiccup

**Dose:** Initially a 125 mg dose taken 1 hour before chemotherapy, then 80 mg once daily for 2 days, consult product literature for dose of concomitant corticosteroid and 5HT3-antagonist.

**Preparations**
Aprepitant capsules, 80 mg cap.
Aprepitant capsules, 125 mg cap.

4 H: Drugs for management of substance dependence.

**Clomethiazole (Chlormethiazole) (Controlled /restricted)**

**Indications:** alcohol dependence; others see sec. 4 E.2.

**Contra-indications, cautions and side-effects:** see under sec. 4 E.2

**Dose:** orally, for alcohol withdrawal, initially 600-1200 mg repeated if necessary after few hours
Day 1, 2.4-3.6 g in 3-4 divided doses
Day 2, 1.8-2.4 g in 3-4 divided doses,
Day 3, 1.2-1.8 g in 3-4 divided doses, then reduce gradually over 4-6 days, total treatment period not more than 9 days.

**Preparations**
Clomethiazole edisylate capsule, 300 mg cap.

4 I: Drugs used for attention deficit hyperactivity disorder

**Atomoxetine**

**Indications:** for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

**Contra-indications:** narrow angle glaucoma, concomitant use with Monoamine Oxidase Inhibitors (MAOI).

**Cautions:** all paediatric patients being treated with should be monitored closely for suicide potential, clinical deterioration, and unusual changes in behaviour, liver impairment, cardiovascular disease, history of seizures, pregnancy and breast-feeding, monitor growth in children.

**Side-effects:** gastrointestinal disorders, headache, dermatitis, palpitations, sleep disorders, menstruation irregularity, sexual dysfunction, urinary retention, hot flushes.

**Dose:**
Children over 6 years and adolescents up to 70 kg body weight, initially 500 microgram/kg and increased after 7 days to a target total daily dose of approximately 1.2 mg/kg administered either as a single daily dose in the morning or as divided doses in the morning and late afternoon/early evening.
Children and adolescents over 70 kg body weight, should be initiated at a total daily dose of 40 mg and increased after 7 days to a target total daily dose of approximately 80 mg administered either as a single daily dose in the morning or as divided doses in the morning and late afternoon/early evening.
afternoon/early evening; the maximum recommended total daily dose is 100 mg.

Preparations
Atomoxetine capsules, 10 mg cap.
Atomoxetine capsules, 18 mg cap.
Atomoxetine capsules, 25 mg cap.

**Methylphenidate (Restricted)**

**Indications:** Attention deficit hyperactivity disorder (initiated under specialist supervision)

**Contra-indications:** Anorexia nervosa; arrhythmias; cardiomyopathy; cardiovascular disease; cerebrovascular disorders; heart failure; hyperthyroidism; phaeochromocytoma; psychosis; severe depression; severe hypertension; structural cardiac abnormalities; suicidal ideation; uncontrolled bipolar disorder; vasculitis.

**Cautions:** Agitation; alcohol dependence; anxiety; drug dependence; epilepsy (discontinue if increased seizure frequency); family history of Tourette syndrome; susceptibility to angle-closure glaucoma; tics.

**Side-effects:** Abdominal pain; aggression; alopecia; anorexia; arrhythmias; arthralgia; asthenia; changes in blood pressure; cough; depression; diarrhoea; dizziness; drowsiness; dry mouth; dyspepsia; fever; growth restriction; headache; insomnia; irritability; movement disorders; nasopharyngitis; nausea; nervousness; palpitation; pruritus; rash; reduced weight gain; tachycardia; tics; vomiting; abnormal dreams; confusion; constipation; dyspnoea; epistaxis; haematuria; muscle cramps; suicidal ideation; urinary frequency

**Dose:** Child 6–17 years. Initially 5 mg 1–2 times a day, increased in steps of 5–10 mg daily if required, at weekly intervals, increased if necessary up to 60 mg daily in 2–3 divided doses, increased if necessary up to 2.1 mg/kg daily in 2–3 divided doses, the licensed maximum dose is 60 mg daily in 2–3 doses, higher dose under the direction of a specialist, discontinue if no response after 1 month, if effect wears off in evening (with rebound hyperactivity) a dose at bedtime may be appropriate (establish need with trial bedtime dose). Treatment may be started using a modified-release preparation; maximum 90 mg per day.

Preparations
Methylphenidate tablets 5 mg tab
Methylphenidate tablets 10 mg tab
Methylphenidate tablets 20 mg tab

**Donepezil (Restricted)**

**Indications:** Mild to moderate dementia in Alzheimer's disease

**Cautions:** Asthma; chronic obstructive pulmonary disease; sick sinus syndrome; supraventricular

4 J: Dementia
4. Central nervous system

Conduction abnormalities; susceptibility to peptic ulcers.

**Side-effects:** Abnormal dreams; aggression; agitation; anorexia; diarrhoea; dizziness; fatigue; hallucinations; headache; insomnia; muscle cramps; nausea; pruritus; rash; syncope; urinary incontinence; vomiting; Bradycardia; duodenal ulcers; gastric ulcers; gastro-intestinal haemorrhage; seizures; AV block; extrapyramidal symptoms; hepatitis; potential for bladder outflow obstruction; sino-atrial block

**Dose:** Initially 5 mg once daily for one month, then increased if necessary up to 10 mg daily, doses to be given at bedtime

**Preparations**

Donepezil hydrochloride tablets 5 mg tab

**Galantamine (Restricted)**

**Indications:** Dementia in Alzheimer’s disease

**Cautions:** Avoid in gastro-intestinal obstruction; avoid in urinary outflow obstruction; avoid whilst recovering from bladder surgery; avoid whilst recovering from gastro-intestinal surgery; cardiac disease; chronic obstructive pulmonary disease; congestive heart failure; electrolyte disturbances; history of seizures; history of severe asthma; pulmonary infection; sick sinus syndrome; supraventricular conduction abnormalities; susceptibility to peptic ulcers; unstable angina.

**Side-effects:** Abdominal pain; bradycardia; decreased appetite; depression; diarrhoea; dizziness; dyspepsia; fall; fatigue; hallucination; headache; hypertension; laceration; malaise; muscle spasm; nausea; syncope; tremor; vomiting; weight loss; Arrhythmias; blurred vision; dehydration; first-degree AV block; flushing; hypersensitivity; hypersomnia; hypotension; muscular weakness; palpitation; paraesthesia; retching; seizures; sweating; taste disturbance; tinnitus.

**Dose:** Immediate release tablets: mild to moderately dementia in Alzheimer’s disease. Initially 4 mg twice daily for 4 weeks, increased to 8 mg twice daily for 4 weeks; maintenance 8–12 mg twice daily.

**Preparations**

Galantamine hydrobromide tablets 8 mg tab

**Rivastigmine (Restricted)**

**Indications:** Mild to moderate dementia in Alzheimer’s disease. Mild to moderate dementia in Parkinson’s disease

**Cautions:** Bladder outflow obstruction; conduction abnormalities; duodenal ulcers; gastric ulcers; history of asthma; history of chronic obstructive pulmonary disease; history of seizures; risk of fatal overdose with patch administration errors; sick sinus syndrome; susceptibility to ulcers
4. Central nervous system

Side-effects: Abdominal pain; agitation; anorexia; anxiety; bradycardia; confusion; diarrhoea; dizziness; drowsiness; dyspepsia; extrapyramidal symptoms; headache; increased salivation; insomnia; malaise; nausea; sweating; tremor; urinary incontinence; vomiting; weight loss; worsening of Parkinson’s disease; Atrial fibrillation; AV block; depression; syncope; Angina; duodenal ulceration; gastric ulceration; rash; seizures.

Dose: Mild to moderate dementia in Alzheimer’s disease. Initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily, dose to be increased at intervals of at least 2 weeks according to response and tolerance; usual dose 3–6 mg twice daily (max. per dose 6 mg twice daily), if treatment interrupted for more than several days, retitratae from 1.5 mg twice daily.

Mild to moderate dementia in Parkinson's disease. Initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily, dose to be increased at intervals of at least 2 weeks according to response and tolerance; usual dose 3–6 mg twice daily (max. per dose 6 mg twice daily), if treatment interrupted for more than several days, retitratae from 1.5 mg twice daily.

Preparations

Rivastigmine hydrogen tartrate capsules 3 mg cap
Rivastigmine hydrogen tartrate capsules 6 mg cap

Note: Ministry of Health policy is that only one of the above medicines for dementia will be supplied at any given time.
5. Infections

Section 5: Infections
- Antibacterial drugs
- Antifungal drugs
- Antiviral drugs
- Antiprotozoal drugs
- Anthelmintics

The antibiotics policy

The use of antibiotics in the Sultanate of Oman follows specific rules and guidelines. These guidelines should be referred to along side the information that is published in the ONF to ensure local up-to-date policies are being adhered to.

Selection of antimicrobial drugs

A thoughtful selection of antimicrobial agent for treatment of infectious diseases requires clinical judgement and detailed knowledge of pharmacological and microbiological factors and the cost. Unfortunately, the decision to use antibiotics frequently is made lightly by practicing medical staff, without regards to the potential infecting microorganism or the pharmacological characteristics of the antibiotic. The most expensive antibacterial drugs are often erroneously considered as most effective. Antibiotics are used in 2 general ways, as empirical therapy and as definitive therapy. When used empirically a broad-spectrum antibiotic or a combination is used to cover a wide possible range of infective microorganisms since the causative microorganism has not been identified. However, once the infective microorganism is identified, definitive antimicrobial therapy should be employed.

Before starting therapy, the first decision to be made is whether administration of an antibacterial agent is truly indicated. Many physicians reflexly associate fever with treatable infections and prescribe antibiotic therapy, without further evaluation. This practice is irrational and potentially dangerous; the diagnosis may be masked if appropriate culture is not taken prior to therapy; antibiotics can cause serious toxic effects.

To prescribe an antibiotic the following points should be considered:
- Which organism is the likely cause of the infection?
- What is the clinical diagnosis and what other measures are taken to increase diagnostic precision?
- Which antibiotics are effective and available? Is their range of antimicrobial activity appropriate and what information is available about the likelihood of drug resistance?
- What are the undesirable effects of the selected antibiotic?
- What is the correct dose and dose interval, and what is the best route of administration?
- What is the duration of treatment?
Considering all the above, the treatment remains to be monitored to evaluate its effectiveness.

A rational choice of an antibacterial drug is judged through careful consideration of the patient and drug-related variables. Following is a general discussion of some of these variables.

**Drug related variables**

The *site of infection* may determine the choice of antibiotic, depending on its pharmacokinetic properties. For example, cephalosporins (except new third generation members), aminoglycosides and amphotericin B do not reach the cerebrospinal fluid in sufficient amount to counter infections in the brain or the meninges. Erythromycin is only partly excreted in the urine and therefore not useful in urinary tract infections. Ampicillin, amoxicillin, cefalexin and rifampicin are sufficiently concentrated in the bile and hence may be effective in biliary tract infections. The site of infection may also determine the dose and route of administration. Drugs poorly penetrate the eye, prostate and bone; therefore infections in such sites require higher dosage of antimicrobials. Parenteral administration is recommended for drugs of poor gastrointestinal absorption in serious systemic infections or in unconscious patients. Penetration of antibiotic agents into infected areas such as abscess cavities is impaired, since the vascular supply is reduced; successful therapy of abscesses usually requires drainage.

When antibacterials are used to treat an infection, the success of the treatment depends on the concentration achieved at the site of infection that is sufficient enough to inhibit bacterial growth. When host defences are maximally effective, it might only be needed to achieve a minimal inhibitory effect, such as that provided by bacteriostatic agents. On the other hand when host defences are impaired the need arises for a more bactericidal effect to achieve complete antibiotic-mediated killing effects. The dose of the drug must be sufficient enough to produce the necessary effects on the microorganism without inducing toxic effects to the human cells. In such cases the microorganism is said to be susceptible to the antimicrobial. If the concentration of drug required to inhibit or kill the microorganism is greater than the concentration that can be safe to the patient, the microorganism is said to be resistant to the antimicrobial. Most *in vitro* sensitivity tests are standardized on the basis of the drug concentration that can safely be achieved in the plasma. They do not reflect concentrations that can be attained at site of infection; nor do they take into consideration the
local factors that may affect the activity of the drug. Such a limitation should always be kept in mind when reading laboratory results of culture and sensitivity tests.

The most frequent adverse effects of antibiotics are:
- hypersensitivity reactions (not dose related)
- toxic and irritative effects (dose related)
- superinfections

If a choice exists between drugs, the least toxic is to be selected.

Antibiotic combinations are frequently used and mostly as a cover for imprecise diagnosis. Every effort must be made towards accurate diagnosis and the administration of more than one antibiotic should be generally avoided. However, combinations are indicated in the following situations:
- mixed infection such as in peritonitis, when one drug is not effective against all pathogens
- a temporary measure during the investigation of an obscure illness.
- to prevent the development of resistance in long-term therapy as in tuberculosis.
- to achieve potentiation or synergism
- to permit dose reduction of potentially toxic drugs.

Most combinations result in indifference or summation; occasionally the result may be antagonism or synergism. Few combinations act synergistically and none do invariably. No particular combination can be specified as generally synergistic but may be synergistic in relation to particular bacteria. Synergism occurs usually with bactericidal drugs.

Mixing of antibiotics with other drugs in the same syringe or container may result in incompatibilities due to physical and chemical interactions. The examples are too numerous to be remembered by the physician; it is better to avoid mixing drugs in the same syringe. Mixing antibiotics with intravenous solutions can also result in precipitation or instability of antibiotics due to chemical interactions or as a result of changes in the pH.

Resistance to antimicrobial agents

Pathogens develop resistance to antimicrobials through a process known as natural selection. When a microbial population is exposed to an antibiotic, more susceptible organisms will perish leaving behind only those resistant to the antimicrobial-mediated killing effect. These organisms can then either pass on their resistance genes to their new generation by replication, or to other related bacteria through a conjugation process whereby plasmids carrying the genes are transferred from one organism to
another. This process is a natural and unstoppable phenomenon which can be exacerbated by abuse, misuse and overuse of antimicrobials in the treatment of human illness and in animal and agricultural industries. It is the medical profession’s great challenge to slow the rate at which resistance develops and spreads through the adoption of a rational selection and use of effective antimicrobials.

**Patient related variables**

The age of the patient is an important determinant of pharmacokinetic properties of antimicrobial agents. Mechanisms of elimination, especially renal excretion and hepatic metabolism are poorly developed in newborns, especially in premature infants. Failure to make adjustment for such differences can have serious consequences. Elderly patients also may have reduced rate of creatinine clearance and drug metabolism. Also, elderly patients are more susceptible to the ototoxic effects of aminoglycosides.

**Renal function** is a major factor in the choice of antimicrobials and the determination of the dose and its frequency. It is important that the renal function is assessed before and during the entire course of treatment, especially when nephrotoxic drugs are used. Drugs that are renally eliminated should be given less frequently in the presence of renal impairment; serum creatinine level and drug concentration in the blood are used for such assessment.

**Hepatic function** is a major factor in the choice of antimicrobials that are eliminated by the bile or inactivated in the liver. For examples, the doses of erythromycin, chloramphenicol, metronidazole, doxycycline and rifampicin should be reduced in hepatic failure.

Certain **genetic factors** may determine the rate of biotransformation of some antibacterials. Rapid acetylators may need to have high doses of isoniazid to obtain therapeutic effects. However, patients with deficiency of G6PD may develop haemolytic anaemia with sulphonamides, chloramphenicol and nitrofurantoin.

**Pregnancy** imposes an additional risk of reaction to some antimicrobial agents both for mother and foetus. Penicillins, cephalosporins and erythromycins are probably safe during pregnancy; others are either contra-indicated or prescribed with caution.

The lactating mother can pass antimicrobials to her nursing child. Sulphonamides and nalidixic acids taken by mothers have been associated with haemolytic anaemia in G6PD deficient infants.
5. Infections

Host defence mechanisms are a critical determinant of the therapeutic effectiveness of antimicrobial agents. Both humoral and cellular immunity are important. Inadequacy of type, quality and quantity of immunoglobulins, alteration in cellular immune system or a quantitative and qualitative defect in phagocytic cells may result in therapeutic failure despite the use of otherwise appropriate and effective drugs. If host defences are impaired, then bactericidal antimicrobials agents have to be applied for cure.

Superinfection. In general broad spectrum antibacterial drugs such as the cephalosporins, tetracycline, chloramphenicol or their combinations are more likely to be associated with adverse reactions related to the prevalence of resistant organisms causing for examples, fungal infections or antibiotic-associated pseudo-membranous colitis; other problems associated with superinfection include vaginitis and pruritus ani.

5 A: Antibacterials

5 A.1: Penicillins

The penicillins are bactericidal anti-bacterial drugs that interfere with bacterial cell wall synthesis. The various penicillin antibiotics share a common structure and mechanism of action. Their distribution in the body is extensive, but in the cerebrospinal fluid it is poor except when the meninges are inflamed. They are mainly excreted in the urine.

These drugs are remarkably free of toxic effects, but in the presence of renal failure large doses may cause convulsion and coma. The most serious adverse effect of penicillins is hypersensitivity that results in anaphylactic shock; such reaction is sometimes fatal. Cross-sensitivity occurs with all penicillins and beta-lactam compounds (cephalosporins). Diarrhoea frequently occurs with oral penicillins and is more common with broad-spectrum drugs.

5 A.1.1: Benzylpenicillin and phenoxymethylpenicillin

Benzylpenicillin (Penicillin G) is active against many streptococcal, gonococcal and meningococcal infections, and also for anthrax, diphtheria, and gas gangrene. It is inactivated by beta-lactamase.

Procaine penicillin and benzathine benzylpenicillin are meant for intramuscular administration of penicillin with longer duration of actions.

Phenoxymethylpenicillin has a similar antibacterial activity to benzylpenicillin but is less effective and can be used orally.
**Benzylpenicillin (Penicillin G) (Restricted)**

**Indications:** pneumonia, otitis media, meningitis, septic arthritis, anthrax, gas gangrene;

**Contra-indications:** sensitivity to penicillins.

**Cautions:** inadvertent intravascular injecting is dangerous.

**Side-effects:** hypersensitivity reactions see benzylpenicillin; seizure, psychotic reactions.

**Dose:** intramuscularly, 400,000–1,200,000 units daily in 2 divided doses.

**Preparations**

Benzylpenicillin + procaine penicillin injection, powder for reconstitution, 100,000 units + 300,000 units/vial

**Benzathine benzylpenicillin**

**Indications:** prophylaxis in rheumatic fever.

**Contra-indications:** see under benzylpenicillin.

**Cautions:** see under procaine penicillin.

**Side-effects:** see under benzylpenicillin.

**Dose:** intramuscularly, 1.2 million units once monthly.

**Preparations**

Benzathine benzylpenicillin injection, powder for reconstitution, 1.2 million unit/vial.

**Phenoxyethylpenicillin**

**Indications:** streptococcal infections, rheumatic fever prophylaxis.

**Contra-indications:** sensitivity to penicillins.

**Cautions:** inadvertent intravascular injecting is dangerous; acute psychotic disorders.

**Side-effects:** hypersensitivity reactions see benzylpenicillin; seizure, psychotic reactions.

**Dose:** intramuscularly, 400,000–1,200,000 units daily in 2 divided doses.

**Preparations**

Benzylpenicillin + procaine penicillin injection, powder for reconstitution, 100,000 units + 300,000 units/vial

**Procaine penicillin**

**Indications:** infections with *Neisseria gonorrhoea, Treponema pallidum*, and other infections showing sensitivity to benzylpenicillin.
5. Infections

**Cautions and side-effects:** see under benzylpenicillin.

**Dose:** orally, adult 250-500 mg every 6 hours up to 1 g every 6 hours. Child, less than 1 year 62.5 mg every 6 hours, 1-5 years 125 mg 6 hourly, 6-12 years 250 mg 6 hourly. Intravenous injection or slow intravenous infusion, 0.25-2 g every 6 hours. Child under 2 years quarter adult dose, 2-10 years half adult dose.

**Preparations**
- Phenoxymethylpenicillin oral solution, 250 mg/5 mL solution; 100 mL/bottle
- Phenoxymethylpenicillin tablets, 250 mg tab.

5 A.1.2: Penicillinase-resistant penicillins

Cloxacillin is resistant to the penicillinase enzyme produced by most staphylococci. It is acid stable and therefore can be used orally as well as by injection.

**Cloxacillin (Restricted)**

**Indications:** infections caused by penicillinase producing staphylococci; streptococcal pharyngitis, skin and soft tissue infections, osteomyelitis, lower respiratory tract infections and otitis media.

**Contra-indications:** hypersensitivity to penicillins.

**Cautions:** see under benzylpenicillin

**Side-effects:** see under benzylpenicillin; hepatitis and cholestatic jaundice reported.

**Dose:** oral and intramuscular injection, 250-500 mg every 6 hours (oral: at least 30 minutes before meal). Child under 2 years, quarter adult dose, 2-10 years half adult dose.

**Preparations**
- Cloxacillin capsule, 250 mg cap.
- Cloxacillin sodium injection, powder for reconstitution, 250 mg vial
- Cloxacillin sodium injection, powder for reconstitution, 500 mg vial
- Cloxacillin sodium, 125 mg/5 ml suspension, 100 mL/bottle

**Flucloxacillin** *(Restricted)*

**Indications:** infections due to beta-lactamase producing staphylococci including otitis externa; adjunct in pneumonia, impetigo, cellulitis, osteomyelitis and in staphylococcal endocarditis.

**Cautions:** see under benzylpenicillin; cholestatic jaundice may occur up to several weeks after treatment with flucloxacillin has stopped. Administration for more than 2 weeks and increasing age are risk factors.

**Contra-indications:** see under benzylpenicillin. Hypersensitivity to penicillins.

**Side-effects:** see under benzylpenicillin.

**Dose:** by mouth 250–500 mg every 6 hours at least 30 minutes before food; Child under 2 years quarter adult dose; 2-10 years half adult dosage.
dose. By intramuscular injection, 250-500 mg every 6 hours; Child under 2 years quarter adult dose; 2-10 years half adult dose. By slow intravenous injection or by intravenous infusion, 250 mg – 2 g every 6 hours; Child under 2 quarter adult dose; 2-10 years half adult dose. see above charts and tables. May be substituted for cloxacillin.

Preparations
Flucloxacillin capsules, 250 mg cap.
Flucloxacillin suspension 125 mg/5 mL, 100 mL/bottle
Flucloxacillin injection, powder for reconstitution, 250 mg vial

Note: Either cloxacillin or flucloxacillin may be available for use

5. Infections

The broad-spectrum penicillins available are ampicillin, amoxicillin and the mixture of amoxicillin and clavulanic acid known as co-amoxiclav. Ampicillin and amoxicillin are not effective against penicillinase producing microorganisms. Ampicillin and amoxicillin are used alternatively; are orally effective as well as by injections, but amoxicillin is better absorbed from the gastrointestinal tract and is not adsorbed to food particles. Amoxicillin produces diarrhoea less frequently than ampicillin.

The clavulanic acid is a beta-lactamase enzyme inhibitor with no significant antibacterial activity. The co-amoxiclav is more active against beta-lactamase-producing bacteria than amoxicillin alone.

Amoxicillin
Indications: broad spectrum antibacterial activity; otitis media, urinary tract infections, meningitis, various streptococcal infections and respiratory infections.
Contra-indications: penicillin hypersensitivity.
Cautions: renal impairment, history of allergy, skin rash, viral infections.
Side-effects: diarrhoea (discontinue treatment if severe), gastrointestinal discomfort.
Dose: orally, 250-500 mg every 8 hours. Child up to 10 years, 125-250 mg every 8 hours.

Preparations
Amoxicillin capsules, 250 mg cap.
Amoxicillin capsules, 500 mg cap.
Amoxicillin oral suspension, 125 mg/5 mL suspension; 100 mL/bottle

Ampicillin (Restricted)
Indications: see under amoxicillin
Contra-indications, cautions and side-effects: see under amoxicillin
Dose: by intramuscular or intravenous injection or infusion, 500 mg
5. Infections

every 4-6 hours. Child, under 10 years half adult dose.

Preparations
Ampicillin sodium injection, powder for reconstitution, 250 mg vial
Ampicillin sodium injection, powder for reconstitution, 500 mg vial

*Amoxicillin + clavulanic acid*

**Co-amoxiclav (Restricted)**

**Indications:** infections caused by beta-lactamase producing strains where amoxicillin alone is not appropriate as in, respiratory tract infections, genitourinary and gastrointestinal infections, cellulitis, severe dental infection with spreading cellulitis; for antibacterial prophylaxis.

**Contra-indications:** penicillin hypersensitivity.

**Cautions:** see under amoxicillin, hepatic impairment.

**Side-effects:** see under amoxicillin; skin disorders, cholestatic jaundice, headache, dizziness, phlebitis at injection sites.

**Dose:** orally, 375 mg (amoxicillin 250 mg + clavulanic acid 125 mg) 3 times daily or double this dose twice daily. Severe infections and respiratory tract infection 750 mg 3 times daily. The frequency of administration should be reduced in presence of renal failure.

Paediatric dose is 20-45 mg/kg daily in three divided doses calculated as amoxicillin content.

By slow intravenous injection or infusion, adult, 1.2 g (amoxicillin 1 g and clavulanic acid 200 mg) every 8 hours; in severe infections every 6 hours.

For antibacterial prophylaxis, 1.2 g intravenously.

Preparations
Amoxicillin + clavulanic acid tablets, 250 mg + 125 mg tab.
Amoxicillin + clavulanic acid injection, Powder for reconstitution, 500 mg + 100 mg vial
Amoxicillin + clavulanic acid injection, Powder for reconstitution, 1 g + 200 mg vial
Amoxicillin + clavulanic acid suspension, 125 mg + 31 mg/5 mL suspension, 100 mL/bottle

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5 A.1.4: Antipseudomonal penicillins

Piperacillin is the only antipseudomonal penicillin available. It has been used alone or in combination with the beta-lactamase inhibitor tazobactam. It is specifically active against *Pseudomonas aeruginosa* and has an activity against gram-negative and gram-positive microorganisms. The piperacillin and tazobactam combination broadens the antibacterial spectrum to include beta-lactamase producing microorganisms.

Piperacillin and aminoglycosides have synergistic effects when used simultaneously such use is highly recommended in pseudomonas septicemia.
**Piperacillin + Tazobactam (Restricted)**

**Indications:** Infections with beta-lactamase-producing microorganisms resistant to piperacillin, gram-negative and gram-positive infections, anaerobic infections; effective in septicaemia, intra-abdominal infections, gynaecological infections, community-acquired pneumonia, cellulitis.

**Contra-indications, cautions and side-effects:** See under benzylpenicillin

**Dose:** Should be determined according to creatinine clearance. Patients with creatinine clearance greater than 40 mL/minute the dose is, piperacillin 12 g + tazobactam 1.5 g daily divided in 4 doses.

Patients with creatinine clearance of 20-40 mL/minute, the dose is, piperacillin 8 g + tazobactam 1 g daily in 4 divided doses.

Patients with creatinine clearance of less than 20 mL/minute, the dose is, piperacillin 6 g + tazobactam 0.75 g daily in 3 divided doses.

**Preparations**

- Piperacillin + Tazobactam injection, powder for reconstitution, 2 g + 250 mg vial
- Piperacillin + Tazobactam injection, powder for reconstitution, 4 g + 500 mg vial

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5 A.2: Cephalosporins and other beta-lactam antibiotics

Cephalosporins (CS) have a beta-lactam structure, which they share with penicillins as many other characteristics. They have broad-spectrum antibacterial activities although individual CS may possess differing activity against certain microorganisms. They are eliminated mainly by the renal system and few cephalosporins are partially metabolised. They poorly penetrate the CSF unless the meninges are inflamed.

As with penicillins, the major adverse effect of CS is hypersensitivity; cross sensitivity with penicillin is common.

Cephalosporins are classified into four classes or generations.

**First generation** CS include, cefradine and cefalexin, which are available in oral formulations; cefradine is also available as injection. Cefuroxime is a **second generation** CS, which is less susceptible to beta-lactamase inactivation. Cefuroxime is therefore more active than other cephalosporins against *H. influenzae* and *N. gonorrhoea.* It is available in oral and injectable formulations.

The **third generation** CS are more effective against a wider range of microorganisms than second generation CS. Ceftriaxone, cefotaxime and ceftazidime are **3rd generation** CS available in Oman. They are used...
5. Infections

for serious infections in hospitalised patients; the possibility of superinfection with resistant bacteria and fungi is greater.

Ceftriaxone has a longer half-life and therefore is suitable for once daily administration in serious infections such as septicaemia, pneumonia and meningitis. Cefepime is a fourth generation CS that is reserved for highly resistant infections.

5 A.2.1: First generation cephalosporins

**Cefalexin (Cephalexin)**

**Indications:** infections with gram positive and gram negative organisms in the respiratory tract, skin and soft tissues, otitis media and urinary tract.

**Contra-indications:** cephalosporins hypersensitivity, see notes above

**Cautions:** renal impairment, penicillin sensitivity.

**Side-effects:** diarrhoea, pseudomembranous colitis (on higher doses or prolonged use associated with diarrhoea) abdominal pain, nausea and vomiting, headache, allergic reactions.

**Dose:** oral, 250 mg every 6 hours increased to 500 mg every 8-12 hours. Higher doses may be applied in serious infections. Child under 1 year 125 mg twice daily, 1-5 years 125 mg 3 times daily, 6-12 years 250 mg 3 times daily.

Preparations
- Cefalexin capsule, 250 mg cap.
- Cefalexin suspension, 125 mg/5 mL susp.; 100 mL/bottle

**Cefradine (Cephradine)**

**Indications:** antibacterial prophylaxis (); see under cefalexin above

**Contra-indications, caution and side-effects:** see cefalexin above

**Dose:** oral, 250-500 mg 4 times daily; in severe infections 1 g every 6 hours. Child 25-50 mg/kg daily in 2-4 divided doses. Intramuscular, slow intravenous injection or intravenous infusion, 0.5-1 g 4 times daily. Child, 50-100 mg/kg daily in 4 divided doses.

Surgical prophylaxis, by deep intramuscular injection, or intravenous injection, 2 g at induction.

Preparations
- Cefradine capsule, 250 mg cap.
- Cefradine injection, powder for reconstitution, 500 mg vial (Restricted)
- Cefradine syrup, 125 mg/5 mL susp.; 100 mL/bottle

Note: Ministry of health policy is that either of the cephalosporins, cefalexin or cefradine will be purchased and available for use depending on cost effectiveness

5 A.2.2: Second generation cephalosporins

**Cefuroxime (as axetil) tablets, 250 mg tab.**

**Preparations**
- Cefuroxime sodium injection, powder for reconstitution, 750 mg vial
- Cefuroxime sodium injection, powder for reconstitution, 500 mg vial

**Dose**
- Oral: 1 g 4 times daily.
- Intramuscular, slow intravenous injection, or intravenous infusion, 750 mg 3-4 times daily.
- By intramuscular injection or intravenous administration; pain and allergic reactions rarely arrhythmias following rapid administration at site of injection.

In severe life threatening infections, uncomplicated infections, 1 g twice daily. In moderate to severe infections, double the dose in patients with renal impairment. Reduce dose in patients with renal impairment.

Indications

- Infections with gram positive and gram negative organisms; surgical prophylaxis, gonorrhoea, meningitis.

Preparations
- Cefotaxime sodium injection, 500 mg vial
- Cefotaxime sodium injection, 750 mg vial

**Indications**

- Respiratory tract, pelvic inflammatory disease, skin and soft tissues, otitis media, urinary tract.

Preparations
- Cefotaxime sodium injection, powder for reconstitution, 1 g vial
- Cefotaxime sodium injection, powder for reconstitution, 500 mg vial

**Dose**

- By intramuscular injection or intravenous infusion, 1 g 3-4 times daily in severe infections.
- In severe infections, 1.5 g intravenously.
- Gonorrhoea, 1 g single oral dose.
- Surgical prophylaxis, 1.5 g intravenously.

**Ceftazidime (Restricted)**

**Preparations**
- Ceftazidime capsule, 250 mg cap.
- Ceftazidime suspension, 125 mg/5 mL; 70-100 mL/bottle

**Indications**

- Septicaemia; surgical prophylaxis; meningitis, Haemophilus epiglotitis.

5 A.2.3: Third generation cephalosporins

**Ceftriaxone**

**Preparations**
- Ceftriaxone capsule, 250 mg cap.
- Ceftriaxone suspension, 125 mg/5 mL; 70-100 mL/bottle

**Indications**

- Antibacterial prophylaxis, gonorrhoea, meningitis.

**Contra-indications and cautions**

- See under cefalexin above

**Side-effects**

- Septicemia, Haemophilus influenzae

**Surgical prophylaxis**

- 1.5 g intravenously.

**Note:** Ministry of health policy is that either of the cephalosporins, cefalexin or cefradine will be purchased and available for use depending on cost effectiveness.
Cefuroxime (Restricted)
Indications: infections with gram positive and gram negative organisms in the respiratory tract, skin and soft tissues, otitis media, urinary tract, pelvic inflammatory disease, bone and joint infections and septicaemia; surgical prophylaxis; H. influenzae and N. gonorrhoea infections.
Contra-indications cautions and side-effects: see cefalexin above
Dose: orally, (as cefuroxime axetil), 250 mg twice daily for most infections. In severe infections, double the dose. In UTI, 125 mg twice daily, double in pyelonephritis.
Child, 125 mg twice daily, double the dose in severe infections.
Gonorrhoea, 1 g single oral dose. By intramuscular injection or intravenous injection or infusion, 750 mg 3-4 times daily, increased to 1.5 g 3-4 times daily in severe infections. Child, 60 mg/kg daily (range 30-100 mg/kg daily) in 3-4 divided doses.
Gonorrhoea, intramuscularly, 1.5 g single dose.
Surgical prophylaxis, 1.5 g intravenously.
Preparations
Cefuroxime (as axetil) tablets, 250 mg tab.
Cefuroxime sodium injection, powder for reconstitution, 750 mg vial
Cefuroxime (as axetil) suspension, 125 mg/5 mL; 70-100 mL/bottle

5. Infections

Cefotaxime (Restricted)
Indications: infections with gram negative organisms; surgical prophylaxis, gonorrhoea, meningitis, Haemophilus epiglotitis.
Contra-indications and cautions: see cefalexin above
Side-effects: see cefalexin above; rarely arrhythmias following rapid administration; pain and allergic reaction at site of injection.
Dose: by intramuscular or intravenous injection or intravenous infusion, uncomplicated infections, 1 g twice daily. In moderate to severe infections, 1-2 g 3 times daily. Reduce dose in patients with renal impairment.
In severe life threatening infections, up to 12 g daily in divided doses have been used.
Paediatric dose 50-100 mg/kg/day in divided doses.
Gonorrhoea, 500mg as a single intramuscular injection.

Preparations
Cefotaxime sodium injection, powder for reconstitution, 500 mg vial
Cefotaxime sodium injection, powder for reconstitution, 1 g vial

Ceftazidime (Restricted)
Indications: infections with multi- antibiotic resistant gram-negative

5 A.2.3: Third generation cephalosporins
5. Infections

organisms; infections due to *Pseudomonas aeruginosa*.

**Contra-indications, cautions and side-effects:** see cefalexin above

**Dose:** by intramuscular injection or intravenous injection or infusion, 1 g 2-3 times daily. In very severe life threatening infection and meningitis, 2 g 3 times daily. Child under 2 month, 25-60 mg/kg daily in 2 divided doses, over 2 months 30-100 mg/kg daily in 2-3 divided doses.

**Preparations**

Ceftazidime as pentahydrate with sodium carbonate injection, powder for reconstitution, 1 g vial

**Ceftriaxone (Restricted)**

**Indications:** infections with gram-negative multi-antibiotic resistant organisms; meningococcal meningitis.

**Contra-indications, cautions and side-effects:** see cefalexin above; pain, phlebitis and allergic reaction at site of injection.

**Dose:** by deep intramuscular injection or intravenous injection or infusion, 1-2 g once daily or in 2 divided doses.

In meningitis, 100 mg/kg/day (not to exceed 4 g).

Gonorrhoea, uncomplicated, 250 mg single intramuscular dose, disseminated infection, 1 g single intramuscular or intravenous.

**Preparations**

Ceftriaxone injection, powder for reconstitution, 250 mg vial

Ceftriaxone injection, powder for reconstitution, 500 mg vial

Ceftriaxone injection, powder for reconstitution, 1 g vial

5 A.2.4: Fourth generation cephalexopins

**Cefepime (Restricted)**

**Indications:** severe infections resistant to members of the third generation CS.

**Contra-indications, cautions and side-effects:** see cefalexin above

**Dose:** by deep intramuscular injection or slow intravenous injection or infusion, 0.5-2 g twice daily. Child, 50 mg/kg twice daily, maximum 2 g daily.

**Preparations**

Cefepime hydrochloride injection, powder for reconstitution, 1 g vial

5 A.2.5: Other beta-lactam antibiotics

Imipenem and meropenem are beta-lactam antibiotics of the carbapenem group. They possess a broader antibacterial spectrum and greater potency than other beta-lactam drugs.

Imipenem is metabolised by the kidney and is usually combined with cilastatin, a dehydropeptidase inhibitor, to block its renal metabolism. Adverse effects are similar to other beta-lactam compounds. High doses may cause neurotoxicity especially in the presence of renal failure.
Meropenem is similar to imipenem but more stable to the renal metabolism and therefore is used alone without cilastatin. Meropenem is less neurotoxic than imipenem and can be used to treat central nervous system infections. Ertapenem is licensed for treating abdominal and gynaecological infections and for community-acquired pneumonia, but it is not effective against atypical respiratory pathogens and it had limited activity against penicillin resistant pneumococci. Unlike the other carbapenems, ertapenem is not active against *Pseudomonas* or against *Acinetobactor* spp.

**Ertapenem (Restricted)**  
**Indications:** Abdominal infections. Acute gynaecological infections. Community-acquired pneumonia. Diabetic foot infections of the skin and soft tissue. Surgical prophylaxis, colorectal surgery  
**Cautions:** CNS disorders—risk of seizures; elderly  
**Side-effects:** Diarrhoea; headache; injection-site reactions; nausea; pruritus; raised platelet count; rash (also reported with eosinophilia and systemic symptoms); vomiting; abdominal pain; anorexia; antibiotic-associated colitis; asthenia; bradycardia; chest pain; confusion; constipation; dizziness; dry mouth; dyspepsia; dyspnoea; hypotension; melaena; oedema; petechiae; pharyngeal discomfort; raised glucose; seizures; sleep disturbances; taste disturbances.  
**Dose:** Abdominal infections. Acute gynaecological infections. Community-acquired pneumonia 1 g once daily. Diabetic foot infections of the skin and soft tissue 1 g once daily. Surgical prophylaxis, colorectal surgery 1 g for 1 dose, dose to be completed within 1 hour before surgery.

**Preparations**  
Ertapenem injection powder for reconstitution, 1 g vial

**Imipenem + cilastatin (Restricted)**  
**Indications:** severe aerobic and anaerobic gram-negative and gram-positive infections and in multi-antibiotic resistant infections; alone or in combination with aminoglycosides in serious mixed infections including pulmonary, intra-abdominal, soft tissue and pseudomonas infections; surgical prophylaxis.  
**Contra-indications:** hypersensitivity to beta-lactam compounds; breast-feeding.  
**Cautions:** renal impairment; CNS disorders; pregnancy.  
**Side-effects:** nausea, vomiting, diarrhoea, tooth and tongue discolouration, hearing loss; allergic reactions; CNS disturbances.  
**Dose:** imipenem and cilastatin are mixed 1:1 and doses quoted hence after will refer to imipenem content.
5. Infections

Intravenous injection or infusion, 500 mg 3-4 times daily. Half this dose is used in mild uncomplicated infections. In severe life threatening infections, 1 g 3-4 times daily. Daily doses should not exceed 50 mg/kg or a total of 4 g whichever is lower.

Child 60 mg/kg (up to 2g) daily in 4 divided doses (every 6 hours)

Preparations
Imipenem + cilastatin intravenous injection, powder for reconstitution, 500 mg + 500 mg vial

Meropenem (Restricted)

Indications: see under imipenem; febrile neutropenia, urinary tract infections and in meningitis caused by gram-negative bacilli.

Contra-indications: hypersensitivity to meropenem; and beta-lactam antibiotics.

Cautions: hepatic and renal impairment; pregnancy and breast-feeding.

Side-effects: headache, nausea, vomiting, abdominal pain, diarrhea; liver function test abnormalities; hypersensitivity reactions.

Dose: by intravenous injection or infusion, 0.5-1 g 3 times daily. In meningitis, 2 g 3 times daily.

Child 20 mg/kg every 8 hours for intra-abdominal infections, and 40 mg/kg every 8 hours in meningitis.

Preparations

Meropenem trihydrate injection, powder for reconstitution, 500 mg vial
Meropenem trihydrate injection, powder for reconstitution, 1 g vial

5 A.3: Aminoglycosides

This group of antibacterial drugs include streptomycin, gentamicin, amikacin and netilmicin. Neomycin use has greatly declined though it is sometimes used in special procedures. This group is usually administered by injection since they are poorly absorbed from the gastrointestinal tract. Aminoglycosides do not penetrate the cerebrospinal fluid and hence are not suitable in meningitis. They are mainly eliminated by the renal system without being metabolised by the liver. Renal function is an important factor in determining frequency of dosing and the degree of toxicity.

The most toxic effects of aminoglycosides are ototoxicity and to a lesser extent nephrotoxicity. Degree of toxicity is related to the dose (frequency of doses) and the status of renal function. There is a great risk of foetal ototoxicity when used during pregnancy.
Synergistic effects on ototoxicity may result from simultaneous use of other ototoxic drugs (furosemide, ethacrynic acid) with aminoglycosides. In high doses, aminoglycosides may induce a curare-
5. Infections

Gentamicin (Restricted)

Indications: severe gram-negative infections see notes above.
Contra-indications: myasthenia gravis.
Cautions: pregnancy; renal impairment, infants and elderly (adjust dose and frequency); avoid prolong therapy.
Side-effects: ototoxic and nephrotoxic effects, neuromuscular blocking effect, allergic reactions.

Dose: in normal renal function, intramuscular, slow intravenous injection or intravenous infusion, 3-5 mg/kg daily in a single dose or 2-3 divided doses. A dose adjustment is required in renal impairment and the elderly.
Child, 2 weeks to 12 years, 2 mg/kg every 8 hours.
For other uses

Preparations
Gentamicin sulphate injection, 20 mg vial Gentamicin sulphate injection, 80 mg vial

Amikacin (Restricted)

Indications: serious gram-negative infections resistant to gentamicin; others, see under gentamicin and notes above
Contra-indications, cautions and side-effects: see under gentamicin and notes above
Dose: dosing adjustment is required in renal impairment, in alcoholics, and in cirrhotic patients.
Intramuscular, or slow intravenous injection or by infusion, 15 mg/kg

like effect on neuromuscular junction when used postoperatively. They may induce allergic reactions and superinfections. Aminoglycosides are bactericidal drugs and active against some gram-positive and many gram-negative organisms. Amikacin and gentamicin are also active against Pseudomonas aeruginosa. Streptomycin is almost entirely reserved for the treatment of tuberculosis.

Gentamicin is indicated in the treatment of severe gram-negative infections including, complicated urinary tract infections, bacteremia in burn patients, respiratory tract infections, endophthalmitis, osteomyelitis, and in endocarditis in combination with beta-lactam drugs. It is not effective against anaerobes and when used for the blind treatment of undiagnosed serious infections should be combined with metronidazole or penicillin or both. Amikacin has a similar activity to gentamicin with an advantage that it is more stable to enzymatic degradation than gentamicin. It is mainly used in the treatment of infection with gentamicin-resistant gram-negative bacilli.

Netilmicin has similar activity to gentamicin but causes less ototoxicity; it is more suitable for long-term therapy. Netilmicin is active against a number of gentamicin-resistant gram-negative bacilli but is less active against Pseudomonas aeruginosa.
5. Infections

daily as a single dose or in 2-3 divided doses. Neonates, loading intramuscular or intravenous dose of 10 mg/kg, with 7.5 mg/kg 2 times daily for maintenance. Infants older than 7days and child, 22.5 mg/kg daily in 3 divided doses.

Preparations
Amikacin sulphate injection, 250 mg/mL; 2 mL vial

Streptomycin (Restricted)  
Indications: tuberculosis in combination with other antituberculous drugs; adjunct to doxycycline in brucellosis; plague, Ménière’s disease, mycobacterial infections, tularemia.
Contra-indications and cautions: see gentamicin and notes above  
Side-effects: see gentamicin and notes above  
Dose: for tuberculosis, intramuscular injection of 15 mg/kg (maximum 1 g) daily. Dose is reduced in underweight patients and in those over 40 years or in the presence of renal impairment.

Preparations
Streptomycin sulphate injection, powder for reconstitution, 1 g vial

Tobramycin (Restricted)  
Indications: see under gentamicin and notes above, the inhaled form is used to improve lung function and reduce exacerbations in cystic fibrosis patients.  
Contraindications: see under gentamicin and notes above  
Cautions: see under gentamicin and notes above, other inhaled drugs should be administered before tobramycin; monitor for bronchospasm with initial dose, measure peak flow before and after nebulisation. If bronchospasm occurs, repeat test using bronchodilator; monitor renal function before treatment and then annually; severe haemoptysis.
Side-effects: see under gentamicin and notes above, on inhalation, mouth ulcers, voice alteration, cough, bronchospasm.  
Dose: chronic pulmonary Pseudomonas aeruginosa infection in cystic fibrosis patients, by inhalation of nebulised solution, adult and child over 6 years, 300 mg every 12 hours for 28 days, courses repeated after 28-day interval.

Preparations
Tobramycin nebuliser solution, 60 mg/mL solution, 5 mL vial

5 A.4: Macrolides

Macrolides include erythromycin, azithromycin and clarithromycin, which are basically bacteriostatic antibacterial drugs. They have bactericidal activity against some microorganisms in high concentration.
Erythromycin has a similar but not identical antibacterial spectrum to penicillin. It has been used as an alternative to penicillin in hypersensitive patients. It is active against gram-positive bacteria, Neisseria spp., legionella spp., chlamydia aricketsiae and moderately active against anaerobes and mycoplasma. It is not active against most aerobic enteric gram-negative bacilli.

Azithromycin has been applied in the treatment of chlamydia trachomatis with an advantage over erythromycin of being long acting and once daily dose is recommended.

Clarithromycin is an erythromycin derivative with slightly greater activity than its parent compound. It is more potent against erythromycin-sensitive strains of streptococci and staphylococci. Effectively used in H. pylori eradication regimen. Clarithromycin and azithromycin cause less gastrointestinal disturbances than erythromycin.

**Erythromycin**

**Indications:** as alternative to penicillin in allergic patients; campylobacter enteritis, acne vulgaris, pneumonia, legionnaires’ disease, neonatal conjunctivitis, chlamydia infections, mycoplasma infections, pre-operative bowel preparation, syphilis and most infections with gram-positive organisms.

**Contra-indications:** hepatic disease; pregnancy.

**Cautions:** renal impairment; breast-feeding.

**Side-effects:** diarrhoea, nausea and vomiting, abdominal pain, allergic reactions, cholestatic jaundice.

**Dose:** orally, 250-500 mg 4 times daily.

Child, up to 2 years 125 mg 4 times daily, 2-8 years 250 mg 4 times daily.

Doses are doubled in severe infections.

By intravenous infusion, severe infections, 50 mg/kg daily by continuous infusion, or in divided dose every 6 hours.

**Preparations**

Erythromycin stearate tablets, 250 mg tab.

Erythromycin as ethyl succinate oral suspension, 200 mg/5 mL; 100 mL/bottle

Erythromycin as lactobionate injection, powder for reconstitution, 1 g vial (Restricted)

**Azithromycin** *(Restricted)*

**Indications:** adjunct to Pyrimethamine in toxoplasmosis; chlamydia infections (specifically, Chlamydia trachomatis).

**Contra-indications, cautions:** see erythromycin above

**Side-effects:** see erythromycin above; anorexia, dyspepsia; headache, drowsiness; photosensitivity.

**Dose:** seek expert advise on the dose range and regimen.
5. Infections

Preparations
Azithromycin capsule, 250 mg cap.
Azithromycin suspension, 200 mg/5 mL, 15 mL/bottle

Clarithromycin (Restricted)
Indications: adjunct to Pyrimethamine in toxoplasmosis; H. pylori eradication.
Contra-indications and cautions: see erythromycin above; reduce dose in renal impairment.
Side-effects: see erythromycin and azithromycin above; tooth and tongue discoloration, confusion, hypoglycaemia.
Dose: seek expert advise on the dose range and regimen.

Preparations
Clarithromycin tablets, 250 mg tab.
Clarithromycin suspension, 125 mg/5 mL.
Clarithromycin suspension, 250 mg/5 mL.
Clarithromycin injection powder for reconsititution, 500 mg vial

5 A.5: Other antibacterials

5 A.5.1: Sulphonamides and trimethoprim

More effective and less toxic antibacterials have superseded sulphonamide use. Sulphamethoxazole and trimethoprim (co-trimoxazole) has a synergistic antibacterial activity. However, the increasing bacterial resistance and the high incidence of sulphonamide–related adverse effects have diminished the value of co-trimoxazole.

Trimethoprim + Sulphamethoxazole (Co-trimoxazole) (Restricted)
Indications: chronic bronchitis, nocardiosis, brucellosis, prostatitis, urinary tract infections, granuloma inguinale, Pneumocystis carinii infection.
Contra-indications: porphyria; sensitivity to sulphonamides.
Cautions: hepatic and renal impairment; blood disorders; predisposition to folate deficiency; asthma; G6PD deficiency.
Side-effects: nausea, vomiting, skin reactions, blood disorders, hypoglycaemia, diarrhoea and antibiotic-associated colitis.
Dose: orally, 960 mg twice daily. Child 6 weeks-5months, 120 mg, 6 months–5years 240 mg, 6-12 years 480 mg twice daily for all age ranges. Intravenous infusion, in Pneumocystis carinii pneumonia, 96-120 mg/kg/day divided in 3-4 equal doses.

Preparations
Trimethoprim + Sulphamethoxazole tablets, 160 mg + 800 mg tab.
Trimethoprim + Sulphamethoxazole oral suspension, 40 mg + 200 mg/5 mL, 50-60 mL /bottle
Trimethoprim + Sulphamethoxazole intravenous injection, 16 + 80 mg/mL, 5 mL ampoule (co-trimoxazole 480 mg total in one ampoule)
5. Infections

5 A.5.2: Metronidazole

Metronidazole is active against anaerobic bacteria and protozoal parasites. It is effective in the treatment of trichomoniasis, bacterial vaginosis, Entamoeba histolytica and Giardia lamblia infections. It is also used in surgical and gynaecological sepsis and in antibiotic-associated colitis. It is available in oral, parenteral, topical and rectal formulations.

**Metronidazole**

**Indications:** alone or in combination with other antibacterials; trichomoniasis, bacterial vaginosis, surgical and gynaecological sepsis, pseudomembranous colitis, gingivitis; giardiasis, amoebiasis; other uses,

**Cautions:** alcohol intolerance; hepatic impairment and hepatic encephalopathy, pregnancy and breast-feeding.

**Side-effects:** nausea and vomiting, unpleasant metallic taste, gastrointestinal disturbances, drowsiness and headache, darkening of urine, pruritus, urticaria.

**Dose:** in anaerobic infections, intravenous infusion, initially 15 mg/kg followed by 7.5 mg/kg every 6-8 hours. Orally, 800 mg initially followed by 400 mg OR 500 mg 3 times daily. Rectally, 1 g every 8 hours for 3 days and then 1 g every 12 hours. Treatment should be for 7-10 days.

Child, intravenously or orally, 7.5 mg/kg every 8 hours. Rectally, 3 times daily for 3 days then twice daily, up to 1 year 125 mg, 1-5 years 250 mg, 5-10 years 500 mg. Treatment for 7-10 days.

Oral gel, apply 1-2 times daily.

**Preparations**

Metronidazole injection, 5 mg/mL 100 mL vial (Restricted)
Metronidazole suppository, 500 mg supp.
Metronidazole suspension, 125-200 mg/5 mL; 100-120 mL/bottle
Metronidazole tablets, 200-250 mg tab.
Metronidazole oral gel, 2.5%

5 A.5.3: Quinolones

Nalidixic acid is the older member of this group, which has been used for urinary tract infections. Fluorinated quinolones such as ciprofloxacin, which has a broad antibacterial spectrum, is used for the treatment of a wide variety of infections. Few side-effects have been associated with the use of fluoroquinolones, and microbial resistance to their action does not develop rapidly. Ciprofloxacin is well absorbed after oral administration and mainly eliminated by the renal route. Renal impairment requires a dose adjustment of ciprofloxacin but not for nalidixic acid.

**Ciprofloxacin (Restricted)**
5. Infections

**Indications:** gram-negative and gram-positive microorganisms; urinary tract infections, chronic prostatitis, gonorrhoea, pseudomonal lower respiratory tract infections; enteric fever; anthrax. **Cautions:** renal impairment; patients with history of seizure or epilepsy, G6PD deficiency, pregnancy and breast-feeding, young children; patients should be advised to discontinue treatment at the first sign of pain or inflammation in the limbs and have some rest. **Side-effects:** nausea and vomiting, gastrointestinal disturbances; headache, dizziness, sleep disturbances; hyperglycaemia; tremor; tendonitis (see cautions above)

**Dose:** orally, most infections, 250-750 mg twice daily. 
Gonorrhoea, 500 mg single dose. 
Chronic Prostatitis, 500 mg twice daily for 28 days.
By intravenous infusion, slow over 30-60 minutes, 200-400 mg twice daily.
Child under 5 years, not recommended, 5-17 years, up to 10 mg/kg 3 times daily, maximum 1.2 g daily.

**Preparations**
Ciprofloxacin tablets, 250 mg tab.
Ciprofloxacin infusion, 2 mg/mL; 100 mL bottle

**Levofloxacin (Restricted)**

**Indications:** community acquired pneumonia, complicated urinary tract infection, infection of skin and/or subcutaneous tissue, chronic prostatitis, exacerbation of chronic bronchitis.

**Cautions:** see under ciprofloxacin. Predisposition to QT interval prolongation (including cardiac disease, congenital long QT syndrome, electrolyte disturbances, concomitant use with other drugs known to prolong QT interval).

**Driving:** may cause drowsiness and affect performance of skilled tasks.

**Side-effects:** see under ciprofloxacin, also flatulence, constipation, tachycardia, pneumonitis, peripheral neuropathy, rhabdomyolysis, potentially life-threatening hepatic failure; local reactions and transient hypotension.

**Dose:** orally and intravenously, the average dose is usually between 250-500 mg once or twice daily for 7-14 days depending on the type and severity of infection.

**Preparations**
Levofloxacin tablets, 500 mg tab.
Levofloxacin injection (intravenous infusion), 5 mg/mL, 100 mL bottle

**Moxifloxacin (Restricted)**

**Indications:** used as a second line when conventional therapy has failed or contraindicated in acute bacterial exacerbation of chronic bronchitis, sinusitis, community acquired pneumonia.

**Contra-indications:** history of QT-interval prolongation, bradycardia, symptomatic arrhythmias,
electrolytes disturbances, heart failure with reduced ejection fraction, severe hepatic impairment.
N.B: No dosage adjustment is required in renally impaired patients.
Cautions: conditions predisposing to arrhythmias.
Driving: may cause drowsiness and affect performance of skilled tasks.
Side-effects: stomatitis, glossitis, palpitations, blood pressure changes, constipation, dyspnoea, anxiety, peripheral oedema.
Dose: 400 mg once daily for 5-10 days.

Preparations
Moxifloxacin tablets, 400 mg tab.
Moxifloxacin injection (intravenous infusion), 400 mg/250 mL

Nalidixic acid (Restricted)
Indications: urinary tract infection; bacterial dysentery.
Cautions: see under ciprofloxacin. Liver disease; monitor blood count, liver and renal function if treatment exceeds 2 weeks.
Side-effects: see under ciprofloxacin; also, psychosis, intracranial hypertension, metabolic acidosis.
Dose: orally, for suppressive therapy 500mg 4 times daily. Child 33 mg/kg/day in divided doses. For acute therapy, 4 g daily in 4 divided doses. Child, 55-60 mg/kg/day in 4 divided doses.

Preparations
Nalidixic acid tablets, 500 mg tab.
5. Infections

terococci, but Pseudomonas aeruginosa and many strains of Proteus spp are resistant to tigecycline.

**Doxycycline**

*Indications*: rosacea, mycoplasma infections, Chlamydia infections, brucellosis, cholera; brucellosis with aminoglycosides, pelvic inflammatory disease, syphilis, sinusitis; rickettsia; acne; lyme disease; anthrax; prophlaxis of malaria

*Contra-indications*: breast-feeding; children under 12 years.

*Cautions*: hepatic impairment; renal impairment; alcohol dependence.

*Side effects*: nausea and vomiting, gastrointestinal disturbances, allergic skin reactions; headache and visual disturbances may indicate intracranial hypertension; teeth discoloration, anorexia; tinnitus, dry mouth; anxiety; flushing; fungal superinfection.

*Dose*: orally, for general use, 100 mg twice daily for 1 day and then 100 mg once daily. In severe infections, 100 mg twice daily.

**Preparations**

Doxycycline capsules/tablets, 100 mg cap/tab.

**Minocycline**

*Indications*: rosacea, mycoplasma infections, Chlamydia infections, brucellosis, cholera; meningooccal carrier state, non-gonococcal urethritis; acne.

*Contra-indications*: see under doxycycline.

*Cautions*: hepatic impairment; alcohol dependence; systemic lupus erythematosus; renal impairment; monitor blood picture if used for more than 6 months period.

*Side-effects*: nausea and vomiting, gastrointestinal disturbances, allergic skin reactions; headache and visual disturbances may indicate intracranial hypertension; teeth discoloration; tinnitus, vertigo, anorexia and dizziness; discoloration of conjunctiva, tears and sweat.

*Dose*: 100 mg twice daily.

**Preparations**

Minocycline capsules, 100 mg cap.

**Tigecycline (Restricted)**

*Indications*: Treatment of complicated skin and soft-tissue infections and complicated abdominal infections caused by multiple-antibacterial resistant organisms when other antibacterials cannot be used.

*Cautions*: Cholestasis; pregnancy; breastfeeding; hepatic impairment.

*Side-effects*: Abdominal pain; anorexia; bilirubinaemia; diarrhoea; dizziness; dyspepsia; headache; hypoglycaemia; injection-site reactions; nausea; prolonged activated partial thromboplastin time; prolonged prothrombin time; pruritus; rash; vomiting

*Dose*: Initially 100 mg, then 50 mg every 12 hours for 5–14 days, not recommended for the treatment of foot infections in patients with diabetes.

Maintainance dose should be reduced by one half in patients with...
5. Infections

severe hepatic dysfunction. No dose adjustment is required in renally impaired or hemodialysis patients.

Preparations
Tigecycline injection, 50 mg

5 A.5.5: Chloramphenicol and other antibiotics

5 A.5.5.1: Chloramphenicol

Chloramphenicol is a potent bactericidal antibiotic, which should be reserved for life-threatening infections. Its use is associated with serious adverse effects and therefore should not be used for prolonged or repeated treatment courses. It is mainly reserved for enteric fever and typhoid (; it should not be used indiscriminately for minor infections. Chloramphenicol should be avoided in hepatic failure and during pregnancy or breast-feeding. Toxicity in neonates and infants has resulted in grey-baby syndrome with concentration exceeding 25 mg/kg daily.

**Chloramphenicol (Restricted)**

**Indications:** typhoid, enteric fever, meningitis.

**Contra-indications:** pregnancy, breast-feeding, porphyria.

**Cautions:** see notes above

**Side-effects:** blood disorders, peripheral neuritis, optic neuritis, nausea, vomiting, diarrhoea, stomatitis.

**Dose:** orally or by intravenous injection or infusion, 50 mg/kg daily in 4 divided doses, the dose can be doubled in severe infections but should be reduce as soon as clinical conditions improve.

Child, less than 2 weeks, 25 mg/kg/day in 4 divided doses, 2 weeks-1 year and older children, 50 mg/kg daily in 4 divided doses.

**Preparations**
Chloramphenicol capsules, 250 mg cap.

5 A.5.5: Other antibiotics

Fusidic acid is a narrow-spectrum antibiotic. It is effective against most gram-positive bacteria and gram-negative cocci. Its main use is in treatment of infections caused by penicillin resistant staphylococci especially in osteomyelitis, as it is highly concentrated in the bone. A second anti-staphylococcal antibiotic is preferably used with fusidic acid to prevent the emergence of resistance.

Fusidic acid is well absorbed from the gut and is metabolised in the liver to inactive metabolite.

Linezolid, an oxazolidinone antibacterial, is active against Gram-positive bacteria including meticillin-resistant Staphylococcus aureus (MRSA), and glycopeptide-resistant enterococci. Resistance to linezolid can develop with prolonged treatment or if the dose is...
5. Infections

less than that recommended. Linezolid is not active against common Gram-negative organisms; it must be given in combination with other antibacterials for mixed infections that also involve Gram-negative organisms.

**Fusidic acid and sodium fusidate (Restricted)**

**Indications:** osteomyelitis, skin and soft tissue infection due to penicillin-resistant *Staphylococcus aureus*.

**Cautions:** hepatic impairment; pregnancy; breast-feeding.

**Side-effects:** nausea and vomiting, reversible jaundice after large doses or rapid infusion.

**Dose:** orally, (as sodium fusidate) 500 mg every 8 hours, doubled in severe infections. Child (as fusidic acid suspension) up to 1 year, 50 mg/kg daily in 3 divided doses, 1-5 years, 250 mg every 8 hours, 6-12 years 500 mg every 8 hours.

**Preparations**

- Fusidic acid suspension, 250 mg/5 mL susp, 90 mL/bottle
- Sodium fusidate tablets, 250 mg tab.

**Vancomycin and Teicoplanin**

Vancomycin is effective against gram-positive organisms but relatively ineffective against gram-negative organisms. It is specifically useful in treatment of methicillin-resistant *S. aureus* (MRSA) infections. It is also useful in endocarditis and pseudomembranous colitis caused by *Clostridium difficile*. It has a long duration of action that permits twice daily administration. Orally, its absorption is minimal and is used for its local effect as in pseudomembranous colitis; for serious infections, it is given by intravenous route.

Teicoplanin is an alternative to Vancomycin with a longer duration of action. It is administered by intravenous and intramuscular injection but not orally.

**Vancomycin (Restricted)**

**Indications:** see notes above, endocarditis prophylaxis and treatment, serious infection with staphylococci.

**Cautions:** avoid rapid infusion; renal impairment; avoid in elderly with a history of deafness; blood count.

**Side-effects:** nephrotoxicity, ototoxicity, blood disorders; anaphylaxis reactions; red-man syndrome (flushing of the upper body); nausea and vomiting.

**Dose:** orally in pseudomembranous colitis, 125 mg every 6 hours for 7-10 days. Child up to 5 years, 5 mg/kg every 6 hours; more than 5 years, half adult dose.
5. Infections

By intravenous infusion over 30-60 minutes, 500 mg every 6 hours or 1 g every 12 hours. Neonates, 15 mg/kg, then 10 mg/kg every 12 hours; Infants 1-4 weeks, initially 15 mg/kg and then 10 mg/kg every 8 hours; Child over 1 month, 10 mg/kg every 6 hours.

Preparations
Vancomycin hydrochloride injection, powder for reconstitution, 500 mg vial

**Teicoplanin (Restricted)**

**Indications:** see vancomycin

**Cautions:** vancomycin sensitivity, renal and liver function tests, monitor for ototoxicity.

**Side-effects:** nausea, vomiting, diarrhoea; blood disorders; tinnitus and temporary hearing loss; sensitivity reactions.

**Dose:** by intramuscular injection or intravenous injection or infusion, initially 400 mg and then 200 mg daily. In severe infections, initially 400 mg twice daily then 400 mg once daily. Child over 2 months, initially 10 mg/kg every 12 hours then 6 mg/kg daily.

Preparations
Teicoplanin injection, powder for reconstitution, 200 mg vial

**Clindamycin (Restricted)**

**Indications:** staphylococcal joint and bone infections such as osteomyelitis, intra-abdominal sepsis, an alternative to macrolides for erysipelas or cellulitis in penicillin allergic patients, infections associated with meticillin resistant *Staphylococcus aureus* (MRSA) in bronchiectasis, bone and joint infections, skin and soft tissue infections.

**Contraindications:** diarrhoeal states; avoid injections containing benzyl alcohol in neonates.

**Cautions:** bacterial overgrowth may occur; risk of *Clostridium difficile* induced diarrhoea and pseudomembranous colitis, concomitant use with erythromycin is not recommended, diarrhoea may occur two or more months after discontinuation of therapy, monitor liver and renal function on prolonged therapy and in neonates and infants, pregnancy, breast-feeding, avoid rapid intravenous administration, avoid in acute porphyria

**Side-effects:** diarrhoea (discontinue treatment), abdominal discomfort, oesophagitis, oesophageal ulcers, taste disturbances, nausea, vomiting, antibiotic-associated colitis; jaundice; leucopenia, eosinophilia, thrombocytopenia, rash, pruritus, urticaria, anaphylactoid reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative and vesiculobullous dermatitis, pain, induration, and abscess after intramuscular injection; thrombophlebitis after intravenous injection.

**Dose:** orally, 150–300 mg every six hours; up to 450 mg every 6 hours in severe infections; child, 3–6
5. Infections

mg/kg every 6 hours. By deep intramuscular injection or by intravenous infusion, 0.6–2.7 g daily (in 2–4 divided doses); life-threatening infection, up to 4.8 g daily; single doses above 600 mg by intravenous infusion only; single doses by intravenous infusion not to exceed 1.2 g; child over 1 month, 15 mg/kg daily in 3–4 divided doses; severe infections, at least 300 mg daily regardless of weight.

Preparations
Clindamycin capsule, 150 mg cap.
Clindamycin suspension, 75 mg / 5 mL
Clindamycin injection, 150 mg/mL; 2 mL ampoule

**Colistin (Restricted)**

**Indications:** active against Gram-negative organisms including *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and *Klebsiella pneumoniae* (should be reserved for Gram-negative infections resistant to other antibacterials).

**Contraindications:** myasthenia gravis, pregnancy, breast-feeding.

**Cautions:** renal impairment, acute porphyria, risk of bronchospasm on inhalation (may be prevented or treated with a selective beta₂ agonist), plasma concentration monitoring required in neonates, renal impairment, and in cystic fibrosis; recommended peak plasma colistin concentration (approx. 30 minutes after intravenous injection or infusion) 10–15 mg/litre (125–200 units/mL).

**Side-effects:** neurotoxicity, nephrotoxicity, hypersensitivity reactions.

**Dose:** by slow intravenous injection into a totally implantable venous access device, or by intravenous infusion; adult and child body weight under 60 kg, 50,000–75,000 units/kg daily in three divided doses; body-weight over 60 kg, 1–2 million units every 8 hours. By mouth, bowel sterilisation, 1.5–3 million units every 8 hours. By inhalation of nebulised solution, adult and child over 2 years, 1–2 million units every 12 hours; child under 2 years, 0.5–1 million units every 12 hours.

Preparations
Colistin, injection, powder for reconstitution, 1 million unit vial

**Linezolid (Restricted)**

**Indications:** Pneumonia (when other antibacterials e.g. a glycopeptide, such as vancomycin, cannot be used) (initiated under specialist supervision)

Complicated skin and soft-tissue infections caused by Gram-positive bacteria, when other antibacterials cannot be used (initiated under specialist supervision)

**Cautions:** Pregnancy; breastfeeding; contaminant MAOIs; severe optic neuropathy may occur rarely, particularly if linezolid is used for longer than 28 days. Patients should be warned to report symptoms of visual impairment (including blurred vision, visual field defect,
changes in visual acuity and colour vision) immediately. Monitor full blood count (including platelet count weekly). Acute confusional states; bipolar depression; carcinoid tumour; elderly (increased risk of blood disorders); history of seizures; phaeochromocytoma; schizophrenia; thyrotoxicosis; uncontrolled hypertension. Unless close observation and blood pressure monitoring possible, linezolid should be avoided in uncontrolled hypertension, phaeochromocytoma, carcinoid tumour, thyrotoxicosis, bipolar depression, schizophrenia, or acute confusional states.

**Side-effects:** Diarrhoea; eosinophilia; headache; nausea; taste disturbances; vomiting, anaemia; antibiotic-associated colitis; convulsions; hyponatraemia; lactic acidosis; optic neuropathy reported on prolonged therapy; pancytopenia; peripheral neuropathy reported on prolonged therapy; Stevens-Johnson syndrome; tooth discoloration; toxic epidermal necrolysis; myelosuppression.

**Dose:** 600 mg every 12 hours usually for 10–14 days (maximum duration of treatment 28 days).

**Preparations**
- Linezolid tablets, 600 mg tab.
- Linezolid suspension 100 mg / 5 mL.
- Linezolid injection, 2 mg / mL injection.

### 5. Infections

#### 5 A.6: Antituberculous and antileptotic drugs

#### 5 A.6.1: Antituberculous drugs

**For tuberculosis (TB) treatment protocols and procedures, refer to MOH TB treatment manual**

Patients with TB are categorized into 4 categories and treatment is usually of 2 phases, initial phase and continuous phase.

**Category I:** new cases of smear-positive pulmonary TB and other newly diagnosed seriously ill patients with severe forms of TB.

**Initial phase:** INH, Rifampicin, Pyrazinamide and either Streptomycin or Ethambutol daily for 2 months

**Continuous phase:** INH and Rifampicin daily for 4 months

**Category II:** Relapse and treatment failure (smear-positive)

**Initial phase:** INH, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin daily for 2 months followed by INH, Rifampicin, Pyrazinamide and Ethambutol for 1 month.

**Continuous phase:** INH, Rifampicin and Ethambutol daily for 5 months.

**Category III:** Pulmonary smear-negative TB with limited parenchymal involvement and extra-pulmonary TB/ other than the forms in...
5. Infections

category I, TB in children and young people who develop primary TB usually appearing as pleural effusion or small parenchymal lesions in lungs.

**Initial phase:** INH, Rifampicin, Pyrazinamide, Ethambutol daily for 2 months

**Continuous phase:** INH, Rifampicin daily for 4 months.

**Category IV:** Chronic cases. Patients of this category are managed at specialized centres as per individual case as most of these patients are resistant to conventional therapy.

### Dosage, schedule and route of TB drugs

<table>
<thead>
<tr>
<th>Drug strength</th>
<th>Route</th>
<th>Dose daily frequency</th>
<th>Adult daily dose</th>
<th>Child Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH, 100 &amp; 300 mg</td>
<td>Oral</td>
<td>1</td>
<td>5 mg/kg. Max. 300 mg</td>
<td>10-15 mg/kg, max. 300 mg</td>
</tr>
<tr>
<td>Rifampicin, 150 &amp; 300 mg</td>
<td>Oral</td>
<td>1 (to be taken early morning)</td>
<td>10 mg/kg if body weight &lt;50 kgs (Max. 450 mg)</td>
<td>10-20 mg/kg, max. 600 mg</td>
</tr>
<tr>
<td>Ethambutol 400 mg</td>
<td>Oral</td>
<td>1</td>
<td>25 mg/kg for not more than 2 months. 15 mg/kg if longer than 2 months</td>
<td>15-25 mg/kg, max. 2.5 g</td>
</tr>
<tr>
<td>Streptomycin 1 g</td>
<td>IM</td>
<td>1</td>
<td>15 mg/kg</td>
<td>20-40 mg/kg, max. 1 g</td>
</tr>
<tr>
<td>Pyrazinamide 500 mg</td>
<td>Oral</td>
<td>1</td>
<td>25 mg/kg</td>
<td>20-40 mg/kg, max. 2 g</td>
</tr>
</tbody>
</table>

_N.B._ Antituberculous drugs are made available to Health Centres wherever TB cases are on treatment within their catchment area.
5. Infections

**Ethambutol (Restricted)**

**Indications:** TB treatment regimen.

**Contra-indications:** optic neuritis, poor vision.

**Cautions:** renal impairment, avoid in young and elderly, monitor for visual disturbances.

**Side-effects:** decreased visual acuity (reversible), optic neuritis, peripheral neuritis, gastrointestinal disturbances, confusion, hallucination.

**Dose:** see the table

**Preparations**
- Ethambutol hydrochloride tablets, 400 mg tab.

**Isoniazid (Isonicotinic acid hydrazide, INH)**

**Indications:** TB treatment regimen.

**Cautions:** renal and hepatic function, diabetes, epilepsy, pregnancy and breast-feeding.

**Side-effects:** peripheral neuritis, optic neuritis, nausea and vomiting, impairment of memory, psychosis, allergic reactions, blood disorders.

**Dose:** see table above; consider concurrent pyridoxine administration in malnourished, diabetics, alcoholics, and slow acetylators to prevent peripheral neuritis.

**Preparations**
- Isoniazid tablets, 100 mg tab.
- Isoniazid elixir, 50 mg/5 mL, 500 mL/bottle

**Pyrazinamide (Restricted)**

**Indications:** TB treatment regimen.

**Contra-indications:** liver disease.

**Cautions:** pregnancy, hepatic impairment, gout, diabetes.

**Side-effects:** hepatotoxicity, urticaria, arthralgia, rash, nausea and vomiting.

**Dose:** see the table

**Preparations**
- Pyrazinamide tablets, 500 mg tab.

**Rifabutin (Restricted)**

**Indications:** Prophylaxis of Mycobacterium avium complex infections in immunosuppressed patients with low CD4 count. Treatment of non-tuberculous mycobacterial disease, in combination with other drugs. Treatment of pulmonary tuberculosis, in combination with other drugs.

**Cautions:** Acute porphyrias; discolours soft contact lenses

**Side-effects:** Anaemia; blood disorders; leucopenia; myalgia; nausea; pyrexia; rash; thrombocytopenia, arthralgia; body secretions coloured orange-red; bronchospasm; corneal deposits; eosinophilia; hypersensitivity reactions; jaundice; raised liver enzymes; saliva coloured orange-red; skin coloured orange-red; urine coloured orange-red; uveitis (especially following high doses or concomitant use with drugs that increase plasma concentration); vomiting.
5. Infections

**Dose**: Prophylaxis of Mycobacterium avium complex infections in immunosuppressed patients with low CD4 count, 300 mg once daily, also consult product literature. Treatment of non-tuberculous mycobacterial disease, in combination with other drugs 450–600 mg once daily for up to 6 months after cultures negative. Treatment of pulmonary tuberculosis, in combination with other drugs, 150–450 mg once daily for at least 6 months.

**Preparations**
Rifabutin tablets, 150 mg tabs

**Rifampicin (Restricted)**

**Indications**: TB treatment regimen; brucellosis and legionnaire’s disease in combination with other antibiotics; leprosy; prevention of meningococcal meningitis.

**Contra-indications**: sensitivity to rifampicin, jaundice.

**Cautions**: hepatic impairment; renal impairment; pregnancy and breast-feeding; porphyria; discolour soft contact lenses, brown-red colouration of faeces, urine and saliva; due to its ability to induce metabolic enzymes, contraceptive users should be advised to seek additional protection; enhances metabolism of warfarin, dapsone, oral hypoglycaemic drugs, and corticosteroids.

**Side-effects**: gastrointestinal disturbances, headache, drowsiness, dizziness, visual disturbances, confusion, fatigue, menstrual irregularities, ataxia, pain in the extremities. Intermittent use of rifampicin may rarely induce flu-like syndrome, acute haemolytic anaemia, acute renal failure, hepatitis, skin reactions. Thrombocytopenia indicates the need to stop therapy and never to use rifampicin again in the same patient.

**Dose**: for TB, see tables above. Brucellosis, Legionnaires’ disease and serious staphylococcal infections in combination with other antibiotics, 0.6-1.2 g daily in 2-4 divided doses.
Leprosy, see sec. 5A.6.2

**Preparations**
Rifampicin capsule, 150 mg cap.
Rifampicin capsule, 300 mg cap.
Rifampicin syrup, 100 mg/5 mL, 50-60 mL/bottle

**Streptomycin (Restricted)**

**Indications**: TB treatment regimen; see sec. 5A.3

**Contra-indications, cautions and side-effects**: see sec. 5A.3 and
**Dose**: see table

**Preparations**
Streptomycin sulphate injection, powder for reconstitution, 1 g vial

**Complementary drugs for the treatment of TB include:**

**Capreomycin Sulphate (C.D.L)**

**Indications**: adjunct to other TB treatment in TB cases resistant to conventional therapy.
5. Infections

**Cautions**: renal, hepatic or auditory impairment; pregnancy and breast-feeding.

**Side-effects**: hypersensitivity reactions; tinnitus, hearing loss; hepato-toxicity; nephrotoxicity.

**Dose**: by deep intramuscular injection, 1 g daily. Consult specialist for dose and duration of therapy.

Preparations
Capreomycin sulphate injection, powder for reconstitution, 1 g (1 million unit) vial

**D-cycloserine (C.D.L)**

**Indications**: adjunct to other TB treatment in TB resistant to conventional therapy.

**Contra-indications**: severe renal impairment; psychotic and neurogenic disorders.

**Cautions**: monitor renal, hepatic and haematological functions; pregnancy and breast-feeding.

**Side-effects**: headache, vertigo, sedation, psychosis.

**Dose**: 250 mg twice daily, increased if necessary to 1 g daily in divided doses. Consult specialist for dose and duration of therapy.

Preparations
D-cycloserine capsule, 250 mg cap.

**Protionamide (Prothionamide) (C.D.L)**

**Indications**: adjunct to other TB treatment in TB resistant to conventional therapy.

**Contra-indications**: severe hepatic impairment; hypersensitivity.

**Cautions**: hepatic disease; depression and other psychotic illness; monitor blood glucose, thyroid function and visual disturbances.

**Side-effects**: gastrointestinal disturbances; mental disturbances; peripheral and optic neuritis; hypersensitivity reactions.

**Dose**: orally, 250 mg twice daily increased if necessary to 1 g daily in divided doses. Consult specialist for dose and duration of therapy.

Preparations
Protionamide tablets, 250 mg tab.

**Rifampicin and isoniazid are combined in one single oral formulation for the national TB control programme as follows:**

Rifampicin 150 mg + isoniazid 75 mg tablets
Rifampicin 150 mg + isoniazid 100 mg tablets
Rifampicin 300 mg + isoniazid 150 mg tablets
Rifampicin 150 mg + isoniazid 75 mg + pyrazinamide 400 mg + ethambutol 275 mg tablets

5 A.6.2: Antileprotic drugs

For leprosy treatment protocols and procedures, refer to MOH leprosy treatment manual
The recommended treatment protocol involves a multi-drug therapy
5. Infections

Escherichia coli, is the most common cause of urinary tract infection. Other organisms may be involved, and identification of the causative organism and its susceptibility are very important determinants of treatment. However, acute and disabling attacks in women may call for prompt empirical therapy while awaiting laboratory results. Most cases of uncomplicated urinary tract infections are efficiently treated with nalidixic acid, co-trimoxazole, nitrofurantoin, and ciprofloxacin. Complicated cases may require a combined therapy mostly of penicillins and aminoglycosides.

Prophylaxis of chronic urinary tract infections can be achieved with low doses of nitrofurantoin. Certain measures can contribute to therapy and reduce the incidence of urinary tract infection. A dose of the drug given immediately before retiring to bed, after having emptied the bladder completely, may control the regrowth of bacteria overnight. Large volume of fluid intake and frequent micturition help eliminate bacteria and reduce pain. Use of yoghurt, which is rich in non-pathogenic Lactobacilli, reduces the E. coli population in the bowel and hence mitigates urinary tract infection in women.

Drugs other than nitrofurantoin used in urinary tract infections have been discussed under relevant sections above.

Nitrofurantoin
Indications: urinary tract infections.
Contraindications: impaired renal function; infants less than 3 months of age, G6PD deficiency.
Cautions: anaemia, diabetes mellitus, pulmonary disease, hepatic impairment.
Side-effects: gastrointestinal disturbances; pulmonary reactions, peripheral neuropathy, blood disorders, skin reactions.
Dose: Acute uncomplicated urinary tract infection, 50-100 mg 4 times daily. Child, 3 mg/kg daily in 4 divided doses. Prophylaxis, 100 mg single dose at night. Child 1 mg/kg single dose at night.
Preparations
Nitrofurantoin tablets 100 mg tab.

Amphotericin and nystatin are not absorbed from gut and when applied orally they are effective only on the gastrointestinal tract. However, amphotericin is effective against systemic fungal infections when administered intravenously. It has a high toxicity and has been

5 B: Antifungals

5 B.1: Polyene antifungals

The recommended treatment approach. The principal drugs in this protocol are, rifampicin, dapsone and clofazimine. Drugs such as minocycline, ofloxacin and clarithromycin, though not effective as rifampicin, are kept as second line therapy.

The recommended treatment protocol for multibacillary leprosy involves 3 drugs for a minimum period of 12 months as follows:

**Rifampicin**
300 mg once a month

**Dapsone**
100 mg daily (1-2 mg/kg daily)

**Clofazimine**
300 mg once a month + 100 mg on alternate days

The recommended treatment protocol for paucibacillary leprosy involves 2 drugs for a minimum period of 6 months as follows:

**Rifampicin**
600 mg once a month (adult), 300 mg (child up to 6 years)
450 mg (child 6-12 years)

**Dapsone**
100 mg daily (1-2 mg/kg daily)

If treatment is interrupted the regimen should be restarted where it was left off to complete the full course.

**Clofazimine (Restricted)**
Indications: leprosy in combination with other drugs.
Cautions: Clofazimine should be reduced or discontinued if gastrointestinal symptoms such as abdominal pain or burning, nausea, vomiting, or diarrhea appear.
Side-effects: gastrointestinal disturbances; brownish discoloration of lesions and exposed skin to light; coloration of faeces, urine and other body fluids; skin reactions.
Dose: see notes above

Preparations
Clofazimine capsule, 100 mg cap.

**Dapsone (Restricted)**
Indications: leprosy in combination with other drugs.
Cautions: cardiac and pulmonary disease, anaemia; G6PD deficiency; pregnancy and breast-feeding.
Side-effects: dose related haemolytic anaemia, methaemoglobinemia, skin reactions, gastrointestinal disturbances, neuropathy; dapsone syndrome characterized by rash with fever and eosinophilia (lepromatous reaction).
Dose: see notes above

Preparations
Dapsone tablets, 100 mg tab.

**Rifampicin (Restricted)**
For indications, contraindications, cautions and side-effects: see sec 5 A.6.1 under Rifampicin
Dose: in leprosy, see notes above.

5 A.7: Urinary tract antiseptics
5. Infections

_Escherichia coli_, is the most common cause of urinary tract infection. Other organisms may be involved, and identification of the causative organism and its susceptibility are very important determinants of treatment. However, acute and disabling attack in women may call for prompt empirical therapy while awaiting the laboratory results. Most cases of uncomplicated urinary tract infections are efficiently treated with nalidixic acid, co-trimoxazole, nitrofurantoin, and ciprofloxacin. Complicated cases may require a combined therapy mostly of penicillins and aminoglycosides.

Prophylaxis of chronic urinary tract infections can be achieved with low doses of nitrofurantoin. Certain measures can contribute to therapy and reduce the incidence of urinary tract infection. A dose of the drug given immediately before retiring to bed, after having emptied the bladder completely may control the regrowth of bacteria overnight. Large volume of fluid intake and frequent micturition help eliminate bacteria and reduces pain. Use of yoghurt, which is rich in non-pathogenic _Lactobacilli_, reduces the _E. coli_ population in the bowel and hence mitigates urinary tract infection in women.

**Drugs other than nitrofurantoin used in urinary tract infections** have been discussed under relevant sections above.

### Nitrofurantoin

**Indications:** urinary tract infections.

**Contra-indications:** impaired renal function; infants less than 3 months of age, G6PD deficiency.

**Cautions:** anaemia, diabetes mellitus, pulmonary disease, hepatic impairment.

**Side-effects:** gastrointestinal disturbances; pulmonary reactions, peripheral neuropathy, blood disorders, skin reactions.

**Dose:** Acute uncomplicated urinary tract infection, 50-100 mg 4 times daily. Child, 3 mg/kg daily in 4 divided doses.

Prophylaxis, 100 mg single dose at night. Child 1 mg/kg single dose at night.

**Preparations**

Nitrofurantoin tablets 100 mg tab.

### 5 B: Antifungals

#### 5 B.1: Polyene antifungals

Amphotericin and nystatin are not absorbed from gut and when applied orally they are effective only on the gastrointestinal tract. However, amphotericin is effective against systemic fungal infections when administered intravenously. It has a high toxicity and has been
5. Infections

superseded by new generation of antifungals.
Various lipid formulations have been applied to reduce amphotericin toxicity.
Nystatin is effective against Candida albicans infections of the skin and mucous membrane, including oesophageal and intestinal candidiasis.

Amphotericin (Restricted) (Amphotericin B)
Indications: oropharyngeal fungal infections; systemic fungal infections.
Contra-indications: concurrent use of nephrotoxic drugs.
Caution: (when given intravenously) monitor renal and hepatic function and blood count; corticoids; pregnancy and breast-feeding.
Side-effects: (when given intravenously) gastrointestinal disturbances, anaphylaxis; nephrotoxicity; headache, muscle and joint pain; blood disorders.
Dose: oropharyngeal fungal infections, see sec. 12C.2
Systemic fungal infections, intravenous infusion, initial test dose of 1 mg over 20-30 minutes, then 250 micrograms/kg daily. Increase gradually, maximum dose 1.5 mg/kg daily.

Preparations
Amphotericin sodium deoxycholate complex injection, powder for reconstitution, 50 mg vial

Nystatin
Indications: candidiasis; (for vaginal and skin candidiasis see sec 7B and 13G.2.2)
Side-effects: nausea and vomiting, diarrhoea; oral burning sensation.
Dose: oral, 500,000 units 4 times daily. Child, 100,000 units 4 times daily.
Prophylaxis, 1 million units once daily.

Preparations
Nystatin oral suspension, 100,000 units/mL; 24-30 mL/bottle

5 B.2: Triazole antifungals

Triazole derivatives such as fluconazole and itraconazole have similar activity to imidazole antifungals. They are orally effective, slowly metabolised and have less hepatotoxicity.

Fluconazole (Restricted)
Indications: vaginal candidiasis, candidal balanitis, mucosal candidiasis, invasive candidal infections, prophylaxis in fungal infection in immunosuppressed.
Caution: renal impairment, pregnancy and breast-feeding; monitor hepatic function.
5. Infections

**Side-effects**: gastrointestinal disturbances; headache, dizziness; hepatic disorders; rash, anaphylaxis, blood disorders.

**Dose**: orally, for vaginal candidiasis, candidal balanitis, 150 mg single dose.

Mucosal candidiasis, orally 50 mg daily for 1-2 weeks.

Tinea infections and dermal candidiasis, orally 50 mg daily for 2-4 weeks.

Invasive candidal infections and cryptococcal meningitis, orally or by intravenous infusion, 400 mg initially, then 200 mg daily. Increase if necessary to 400 mg. Treatment assessment according to response. Child 6-12 mg/kg daily.

Prophylaxis in immunosuppressed, orally 50-400 mg daily adjusted according to severity of infection.

**Preparations**

Fluconazole capsule, 50 mg cap.

Fluconazole tablets, 150 mg tab.

Fluconazole intravenous infusion, 2 mg/mL; 100 mL vial

**Itraconazole (Restricted)**

**Indications**: onchomycosis.

**Cautions**: liver disease; renal impairment; pregnancy and breastfeeding.

**Side-effects**: gastrointestinal disturbances, liver disease, peripheral neuropathy.

**Dose**: orally, by pulse therapy regimen, 200 mg twice daily for 7 days, repeated 21 day intervals.

**Preparations**

Itraconazole tablets/capsule, 100 mg tab/cap.

**Voriconazole (Restricted)**

**Indications**: Invasive aspergillosis

Serious infections caused by Scedosporium spp., Fusarium spp., or invasive fluconazole-resistant Candida spp. (including C. krusei)

**Contra-indications**: Acute porphyrias.

**Cautions**: Avoid exposure to sunlight; bradycardia; cardiomyopathy; electrolyte disturbances; history of QT interval prolongation; patients at risk of pancreatitis; symptomatic arrhythmias. Monitor liver function before starting treatment, then at least weekly for 1 month, and then monthly during treatment. Monitor renal function.

**Side-effects**: Abdominal pain; acute renal failure; agitation; alopecia; altered perception; anaemia; anxiety; asthenia; blood disorders; blurred vision; cheilitis; chest pain; confusion; depression; diarrhoea; dizziness; haematuria; hallucinations; headache; hypoglycaemia; hypokalaemia; hypotension; influenza-like symptoms; jaundice; leucopenia; nausea; oedema; pancytopenia; paraesthesia; photophobia; photosensitivity; pruritus; rash; respiratory distress syndrome; sinusitis; thrombocytopenia; tremor; visual disturbances; vomiting; adrenocortical insufficiency; arrhythmias; arthritis; ataxia; blepharitis; cholecystitis; constipation; duodenitis;
5. Infections

dyspepsia; flushing; fulminant hepatic failure; gingivitis; glossitis; hepatitis; hypersensitivity reactions; hypoaesthesia; hypoglycaemia; nystagmus; optic neuritis; pancreatitis; psoriasis; QT interval prolongation; raised serum cholesterol; scleritis; Stevens-Johnson syndrome; syncope

**Dose:** Orally (body-weight up to 40 kg) 200 mg every 12 hours for 2 doses, then 100 mg every 12 hours, increased if necessary to 150 mg every 12 hours. Orally (body-weight 40 kg and above) 400 mg every 12 hours for 2 doses, then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours.

By intravenous infusion. Initially 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours for max. 6 months; reduced if not tolerated to 3 mg/kg every 12 hours.

**Preparations**

Voriconazol tablets, 200 mg tabs  
Voriconazole powder for injection, 200 mg vial

5 B.3: Other antifungals

**Anidulafungin (Restricted)**  
**Indications:** invasive candidiasis  
**Cautions:** pregnancy, breast-feeding  
**Side effects:** diarrhoea, nausea, vomiting, flushing, convulsion, headache, coagulopathy, hypokalaemia, raised serum creatinine, rash, abdominal pain, cholestasis, hypertension, hyperglycaemia, urticaria, injection site pain, hypotension, dyspnoea, bronchospasm, hepatitis

**Dose:** by intravenous infusion, adult over 18 years, 200 mg on first day then 100 mg once daily

**Preparations**

Anidulafungin injection, powder for reconstitution, 100 mg vial

**Caspofungin (Restricted)**  
**Indications:** invasive aspergillosis, invasive candidiasis, empirical treatment of systemic fungal infections in patients with neutropenia  
**Cautions:** hepatic impairment, pregnancy, breast feeding  
**Side effects:** nausea, diarrhoea, vomiting, dyspnoea, headache, hypokalaemia, arthralgia, rash, sweating, injection site reactions, abdominal pain, dyspepsia, dry mouth, dysphagia, taste disturbances, anorexia, constipation, flatulence, cholestasis, hepatic dysfunction, ascites, palpitation, arrhythmia, chest pain, heart failure, thrombophlebitis, flushing, hypotension, hypertension, bronchospasm, cough, dizziness, fatigue, paraesthesia, hypoaesthesia, sleep disturbances, tremor, anxiety, disorientation, hyperglycaemia, renal failure, hypomagnesaemia, hypocalcaemia, metabolic acidosis, anaemia, thrombocytopenia, leucopenia, myalgia, muscular weakness, blurred vision, anderythema multiforme, adult respiratory distress syndrome, anaphylaxis
5. Infections

**Dose:** by intravenous infusion, 70 mg on first day then 50 mg once daily (70 mg once daily if body weight over 80 kg)

**Preparations**
Caspofungin injection, powder for reconstitution, 50 mg vial

**Griseofulvin (Restricted)**
**Indications:** dermatophytes infections when topical treatment is ineffective.
**Contra-indications:** severe liver disease, pregnancy; avoid pregnancy during and 1 month after treatment. When a man is treated, contraceptive protection by spouse during and 6 months after treatment.
**Cautions:** breast-feeding.
**Side-effects:** headache, nausea, vomiting, dizziness; skin reactions, photosensitivity; blood disorders.
**Dose:** 500 mg daily once daily, or in divided doses. In severe cases, dose can be doubled. Child, 10-15 mg/kg daily as a single dose or in divided doses.

**Preparations**
Griseofulvin tablets, 125 mg tab.

**Terbinafine (Restricted)**
**Indications:** dermatophytes infections in adults when topical treatment is ineffective.
**Cautions:** hepatic and renal impairment; pregnancy and breast-feeding; psoriasis.

**Side-effects:** gastrointestinal disturbances; headache; skin reactions; taste disturbances.
**Dose:** orally, 250 mg daily for 2-6 weeks.

**Preparations**
Terbinafine tablets, 250 mg tab.

5 C: Antiviral drugs

5 C.1: Herpes simplex and Varicella-zoster

Aciclovir has replaced the old antiviral vidarabine. It has proved effective in treating systemic Varicella-zoster and systemic and topical herpes simplex infections of skin and the mucous membrane; it is also used topically on the eye. It is a life saving antiviral in immunocompromised patients with recurrent viral infections.

Other antivirals of similar activity to aciclovir include, famciclovir, which is a pro-drug of penciclovir, and valaciclovir, which is a pro-drug of aciclovir.

Antivirals are more effective in treating viral infections at the onset of episode and are of less value in recurrent infections.

**Aciclovir (Acyclovir) (Restricted)**
**Indications:** herpes simplex and Varicella –zoster infections.
**Cautions:** renal failure; maintain good hydration; pregnancy and breast-feeding.
5. Infections

**Side-effects:** nausea and vomiting, abdominal pain, headache, fatigue, skin reactions; on intravenous infusion, severe local irritation, fever, tremor.

**Dose:** orally, herpes simplex, 200 mg (400 mg in immunocompromised) 5 times daily for 5 Days. Child under 2 years, half adult dose; Child over 2 years, adult dose.

Prevention of recurrence of herpes simplex infection, 200 mg 4 times daily, monitor dose according to response.

Prophylaxis of herpes simplex in the immunocompromised, 200-400 mg 4 times daily. Child under 2 years, half adult dose; Child over 2 years adult dose.

Varicella-zoster infections, 800 mg 5 times daily for a week; Child, Varicella, 20 mg/kg 4 times daily for 5 Days.

By intravenous infusion, 5 mg/kg doubled in immunocompromised, simplex encephalitis, and severe initial genital herpes, over 1 hour, every 8 hours for 5-10 days. Child 3 months - 12 years, 250 mg/m² every 8 hours for 5-10 days.

**Preparations**

- Aciclovir tablets, 200 mg tab.
- Aciclovir injection, powder for reconstitution, 250 mg vial
- Aciclovir oral Suspension, 200 mg/5 mL, 125 mL bottle

**Famciclovir (Restricted)**

**Indications:** herpes zoster, acute genital herpes simplex and suppression of recurrent genital herpes.

**Cautions and side-effects:** see Aciclovir above

**Dose:** herpes zoster, 250 mg 3 times daily or 750 mg once daily for 7 days, increase in immunocompromised.

Genital herpes, first episode, 250 mg 3 times daily for 5 Days. Recurrent infection, 125 mg twice daily for 5 Days, in immunocompromised, all episodes, 500 mg twice daily for seven days.

**Preparations**

- Famciclovir tablets, 250 mg tab.

**Valaciclovir (Restricted)**

**Indications:** treatment of initial and suppression of recurrent herpes simplex infection of the skin and mucous membranes including genital herpes.

**Cautions and side-effects:** see Aciclovir above

**Dose:** herpes simplex, initial episode and recurrent infection, 500 mg twice daily for 5 Days.

Herpes simplex suppression, 500 mg daily in 1-2 divided doses. Increase in immunocompromised.

**Preparations**

- Valaciclovir tablets, 500 mg tab.

5 C.2: Human Immunodeficiency Virus

No cure is yet available for human immunodeficiency virus (HIV), but a number of drugs slow and, if used very early, may halt the progression
5. Infections

Indications: HIV infection in combination with other antiretroviral agents.
Contra-indications: breast feeding.
Cautions: hepatic impairment, hepatitis B or C, renal impairment, pregnancy.
Side-effects: gastrointestinal disturbances, liver damage, lactic acidosis, pancreatitis, insomnia, blood disorders, rash, osteonecrosis, lipodystrophy syndrome, hypersensitivity reactions.
Dose: orally; 300 mg twice daily or 600 mg once daily

Preparations
Abacavir tablets, 300 mg tab.

Didanosine (Restricted)
Indications: HIV infection in combination with other antiretroviral agents.
Contra-indications: breast feeding.
Cautions: see under abacavir; also history of peripheral neuropathy, hyperuricaemia or pancreatitis.
Side-effects: see under abacavir; also peripheral neuropathy, diabetes mellitus, hypoglycaemia, acute renal failure, rhabdomyolysis, optic nerve and retinal changes, alopecia, parotid gland enlargement.
Dose: orally; if weight is ≥ 60 kg, 400 mg daily, if < 60 kg, 250 mg daily (1-2 divided doses). N.B: to be taken on an empty stomach at least 2 hours before or 2 hours after food.
5. Infections

Preparations
Didanosine tablets, 200 mg tab.

**Stavudine (Restricted)**
**Indications:** HIV infection in combination with other antiretroviral agents.
**Contra-indications:** breast feeding.
**Cautions:** see under abacavir; also, history of peripheral neuropathy or pancreatitis, concomitant use with didanosine (high risk of lactic acidosis).
**Side-effects:** see under abacavir, peripheral neuropathy, cognitive dysfunction, depression, pruritus.
**Dose:** orally; if weight is ≥ 60 kg, 40 mg twice daily. If < 60 kg, 30 mg twice daily.

Preparations
Stavudine capsules, 40 mg cap.

**Tenofovir Disoproxil (Restricted)**
**Indications:** HIV infection in combination with other antiretroviral agents.
**Contra-indications:** breast feeding.
**Cautions:** see under abacavir; also, renal impairment, concurrent or recent use of a nephrotoxic drugs.
**Side-effects:** see under abacavir; also renal failure, hypophosphataemia, reduced bone density.
**Dose:** orally; 245 mg once daily.

Preparations
Tenofovir tablets, 245 mg tab.

**Tenofovir with Efavirenz and Emtricitabine (Restricted)**

**Indications:** HIV infection stabilised on antiretroviral therapy for more than 3 months
**Contra-indications:** See individual agents
**Cautions:** See individual agents
**Side-effects:** See individual agents
**Dose:** 1 tablet once daily

Preparations
Tenofovir disproxil with Efavirenz and Emtricitabine tablets, 300/600/200 mg tabs

**Zidovudine (Restricted)**
**Indications:** HIV infection, alone or in combination with other drugs.
**Contra-indications:** blood disorders, liver disease, breast-feeding.
**Cautions:** monitor for haematological toxicity; renal and hepatic impairment; elderly; pregnancy.
**Side-effects:** anaemia, neutropenia and leucopenia, nausea and vomiting and gastrointestinal disturbances, liver disorders, pancreatitis.
**Dose:** orally 500-600 mg daily in 2-3 divided doses. Seek specialist advice for other treatment regimens.

Preparations
Zidovudine capsule, 100 mg cap.
Zidovudine syrup, 10 mg / mL

**With Lamivudine:** for Contra-indications, Cautions and side-effects see under individual drugs
**Dose:** one tablet twice daily.

Preparations
Zidovudine/ Lamivudine tablets, 300 mg/150 mg tab.

5 C.2.b: Non-nucleoside reverse transcriptase inhibitors (NNRTI)

The non-nucleoside reverse transcriptase inhibitors efavirenz and nevirapine are used in the treatment of HIV-1 infection, but not against the subtype HIV-2. Nevirapine is associated with a high incidence of rash (including Stevens-Johnson syndrome) and occasionally fatal hepatitis. Rash is also associated with efavirenz but it is usually milder. Psychiatric or CNS disturbances are common with efavirenz; CNS disturbances are often self-limiting and can be reduced by taking the dose at bedtime (especially in the first 2–4 weeks of treatment). Efavirenz has also been associated with an increased plasma-cholesterol concentration.

Efavirenz (Restricted)
Indications: HIV infection in combination with other antiretroviral agents.
Contra-indications: pregnancy and breast feeding.
Cautions: renal impairment, hepatic impairment, hepatitis B or C, pregnancy, elderly, psychiatric disorders or seizures.
Side-effects: rash, gastrointestinal disturbances, depression, sleep disturbances, pruritus.

Dose: orally; 600 mg once daily (body weight > 40 kg).

Preparations
Efavirenz capsules, 50 mg cap.
Efavirenz capsules, 200 mg cap.
Efavirenz tablets, 600 mg tab.

Nevirapine (Restricted)
Indications: advanced HIV infection in combination with other antiretroviral agents.
Contra-indications: breast feeding, post exposure prophylaxis.
Cautions: hepatic impairment, chronic hepatitis B or C, pregnancy, high CD4 cell count (>250 cells/mm³ in women and >400 cells/mm³ in men).
Side-effects: rash, nausea, headache, hepatitis.
Dose: orally; 200 mg once daily for two weeks, if no rash increase the dose to 200 mg twice daily.

Preparations
Nevirapine tablets, 200 mg tab.
Nevirapine suspension, 10 mg/mL.

5 C.2.c: protease inhibitors

Darunavir (Restricted)
Indications: HIV infection
Contra-indications: Acute porphyrias
Cautions: Diabetes; haemophilia (increased risk of bleeding)
Side-effects: Abdominal pain; anaemia; anaphylaxis; anorexia;
5. Infections

blood disorders; diarrhoea; dizziness; fatigue; flatulence; gastrointestinal disturbances; headache; hepatic dysfunction; hypersensitivity reactions; lipodystrophy; Lipodystrophy Syndrome; metabolic effects; myalgia; myositis; nausea; neutropenia; osteonecrosis; pancreatitis; paraesthesia; pruritus; rash; rhabdomyolysis; sleep disturbances; Stevens-Johnson syndrome; taste disturbances; thrombocytopenia; vomiting.

Dose: 600 mg twice daily, alternatively 800 mg once daily, once daily dose only to be used if no resistance to darunavir, if plasma HIV-RNA concentration less than 100 000 copies/mL, and if CD4 cell count greater than 100 cells×10⁶/litre.

Preparations
Darunavir tablets, 300 mg tabs

**Indinavir (Restricted)**

Indications: HIV infection in combination with other antiretroviral agents.

Contra-indications: breast feeding.

Cautions: hepatic impairment, chronic hepatitis B or C, pregnancy, hyperglycaemia, haemophilia, ensure adequate hydration (risk of nephrolithiasis).

Side-effects: gastrointestinal disturbances, pancreatitis, liver damage, blood disorders, rash, osteonecrosis, lipodystrophy syndrome, hypersensitivity reactions, rhabdomyolysis, sleep disturbances, pruritus, dry mouth and skin, hyperpigmentation, alopecia, paronychia, pyelonephritis.

Dose: orally; 800 mg thrice daily.

Preparations
Indinavir capsules, 400 mg cap.

**Lopinavir with Ritonavir (Restricted)**

Indications: HIV infection in combination with other antiretroviral agents.

Contra-indications: breast feeding.

Cautions: see under Indinavir; also, concomitant use with drugs that prolong QT interval.

Side-effects: see under Indinavir; also, electrolytes disturbances, weight changes, hypertension, myocardial infarction, depression, extrapyramidal effects, influenza like syndrome, Cushing syndrome, abnormal vision, tinnitus.

Dose: Tablets, 400/100 mg twice daily, alternatively 800/200 mg once daily in adults with a HIV strain that has less than 3 mutations to protease inhibitors

Oral solution, 400/100 mg twice daily with food.

Preparations
Lopinavir / Ritonavir capsules, 133.3 m g / 33.3 mg cap.
Lopinavir / Ritonavir capsules, 100 mg / 25 mg tab
Lopinavir / Ritonavir capsules, 200 mg / 50 mg tab
Lopinavir / Ritonavir syrup, 80 mg / 20 mg per mL.
5. Infections

**Nelfinavir (Restricted)**
**Indications:** HIV infection in combination with other antiretroviral agents.
**Contra-indications:** breast feeding.
**Cautions:** see under indinavir.
**Side-effects:** see under indinavir; also, fever.
**Dose:** orally; 1250 mg twice daily or 750 mg thrice daily.

**Preparations**
Nelfinavir tablets, 250 mg tab.

**Ritonavir (Restricted)**
**Indications:** HIV infection in combination with other antiretroviral agents.
**Contra-indications:** breast feeding.
**Cautions:** see under indinavir, avoid in porphyria.
**Side-effects:** see under indinavir; also, diarrhoea, vasodilatation, local throat irritation, paraesthesia, sweating, raised uric acid, decreased thyroxine level, renal failure.
**Dose:** orally; started at no less than 300 mg twice daily and increased at 2 to 3 day intervals by 100 mg twice daily. The recommended dosage of ritonavir is 600 mg twice daily.

**Preparations**
Ritonavir tablets, 100 mg tab.

5 C.3: Other Antivirals

**Adefovir dipivoxil**
**Indications:** chronic hepatitis B infection with either compensated liver disease with evidence of viral replication, and histologically documented active liver inflammation and fibrosis or decompensated liver disease.
**Contraindications:** breast-feeding.
**Cautions:** monitor liver function tests every 3 months, and viral and serological markers for hepatitis B every 3–6 months; discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis; recurrent hepatitis may occur on discontinuation; monitor renal function every 3 months, more frequently in renal impairment or in patients receiving nephrotoxic drugs; pregnancy; elderly; HIV.
**Side-effects:** nausea, vomiting, dyspepsia, abdominal pain, flatulence, diarrhoea; asthenia, headache; renal failure; hypophosphataemia; rash and pruritus; pancreatitis.
**Dose:** adult over 18 years, 10 mg once daily.

**Preparations**
Adefovir tablets, 10 mg tab.

**Entecavir**
**Indications:** chronic hepatitis B infection with compensated liver disease, evidence of viral replication,
5. Infections

and histologically documented active liver inflammation or fibrosis.

**Contraindications:** breast-feeding.

**Cautions:** monitor liver function tests every 3 months, and viral and serological markers for hepatitis B every 3-6 months; discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis; recurrent hepatitis may occur on discontinuation; renal impairment; pregnancy.

**Side-effects:** nausea, vomiting, dyspepsia, diarrhoea, raised serum amylase and lipase; headache, fatigue, dizziness, sleep disturbances; thrombocytopenia.

**Dose:** adult over 18 years, not previously treated with nucleoside analogues, 500 micrograms once daily.

Adult over 18 years with lamivudine-resistant chronic hepatitis B, 1 mg once daily

Counselling: To be taken at least 2 hours before or 2 hours after food

Preparations
Entecavir tablets, 500 micrograms tab.
Entecavir tablets, 1 mg tab.

**Ganciclovir (C.D.L)**

**Indications:** life-threatening or sight-threatening cytomegalovirus infections.

**Contra-indications:** pregnancy; avoid pregnancy during treatment; breast feeding; abnormally low neutrophil or platelet counts.

**Cautions:** monitor for haematological toxicity; renal impairment; ensure adequate hydration.

**Side-effects:** nausea, diarrhoea, abdominal pain, leucopenia, anaemia, asthenia.

**Dose:** by intravenous infusion, 5 mg/kg every 12 hours. Consult product literature for dosing schedules.

Preparations
Ganciclovir intravenous infusion, freeze-dried powder for reconstitution, 500 mg vial

**Lamivudine (3TC) (Restricted)**

**Indications:** chronic hepatitis B infection.

**Contra-indications:** breast-feeding.

**Cautions:** renal impairment; hepatic disease; pregnancy.

**Side-effects:** nausea and vomiting, diarrhoea; cough; headache; insomnia malaise and muscle disorders; alopecia.

**Dose:** orally, adult over 16 years, 100 mg daily.

Preparations
Lamivudine tablets, 100 mg tab.
Lamivudine tablets, 150 mg tab.
Lamivuine solution 10 mg/ml

**Oseltamivir**

**Indications:** treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days, for the
prophylaxis of influenza in patients 1 year and older.

**Contraindications:** known hypersensitivity to any of the components of the product.

**Cautions:** renal impairment, pregnancy, breast-feeding.

**Side-effects:** nausea, vomiting, abdominal pain, dyspepsia, diarrhoea; headache, fatigue, insomnia, dizziness, conjunctivitis, epistaxis, rash; hepatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, neuropsychiatric disorders.

**Dose:** Prevention of influenza, adult and adolescent over 13 years, 75 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic; child 1–13 years, body-weight under 15 kg, 30 mg once daily, body-weight 15–23 kg, 45 mg once daily, body-weight 23–40 kg, 60 mg once daily, body-weight over 40 kg, adult dose.

Treatment of influenza, adult and adolescent over 13 years, 75 mg every 12 hours for 5 days; child 1–13 years, body-weight under 15 kg, 30 mg every 12 hours, body-weight 15–23 kg, 45 mg every 12 hours, body-weight 23–40 kg, 60 mg every 12 hours, body-weight over 40 kg, adult dose.

**Preparations**

Oseltamivir tablets, 75 mg tab.

Ribavirin (Tribavirin) *(Restricted)*

**Indications:** chronic hepatitis C in combination with other drugs.

**Contra-indications:** pregnancy; severe cardiac disease.

**Cautions:** avoid pregnancy during treatment; monitor for cardiac disease; haematological monitoring; gout; liver disease.

**Side-effects:** nausea, vomiting, dry mouth, anaemia, weight loss, cough, rhinitis, pharyngitis, sleep disturbance, asthenia.

**Dose:** orally, adult over 18 years, body weight under 65 kg, 400 mg twice daily. Body weight 65-85 kg, 400 mg in the morning and 600 mg in the evening. Body weight over 85 kg, 600 mg twice daily.

**Preparations**

Ribavirin capsule, 200 mg cap.

**Valganciclovir**

(Valganciclovir is a pro-drug of ganciclovir)

**Indications:** induction and maintenance treatment of cytomegalovirus retinitis in AIDS patients; prevention of cytomegalovirus disease following solid organ transplantation from a cytomegalovirus positive donor.

**Cautions:** see under ganciclovir

**Side-effects:** see under ganciclovir

**Dose:** CMV retinitis, induction, 900 mg twice daily for 21 days then 900 mg once daily; induction regimen may be repeated if retinitis progresses, prevention of cytomegalovirus disease following solid organ transplantation (starting within 10 days of transplantation), 900 mg
once daily for 100 days, child under 18 years not recommended

Preparations
Valganciclovir tablets, 450 mg tab.

5 D: Antiprotozoal drugs

5 D.1: Antimalarials

The MOH manual for treatment of malaria and its complications should be consulted for treatment protocols. In this section of the formulary, antimalarials applied in malaria treatment protocols are discussed with as much information as possible about their characteristics. Investigative and intervention measures related to malaria treatment and control are best referred to in the MOH manual.

The recommended standard prophylaxis and treatment of malaria cases among all age groups involves the use of chloroquine. Chloroquine is usually given in a 3-day course for curative treatment of P. malariae and for the termination of an acute attack of P. vivax and P. ovale malaria. The treatment regimen consists of 10 mg/kg chloroquine base as a first dose, followed by 5 mg/kg 6-8 hours later and 5 mg/kg on each of the next two days. Taken in proper doses, chloroquine is an extraordinarily safe drug. However, chloroquine is no longer recommended for the treatment of P. falciparum owing to widespread resistance. Acute chloroquine toxicity is most frequent when therapeutic or high doses are administered too rapidly by parenteral routes. Chloroquine has been considered safe during pregnancy, as risk of non-treatment is far more serious than drug induced adverse effects. It has been applied in the treatment of malaria in pregnant women starting at the 3-4 month of pregnancy.

Cerebral malaria is the most important and usually fatal complication of P. falciparum malaria. It is a medical emergency that calls for intensive care. Intravenous infusion of quinine should be commenced as soon as the diagnosis is confirmed.

Chemoprophylaxis in malaria is aimed at reducing morbidity and to prevent fatalities among persons at high risk from severe malaria. Basically this covers the non-immune travellers in areas of malaria transmission as well as pregnant women. Chloroquine with or without proguanil has been used for this purpose.

Malaria cases resistant to chloroquine have been reported. It is important to exclude other reasons for lack of response to chloroquine before starting other treatment protocols with drugs such as quinine, pyrimethamine and sulfadoxine or mefloquine.
5. Infections

**Artesunate (Restricted)**

**Indications:** Severe falciparum malaria

**Cautions:** The powder for injection is difficult to dissolve and care should be taken to ensure that it is completely dissolved before parenteral administration. It should always be used immediately following reconstitution. If the solution is cloudy or a precipitate is present, the parenteral preparation should be discarded.

**Side-effects:** Fever, gastrointestinal disturbances, pruritus; dizziness; headache; tinnitus, neutropenia; elevates liver enzyme levels; ECG abnormalities

**Dose:** A loading dose of 2 mg/kg should be followed by 1 mg/kg after 4 hours and 24 hours. Thereafter a dose of 1 mg/kg should be given daily until the patient is able to tolerate oral artesunate or for a maximum of 7 days.

**Preparations**

Artesunate injection 60 mg

**Chloroquine**

**Indications:** treatment and prophylaxis of malaria.

**Contra-indications:** epilepsy, hypersensitivity, psoriasis.

**Cautions:** renal and hepatic impairment; pregnancy; gastrointestinal disorders; neurological disorders.

**Side-effects:** gastrointestinal disturbances, headache, visual disturbances, skin reaction.

**Dose:** see notes above and MOH protocols.

**Preparations**

Chloroquine phosphate tablets, 250 mg tab. (150 mg chloroquine base)

Chloroquine sulphate syrup, 50 mg (base)/5 ml syrup, 60-100 mL/bottle

Chloroquine sulphate injection, 40 mg (base)/mL ampoule

**Mefloquine**

**Indications:** chloroquine resistant *P. falciparum* malaria.

**Contra-indications:** history of neuropsychiatric disorders, treatment with mefloquine in the previous 4 weeks, in those who are performing activities requiring fine coordination and spatial discrimination, risk of bradycardia with concomitant use of beta-blockers, calcium-channel blockers and digoxin.

**Cautions:** pregnancy, breast-feeding, cardiac conduction disorders; severe hepatic impairment; epilepsy.

**Side-effects:** mainly dose related: nausea, vomiting, abdominal pain, diarrhoea; headache, sleep disturbances, and loss of balance; neuropsychiatric disorders (such as depression, anxiety, panic attack, hallucination, psychosis, convulsion).

**Dose:** 15-25 mg/kg as single dose or in two divided doses 12 hours apart.
5. Infections

Preparations
Mefloquine hydrochloride tablets, 250 mg tab.

Quinine
Indications: treatment of P. falciparum malaria; malaria of unknown origin.
Contra-indications: optic neuritis.
Cautions: cardiac conduction defects, heart block, G6PD deficiency, monitor glucose level during parenteral administration.
Side-effects: giddiness, tinnitus, blurred vision, tremor, abdominal pain, hot skin and flushes.
Dose: orally, 600 mg 3 times daily for 7-10 days; Child, 10 mg/kg every 8 hours for 7 days.

By intravenous infusion, in severe cases, initially 10 mg/kg diluted in 5% glucose, over a period of 4 hours. Maintenance dose, 5 mg/kg in 5% glucose over a period of 4-6 hours every 12 hours, to be repeated until patient is capable to swallow. Oral dose, 10 mg/kg every 8 hours to complete a 7-day course. Dose can be doubled in very severe cases.

Preparations
Quinine dihydrochloride injection, 300 mg/mL; 1-2 mL ampoule
Quinine dihydrochloride tablets, 300 mg tab.

Primaquine
Indications: anti-relapse treatment of P. vivax and P. ovale cases of malaria; as gametocytocide for P. falciparum.

Contra-indications: rheumatoid arthritis; lupus erythematosus.
Cautions: G6PD deficiency; pregnancy and breast-feeding.
Side-effects: nausea and vomiting, anorexia, haemolytic anaemia, methaemoglobinaemia.
Dose: orally, for anti-relapse therapy, 15 mg daily (as a base), for 14 days, or 21-28 days for cases from south East Asia or Oceania. As a gametocytocide for P. falciparum, a single dose of 30-45 mg (as a base).

Preparations
Primaquine phosphate tablets, 7.5 mg tab..

Proguanil (Restricted)
Indications: prophylaxis of malaria in combination with chloroquine.
Cautions: renal impairment; folate supplementation during pregnancy (safe during pregnancy).
Side-effects: nausea and vomiting, mouth ulceration, anorexia.
Dose: orally, 200 mg as single dose with chloroquine. Child, 3-5 mg/kg single dose.

Preparations
Proguanil hydrochloride tablets, 100 mg tab.

Sulfadoxine + pyrimethamine (Restricted)
Indications: adjunct to quinine in P. falciparum resistant cases.
Cautions: haemolytic disorders; neurological disorders.
Side-effects: vomiting, anorexia, abdominal discomfort, tremor, seizure, megaloblastic anaemia due to folic acid deficiency.

Dose: orally, 3 tablets (each tablet of sulfadoxine 500 mg + pyrimethamine 25 mg). Child, 5-10 kg 0.5 tablet, 11-15 kg 1 tablet, 16-25 kg 1 and quarter of a tablet, 26-40 kg 1 and a half tablet, 41-50 kg 2 tablets.

Preparations
Sulfadoxine + pyrimethamine tablets, 500+25 mg tab.
Sulfadoxine + pyrimethamine injection, 500+25 mg/2.5 mL ampoule

Artemether/ lumefantrine (Restricted)

Indications: Treatment of acute uncomplicated falciparum malaria. Treatment of chloroquine-resistant non-falciparum malaria
Contra-indications: Family history of congenital QT interval prolongation; family history of sudden death; history of arrhythmias; history of clinically relevant bradycardia; history of congestive heart failure accompanied by reduced left ventricular ejection fraction
Cautions: Avoid in acute porphyrias; electrolyte disturbances
Side-effects: Abdominal pain; anorexia; arthralgia; asthenia; cough; diarrhoea; dizziness; headache; myalgia; nausea; palpitation; paraesthesia; prolonged QT interval; pruritus; rash; sleep disturbances; vomiting

Dose: Initially 4 tablets, followed by 4 tablets for 5 doses each given at 8, 24, 36, 48 and 60 hours (total 24 tablets over 60 hours)

Preparations
Artemether/ lumefantrine tablets, 20 mg Artemether/ 120 mg lumefantrine tab.

5 D.2: Leishmaniacides

Cutaneous, mucocutaneous and visceral types of leishmaniasis are treated with pentavalent antimonial drugs. Intramuscular or intravenous therapy with sodium stibogluconate has been found safe and effective in most cases. In visceral leishmaniasis, a 20-day treatment course with 20 mg/kg daily is commonly applied; 10-day treatment course for cutaneous infection.

Sodium stibogluconate (C.D.L)
Indications: leishmaniasis.
Contra-indications: severe renal impairment; breast-feeding.
Cautions: avoid rapid intravenous administration; heart disease, hepatic impairment.
Side-effects: pain at site of intramuscular injection, gastrointestinal disturbances, stiffness of joints, delayed muscle pain; ECG changes may precede arrhythmias.
Dose: see notes above.
5. Infections

Preparations
Sodium stibogluconate injection, 100 mg/mL 100 mL bottle

5 D.3: Drugs for pneumocystis pneumonia

Pneumocystis pneumonia is more common among immunocompromised patients. It is mainly treated with co-trimoxazole (see sec 5A.5). Pentamidine is associated with high toxicity and should be used by specialists in cases resistant or intolerant to co-trimoxazole.

**Pentamidine Isethionate (C.D.L)**

**Indications**: pneumocystis pneumonia (see notes above)

**Cautions**: risk of hypotension; hepatic and renal impairment; blood disorders; pregnancy and breastfeeding (check with product literature).

**Side-effects**: severe reactions due to hypotension, hypoglycaemia, pancreatitis, and arrhythmias; blood disorders; acute renal failure.

**Dose**: intravenous infusion, 4 mg/kg daily for at least 14 days. Inhalation: Adult 300 mg every four weeks or 150 mg every 2 weeks, using suitable equipment – consult the product literature.

Preparations
Pentamidine Isethionate injection, powder for reconstitution, 300 mg vial
Pentamidine Isethionate solution for inhalation, 300 mg vial

5 D.4: Anti-bilharziasis

**Praziquantel (C.D.L)**

**Indications**: schistosomiasis.

**Contra-indications**: hepatic impairment.

**Cautions**: monitor for ocular abnormalities; avoid tasks requiring mental alertness during therapy; reduce dose in liver disease.

**Side-effects**: abdominal disturbances, headache, dizziness, drowsiness.

**Dose**: orally, 40 mg/kg in 2 divided doses 4-6 hours apart on one day.

Preparations
Praziquantel tablets, 600 mg tab.

5 E: Anthelmintics

The availability of broad spectrum Anthelmintics has lead to a better control of helminthic infections. Mebendazole is a widely used safe anthelmintic, which is highly effective against single or mixed infections with threadworms, hookworms and common roundworms. Albendazole, like mebendazole is safe and effective against the same range of helminthic infections. It has also been found useful in inoperable cases of hydatid cyst or in conjunction with surgery to prevent relapses.

Tapeworm infection is safely treated with niclosamide, an effective taenicide drug.

Filarial parasites infections are best treated with diethylcarbamazine.
Medical care is required in the early stages of treatment.

### 5 E.1: Drugs for round worms


**Mebendazole**

**Indications:** mixed or single infections with threadworm, roundworm, whipworm and hookworm *(see notes above)*

**Cautions:** pregnancy and breast-feeding, avoid in children under 2 years.

**Side-effects:** very rare due to low systemic bioavailability. Abdominal pain.

**Dose:** doses for adult and child over 2 years are the same.

- Threadworms, 100 mg as single dose. Repeat if necessary 2-3 weeks later.
- Whipworms, roundworms or hookworms, 100 mg twice daily for 3 days.

**Preparations**
- Mebendazole suspension, 2% (20 mg/mL) susp. 20-30 mL/bottle

**Albendazole**

**Indications:** see under mebendazole; hydatid cyst *(see notes above)*

**Contra-indications:** hepatic cirrhosis; pregnancy and breast-feeding.

**Cautions:** children under 2 years; monitor liver function when used for protracted therapy.

**Side-effects:** on long-term use as for hydatid cysts, abdominal discomfort, headache, fatigue, fever, loss of hair.

**Dose:** for mixed or single intestinal helminths infection, 400 mg single dose. In heavy infections therapy may be needed for 2-3 days.

- In hydatid cysts, 10 mg/kg daily in divided doses for 28 consecutive days. Treatment course may be repeated 2-3 times if necessary at 2-week intervals.

**Preparations**
- Albendazole suspension, 100 mg/5 mL susp.; 20-30 mL/bottle
- Albendazole tablets, 200 mg tab.
Diabetes mellitus results from relative or absolute deficiency of insulin. It has emerged as a major and growing health problem in the Sultanate of Oman. The National Health Survey of diabetes, which was conducted in 1991 showed that the prevalence rate was 9.75%, while the national health survey in the year 2000 showed that rate of prevalence had increased to 11.6% among adults over 20 years.

In clinical practice, diabetes is presented as the commonest metabolic disorder. There are two principal types of diabetes;-
- Type I also known as insulin-dependent diabetes mellitus (IDDM), is characterized by subnormal or undetectable insulin secretion and requires daily insulin injection for treatment.
- Type II also known as non-insulin-dependent diabetes mellitus (NIDDM), is due to reduced secretion of insulin or to peripheral resistance to the effects of insulin. A good proportion of patients affected with this type are obese and may respond to diet control and weight reduction alone. However, many patients need to receive oral antidiabetic drugs to keep hyperglycaemia under control.

Treatment of diabetes mellitus is aimed at reducing symptoms and minimizing the risk of long-term complications by appropriate management protocols. Diabetes represents a high risk factor for cardiovascular disease. Other risk factors such as smoking, obesity, hyperlipidaemia and hypertension should also be considered.

Uncontrolled diabetes, will in the long run result in serious complications that involves the renal, nervous and microvascular systems. In all types of diabetes, measures other than drugs are used to optimise treatment such as diet control and physical exercises.

Patient education is the cornerstone for long-lasting optimal glycaemic control. Without the patients understanding of the metabolic changes involved in diabetes, treatment and control become difficult.

Preparations of insulin are used for the treatment of type I and under particular circumstances for type II diabetes mellitus. Oral antidiabetic drugs such as sulphonylurea and biguanides are exclusively available for the treatment of type II diabetes mellitus.
Diabetes mellitus results from relative or absolute deficiency of insulin. It has emerged as a major and growing health problem in the Sultanate of Oman. The National Health Survey of diabetes, which was conducted in 1991 showed that the prevalence rate was 9.75%, while the national health survey in the year 2000 showed that rate of prevalence had increased to 11.6% among adults over 20 years. In clinical practice, diabetes is presented as the commonest metabolic disorder. There are two principal types of diabetes;

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Physiologically, insulin is synthesized in the beta islet cells of the pancreas and released mainly in response to changes in blood glucose level. It plays a key role in the regulation of carbohydrate, fat and protein metabolism. For therapeutic uses, insulin has been extracted from animal pancreas and most recently biosynthesized. The animal insulin slightly differs in the amino acid number and sequence from human insulin. Nowadays, most of the available preparations are recombinant human insulin with the strength of 100 units/mL.

Insulin has a short half-life of 4-5 minutes due to hepatic and renal elimination. Gastrointestinal proteolytic enzymes degrade insulin, and therefore it is ineffective by mouth. An insulin preparation is an acidic solution of crystalline insulin with a variable amount of zinc and is normally administered by injection. The subcutaneous route is the common route for routine administration. However, it can also be administered by intramuscular route and for the soluble insulin by the intravenous route. To prolong its effect insulin is mixed with proteins such as protamine or globulin to form complexes that delay its absorption.

Animal insulin preparations are antigenic. The synthesis of human insulin is thought to reduce this antigenicity, a claim which has not been substantiated in clinical practice.

**Indications** for insulin are;
- type I diabetes mellitus.
- uncontrolled hyperglycaemia in type II diabetes mellitus.
- when diet has failed during pregnancy.
- during stressful situation like infection, trauma, surgery and myocardial infarction.
- Ketoacidosis.

**Insulin preparations**: There are 3 types of insulin preparation;
- **Short acting** that has a relatively rapid onset such as regular or soluble insulin.
- **Intermediate acting** such as isophane and insulin zinc suspension.
- **Long acting**, with slower onset and prolonged duration such as glargine insulin suspension.

Variations in the duration and onset of action from one patient to another necessitate that patients are individually assessed.

**Insulin dose regimens**
- There are no rules of insulin dosage, but average requirements are often 0.5-1 unit/kg/day. The following are some regimens for insulin use:

The majority of patients will require more than one daily injection.
if good glycaemic control is to be achieved. However, a one-daily injection of an intermediate acting preparation may be effectively used in some patients.

- Twice daily mixture of short and intermediate-acting insulin is a commonly used regimen.
- In some cases, a mixture of short and intermediate acting insulins may be given in the morning. Further doses of short acting insulin are given before lunch and evening meal and an evening dose of intermediate acting insulin is given at bed time. This may be used particularly when a strict glycaemic control is mandatory.
- The dose of insulin preparations is adjusted according to the blood glucose levels. Blood glucose monitoring should be intensified during intercurrent illness and other stressful conditions and insulin doses may have to be increased.

**Side-effects:** Hypoglycaemia is the most serious side effect of insulin and patients should carefully be directed to avoid it. It could result from an overdose of insulin, missed meal or an unusual physical activity. The early symptoms of hypoglycaemia are; fatigue, dizziness, cold, sweat, headache, hunger, weakness, nervousness, mental lapse and if not treated may lead to convulsion and coma.

Other side-effects include, local reaction and lipotrophy at the site of injection. It is advisable to frequently change the site of injection.

Routes of administration: the subcutaneous route is the most common route for all types of insulin. However, the soluble regular insulin can also be administered intramuscularly and intravenously. The abdominal wall is preferably used for faster absorption of short acting insulin. The thigh and the upper lateral gluteal region are preferred for slower absorption of intermediately acting insulins.

**Insulin (Restricted)**

Preparations

Recombinant regular human insulin injection, 100 unit/mL, 10 mL vial and 3 mL pen

Recombinant NPH (Neutral Protamine Hagedorn) human insulin injection (isophane suspension), 100 unit/mL, 10 mL vial and 3 mL pen

Recombinant regular human insulin 30% and NPH human insulin 70% (insulin mixture) injection, 100 unit/mL, 10 mL vial and 3 mL pen

Insulin Aspart injection, 100 units/mL, prefilled pen

Insulin Lispro injection, 100 units/mL, prefilled pen

(Note: Aspart & Lispro are short acting insulin analogues and approved as a group)

Biphasic insulin aspart (50%/ 50%) injection, prefilled pen
Endocrine system

6 A.2.1: Sulphonylureas

The sulphonylureas stimulate the release of insulin from the beta cells of the pancreas and on long-term therapy improve sensitivity to insulin through extra-pancreatic mechanisms. Hypoglycaemia may be induced with sulphonylureas as a side effect resulting from overdose or inadequate food intake.

The choice of sulphonylurea drug is determined by the potency, duration of action, cost, side-effects and potential interactions with other drugs. The patient’s nutritional status, dietary habits and age associated medical conditions must be also considered.

Contra-indications:
- type I diabetes mellitus.
- severe renal and hepatic impairment.
- allergy to sulfa drugs.
- pregnancy and breast feeding.
- patients undergoing stressful conditions such as surgery, severe infection, trauma and myocardial infarction.
- ketoacidosis.

Side-effects: The main side-effects associated with the use of sulphonylureas are:
- hypoglycaemia.
- gastrointestinal disturbances such as nausea, vomiting and constipation.
- allergic skin reaction, renal, hepatic and blood disorders are more frequent side-effects with the older generation of long acting sulphonylureas.

The sulphonylureas available in Oman are:

- Glibenclamide, a long acting drug, which should be avoided in the elderly because of the danger of hypoglycaemia.
- Glimepride is of intermediate duration of action.
- Gliclazide is more useful in presence of renal impairment since it is mainly eliminated by liver metabolism.

Glibenclamide

Indications: type II diabetes mellitus.

Contra-indications, cautions and side-effects: see notes above

Dose: initially, 5 mg daily with or immediately after breakfast, adjust according to response. Reduce in elderly; see notes above. Maximum, 15 mg daily.

Preparations: Glibenclamide tablets, 5 mg tab.

Gliclazide (Restricted)

Indications: type II diabetes mellitus.

Contra-indications, cautions and side-effects: see notes above

Dose: initially, 40-80 mg daily with breakfast, adjust if necessary to 160 mg daily. Maximum daily dose 320 mg in divided doses.

Preparations: Gliclazide tablets, 80 mg tab.

Glimepride

Indications: type II diabetes mellitus.

Contra-indications: see notes above

Cautions: regular haematological and hepatic monitoring is recommended.

Side-effects: see notes above

Dose: initially, 1 mg daily shortly before or with breakfast. Increase if necessary in 1 mg steps every 1 - 2 week to a maximum of 4 mg daily.

Preparations: Glimepride tablets, 2 mg tab.

6 A.2: Oral antidiabetic drugs

Oral antidiabetic drugs are used for the treatment of type II diabetes mellitus. Drug treatment with oral antidiabetic drugs is only considered after regimen of dietary treatment combined with exercise has failed to achieve the therapeutic target.

The choice of oral antidiabetic drugs depends on the individual patient. Sulphonylureas are effective in reducing blood glucose level in patients uncontrolled by dietary restriction and exercises. Biguanides on the other hand, are more useful in obese patients when diet restriction is a problem. Biguanides interfere with carbohydrate metabolism, by increasing peripheral utilization of glucose and decreasing gluconeogenesis. They act in the presence of insulin and for this reason they are effective in diabetic patients with residual functioning therapeutic beta cells. They do not, in normal doses, induce hypoglycaemia in normal people.
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The sulphonylureas stimulate the release of insulin from the beta cells of the pancreas and on long-term therapy improve sensitivity to insulin through extra-pancreatic mechanisms. Hypoglycaemia may be induced with sulphonylureas as a side effect resulting from overdose or inadequate food intake.

The choice of sulphonylurea drug is determined by the potency, duration of action, cost, side-effects and potential interactions with other drugs. The patient’s nutritional status, dietary habits and age associated medical conditions must be also considered.

**Contra-indications:**
- type I diabetes mellitus.
- severe renal and hepatic impairment.
- allergy to sulfa drugs.
- pregnancy and breast feeding.
- patients undergoing stressful conditions such as surgery, severe infection, trauma and myocardial infarction.
- ketoacidosis.

**Side-effects:** The main side-effects associated with the use of sulphonylureas are, hypoglycaemia, gastrointestinal disturbances such as nausea, vomiting and constipation. Allergic skin reaction, renal, hepatic and blood disorders are more frequent side-effects with the older generation of long acting sulphonylureas.

The sulphonylureas available in Oman are:

**Glibenclamide**, a long acting drug, which should be avoided in the elderly because of the danger of hypoglycaemia. **Glimepride** is of intermediate duration of action.

**Gliclazide** is more useful in presence of renal impairment since it is mainly eliminated by liver metabolism.

**Glibenclamide**

**Indications:** type II diabetes mellitus.
Contra-indications, cautions and side-effects: see notes above

**Dose:** initially, 5 mg daily with or immediately after breakfast, adjust according to response. Reduce in elderly; see notes above. Maximum, 15 mg daily.

**Preparations**
Glibenclamide tablets, 5 mg tab.

**Glimepride**

**Indications:** type II diabetes mellitus.
Contra-indications: see notes above

**Cautions:** regular haematological and hepatic monitoring is recommended.

**Side-effects:** see notes above

**Dose:** initially, 1 mg daily shortly before or with breakfast. Increase if necessary in 1 mg steps every 1-2 week to a maximum of 4 mg daily.

**Preparations**
Glimepride tablets, 2 mg tab.

**Gliclazide (Restricted)**

**Indications:** type II diabetes mellitus.
Contra-indications, cautions and side-effects: see notes above

**Dose:** initially, 40-80 mg daily with breakfast, adjust if necessary to 160 mg daily. Maximum daily dose 320 mg in divided doses.

**Preparations**
Gliclazide tablets, 80 mg tab.

**6 A.2.2: Biguanides**

Biguanides differ from sulphonylureas in their mechanism of action. Metformin is the only biguanide available for use in Oman. It acts through decreasing gluconeogenesis and by increasing peripheral carbohydrate utilization. Metformin is only used in type II diabetes mellitus.

Diabetic obese patients benefit more with metformin. When sulphonylureas and diet restriction fail
6: Endocrine system

to bring glycaemic control, metformin is an alternative. Hypoglycaemia is not a serious side effect with metformin and there is no weight gain. Metformin may cause lactic acidosis, which is more often in patients with impaired renal function.

**Metformin**

**Indications**: type II diabetes mellitus.

**Contra-indications**: severe hepatic or renal impairment, ketoacidosis, heart failure, alcohol dependence, dehydration.

**Side-effects**: gastrointestinal disturbances, such as anorexia, nausea, vomiting, diarrhoea, metallic taste, decreased vitamin B₁₂ absorption.

**Dose**: initially, 500 mg with breakfast for 1 week, then 500 mg with breakfast and dinner for 1 week, then 500 mg three times daily with meals. Maximum 3g daily in divided doses.

**Preparations**

Metformin hydrochloride tablets, 500 mg tab.

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6 A.2.3: Dipeptidylpeptidase-4 inhibitors

Dipeptidylpeptidase-4 inhibitors (gliptins) impair the degradation of incretin hormones, which play a role in glucose homoeostasis by increasing insulin synthesis and release, and reducing glucagon secretion. They are used in the management of type 2 diabetes mellitus.

**Sitagliptin**

**Indications**: type II diabetes mellitus.

**Contra-indications**: Ketoacidosis

**Side-effects**: Gastro-intestinal disturbances; nasopharyngitis; pain; peripheral oedema; upper respiratory tract infection; anorexia; dizziness; drowsiness; dry mouth; headache; hypoglycaemia; osteoarthritis; cutaneous vasculitis; pancreatitis; rash; Stevens-Johnson syndrome

**Dose**: 100 mg once daily.

**Note**: Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).

**Preparations**

Sitagliptin phosphate tablets, 100 mg tab.

**Vildagliptin**

**Indications**: type II diabetes mellitus.

**Contra-indications**: Ketoacidosis

**Cautions**: Manufacturer advises avoid in severe heart failure
**Endocrine system**

**Side-effects**: Arthralgia; constipation; hypoglycaemia; hepatic dysfunction; nasopharyngitis; upper respiratory tract infection; bullous skin reactions; exfoliative skin reactions; pancreatitis

**Dose**: 50 mg twice daily, but if taken in combination with a sulphonylurea 50 mg once daily

**Note**: Monitor liver function before treatment and every 3 months for first year and periodically thereafter. Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).

**Preparations**

Vildagliptin tablets, 50 mg tab.

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**Ministry of Health policy is that only one of the above gliptins will be purchased and made available for use**

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**6 A.2.4: Glucagon-Like Peptide 1 Receptor Agonists**

Glucagon-Like Peptide 1 Receptor Agonist binds to, and activates, the GLP-1 (Glucagon-Like Peptide 1) receptor to increase insulin secretion, suppresses glucagon secretion, and slows gastric emptying.

**Exenatide**

**Indications**: treatment of type 2 diabetes mellitus in combination with metformin or a sulfonylurea, or both, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination

**Contra-indications**: ketoacidosis, severe gastro-intestinal disease, pregnancy

**Cautions**: elderly, pancreatitis, may cause weight loss greater than 1.5 kg weekly, breastfeeding, renal impairment

**Side effects**: gastro-intestinal disturbances including nausea, vomiting, diarrhoea, dyspepsia, abdominal pain and distension, gastro-oesophageal reflux disease, decreased appetite, weight loss, headache, dizziness, agitation, asthenia, hypoglycaemia, increased sweating, injection site reactions, antibody formation, pancreatitis

**Dose**: By subcutaneous injection, adult over 18 years, initially 5 micrograms twice daily within 1 hour before 2 main meals (at least 6 hours apart), increased if necessary after at least 1 month to max. 10 micrograms twice daily

**Counselling**: If a dose is missed, continue with the next scheduled dose (do not administer after a meal). Some oral medications should be taken at least 1 hour before or 4 hours after exenatide injection (consult product literature for details)

**Note**: Dose of concomitant sulfonylurea may need to be reduced

**Preparations**

Exenatide Injection, 5 microgram/dose (60 doses) in prefilled pen
**6: Endocrine system**

**Liraglutide**

**Indications:** treatment of type 2 diabetes mellitus in combination with metformin or a sulfonylurea, or both, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination

**Contra-indications:** ketoacidosis; inflammatory bowel disease; diabetic gastroparesis

**Cautions:** discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain), pregnancy, breastfeeding, hepatic impairment, renal impairment

**Side effects:** gastro-intestinal disturbances including nausea, vomiting, constipation, diarrhoea, dyspepsia, abdominal pain and distension, flatulence, gastritis, gastro-oesophageal reflux disease, decreased appetite; headache, dizziness, fatigue; fever, bronchitis, nasopharyngitis; hypoglycaemia; injection site reactions; acute pancreatitis; thyroid neoplasm, goitre, increased blood calcitonin, angiœdema

**Dose:** By subcutaneous injection, adult over 18 years, initially 0.6mg once daily, increased after at least 1 week to 1.2mg once daily, further increased if necessary after an interval of at least 1 week to max. 1.8mg once daily

Note Dose of concomitant sulfonylurea may need to be reduced

**Preparations**

Liraglutide injection, 6 mg/mL, 3 mL prefilled pens

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**Ministry of Health policy is that only one of the GLP-1 receptor agonists above will be purchased and made available for use**

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**6 A.2.5: Treatment of hypoglycaemia**

Management of hypoglycaemia in a conscious patient could start with oral glucose in the form of sweetened drinks or as granulated sugar. In unconscious patients, intravenous glucose should be given; it is best to start with concentrated (50%) intravenous solution when available, otherwise, 5-10% glucose is an alternative although large volumes are required; and transfer the patients to higher level of health service.

When facilities for intravenous administration of glucose are not available, use 1 mg of glucagon intramuscularly, intravenously or subcutaneously and transfer the patients to a higher level of health service. See also sec 6 A.1 above.

**Glucagon (Restricted)**

**Indications:** acute insulin-induced hypoglycaemia.

**Contra-indications:** phaeochromocytoma.

**Cautions:** ineffective in chronic hypoglycaemia, starvation.
6: Endocrine system

**Side-effects**: nausea, vomiting, diarrhoea, hypokalaemia.

**Dose**: by intramuscular, subcutaneous or intravenous injection, adult and child over 8 years, 1 mg; Child under 8 years or body weight less than 25 kg, 500 mg.

**Preparations**

Glucagon hydrochloride injection, powder for reconstitution, 1 mg vial

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6 B: Thyroid hormones and antithyroid drugs

6 B.1: Thyroid hormones

The thyroid gland synthesises thyroxine or tetra-iodothyronine (T₄) and tri-iodothyronine (T₃), which are available commercially for treatment of hypothyroidism. T₃ is more potent and has a shorter half-life than T₄, which has a longer duration and slower onset of action. Thyroxine is clinically used for maintenance therapy in hypothyroidism.

**Levothyroxine sodium (Thyroxine sodium)**

**Indications**: hypothyroidism.

**Contra-indications**: thyrotoxicosis.

**Cautions**: cardiovascular disease, elderly, diabetes mellitus and diabetes insipidus.

**Side-effects**: usually seen with excessive doses; tachycardia, arrhythmias, anginal pain, tremor, excitation, diarrhoea, heat intolerance, sleep disturbances.

**Dose**: initially, do not exceed 100 micrograms daily. Adjust dose according to response, by a 25-50 micrograms increment not before a month use. Maintenance dose is 100-200 micrograms daily.

In children and infants doses of thyroxine have to be titrated according to clinical response.

**Preparations**

Levothyroxine sodium tablets, 25 micrograms tab.
Levothyroxine sodium tablets, 50 micrograms tab.
Levothyroxine sodium tablets, 100 micrograms tab.
Levothyroxine sodium, oral solution, 100 micrograms / 5 mL

6 B.2: Antithyroid drugs

Hyperthyroidism can be treated with antithyroid drugs, but other treatment options include surgically removing the gland or treating it with radioactive iodine.

The thyroid gland needs iodine in small quantity to function properly. Large quantities of iodine may reduce thyroid hormone production and the vascularity of the gland, which helps in safe surgical manipulation. Iodine is not used for routine treatment of hyperthyroidism.

Carbimazole is a commonly used drug in hyperthyroidism, which slows down the gland’s production.
of thyroid hormone. It is very effective and can control thyroid function in 6-8 weeks. Treatment may continue for 12-18 months with an adjustment of the dose according to response. Allergic reaction is the most common side effect that mandates shifting the patients to other types of therapy.

Propylthiouracil is an alternative in patients allergic to carbimazole. Antithyroid drugs are orally effective and once daily dose is needed because of their long duration of action.

Physical symptoms of hyperthyroidism such as tremor, palpitation, sweating and insomnia can be managed with propranolol at the initial stages of treatment with antithyroid drugs.

**Carbimazole**

*Indications*: hyperthyroidism.

*Cautions*: liver disorders, pregnancy, breast-feeding, monitor blood tests; warn patients to report immediately any sore throat, mouth ulcers, fever, or any non-specific illness.

*Side-effects*: allergic reactions, skin rash, pruritus; nausea, headache, bone marrow suppression.

*Dose*: adult, 15-40 mg daily for 4-8 weeks or when the patient becomes euthyroid. Reduce dose for maintenance, usually 5-15 mg daily.

Child, initially 250 microgram/kg daily in divided doses, adjust according to response.

Preparations

Carbimazole tablets, 5 mg tab.

Carbimazole tablets, 20 mg tab.

**Iodine and iodide**

*Indications*: thyrotoxicosis (pre-operative).

Contra-indications: breast-feeding.

*Cautions*: pregnancy, young children, not for long course of therapy.

*Side-effects*: skin and mucous membrane irritation, headache, weakness, erythema.

*Dose*: 0.1-0.3 mL 3 times daily of aqueous iodine solution diluted with milk or water.

Preparations

Aqueous iodine oral solution (Lugol’s solution), contains 5% iodine and 10% potassium iodide in water; 500 mL/bottle.

**Propylthiouracil (Restricted)**

*Indications*: hyperthyroidism.

*Cautions*: renal impairment, see under carbimazole.

*Side-effects*: see under carbimazole, blood disorders.

*Dose*: adult, 200-400 mg daily until patient becomes euthyroid. Reduce dose gradually, for maintenance usually 50-150 mg daily.

Child, not recommended.

Preparations

Propylthiouracil tablets, 50 mg tab.
6 C: Corticosteroids

The adrenocorticotropic hormone (ACTH) stimulates the adrenal cortex to secrete 3 groups of corticosteroids namely, glucocorticoids, mineralocorticoids and weak androgens that can be converted peripherally to more potent androgens. Glucocorticoids (cortisone and hydrocortisone) exert a number of physiological actions on carbohydrate, protein, and fat metabolism; contribute to the maintenance of normal blood pressure, maintain normal balance of body fluids and electrolyte and suppress inflammation. Mineralocorticoids such as aldosterone are mainly involved in water and electrolyte regulation. In addition to the naturally occurring corticosteroids, a large number of synthetic derivatives have been introduced. Although their effectiveness is well recognised in some clinical conditions, they are generally used indiscriminately in clinical practice causing serious complications. They are available in various formulations. Those orally administered are well absorbed from the gastrointestinal tract. Topical, rectal and inhalational preparations are well absorbed from the site of administration and may cause systemic effects. Absorbed, corticosteroids are bound to plasma protein, metabolised in the liver and kidney and excreted in the urine.

Therapeutic indications: With the exception of replacement therapy in deficiency states, the use of glucocorticoids is largely empirical, not curative but merely palliative. Small physiological doses are needed in replacement therapy, but larger doses are needed to suppress inflammatory and immune responses. Based on extensive clinical experience with corticosteroids it has been proposed that due to the number and severity of potential side-effects, the decision to institute therapy with corticosteroids always requires a careful consideration of the relative risk and benefits in each patient. For any disease and in any patient the appropriate dose to achieve a therapeutic effect must be determined by trial and error and must be re-evaluated periodically as the underlying disease changes or the complications of therapy arise. If the use of corticosteroids can save life as in exfoliative dermatitis, pemphigus, leukaemia or acute transplant rejection, high doses may need to be given irrespective of the side-effects. However, when corticosteroids are used to relieve pain, as in rheumatoid arthritis, the initial dose should be small and increased gradually until pain has been reduced to a tolerable level.
The mineralocorticoids effects of the selected corticosteroids should always be considered. The relative potencies of the various drugs are listed.

**Relative potencies and doses of corticosteroids**

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Glucocorticoid effect</th>
<th>Mineralo Equivalent effect</th>
<th>dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>1</td>
<td>20mg</td>
</tr>
<tr>
<td>Cortisone</td>
<td>0.8</td>
<td>0.8</td>
<td>25mg</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>10</td>
<td>125</td>
<td>25mg</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
<td>0.8</td>
<td>5</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25</td>
<td>0.0</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**not applied as a glucocorticoid**

**Replacement therapy**

Cortisone has been used, but hydrocortisone (cortisol) is preferred in primary adrenal insufficiency (Addison’s disease). The daily dose of hydrocortisone is 20-30 mg in divided doses. Two thirds of the daily dose is given in the morning and the rest is in the evening to simulate the normal diurnal rhythm. The maintenance dose is determined by the clinical response and the well being of the patient. To correct the mineralocorticoid effects, a small dose of fludrocortisone 100-200 micrograms orally, is given in addition, as single daily dose.

Acute adrenal insufficiency (Addisonian crisis) is a medical emergency which is treated by, fluid and electrolyte replacement, correction of hypoglycaemia and the intravenous administration of hydrocortisone 100 mg initially and then at 6 hourly intervals. The precipitating cause should be identified and treated such as trauma, infection, haemorrhage.

Iatrogenic adrenal insufficiency is caused by suppression of the hypothalamic-pituitary-adrenal function due to prolonged use of high doses of corticosteroids. Sudden cessation of therapy or intercurrent disease will lead to cortical insufficiency. Abrupt withdrawal also leads to relapse of the disease that was being treated. In such situation, intravenous injection of 100 mg hydrocortisone is given followed by further injection until blood pressure is maintained at a safe level.

**Indications in non-endocrine conditions:** Corticosteroids are widely indicated for various clinical conditions as a result of their anti-inflammatory and immunosuppressive nature. Such clinical conditions include; allergic reactions, collagen diseases, bronchial asthma, some skin disease, some neoplastic diseases, cerebral oedema, some blood disorders, active chronic hepatitis, ulcerative colitis, and acute resistant gout.

**Cautions:** Whenever possible local treatment with creams, intra-articular injection, inhalational, eye drops or enemas should be used in preference to systemic treatment. Taking the corticosteroid in the morning
has less suppressive effects on endogenous hormones. To attempt reducing pituitary-adrenal suppression further, the total dose of two days can sometimes be taken as a single dose on alternate days; alternate-day administration has not been proven to be effective in asthma. Gradual withdrawal is recommended in those whose disease is unlikely to relapse and have:
- recently received repeated courses.
- received more than 40 mg daily prednisolone or equivalent.
- been given repeat doses in the evening.
- being on treatment for more than three weeks.
Caution should be considered when prescribing to children, adolescents, elderly, during breast-feeding and pregnancy. Frequent monitoring is required if there is a history of tuberculosis, hypertension, diabetes mellitus, cardiac disease, osteoporosis, peptic ulceration, glaucoma, affective disorders.

**Side-effects:** diabetes mellitus, osteoporosis, water and electrolyte retention, hypertension, mental disturbances with an increased risk of suicidal tendencies, muscle wasting, peptic ulceration, glaucoma, increased susceptibility for infections, skin atrophy, acne. Chronic use in children may lead to growth retardation.

**Hydrocortisone**

**Indications:** adrenal insufficiency; anaphylactic and angioedema; for other indications see notes above and relevant sections.

**Contra-indications:** systemic infections.

**Cautions:** see notes above

**Side-effects:** see notes above

**Dose:** orally, for replacement therapy, 20-30 mg daily in divided doses, see notes above.

By intramuscular injection or slow intravenous injection or infusion, 100-500 mg 3-4 times in 24 hours or as required.

Child, by slow intravenous injection up to 1-year 25 mg, 1-5 years 50 mg, 6-12 years 100 mg.

**Preparations**

Hydrocortisone sodium succinate injection, powder for reconstitution, 100 mg vial.

Hydrocortisone tablets, 10 mg tab.

**6 C.2: Synthetic adrenocorticosteroids**

**Dexamethasone (Restricted)**

**Indications:** suppression of inflammatory and allergic disorders;
6: Endocrine system

Dexamethasone tablets, 2 mg tab.
Dexamethasone tablets, 0.5 mg tab.

Preparations
Injection, 4-5 mg/mL, 1 mL ampoule
Dexamethasone sodium phosphate injection, 4-5 mg/mL, 1 mL ampoule
Dexamethasone sodium phosphate injection, 4-5 mg/mL, 2 mL ampoule

Contra-indications: severe infections.
Cautions: see notes above; very large intravenous doses have been associated with cardiac collapse.
Side-effects: see notes above
Dose: by intramuscular injection, for depot preparation, 40-120 mg repeated if necessary after 2-3 weeks.
By intramuscular or intravenous injection or infusion, for soluble preparations, 10-500 mg as required. May be repeated if necessary.

Preparations
Methylprednisolone acetate depot injection, 40 mg/mL vial
Methylprednisolone sodium succinate injection, powder for reconstitution, 500 mg vial

Prednisolone (Restricted)
Indications: suppression of inflammatory and allergic disorders; see also notes above
Contra-indications: severe infections.
Cautions: see notes above
Side-effects: see notes above
Dose: varies widely according to condition and its severity, usual range 5-20 mg daily, in very severe condition up to 60 mg daily.

Preparations
Prednisolone tablets, 5 mg tab
Prednisolone tablets, 20 mg tab
**Triamcinolone**

**Indications:** for alleviating the joint pain, swelling and stiffness associated with rheumatoid arthritis and osteoarthritis; also for bursitis, epicondylitis, tenosynovitis, lichen simplex chronicus (neuro-dermatitis), granuloma annulare, lichen planus, keloids, alopecia areata and hypertrophic scars.

**Contra-indications:** see notes above; administration by intravenous, intrathecal or intraocular injection, hypersensitivity to any of the ingredients.

**Cautions:** see notes above; should not be injected into unstable joints. avoid given over a long period of time, recent intestinal anastomoses, diverticulitis, thrombophlebitis, existing or previous history of severe affective disorders (especially previous steroid psychosis), exanthematous disease, renal insufficiency, metastatic carcinoma, osteoporosis (post-menopausal females are particularly at risk); in patients with peptic ulcer, myasthenia gravis, latent or healed tuberculosis; in the presence of local or systemic viral infection, systemic fungal infections or in active infections not controlled by antibiotics, hypertension, congestive heart failure, glaucoma, previous steroid myopathy, epilepsy, liver failure.

**Side-effects:** see notes above

**Dose:** by deep intramuscular injection, 40 mg; maximum 100 mg as a single dose.

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**Preparations**

**Triamcinolone injection, 10 mg/mL**

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**6 C.3: Naturally-occurring mineralocorticoids and related drugs**

**Fludrocortisone (Restricted)**

**Indications:** mineralocorticoid replacement in adrenal insufficiency.

**Cautions:** to be used with hydrocortisone.

**Dose:** 50-300 micrograms daily; Child, 5 micrograms/kg daily.

**Preparations**

**Fludrocortisone tablets, 100 micrograms tab.**

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**6 D: Sex hormones**

**6 D.1: Female sex hormones**

**6 D.1.1: Oestrogens and hormonal replacement therapy HRT**

Oestrogens are available in natural and synthetic forms. Synthetic oestrogens are more potent than natural preparations and therefore are not routinely recommended for women in menopause. Only small doses of natural oestrogens are needed to alleviate somatic symptoms and vaginal dryness of menopause and to prevent osteoporosis.

Oestrogens may be given in tablet form or skin gel and patches. Vaginal creams are applied when they
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are primarily used to prevent thinning of the vaginal lining, thereby prevent urinary tract infections and incontinence and also prevent painful intercourse. Oestrogen is well absorbed from skin, vaginal wall and gastrointestinal tract. Systemic side-effects may be experienced after local administration. Hormonal replacement therapy (HRT) in menopause may be initiated after careful assessment of the risks and benefit of oestrogens. Prolonged use of oestrogen is associated with some serious side-effects such as thromboembolic disorders, breast and endometrial cancers. However, side-effects such as, nausea, migraine-like headache, breast discomfort and mood changes are associated with small doses and short period of oestrogen use.

In menopausal women with intact uterus, the use of progestogen with oestrogen is recommended. Such combination significantly reduces the risk of developing endometrial cancer.

Long term HRT is almost certainly favourable in risk-benefit terms for menopausal women without a uterus, because they do not require additional progestogen therapy.

Contra-indications:
- thromboembolic disorders; undiagnosed vaginal bleeding.
- disorders; pre-existing endometriosis, hypertension, diabetes, affective disorders.

Side-effects:
- nausea and vomiting, headache, migraine, mood changes, lipid and carbohydrate metabolic changes, body weight changes; see notes above

Dose: orally, for menopausal symptoms and osteoporosis prophylaxis, 0.625-1.25 mg daily.

Preparations
Conjugated oestrogen tablets, 625 microgram tab.

Betaestradiol

Indications: hormonal replacement therapy in menopause.

Contra-indications, cautions and side-effects: see under oestrogens

Dose: topical gel applications, 1–2 mg spread over the dry clean skin of the shoulder, thigh or arms, allow to dry for 5 minutes before covering with clothing. Avoid application near the eyes, breast or vulval region. Do not wash for at least one hour after application.

Preparations
Betaestradiol gel, 60 mg/100g gel

Estradiol (Restricted)

Indications: improve the vaginal epithelium in menopausal atrophic vaginitis. Postmenopausal urogenital conditions (not suitable for vasomotor symptoms or osteoporosis prophylaxis).
Contra-indications: active arterial thromboembolic disease (e.g. angina or myocardial infarction); active thrombophlebitis; Dubin-Johnson syndrome (or monitor closely); history of breast cancer; history of recurrent venous thromboembolism (unless already on anticoagulant treatment); oestrogen-dependent cancer; recent arterial thromboembolic disease (e.g. angina or myocardial infarction); Rotor syndrome (or monitor closely); thrombophilic disorder; undiagnosed vaginal bleeding; untreated endometrial hyperplasia; venous thromboembolism

Cautions: interrupt treatment periodically to assess need for continued treatment; acute porphyrias; diabetes (increased risk of heart disease); history of breast nodules—closely monitor breast status (risk of breast cancer); history of endometrial hyperplasia; factors predisposing to thromboembolism; history of fibrocystic disease—closely monitor breast status (risk of breast cancer); hypophyseal tumours; increased risk of gall-bladder disease; migraine (or migraine-like headaches); presence of antiphospholipid antibodies (increased risk of thrombotic events); prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer; risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative); symptoms of endometriosis may be exacerbated; uterine fibroids may increase in size.

Side-effects: local irritation; abdominal bloating; abdominal cramps; altered blood lipids (may lead to pancreatitis, rashes and chloasma); breast enlargement; breast tenderness; changes in libido; cholestatic jaundice; contact lenses may irritate; depression; dizziness; fluid retention; glucose intolerance; headache; headache (on vigorous exercise); leg cramps (rule out venous thrombosis); migraine; mood changes; nausea; premenstrual syndrome; sodium retention; vaginal candidiasis; vomiting; weight changes.

Dose: Improve the vaginal epithelium in menopausal atrophic vaginitis 1 tablet daily for 2 weeks, then reduced to 1 tablet twice weekly. Postmenopausal urogenital conditions (not suitable for vasomotor symptoms or osteoporosis prophylaxis). To be inserted into upper third of vagina and worn continuously; replace after 3 months; max. duration of continuous treatment 2 years

Preparations
Estradiol pessary, 10 microgram
Estradiol pump, 750 microgram pack
Progestogens include the naturally occurring progesterone and a number of frequently used synthetic compounds with progestogenic activities. Progestogens are most often used in conjunction with oestrogens for hormone replacement therapy in postmenopausal women and either alone or combined with oestrogen for contraception (see sec 7C). Endometriosis, menstrual disorders and some malignancies may be treated with progestogens. Progestogens are contra-indicated in presence of severe liver disease, progestogen-dependent genital or breast cancer or vaginal bleeding. Progestogens may induce acne, gastrointestinal disturbances, oedema, changes in libido, breast tenderness, mood changes, irregular menstrual cycles. They should be used with caution in the presence of diabetes, hypertension, epilepsy and cardiac, hepatic or renal disease.

**Medroxyprogesterone acetate**

**Indications:** endometriosis; dysfunctional bleeding; contraception (see sec 7C); malignancies; progestogenic opposition of oestrogen HRT.

**Contra-indications, cautions and side-effects:** see notes above

**Dose:** endometriosis, mild to moderate cases, 10 mg 3 times daily for 90 consecutive days, beginning of day 1 of a cycle. Dysfunctional uterine bleeding, 2.5-10 mg daily for 5-10 days beginning on day 16 to 21 of cycle, repeated for 2 cycles. Progestogenic opposition of oestrogen HRT, 10 mg daily for the last 14 days of each 28-day oestrogen HRT cycle.

Malignancies, consult product literature.

**Preparations**

Medroxyprogesterone acetate tablets, 5 mg tab.

Medroxyprogesterone acetate tablets, 10 mg tab.

Medroxyprogesterone acetate injection, 150 mg vial

**Megestrol acetate (Restricted)**

**Indications:** breast cancer, endometrial cancer.

**Contra-indications, cautions and side-effects:** see notes above

**Dose:** breast cancer, 160 mg daily in single or divided doses. Endometrial cancer, 40-320 mg daily in divided doses.

**Preparations**

Megestrol acetate tablets, 160 mg tab.

**Norethisterone acetate**

**Indications:** endometriosis, HRT, menstrual disorders

**Contra-indications, cautions and side-effects:** see notes above

**Dose:** endometriosis, 10-15 mg daily starting on day 5 of cycle; if spotting appears, increase dose to 20-25 mg daily and reduce when bleeding stops.
Dysfunctional uterine bleeding, 5 mg 3 times daily for 10 days
Dysmenorrhoea, 5 mg 3 times daily from day 5 to 25 for 3-4 cycles
Postponement of menstruation, 5 mg 3 times daily starting 3 days before anticipated onset
Progestogenic opposition of oestrogen in oestrogen HRT, 0.32-1 mg daily starting on day 15-26 of each 28-day oestrogen HRT cycle.

Preparations
Norethisterone acetate tablets, 5 mg tab

6 D.1.3: Oestrogens-progestogens preparations

**Estradiol valerate + norgestrel**

*Indications:* HRT in postmenopausal and osteoporosis prophylaxis in women with uterus.

*Contra-indications, cautions and side-effects:* see notes under oestrogens and progestogens

*Dose:* each calendar pack contains, 11 tablets estradiol valerate 2 mg, and 10 tablets of estradiol valerate 2 mg + norgestrel 0.5 mg. One tablets daily starting at day 5 of cycle (or any day if cycle has ceased or infrequent), followed by 7-day interval.

Preparations
Estradiol valerate 2 mg tab (11 tablets), and estradiol valerate 2 mg + norgestrel 0.5 mg tablets (10 tablets)/packet

**Conjugated oestrogen + norgestrel**

*Indications:* HRT in postmenopausal and osteoporosis prophylaxis in women with uterus.

*Contra-indications, cautions and side-effects:* see notes under oestrogens and progestogens

*Dose:* each pack contains 28 tablets (maroon colour) of conjugated oestrogens 625 micrograms, and 12 tablets (brown colour) of norgestrel 150 micrograms. One maroon tablets daily continuously starting on day 1 of cycle or at any time if cycle has ceased, and one brown tablets on days 17-28 of each 28-day treatment cycle, subsequent courses are repeated without interval.

Preparations
Conjugated oestogens tablets, 625 micrograms (28 tablets), and norgestrel 150 micrograms tablets (12 tablets)

6 D.2: Male sex hormones and antagonists

6 D.2.1: Male sex hormones

Testosterone, or testosterone esters, replacement therapy is the standard treatment for primary hypogonadism due to testicular or pituitary disease. In the normal male, androgens inhibit pituitary gonadotrophin secretion and depress spermatogenesis.
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Androgens should not be used for the treatment of impotence unless evidence of hypogonadism is confirmed.

Other uses of androgens include metastatic carcinoma of the breast, osteoporosis and delayed puberty in children. In children, caution should be practiced to avoid early closure of epiphyses with the result of short stature.

Testosterone is often given as an intramuscular depot injection of the esters although subcutaneous implants and oral preparations are also employed. More recently, transdermal implants and topical gel have been developed.

Androgens are contra-indicated in men with prostatic or breast cancer, and during pregnancy and breastfeeding.

They should be used with caution in patients with cardiac, renal and hepatic impairment; hypertension, migraine, epilepsy, diabetes or thyroid diseases; elderly, pre-pubertal boys.

The main side-effects encountered with the use of androgens include sodium and water retention, increased skeletal growth, hypercalcaemia and hypercalciuria, prostate abnormalities and probably cancer, changes in libido. In women it may cause virilisation and suppression of ovulation.

### Testosterone (Restricted)

**Indications:** androgen deficiency, see notes above

**Contra-indications, cautions and side-effects:** see notes above

**Dose:** orally, in androgenic deficiency, initially 120-160 mg daily of testosterone undecanoate; maintenance 40-120 mg daily.

By intramuscular injection, testosterone esters in depot preparation 250 mg every 2-4 weeks

**Preparations**

Testosterone depot injection, 250 mg/mL of various testosterone esters in oily solution, 1 mL ampoule

Testosterone undecanoate capsules, 40 mg cap.

### Oxandrolone (C.D.L)

**Indications:** (specialist use only), for the treatment of constitutional delay of growth and puberty in boys and Turner’s syndrome in girls.

**Contra-indications, cautions and side-effects:** see notes above; short course of treatment to avoid the risk of epiphyseal closure.

**Dose:** 1.25-2.5mg daily for 3 months, longer duration may be required.

**Preparations**

Oxandrolone tablets, 2.5 mg tab.

6 D.2.2: Anti-androgens
Anti-androgens are used to treat disorders associated with excessive androgen or when lower than normal androgens level is desirable. Cyproterone is used in treatment of severe hypersexuality and sexual deviation in the male. It may also be used in the treatment of acne and hirsutism in women. Finasteride interferes with testosterone metabolism by inhibiting the enzyme 5α-reductase, which metabolises testosterone into the more potent androgen, dihydrotestosterone. Reducing the level of testosterone in the prostate results in reducing its size and an improvement of urinary flow rate and in obstructive symptoms.

**Cyproterone (Restricted)**

**Indications:** hypersexuality in the male; severe acne and hirsutism in women.

**Contra-indications:** hepatic disease; malignant or wasting disease; severe diabetes with vascular changes; youths under 18 years.

**Cautions:** sedation may impair psychomotor performances; chronic alcoholism; regularly monitor hepatic function, blood count, adrenocortical function.

**Side-effects:** fatigue and lassitude, weight changes, gynaecomastia; inhibition of spermatogenesis; osteoporosis.

**Dose:** orally in male hypersexuality, 50 mg twice daily.

Preparations
Cyproterone tablets, 50 mg tab.

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**Finasteride (Restricted)**

**Indications:** benign prostatic hyperplasia.

**Cautions:** obstructive uropathy, prostate cancer; finasteride may cause feminisation of male foetus, it is recommended to use condom if sexual partner is pregnant (finasteride is excreted in semen).

**Side-effects:** impotence, decreased libido, ejaculation disorders, testicular pain, breast tenderness and enlargement, allergic reactions.

**Dose:** 5 mg daily for 6 months, re-assess treatment then after. Longer therapy period may be needed.

Preparations
Finasteride tablets, 5 mg tab.

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**6 D.2.3: Somatostatin analogues**

Somatostatin, a cyclic polypeptide, secreted from pancreas can regulate pituitary function, thereby acting as a true neurohormone. The therapeutic uses of Somatostatin are confined mainly to blocking hormone release in endocrine-secreting tumours, including insulinomas, VIPomas, glucagonomas, carcinoid tumours, somatotropinomas as in acromegaly. Because of its short half-life, somatostatin has been replaced by octreotide, a long-acting analogue. Octreotide successfully controls excess secretion of growth hormone and reduces the size of pituitary tumours. It has also been
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used for the prevention of complications following pancreatic surgery.

Lanreotide (Restricted)

**Indications**: Acromegaly and neuroendocrine (particularly carcinoid) tumours. Thyroid tumours.

**Cautions**: Cardiac disorders (including bradycardia); patients with carcinoid tumours—exclude the presence of an obstructive intestinal tumour before treatment. Diabetes mellitus (antidiabetic requirements may be reduced); insulinoma (increased depth and duration of hypoglycaemia may occur—observe patients and monitor blood glucose levels when initiating treatment and changing doses); may cause growth hormone-secreting pituitary tumour expansion during treatment (causing serious complications).

**Side-effects**: Alopecia; biliary dilatation; bradycardia; constipation; dizziness; dyspepsia; headache; lethargy; malaise; musculoskeletal pain; myalgia; raised bilirubin; Hot flushes; insomnia; hypothyroidism; Pancreatitis (shortly after administration); Abdominal pain; anorexia; bloating; diarrhoea; flatulence; gallstones (after long-term treatment); gastro-intestinal disturbances; hyperglycaemia (with chronic administration); hypoglycaemia; impaired postprandial glucose tolerance (with chronic administration); irritation at the injection site; nausea; pain at the injection site; steatorrhoea; vomiting

**Dose**: Acromegaly and neuroendocrine (particularly carcinoid) tumours. Initially 30 mg every 14 days, increased to 30 mg every 7–10 days, adjusted according to response.

Thyroid tumours. Initially 30 mg every 14 days, increased to 30 mg every 10 days, adjusted according to response.

**Preparations**

Lanreotide acetate injection, 30 mg vial

Octreotide (C.D.L)

**Indications**: see notes above

**Cautions**: do regular ultrasound examination of gallbladder; monitor glucose tolerance; check on growth hormone abnormal secretion.

**Side-effects**: sinus bradycardia, conduction abnormalities, arrhythmias; diarrhoea; hypo/hyperglycaemia; gallbladder abnormalities.

**Dose**: for doses in various therapeutic indications, consult product literature.

**Preparations**

Octreotide injection, 200 micrograms ampoule.

Octreotide acetate injection, powder and solvent for reconstitution, 20 mg vial

6 E: Hypothalamic and pituitary hormones
6 E.1: Anterior pituitary hormones and anti-oestrogens

6 E.1.1: Anti-oestrogens

The anti-oestrogens tamoxifen and clomifene are used primarily for the treatment of breast cancer and female infertility, respectively. These agents are therapeutically used for their anti-oestrogenic activity, but they are capable of producing anti-oestrogenic as well as oestrogenic effects. They block the oestrogen receptors in the hypothalamus leading to increased pituitary secretion of gonadotrophin.

**Clomifene citrate (Clomiphene citrate)**

**Indications**: anovulatory infertility.

**Contra-indications**: hepatic disease, ovarian cysts, abnormal uterine bleeding, endometrial carcinoma, pregnancy.

**Cautions**: use smallest dose possible in women with polycystic disease; patients should be warned of the possibility of multiple pregnancy; visual disturbances mandates discontinuation of therapy.

**Side-effects**: visual disturbances, hot flushes, gastrointestinal disturbances, liver impairment, ovarian enlargement and cyst formation, breast tenderness.

**Dose**: 50 mg daily for 5 days, starting within about 5 days of onset of cycle or at any time if there is amenorrhoea. If ovulation does not occur the dose may be doubled and treatment course repeated twice if necessary. Long-term cyclical therapy is not recommended.

**Preparations**

Clomifene citrate tablets, 50 mg tab.

**Tamoxifen (Restricted)**

**Indications**: oestrogen-receptor positive breast cancer in women.

**Contra-indications**: pregnancy.

**Cautions**: patients with leucopenia or thrombocytopenia; occasional cystic ovarian swelling in premenopausal women, endometrial changes; breast-feeding.

**Side-effects**: hot flushes, nausea and vomiting, increased tumour pain, vaginal bleeding, endometriosis, blood disorders, masculinisation and hirsutism in females.

**Dose**: 20 mg daily.

**Preparations**

Tamoxifen tablets, 10 mg tab.

6 E.1.2: Anterior pituitary hormones

The peptide hormones of the anterior pituitary are essential for the regulation of growth, reproduction and intermediary metabolism. The synthesis and release of such hormones are controlled by hypothalamic hormones, by peripheral endocrine hormones, by disease, and by many drugs.
**6: Endocrine system**

### Corticotropins (Corticotrophins)

The adrenocorticotropic hormone (ACTH or corticotropin) stimulates the adrenal cortex to secrete glucocorticoids, mineralocorticoids, and androgens.

Tetracosactrin (tetracosactide) is a synthetic analogue of corticotropin that is of therapeutic and diagnostic uses. The use of ACTH and tetracosactide as alternative to corticosteroids is declining due to variable and unpredictable therapeutic response. Presently, they are mainly indicated for the diagnosis of adrenal insufficiency. Plasma cortisol concentration in normal adrenal function tends to rise after the administration of tetracosactrin or ACTH.

**Tetracosactide acetate** (Tetracosactrin acetate) (Restricted)

**Indications**: adrenocortical function test; see notes above

**Contra-indications**: as for corticosteroids; avoid using preparations containing benzyl alcohol in neonates.

**Cautions and side-effects**: as for corticosteroids see sec 6 C

**Dose**: diagnostic, intramuscularly 1 mg single dose.

Therapeutic indications, consult product literature.

**Preparations**

Tetracosactide acetate injection, 250 micrograms/mL, 1 mL ampoule

### Gonadotrophins

The pituitary hormones, luteinising hormone (LH), and follicle-stimulating hormone (FSH) as well as the related placental hormone, chorionic gonadotrophin (CG), are referred to as the gonadotropic hormones because of their actions on gonadal cells. These hormones are nowadays prepared from human urine and no more extracted from cadaverous pituitary glands. Menotrophin, which contains both FSH and LH is obtained from the urine of postmenopausal women and often referred to as human menopausal gonadotropin. Human chorionic gonadotrophin (HCG) is obtained from the urine of pregnant women. Urofollitropin (urofollitrophin) is a menotrophin from which the LH has been removed and thus is primarily FSH.

The main therapeutic use of these hormones is in the treatment of female infertility resulting from hypopituitarism, or those not responded to clomiphene, or in superovulation treatment to assist conception. In the male, they are used for the treatment of hypogonadotropin hypogonadism and associated oligospermia.

**Human chorionic gonadotrophin** (Restricted)
**Indications**: see notes above  
**Contra-indications**: androgen-dependent tumours.  
**Cautions**: cardiac or renal dysfunction, asthma, epilepsy, migraine.  
**Side-effects**: headache, irritability, precocious puberty, gynaecomastia, injection site pain, multiple pregnancy.  
**Dose**: by subcutaneous or intramuscular injection according to patient’s response or need.

**Preparations**  
*Human chorionic gonadotrophin injection*, powder for reconstitution 1500 units/ampoule.  
*Human chorionic gonadotrophin injection*, powder for reconstitution 5000 units/ampoule.

**Human menopausal gonadotrophin (Restricted)**  
**Indications**: see notes above  
**Contra-indications**: undiagnosed abnormal vaginal bleeding, intracranial bleeding, adrenal and thyroid disorders, pre-existing ovarian cysts, primary ovarian or testicular failure, malignancies of breast, uterus, testes or prostate.  
**Cautions**: tumour of the pituitary, rule out infertility caused by adrenal or thyroid disorders, hyperprolactinaemia.  
**Side-effects**: allergic reactions; ovarian enlargement and rupture, increased risk of multiple pregnancies.  
**Dose**: by subcutaneous or intramuscular injection, according to patient’s response or need.

**Preparations**  
*Human menopausal gonadotrophin injection*, powder for reconstitution, 75 units / ampoule

**Urofollitropin (Urofollitrophin) (Restricted)**  
**Indications**: see notes above  
**Contra-indications**, cautions and side-effects: see under human menopausal gonadotrophin  
**Dose**: by subcutaneous or intramuscular injection according to patient’s response or need.

**Preparations**  
*Urofollitropin injection*, powder for reconstitution, 75 units / ampoule

**Growth hormone**  
Somatropin is an analogue of human growth hormone produced by using recombinant DNA technology. Its main therapeutic indication is in growth hormone-deficient children.

**Human growth hormone HGH (Somatropin) (Restricted)**  
**Indications**: growth hormone deficiency.  
**Contra-indications**: closed epiphyses, active tumours, hypersensitivity to m-cresol or glycerin (diluent).
6: Endocrine system

Cautions: diabetes mellitus, papilloedema, history of malignant disease, rotate site of injection to avoid lipoatrophy.
Side-effects: development of antibodies, oedema.
Dose: by subcutaneous injection according to patient’s response or need.

Preparations
Human growth hormone injection, powder for reconstitution, 4 units/ampoule (1.33 mg / ampoule)
Growth Hormone 15 Units pen.

Thyroid stimulating hormone

Thyrotropin alfa is a recombinant form of throtrophin (thyroid stimulating hormone)

Thyrotropin alfa (recombinant thyroid stimulating hormone) (Restricted)
Indications: Detection of thyroid remnants and thyroid cancer in post-thyroidectomy patients, together with serum thyroglobulin testing (with or without radiiodine imaging). To increase radio-iodine uptake for the ablation of thyroid remnant tissue in suitable post-thyroidectomy patients
Cautions: Presence of thyroglobulin autoantibodies may give false negative results
Side-effects: Dizziness; fatigue; headache; nausea; vomiting

Dose: 900 micrograms every 24 hours for 2 doses, dose to be administered into the gluteal muscle, consult product literature for further information on indications and dose.

Preparations
Thyrotropin Alfa injection, powder for reconstitution, 900 microgram vial.

6 E.1.3: Hypothalamic hormones

The hypothalamic hormone gonadorelin, which causes the release of LH and FSH, is mainly used for diagnostic purposes. However, gonadorelin analogues such as goserelin and triptorelin are indicated for the treatment of prostate cancer and endometriosis (see sec 8C).

Protirelin is a hypothalamic-releasing hormone that stimulates the release of thyrotrophin from the pituitary. It is indicated for the diagnosis of mild hyperthyroidism or hypothyroidism.

Gonadorelin (Restricted)
Indications: assessment of pituitary function in adults.
Cautions: pituitary adenoma.
Side-effects: irritation at injection site; hypersensitivity reactions on repeated administration.
Dose: subcutaneous or intravenous injection, 100 micrograms.
6 E.2: Posterior pituitary hormones and antagonists

Antidiuretic hormone (vasopressin) promotes water conservation by the kidney. In large therapeutic doses, it can also cause peripheral vasoconstriction and stimulates the smooth muscles of the intestine, gall bladder and urinary bladder. Lack of this hormone leads to diabetes insipidus with characteristic excessive excretion of diluted urine.

Desmopressin is an analogue of vasopressin with longer duration of action and no vasoconstrictor effects. It is indicated in the treatment and diagnosis of hypothalamic (cranial) diabetes insipidus. Nephrogenic diabetes insipidus is better treated with thiazide diuretics. Desmopressin is also used to boost the effect of factor VIII in haemophilic patients, in the treatment of bleeding oesophageal varices because it decreases hepatic blood flow and portal venous pressure.

Desmopressin (Restricted)  
**Indications:** diagnosis and treatment of hypothalamic diabetes insipidus; boosting Factor VIII in haemophilia.  
**Contra-indications:** cardiac insufficiency and disorders treated with diuretics.  
**Cautions:** migraine, epilepsy, heart failure, asthma; pregnancy; avoid fluid overload.
6: Endocrine system

Side-effects: fluid retention when fluid intake is not restricted, gastric pain, headache, convulsions due to hyponatraemia, nausea and vomiting.


Diagnosis of diabetes insipidus, intranasally, adult and child 20 micrograms. By injection, adult and child 2 micrograms. Restrict fluid intake 1 hour before and 8 hours after administration.

In mild to moderate haemophilia, by subcutaneous or intramuscular injection, consult literature.

Preparations
Desmopressin acetate injection, 4 micrograms/mL, 1 mL ampoule
Desmopressin tablets, 100 microgram tab.
Desmopressin tablets, 200 microgram tab.

Terlipressin (Restricted)

Indications: bleeding from oesophageal varices.
Contra-indications and cautions: see under desmopressin
Side-effects: see under desmopressin, but effects milder

Calcitonin (Salmon) (Salcatonin) (Restricted)

Indications: hypercalcaemia; Paget’s disease; osteoporosis.
Contra-indications: hypersensitivity to synthetic calcitonin.
Cautions: administration may lead to hypocalcaemic tetany; monitor for possible allergic reactions to
calcitonin since it is an exogenous protein; resistance to salmon calcitonin may develop due to antibody formation. **Side-effects**: gastrointestinal disturbances; skin rash; nasal spray may cause local irritation and ulceration, rhinitis sinusitis, epistaxis. **Dose**: hypercalcaemia, by subcutaneous or intramuscular injection, 5-10 units/kg daily in 1-2 divided doses, adjust according to clinical and biochemical response. Paget’s disease of bone, intramuscular or subcutaneous injection, a dose range of 50 units 3 times weekly to 100 units daily are used as single or divided doses. Postmenopausal osteoporosis, intramuscular or subcutaneous injection, 100 units daily. Intranasally, 200 units daily. Supplement of dietary calcium and vitamin D is recommended.

**Preparations**
Calcitonin injection, 50 micrograms mL, 1 mL ampoule
Calcitonin metered nasal spray, 200 units/metered spray

### 6 F.2: Bisphosphonates

Bisphosphonates increase bone mass by reducing the activity of individual osteoclasts and increasing osteoclast apoptosis. They are indicated for, the prevention of bone loss in early menopausal women, treatment of established osteoporosis, and in conditions characterized by increased bone remodelling as in Paget’s disease or hypercalcaemia in malignancies. These drugs should be avoided in the presence of upper gastrointestinal disease, hypocalcaemia and in renal impairment.

**Alendronate (Restricted)**

**Indications**: treatment and prevention of postmenopausal osteoporosis, Paget’s disease.

**Contra-indications**: hypocalcaemia; pregnancy and breast-feeding; upper gastrointestinal disorders.

**Cautions**: upper gastrointestinal disorders, renal impairment, routine check for calcium and other minerals.

**Side-effects**: oesophageal reactions, gastrointestinal disturbances, musculoskeletal pain, headache, rash and photosensitivity.

**Dose**: treatment of postmenopausal osteoporosis, 70 mg once weekly.

**Note**: to be taken on an empty stomach at least 30 minutes before breakfast and patient should stand or sit upright for at least 30 minutes after taking tablet.

**Preparations**
Alendronate tablets, 70 mg tab.
6: Endocrine system

**Clodronate (Restricted)**

**Indications:** hypercalcaemia in malignancies, Paget’s disease, osteolytic lesions and bone pain associated with malignancies.

**Contra-indications:** renal impairment, pregnancy and breast-feeding.

**Cautions:** renal and hepatic disease, elderly; regularly monitor water and electrolytes; concomitant use of NSAIDs may be associated with renal dysfunction.

**Side-effects:** nausea, diarrhoea.

**Dose:** by mouth, 1.6 g daily in single or 2 divided doses, increase if necessary to 3.2 g.

Preparations
Clodronate sodium capsules, 400 mg cap.

**Disodium pamidronate (Restricted)**

**Indications:** hypercalcaemia in malignancies, Paget’s disease, osteolytic lesions and bone associated with malignancies.

**Contra-indications:** see notes above; pregnancy and breast-feeding.

**Cautions:** renal disease, elderly; thyroid dysfunction; regularly monitor water and electrolytes.

**Side-effects:** hypophosphataemia, fever and flu-like symptoms, nausea and vomiting, gastrointestinal discomfort.

**Dose:** by slow intravenous infusion; in hypercalcaemia of malignancy, 15-60 mg in single infusion or in divided doses over 2-4 days according to level of serum calcium.

In Paget’s disease, 30 mg once a week for 6 weeks or 30 mg first week and the 60 mg every other week with a total of 210 mg. Maximum total 360 mg.

In osteolytic lesions and bone pain in bone metastases associated with breast cancer or multiple myeloma, 90 mg every 3-4 weeks.

Preparations
Disodium pamidronate injection, powder for reconstitution, 15 mg vial

**Zoledronic acid**

**Indications:** hypercalcaemia of malignancy, osteoporosis, Paget's disease, multiple myeloma and patients with documented bone metastases from solid tumours, in conjunction with standard antineoplastic therapy.

**Contra-indications:** pregnancy and breast-feeding.

**Cautions:** patient must be adequately rehydrated prior to administration, serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy, if hypocalcaemia, hypophosphataemia, or hypomagnesaeemia occur, short-term supplemental therapy may be necessary.

**Side-effects:** hypophosphataemia, anaemia, influenza like syndrome
including bone pain, gastrointestinal disturbances, headache, renal impairment.

**Dose:** in hypercalcaemia of malignancy, by intravenous infusion, 4 mg as a single dose infused over no less than 15 minutes. In osteoporosis, by intravenous infusion, 5 mg infused over no less than 15 min every 12 months.

**Note:** daily calcium and vitamin D supplements should also be taken.

**Preparations**

Zoledronic acid injection, 4 mg vial
Zoledronic acid injection, 50 micrograms/mL, 100 mL bottle

**Denosumab (Restricted)**

**Indications:** Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, by subcutaneous injection: 60 mg every 6 months, supplement with calcium and vitamin D. Prevention of skeletal related events in patients with bone metastases from solid tumours, by subcutaneous injection: 120 mg every 4 weeks, supplementation of at least Calcium 500 mg and vitamin D 400 units daily should also be taken unless hypercalcaemia is present. Treatment of giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity in adults and skeletally mature adolescent, by subcutaneous injection: 120 mg every 4 weeks, give additional dose on days 8 and 15 of the first month of treatment only, supplementation of at least Calcium 500 mg and vitamin D 400 units daily should also be taken unless hypercalcaemia is present.

**Contra-indications:** Hypocalcaemia, unhealed lesions from dental or oral surgery.

**Cautions:** Atypical femoral fractures; hypocalcaemia; osteonecrosis of the jaw—consider temporary interruption of treatment if occurs.

**Side-effects:** Abdominal discomfort; cataracts; constipation; diarrhoea; dyspnoea; eczema; hypocalcaemia (fatal cases reported); hypophosphataemia; musculoskeletal pain; osteonecrosis of the jaw; pain in extremity; rash; sciatica; sweating; upper respiratory tract infection; urinary tract infection.

**Dose:** Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures and the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, by subcutaneous injection: 60 mg every 6 months, supplement with calcium and vitamin D.

Prevention of skeletal related events in patients with bone metastases from solid tumours, by subcutaneous injection: 120 mg every 4 weeks, supplementation of at least Calcium 500 mg and vitamin D 400 units daily should also be taken unless hypercalcaemia is present.

**Preparations**

Denosumab injection, 60 mg / 1 ml
Denosumab injection 70 mg / 1 ml
6: Endocrine system

6 G: Other endocrine drugs

6 G.1: Bromocriptine

Bromocriptine is a dopaminergic agonist that inhibits the pituitary release of prolactin. It is useful in galactorrhoea and in the treatment of infertility due to hyperprolactinaemia. It may be used to reduce the level of growth hormone in patients with acromegaly. When ordinary measures fail, bromocriptine may be used to suppress lactation. It is also used in treatment of benign breast disorders and prolactinoma.

**Bromocriptine (Restricted)**

**Indications:** see notes above

**Contra-indications:** sensitivity to bromocriptine; toxaemia of pregnancy and hypertension in postpartum women or in puerperium.

**Cautions:** peptic ulcer; mental disorders; cardiovascular disease.

**Side-effects:** nausea, vomiting, constipation; dyskinesia, fatigue; hypotension.

**Dose:** prevention of lactation, orally 2.5 mg on day 1 and then 2.5 mg twice daily for 14 days.

Suppression of lactation, 2.5 mg daily for 2-3 days and then 2.5 mg twice daily for 14 days. Hypogonadism, galactorrhoea, infertility, initial dose of 1-1.25 mg at bed time to minimize the hypotensive effect, increase gradually to 7.5 mg daily in divided doses.

Cyclical benign breast disease, 1-1.25 mg at bedtime, increase gradually to 2.5 mg twice daily.

Acromegaly, initially 1-1.25 mg, increase gradually to 5 mg every 6 hours.

**Preparations**

Bromocriptine tablets, 2.5 mg tab.

**Cabergoline (Restricted)**


**Contra-indications:** Avoid in pre-eclampsia; cardiac valvulopathy (exclude before treatment); history of pericardial fibrotic disorders; history of puerperal psychosis; history of pulmonary fibrotic disorders; history of retroperitoneal fibrotic disorders

**Cautions:** Acute porphyrias; cardiovascular disease; history of peptic ulcer (particularly in acromegalic patients); history of serious mental disorders (especially psychotic disorders); Raynaud’s syndrome. In hyperprolactinaemic patients, the source of the hyperprolactinaemia should be established (i.e. exclude pituitary tumour before treatment).

**Side-effects:** Abdominal pain; angina; breast pain; confusion; constipation; depression; dyspepsia; epigastric pain; gastritis; hallucinations; headache; nausea; syncope

**Dose:** Prevention of lactation 1 mg, to be taken as a single dose on the first day postpartum.
Suppression of established lactation 250 micrograms every 12 hours for 2 days.

Hyperprolactinaemic disorders Initially 500 micrograms once weekly, dose may be taken as a single dose or as 2 divided doses on separate days, then increased in steps of 500 micrograms every 1 month until optimal therapeutic response reached, increase dose following monthly monitoring of serum prolactin levels; usual dose 0.25–2 mg once weekly, usually 1 mg weekly; reduce initial dose and increase more gradually if patient intolerant, doses over 1 mg weekly to be given as divided dose; maximum 4.5 mg per week.

Parkinson's disease Initially 1 mg daily, then increased in steps of 0.5–1 mg every 7–14 days, concurrent dose of levodopa may be decreased gradually while dose of cabergoline is increased; maximum 3 mg per day.

Preparations
Cabergoline tablets, 500 microgram tab.

6 G.2: Trilostane

Danazol is a synthetic androgen with strong antgonadotrophic effects that leads to secondary endometrial atrophy. It is used for the treatment of endometriosis. Danazol possesses an antagonistic effect and hence is used in precocious puberty, gynaecomastia, and menorrhagia. It may be of value in the long-term therapy of hereditary angioedema.

Danazol (Restricted)

Indications: see notes above

Contra-indications: pregnancy; severe renal, hepatic and cardiac disease; thromboembolic disorders; hormone-dependent tumours.

Cautions: epilepsy, diabetes mellitus, migraine, elderly, polycythaemia, hypertension, non-hormonal contraceptive to be used if appropriate.

Side-effects: dizziness, flushes, muscle spasm, hair loss, acne, oedema, mild hirsutism, mood changes, changes in libido, vaginal dryness and irritation, menstrual disturbances, reduction in breast size.

Dose: endometriosis, initially 200-400 mg daily in 2-4 divided doses for 6 months, adjust according to response.

Precocious puberty, 100-400 mg daily in 2-4 divided doses, adjust according to age and response.

Menorrhagia. 100-400 mg in 2-4 divided doses, starting on the first day of cycle, adjust dose according to response, reassess after 3 months.

Gynaecomastia, 400 mg daily in divided doses, for six months. Smaller dose may be used in adolescents.

Preparations
Danazol capsules, 200 mg cap.
7: Obstetrics, gynaecology and urinary tract disorders

Section 7: Obstetrics, gynaecology and urinary tract disorders

- Drugs acting on smooth muscles
- Drugs used in vaginal and vulval conditions
- Contraceptives
- Urinary disorders
- Irrigation fluids and dialysis

7 A: Drugs acting on smooth muscles

7 A.1: Prostaglandins and oxytocics

Drugs such as prostaglandins and oxytocics (oxytocin and ergometrine) are used to induce or augment labour. They are also used to induce abortion or to stop postpartum haemorrhage. The uterine contractions induced vary in strength and duration and the pain caused is contraction dependent.

Dinoprostone (prostaglandin PGE₂) is available in various formulations. Vaginal applications in the form of gel and pessaries are mostly preferred because of low incidence of side-effects. It is used for induction and augmentation of labour at term. Carboprost (prostaglandin PGF₂α) is administered by injection for the treatment of postpartum haemorrhage that is uncontrolled by oxytocin and ergometrine.

Dinoprostone (Restricted)

Indications: induction and augmentation of labour at term; medical induction of therapeutic abortion.

Contra-indications: cardiac, pulmonary, renal, hepatic disease; foetal distress; untreated pelvic infection; placenta praevia or unexplained vaginal bleeding; history of difficult cephalopelvic disproportion or traumatic delivery; foetal malpresentation, grand multipara, multiple pregnancy; history of caesarean section or major uterine surgery.

Cautions: asthma, glaucoma, cardiac, hepatic or renal impairment; hypertension; epilepsy; closely monitor uterine contractility when oxytocin is used in sequence.

Side-effects: nausea, diarrhoea; dizziness; bronchospasm, fever.
backache; severe uterine contraction; pulmonary or amniotic fluid embolism; abruptio placentae, foetal distress, uterine rupture.  
**Dose:** vaginal gel, for induction of labour 1 mg inserted high into posterior fornix, followed after 6 hours by 1-2 mg, maximum 3 mg gel.  
Vaginal tablets, for induction of labour, 3 mg tablets inserted high into posterior fornix, followed after 6-8 hours by another 3 mg tablet, maximum 6 mg as vaginal tablets.  
Injections, consult manufacturer’s literature.

**Preparations**
Dinoprostone vaginal gel, 400 micrograms/mL, 2.5 mL gel application (total 1 mg per application)  
Dinoprostone vaginal gel, 800 micrograms/mL, 2.5 mL gel application (total 2 mg per application)  
Dinoprostone vaginal tablets, 3 mg pessary

**Carboprost (CDL)**  
**Indications:** postpartum haemorrhage due to uterine atony unresponsive to ergometrine and oxytocin.  
**Contra-indications:** renal, cardiac, pulmonary or hepatic disease; untreated pelvic infection.  
**Cautions:** glaucoma, hypertension, hypotension, epilepsy, uterine scar.  
**Side-effects:** see dinoprostone above  
**Dose:** by deep intramuscular injection, 250 micrograms repeated if necessary every 60-90 minutes, total dose should not exceed 2 mg.

**Preparations**  
Carboprost (as trometamol or tromethamine salt) injection, 250 microgram/mL, 1 mL ampoule

**Ergometrine maleate + oxytocin**  
**Indications:** postpartum haemorrhage; to reduce bleeding during surgical uterine evacuation.  
**Contra-indications:** induction of labour; second and third stages of labour; circulatory disease; impaired pulmonary, renal or hepatic functions; sepsis; severe hypertension, eclampsia.  
**Cautions:** multiple pregnancy, toxemia, sepsis.  
**Side-effects:** nausea and vomiting, abdominal pain, dizziness, tinnitus, palpitation, transient hypertension.  
**Dose:** intramuscular injection, single 1 mL ampoule (see preparation).

**Preparations**  
Ergometrine maleate + oxytocin injection, 500 micrograms + 5 units/mL, 1 mL ampoule

**Misoprostol (Restricted)**  
**Indications:** to induce medical abortion, cervical ripening procedure, management of post partum haemorrhage, prophylaxis for NSAID-induced gastric ulcer.  
**Contraindication:** pregnancy, severe asthma requiring corticosteroids, hepatic failure, adrenalfailure, bleeding disorders of concurrent anticoagulation therapy, allergy to misoprostol, suspected ectopic
pregnancy, IUCD in situ, inherited porphyria

**Cautions:** Conditions where hypotension might precipitate severe complications (e.g. cerebrovascular disease, cardiovascular disease); inflammatory bowel disease, renal failure, previous cesarean birth

**Side-effects:** abdominal pain, diarrhoea, indigestion, nausea, cardiac dysrhythmia, anaemia, vaginal bleeding, chills and fever.

**Dose:** Benign gastric ulceration

Benign duodenal ulceration

NSAID-associated ulceration: 800 micrograms daily in 2–4 divided doses continued for at least 4 weeks or may be continued for up to 8 weeks if required, dose to be taken with breakfast (or main meals) and at bedtime.

Prophylaxis of NSAID-induced gastric ulcer. Prophylaxis of duodenal ulcer: 200 micrograms 4 times a day, reduced if not tolerated to 200 micrograms 2–3 times a day/day, use lower dose is less

Termination of pregnancy following mifepristone (gestation up to 49 days) 400 micrograms for 1 dose, dose to be given 24–48 hours after mifepristone.

Termination of pregnancy following mifepristone (gestation 50 to 63 days). Initially by vagina, or by buccal administration, or by sublingual administration 800 micrograms for 1 dose, dose to be given 24–48 hours after mifepristone, if abortion has not occurred 4 hours after first misoprostol dose a further dose may be given, (by mouth or by vagina) 400 micrograms for 1 dose.

Termination of pregnancy following mifepristone (gestation of 9 to 13 weeks). Initially by vagina 800 micrograms for 1 dose, dose to be given 36–48 hours after mifepristone, followed by (by vagina or by mouth) 400 micrograms every 3 hours if required for a maximum of 4 doses.

Termination of pregnancy following mifepristone (gestation of 13 to 24 weeks). Initially by vagina 800 micrograms for 1 dose, dose to be given 36–48 hours after mifepristone, followed by (by vagina or by mouth) 400 micrograms every 3 hours if required for a maximum of 4 doses, if abortion has not occurred 3 hours after the last dose of misoprostol, a further dose of mifepristone may be given, and misoprostol may be recommenced 12 hours later.

Induction of abortion (0-12 weeks): 800 micrograms vaginally every 12 hours (total: 3 doses). Missed abortion (0-12 weeks): 800 micrograms vaginally every 12 hours (total: 3 doses). Incomplete abortion (0-12 weeks): 600 micrograms orally stat and to be repeated every 12 hours (total: 3 doses). Also, patients will need antibiotic cover. Induction of abortion (13-22 weeks): 400 micrograms vaginally to be given every 3 hours (5 doses). Intrauterine fetal death (13-17 weeks): 400 micrograms vaginally every 6-12 hours for 4 doses. Intrauterine fetal
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Death (18-26 weeks): 100 micrograms vaginally every 6-12 hours for 4 doses. Intrauterine fetal death beyond 26 weeks: 25-50 micrograms vaginally every 4 hours up to 6 doses. Postpartum haemorrhage: 800 micrograms stat dose rectally

Preparations
Misoprostol tablets, 200 micrograms tab.

Oxytocin
Indications: induction and augmentation of labour; postpartum haemorrhage; missed or incomplete abortion.
Contra-indications: mechanical obstruction to delivery, hypertonic uterine; when vaginal delivery is contra-indicated; foetal distress.
Cautions: previous caesarean section, multiple pregnancy, multipara, hypertension, concomitant use of prostaglandins, borderline cephalopelvic disproportion.
Side-effects: uterine hyper-stimulation, uterine spasm; nausea and vomiting, water intoxication when infused with large volume of electrolyte-free fluids; amniotic fluid embolism; placenta abruption.
Dose: for induction or augmentation of labour, by slow intravenous infusion, 0.001-0.002 unit/minute; maximum is 5 units per day. Closely monitor foetal heart rate and uterine motility.
For prevention or treatment of postpartum haemorrhage, 5-10 units by slow intravenous injection; in severe cases 5-30 units in 500 mL infusion fluid by slow intravenous infusion.
For missed or incomplete abortion, by slow intravenous injection, 5 units followed if necessary by 0.02-0.04 units/minute or faster.

Preparations
Oxytocin injection, 10 units/mL, 1 mL ampoule

Hydroxyprogesterone hexanoate (Restricted)
Indications: Preterm birth risk reduction
Contra-indications: Current thrombosis or thromboembolic disorders or history of these conditions, known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions, undiagnosed abnormal vaginal bleeding unrelated to pregnancy, cholestatic jaundice of pregnancy, liver tumors, uncontrolled hypertension, herpes.
Cautions: Thromboembolic disorder, sensitivity reactions, allergic reactions, decreased glucose tolerance, fluid retention, depression, jaundice, hypertension
Side-effects: Diarrhea; mild bruising, itching, or pain at the injection site; nausea
Dose: 250 mg once weekly (every 7 days) by slow IM injection. Treatment should begin between 16 weeks 0 days and 20 weeks 6 days of gestation, and continue once weekly until week 37 (through 36
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weeks, 6 days) of gestation or delivery, whichever occurs first.

Hydroxyprogesterone hexanoate
injection, 250 mg / injection

7 A.2: Ductus arteriosus

Ductus arteriosus patency is physiologically maintained by prostaglandins. In neonates with congenital heart defects, alprostadil (prostaglandin E1) is used to maintain and increase pulmonary blood flow and oxygenation of blood.

Alprostadil (CDL)
Indications: congenital heart defect in neonates prepared for corrective surgery.
Cautions: intensive care facility should be available; monitor arterial pressure.
Side-effects: neonatal apnoea, blood pressure changes, disseminated intravascular coagulation, flushing, fever.
Dose: by intravenous infusion, 50-100 nanograms/kg/minute, then decrease to lowest effective dose.

Preparations
Alprostadil injection, 500 micrograms / mL, 1 mL ampoule

7 A.3: Myometrial relaxants

The uterine muscle is rich during pregnancy with β2-receptors. Stimulation of such receptors with β2-agonists leads to uterine muscle relaxation. Salbutamol is commonly used to inhibit uncomplicated premature labour between 24 and 33 weeks of gestation and it may delay delivery at least 48 hours. Prolonged use should be avoided since risk to mother increases after 48 hours of use and there is a lack of evidence of any benefit from further treatment. Oral treatment after initial parenteral therapy is therefore not recommended. The oxytocin receptor antagonist, Atosiban, is licensed for the inhibition of uncomplicated premature labour between 24 and 33 weeks of gestation. Atosiban may be preferable to β2-agonists because it has fewer side-effects.

Atosiban
Indications: uncomplicated premature labour.
Contra indications: cardiac disease, eclampsia and severe pre-eclampsia, intra-uterine infection, intra-uterine fetal death, antepartum haemorrhage, placenta praevia, cord compression, premature rupture of membranes after 30 weeks’ gestation.
Caution: hepatic impairment, renal impairment, intrauterine growth retardation.
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Side-effects: nausea, vomiting, flushing, sweating, tremor, tachycardia.

Dose: by intravenous injection, initially 6.75 mg over 1 minute, then by intravenous infusion 18 mg/hour for 3 hours, then 6 mg/hour for up to 45 hours; max. duration of treatment 48 hours.

Preparations
Atosiban injection, 7.5 mg/mL, 5 mL vial

Salbutamol
See notes in sec 3 A.1.1.

7 B: Drugs used in vaginal and vulval conditions

Vaginal infections: Symptoms of vulvo-vaginitis are likely to be primarily presented as vulvitis but infection almost invariably involves the vagina also. External application of drugs to the vulva alone may give symptomatic relief, without curing the infection. Creams, vaginal ovules and pessaries are applied but not ointments. The natural secretion and evaporation should not be impeded in the vagina during treatment. Systemic treatment is also recommended especially in infections, which are sexually transmitted. Fungal, bacterial and rarely viral infections are treated with specific drugs. Identification of the causative microorganism should be done before selecting a preparation for treatment.

Treatment with creams should involve both the vulva and the vagina. Pessaries or ovules must be inserted high into the vagina.

Fungal infections
Recurrence is common in fungal infections if treatment is not adequate or there are predisposing factors such antibacterial therapy, diabetes mellitus or the use of contraceptive pills. The use of nystatin vaginal tablets, imidazole derivative cream or vaginal tablets are recommended.

Bacterial infections
Bacterial vaginosis is commonly due to gram-negative organisms. It can be treated with systemic metronidazole or amoxicillin. Vaginal antibacterial creams such as Clindamycin or metronidazole are used for bacterial vaginosis and cervicitis. Sexually transmitted bacterial infections are treated systemically.

Trichomonal infections
They commonly involve the lower urinary tract as well as the genital system and needs systemic treatment with metronidazole.

Preparations
Nystatin vaginal tablets, 100,000 IU / vaginal tab.
Dose: one pessary at night for 14-28 days.
Clindamycin vaginal cream, 2%
Dose: one application (5 g) at night for 3-7 Days
Clotrimazole vaginal tablets, 500 mg vaginal tab.
Dose: one pessary single application
Imidazole derivatives vaginal cream (e.g. clotrimazole, econa-zole, miconazole, ketoconazole)
Dose: vulval-vaginal applications once or twice daily for at least 7 Days.

7 C: Contraceptives

7 C.1: Combined oral monophasic contraceptives

These contain oestrogen and progestogen together in one pill and they are the most effective, reliable and reversible method of contraception available. In addition to contraception, these preparations have the following advantages:
- lighter, shorter, regular period with decreased menstrual cramp
- reduced risk of ovarian and endometrial cancers
- decreased benign breast disease
- reduced risk of pelvic inflammatory disease
- decrease the risk of developing functional ovarian tumour
- decrease the risk of ectopic pregnancy
- decreased peri-menopausal bone loss
- improve anaemia.

A fixed concentration of oestrogen and progestogen are contained in each pill; such preparation is also called monophasic. The concentration of oestrogens may vary among different preparations from 25-50 micrograms. There are low, standard and high oestrogen types of pills. Standard type of combined contraceptive pills contains 30-35 micrograms of oestrogens; the approved preparations in Oman are of this type.

There are major and minor adverse effects associated with the use of combined contraceptives. The incidence of complications in women under 30 years of age who do not have risk factors for cardiovascular disease appears to be small. An assessment of the risk benefit ratio for each patient is essential prerequisite for use.

The risks associated with the pill use are directly related to the oestrogen contents, and are low with the low oestrogen type and increase, as oestrogen content gets higher.

There is an increased risk of venous thromboembolism in users of oral contraceptives though this risk remains smaller than any risk associated with pregnancy. The risk of venous thromboembolism increases with age and in presence of other risk factor such as smoking and obesity.

Combined oral contraceptives

Indications: contraception; menstrual symptoms.
Contra-indications: pregnancy; previous history of venous or arterial thromboembolic disorders; cerebral vascular disease; breast cancer, oestrogen-dependent tumours, benign or malignant liver tumour; active liver disease; migraine; ophthalmic vascular disease; sickle cell anaemia; undiagnosed vaginal bleeding; breast feeding; cholestatic jaundice.

Cautions: in women with hypertension, psychic depression, epilepsy, asthma, renal or hepatic dysfunction, cardiac disease, diabetes mellitus, multiple sclerosis, varicose veins; cigarette smoking increases the risk of serious C-V side-effects.

Caution if severe diarrhoea or vomiting occurs during the use of oral contraception, as absorption of content may be incomplete. Travellers on long journeys may take precaution not to stay immobile for more than 5 hours; risk of venous thrombus in the lower extremities is increased. Undergoing surgery necessitates the discontinuation of contraceptive pills and arrangement for other contraceptive methods is sought.

Missing a pill
- **if one active pill is missed, take it as soon as you remember and take the next active pill at the regular time**
- **If two active pills or more are missed, start taking active pills as soon as you remember, and continue on regular schedule. For additional protection from pregnancy use condoms or refrain from sex until you have taken one active pill each day for 7 Days in a row.**
- **If two or more active pills are missed and bleeding has started, stop taking pills and restart a new pack 7 Days later.**
- **If one or more of the inactive (coloured pills in every day pill pack) are missed, throw away the missed pills and continue to take the remaining pills each day until the end of the pack.**

Side-effects: nausea, vomiting, headache, breast tenderness, weight changes, thrombosis, changes in libido, depression, chorea, skin reaction, chloasma, hypertension, liver function impairment, spotting in early cycle.

Dose: A pill is taken at approximately the same time each day; delay of longer than 12 hours may lead to loss of contraceptive protection.

For 21-combined monophasic contraceptives, 1 pill daily for 21 days, subsequent courses repeated after 7 Days interval; first course usually starts at day 1 of the cycle, if delayed further additional precautionary measures are needed for the following seven days.

For every day (28 pill pack) combined monophasic contraceptives, one active pill daily as above; then one coloured (inert) pill is used
daily for the seven days following the full use of the active 21 pills.

Note: Only one of the following preparations will be available at any time depending on cost effectiveness.

Preparations
Ethinylestradiol + desogestrel tablets, 30 micrograms + 150 micrograms pill
Ethinylestradiol + levonorgestrel tablets, 30 micrograms + 150 micrograms pill Ethinylestradiol + Norgestrel tablets, 30 micrograms + 300 micrograms pill (birth spacing programme)
Ethinylestradiol + gestodine tablets, 30 micrograms + 75 micrograms pill

7 C.2: Progestogen-only contraceptives

7 C.2.1: Oral progestogen-only contraceptives

Oral progestogen only contraceptives are suitable alternatives when oestrogens are contraindicated (see notes above). There is a higher failure rate than with combined contraceptives. They are suitable for older women, for heavy smokers, and those with hypertension, valvular heart disease, diabetes and migraine.

Daily use on a continuous basis characterizes this group of oral contraceptives. Starting at the first day of the cycle and continuing uninterrupted, the pill is taken at the same time every day. A delay of longer than three hours may lead to loss of contraceptive protection. In such cases, the woman takes the pill any time she remembers it and adds one microgram of progestogen. Consult MOH guidelines on Birth Spacing.

Oral progestogen-only contraceptives

Indications: contraception, see notes above
Contra-indications: pregnancy, undiagnosed vaginal bleeding, arterial disease.
Cautions: heart disease, sex-steroid dependent cancer, past ectopic pregnancy, functional ovarian cyst, active liver disease, concurrent use of enzyme inducing drugs, history of jaundice in pregnancy.
Side-effects: menstrual irregularities, nausea, vomiting, headache, body weight changes, depression, change in libido.
Dose: one tablet daily at the same time each day starting on day 1 of a cycle then continuously. See notes above.
7: Obstetrics, gynaecology and urinary tract disorders

Note: Only one of the following preparations will be available at any time depending on cost effectiveness.

Preparations
Norethisterone tablets, 350 micrograms tab.
Norgestrel tablets, 75 micrograms tab. (birth spacing programme)
Levonorgestrel tablets, 30 micrograms tab.
Lynestrenol tablets, 500 micrograms tab.

7 C.2.2: Parenteral progestogen only contraceptives

Long-acting progestogen only preparations are as effective as combined oral contraceptives. Patient’s education is an important element as the long term effects may result in menstrual disturbances and a potential for a delay in return to normal fertility.

Medroxyprogesterone acetate, 150 mg depot preparation is a long acting progestogen only injectable contraceptive that is available at MOH; it provides 12-week contraception. For users’ selection see MOH guidelines on Birth Spacing.

Etonogestrel (Restricted)

Indications: Contraception
Contra-indications: Acute porphyria; history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable; severe arterial disease; undiagnosed vaginal bleeding

Cautions: Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice; arterial disease; disturbances of lipid metabolism; history during pregnancy of deterioration of otsclerosis; history during pregnancy of pruritus; history of jaundice in pregnancy; malabsorption syndromes; possible risk of breast cancer; sex-steroid dependent cancer; systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies.

Side-effects: Breast discomfort; changes in libido; depression; disturbance of appetite; dizziness; headache; injection-site reactions; menstrual irregularities; nausea; vomiting

Dose: Contraception (no hormonal contraceptive use in previous month). By subdermal implantation 1 implant inserted during first 5 days of cycle, implant should be removed within 3 years of insertion.

Contraception (postpartum)
By subdermal implantation 1 implant to be inserted 21–28 days after delivery, 1 implant to be inserted after 28 days postpartum in breast-feeding mothers, implant should be removed within 3 years of insertion.

Contraception following abortion or miscarriage in the second trimester 1 implant to be inserted 21–
28 days after abortion or miscarriage, implant should be removed within 3 years of insertion. Contraception following abortion or miscarriage in the first trimester 1 implant to be inserted within 5 days, implant should be removed within 3 years of insertion. Contraception (changing from other hormonal contraceptive). Implant should be removed within 3 years of insertion (consult product literature).

Preparations
Etonogestrel 68 mg intradermal implant

**Medroxyprogesterone acetate depot preparation**

**Indications:** contraception.

**Contra-indications, cautions and side-effects:** see sec Oral preparations above

**Dose:** by deep intramuscular injection, 150 mg within the first 5 days of cycle or within the first 5 days after parturition. It could be delayed to 6 weeks in breast-feeding mothers. Repeat every 12 weeks.

Preparations
Medroxyprogesterone acetate depot injection, 150 mg in aqueous suspension (birth spacing programme)

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**7 D: Urinary disorders**

**7 D.1: Drugs for urinary retention**

Urinary retention may be acute or chronic. Acute urinary retention is best managed by catheterisation. Chronic retention can be managed with drugs such as bethanechol, a parasympathomimetic, that increases detrusor muscle tone. Urinary retention caused by benign prostatic hyperplasia is well treated by alpha-blockers that relax smooth muscles and increase urinary flow rate resulting in an improvement in obstructive symptoms.

**Bethanechol chloride**

**Indications:** urinary retention.

**Contra-indications:** intestinal and urinary obstruction; gastrointestinal ulceration, asthma, hypotension, epilepsy, pregnancy and breast feeding.

**Cautions:** hyperthyroidism, cardiac disorders.

**Side-effects:** nausea, vomiting, intestinal cramp, sweating, bradycardia.

**Dose:** 10-25 mg 3-4 times daily before meal.

Preparations
Bethanechol chloride tablets, 25 mg tab.
Urinary incontinence is treated with various drugs possessing antimuscarinic effects that relax detrusor muscle and increases bladder capacity.

**Solifenacin (Restricted)**

**Indications:** Urinary frequency. Urinary urgency. Urinary incontinence

**Contra-indications:** Gastro-intestinal obstruction; intestinal atony; myasthenia gravis (but some antimuscarinics may be used to decrease muscarinic side-effects of anticholinesterases); paralytic ileus; prostatic enlargement; pyloric stenosis; severe ulcerative colitis; significant bladder outflow obstruction; toxic megacolon; urinary retention; narrow-angle glaucoma

**Cautions:** Acute myocardial infarction; arrhythmias (may be worsened); autonomic neuropathy; cardiac insufficiency (due to association with tachycardia); cardiac surgery (due to association with tachycardia); conditions characterised by tachycardia; congestive heart failure (may be worsened); coronary artery disease (may be worsened); diarrhoea; elderly (especially if frail); gastro-oesophageal reflux disease; hiatus hernia with reflux oesophagitis; hypertension; hyperthyroidism (due to association with tachycardia); individuals susceptible to angle-closure glaucoma; prostatic hyperplasia; pyrexia; ulcerative colitis; neurogenic bladder disorder; susceptibility to QT-interval prolongation

**Side-effects:** Constipation; dilation of pupils with loss of accommodation; dry mouth; photophobia; reduced bronchial secretions; skin dryness; skin flushing; transient bradycardia (followed by tachycardia, palpitation and arrhythmias); urinary retention; urinary urgency, confusion (particularly in the elderly); giddiness; nausea; vomiting.

**Dose:** 5 mg once daily, increased if necessary to 10 mg once daily (Max. 5 mg daily with concomitant potent inhibitors of cytochrome P450 enzyme CYP3A4 such as itraconazole, ketoconazole, or ritonavir).

**Preparations**

Solifenacin succinate tablets 5 mg tab

**Tolterodine tartrate**

**Indications:** urinary frequency, urgency and incontinence.

**Contraindications:** pregnancy and breast-feeding.

**Cautions:** history of QT-interval prolongation; concomitant use with other drugs known to prolong QT interval.

**Side-effects:** chest pain, peripheral oedema; sinusitis, bronchitis; parasthesia, fatigue, vertigo, weight gain, flushing.

**Dose:** adult over 18 years, 2 mg twice daily; reduce to 1 mg twice
daily if necessary to minimise side-effects.

**Preparations**
Tolterodine tartrate tablets, 1 mg tab.
Tolterodine tartrate tablets, 2 mg tab.

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### 7 D.3: Drugs used in urological pain

Ureteric colic can be relieved by an injection of narcotic analgesic or diclofenac sodium. However, alkalinising the urine may promote the relief of pain in cystitis. The following preparation is used to render the pH of urine more alkaline.

Urinary alkaliniser in effervescent granules or syrup form

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### 7 D.4: Drugs used for impotence

Recent development in the treatment of erectile dysfunction has lead to the introduction of many drugs that are orally effective with high efficacy and wider margin of safety. Such drugs have rendered the old generation of drugs that are given by intracavernosal injection obsolete. However, papaverine is still approved and available in Oman for use as an intracavernosal injection for the treatment of erectile dysfunction under strict medical supervision by a specialist.

**Papaverine (Restricted)**

**Indications**: erectile dysfunction.

**Contra-indications**: predisposal for prolonged erection.

**Cautions**: persistent erection for longer than 4 hours calls for an emergency interference.

**Side-effects**: priapism, penile pain, haematoma, local irritation.

**Dose**: by intracavernosal injection, 25-90 mg.

**Preparations**
Papaverine hydrochloride injection, 30 mg/mL, 2 mL ampoule

**Sildenafil (CDL)**

**Indications**: erectile dysfunction, pulmonary hypertension.

**Contra-indications**: in patients receiving nitrates, hypotension (systolic BP < 90 mmHg), recent stroke, myocardial infarction or unstable angina.

**Cautions**: cardiovascular disease, anatomical deformation of the penis, in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), concomitant use of sildenafil with other treatments for erectile dysfunction.

**Side-effects**: dyspepsia, vomiting, headache, flushing, nasal congestion, abnormal vision (non-arteritic anterior ischemic optic neuropathy).

**Dose**: 50 mg taken, as a single dose per day, approximately 1 hour before sexual activity, the dose may
be increased to a maximum dose of 100 mg or decreased to 25 mg.

**Preparations**
- Sildenafil tablets, 25 mg tab.
- Sildenafil tablets, 50 mg tab.

**7 D.5: Irrigation fluids and dialysis concentrates**

*For the following preparations consult manufacturer’s literature for information about contents, strengths, and method of preparations and dilutions.*

**7 D.5.1: Haemodialysis preparations**

**Concentrated haemodialysis solution**
Contents: Na\(^+\) 135 + K\(^+\) 2 + mg\(^++\) 1 + Ca\(^++\) 1.75 + Cl\(^-\) 107.5 + Acetate 35 mmol/litre; 5 litre /jar.
Dilution ratio 1:34

**Peritoneal dialysis solution 2**
Contents: Dextrose 4.25% + Na\(^+\) 135 + Ca\(^++\) 2 + Cl\(^-\) 104.5 + Lactate 35 mmol/litre; 2 or 5 litre/bag

**7 D.5.2: Peritoneal dialysis preparations**

**Peritoneal dialysis solution 1**
Contents: Dextrose 1.5% + Na\(^+\) 134 + K\(^+\) 2.5 + mg\(^++\) 0.75 + Ca\(^++\) 1.75 +
8: Malignant disease and immunosuppression

Section 8: Malignant disease and immunosuppression

- Cytotoxic drugs.
- Drugs affecting the immune response.
- Sex hormone and hormone antagonists in malignant disease.

All drugs included in this section are restricted and intended for use by specialists.

Treatment of tumours with chemotherapy has shown that some are highly responsive but most are not. Due to the high toxicity of cytotoxic drugs, their inappropriate use may lead to increased morbidity and mortality. Cytotoxic drugs do not differentiate between normal and malignant cells. Highly proliferating cells are more seriously affected than non-proliferating cells. Serious side-effects should always be balanced against benefit in determining the regimen for treatment. Chemotherapy is applied with an intention to cure, with the aim to prolong life, or to palliate symptoms. Single agent chemotherapy has been found effective in treatment of only few tumours; combined multiple drug therapy is more often applied for the majority of tumours. Drug combination is more toxic than a single drug but may have the advantage of reducing tumour resistance, enhancing responsiveness and increasing rate of remission.

General side-effects encountered with the use of cytotoxic drugs are discussed hence after. Characteristic side-effects of a single drug will be specified in the relevant section.

Nausea and vomiting are very common distressing side-effects in patients receiving chemotherapy. It could be acute in onset or delayed. Acute nausea and vomiting is easy to treat with conventional anti-emetic agents (see sec 4 G.2). Drugs such as dexamethasone, lorazepam and 5-HT3 antagonists are used with or without conventional anti-emetics in the treatment of severe delayed nausea and vomiting.

Bone marrow depression is caused by all cytotoxic agents except vincristine and bleomycin. Differential blood counts should be performed to determine the degree of neutropenia. Antibacterial therapy may be needed in high-risk patients.

Hyperuricaemia. Tumour cell destruction by cytotoxic drugs will result in high protein catabolism and a rise in uric acid production. Urinary dysfunction may be caused by uric acid crystal deposition in the renal system. To mitigate such complications, allopurinol is administered with chemotherapy; in addition, patients should be kept
well hydrated. The dose of mercaptopurine and azathioprine must be reduced if allopurinol needs to be given concomitantly.

*Alopecia* is a reversible side effect with cytotoxic drugs with variable severity among drugs and individual patients. Pharmacological methods for preventing this side effect are not available.

**Reproductive functions.** Cytotoxic drugs affect male and female reproductive systems causing an often-permanent amenorrhea in premenopausal women and an irreversible azoospermia in men. They are teratogenic and should not be administered during pregnancy. Well-trained staff should carefully carry out intravenous administration of cytotoxic drugs. Extravasation of intravenous cytotoxic solution will cause severe local tissue necrosis.

### 8 A: Cytotoxic drugs

#### 8 A.1: Alkylating drugs

#### 8 A.1.1: Nitrogen mustards

**Chlorambucil**

**Indications:** chronic lymphocytic leukaemia, indolent non-Hodgkin’s lymphomas, Hodgkin’s disease, ovarian cancer.

**Cautions and side-effects:** bone marrow depression; skin rash. If skin rash develops, better stop therapy and replace with other cytotoxic drug.

**Dose:** used alone, 100-200 micrograms / kg daily for 4-8 weeks.

**Preparations**

Chlorambucil tablets, 2 mg tab.

**Cyclophosphamide**

**Indications:** chronic lymphocytic leukaemia, solid tumours, lymphomas.

**Cautions and side-effects:** see notes above; hepatic and renal impairment; haemorrhagic cystitis.

**Preparations**

Cyclophosphamide tablets, 50 mg tab.

Cyclophosphamide injection, powder for reconstitution, 500 mg/vial

**Ifosfamide**

**Indications:** see cyclophosphamide

**Contra-indications:** hepatic impairment.

**Cautions and side-effects:** mesna is routinely given to reduce urothelial toxicity.

**Preparations**

Ifosfamide injection, powder for reconstitution, 500 mg/vial

**Melphalan**

**Indications:** myeloma; solid tumours and lymphomas.

**Cautions and side-effects:** see notes above, bone marrow toxicity is delayed.
8: Malignant disease and immunosuppression

Dose: orally, for multiple myeloma, 150 micrograms / kg daily in divided doses for 4 days, repeated at intervals of 6 weeks.

Preparations
Melphalan tablets, 2 mg tab.
Melphalan injection, powder for reconstitution, 50 mg vial

Bendamustine
Contra-indications: Jaundice; low leucocyte count; low platelet count; major surgery less than 30 days before start of treatment; severe bone marrow suppression.
Cautions: Avoid in acute porphyrias; cardiac disorders—monitor serum potassium and ECG.
Side-effects: Amenorrhea; an-gina; anorexia; arrhythmias; chills; constipation; dehydration; diarrhoea; electrolyte disturbances; haemorrhage; hypertension; hypokalaemia; hypotension; infection; insomnia; malaise; pain; palpitation; pyrexia; respiratory dys-function.
Dose: Consult local protocol.

Preparations
Bendamustine injection, powder for reconstitution, 25 mg / vial
Bendamustine injection, powder for reconstitution, 100 mg / vial

8 A.1.2: Nitrosoureas

Lomustine
Indications: Hodgkin’s disease, solid tumours.
Cautions: bone marrow depression may be permanent with prolonged use.
Side-effects: see notes above
Dose: used alone, 120-130 mg / m² body surface, every 6–8 weeks.

Preparations
Lomustine tablets, 10 mg tab.
Lomustine tablets, 40 mg tab.

8 A.2: Natural products

8 A.2.1: Vinca alkaloids

Vinblastine sulphate
Indications: acute leukaemias, lymphomas, solid tumours.
Contra-indications: not to be administered by intrathecal injection.
Cautions and side-effects: see notes above; dose reduction when neurological toxicity is manifested. Myelosuppression is a dose-limiting side effect.

Preparations
Vinblastine sulphate injection, 1 mg/mL, 10 mL vial

Vincristine sulphate
Indications: acute leukaemias, lymphomas, solid tumours.
### 8: Malignant disease and immunosuppression

**Contra-indications:** see under vincristine

**Cautions and side-effects:** see notes above; hepatic impairment, dose reduction when neurological toxicity is manifested.

**Preparations**
- Vincristine sulphate injection, 1 mg/mL, 1 mL vial

#### 8 A.2.2: Epipodophyllotoxins

**Etoposide**

**Indications:** small cell carcinoma, lymphomas, testicular cancer.

**Cautions and side-effects:** see notes above; treatment should not be repeated before an interval of 21 days.

**Dose:** orally, 120-240 mg/m² daily for 3-5 days.
- Intravenously, double the oral dose.

**Preparations**
- Etoposide capsules, 50 mg cap.
- Etoposide injection, powder for reconstitution, 100 mg vial

#### 8 A.2.3: Enzymes

**Crisantaspase (L-asparaginase)**

**Indications:** acute lymphoblastic leukaemia.

**Cautions:** monitor for hyperglycaemia.

**Side-effects:** liver function and blood lipid changes; CNS depression, anaphylactic reaction.

**Preparations**
- Crisantaspase (Erwina brand) injection, powder for reconstitution, 10,000 units vial

#### 8 A.2.4: Taxanes

**Docetaxel**

**Indications:** is indicated for the treatment of patients with advanced or metastatic breast cancer and lung cancer.

**Contra-indications:** see notes above; in patients with neutrophil counts of < 1500 cells/mm³, severe hypersensitivity.

**Cautions:** see notes above; hepatic impairment.

**Side-effects:** see notes above; myelosuppression, hypersensitivity reactions, fluid retention.

**Preparations**
- Docetaxel injection, 40 mg/mL, 0.5 mL vial
- Docetaxel injection, 40 mg/mL, 2 mL vial

**Paclitaxel**

**Indications:** primary ovarian cancer with cisplatin; metastatic ovarian cancer resistant to platinum compound therapy.

**Cautions:** pre-treatment with corticosteroid, antihistamine and H₂-receptor antagonists are recommended to prevent hypersensitivity reactions.

**Side-effects:** see notes above; bradycardia, hypotension, peripheral neuropathy.
8: Malignant disease and immunosuppression

Preparations
Paclitaxel intravenous infusion, 6 mg/mL 5 mL vial
Paclitaxel intravenous infusion, 100 mg/ 16.7 mL vial
Paclitaxel intravenous infusion 150 mg/25 mL vial

8 A.3: Antimetabolites

Antimetabolites have similarity in their structures to molecules essential for protein synthesis. They combine irreversibly with vital cellular enzymes, preventing normal cellular multiplication. Folic acid, pyrimidine and purine analogues are effective cytotoxic drugs.

8 A.3.1: Folic acid analogues

Methotrexate is the main drug in this group. It acts by inhibiting the enzyme dihydrofolate reductase, which is essential for the synthesis of purine and pyrimidine. It can be orally and parenterally administered.

Methotrexate
Indications: maintenance therapy of childhood lymphoblastic leukaemia; choriocarcinoma, non-Hodgkin’s lymphoma, solid tumours. Intrathecal methotrexate is used in meningeal cancer or lymphoma.
Contra-indications: sever renal impairment, sever hepatic impairment.

Cautions: avoid in pleural effusion or ascites. Administer folinic acid to prevent methotrexate induced mucositis or myelosuppression.
Side-effects: see notes above; myelosuppression which may be prolonged in presence of renal dysfunction.

Preparations
Methotrexate tablets, 2.5 mg tab.
Methotrexate suspension
Methotrexate sodium injection, 50 mg vial
Methotrexate sodium injection, 1 g vial
Methotrexate sodium injection, 10 mg in pre-filled syringe
Methotrexate sodium injection, 20 mg in pre-filled syringe

Pemetrexed
Indications: as a single agent for the treatment of locally advanced or metastatic non-small cell lung cancer, in combination with cisplatin for the treatment of malignant pleural mesothelioma which is unresectable.
Contra-indications: see notes above
Cautions: see notes above; prophylactic folic acid and vitamin B12 supplementation required.
Side-effects: see notes above; myelosuppression, gastro-intestinal toxicity and skin disorders are the commonest adverse effects.

Preparations
Pemetrexed injection; 500 mg vial
8: Malignant disease and immunosuppression

8 A.3.2: Pyrimidine analogues

This group encompasses many drugs with diverse activities; they have the capacity to inhibit the synthesis of pyrimidine nucleotides or mimic these natural metabolites to the extent that they interfere with vital cellular functions.

**Capecitabine**
- **Indications**: colorectal carcinoma, breast carcinoma and gastric carcinoma.
- **Contra-indications**: see notes above; hypersensitivity, severe renal and hepatic impairment.
- **Cautions**: see notes above; cardiovascular diseases, diabetes mellitus.
- **Side-effects**: see notes above; diarrhoea, hand-foot syndrome.

**Preparations**
- Capecitabine tablets, 150 mg tab.
- Capecitabine tablets, 500 mg tab.

**Cytarabine**
- **Indications**: acute leukaemia.
- **Cautions and side-effects**: see notes above; careful haematological monitoring because of potentially severe myelosuppression.

**Preparations**
- Cytarabine injection, 100 mg, 5 mL vial
- Cytarabine injection, 500 mg, 25 mL vial

**5-Fluorouracil**
- **Indications**: gastro-intestinal tract cancers, breast cancer, with folinic acid in colorectal cancer.
- **Cautions and side-effects**: see notes above; irritant to tissues—careful handling.

**Preparations**
- 5-Fluorouracil sodium injection, 50 mg/mL, 5 mL vial

**Gemcitabine**
- **Indications**: used in a wide variety of malignancies, both as a single-agent and in combination with other cytotoxic drugs e.g. pancreatic cancer, ovarian cancer, breast cancer, non-small cell lung cancer and bladder cancer.
- **Contra-indications**: see notes above; hypersensitivity to the drug.
- **Cautions**: see notes above; renal and hepatic impairment, prolongation of the infusion time beyond 60 minutes and more frequent than weekly dosing has been shown to increase toxicity. Side-effects: see notes above; gastrointestinal disturbances, myelosuppression, haemolytic uraemic syndrome.

**Preparations**
- Gemcitabine injection, 1 g vial

8 A.3.3: Purine analogues

Mercaptopurine and thioguanine are important purine analogues with wide therapeutic applications. They are cell cycle specific and interfere with DNA synthesis. They
### 8: Malignant disease and immunosuppression

Possess some immunosuppressive effects and some of their derivatives are effectively used for this purpose.

#### 8 A.4: Antineoplastic antibiotics

#### 8 A.4.1: Dactinomycin group

**Dactinomycin**  
**Indications:** paediatric cancers.  
**Cautions and side-effects:** see notes above; elevated bilirubin concentration is an indication for dose reduction; caution in handling.

**Preparations**  
Dactinomycin injection, powder for reconstitution, 500 microgram vial

#### 8 A.4.2: Anthracyclines

**Doxorubicin**  
**Indications:** acute leukaemias, lymphomas and solid tumours, bladder cancer by bladder instillation.  
**Cautions:** cardiac disease; elevated bilirubin concentration is an indication for dose reduction; cumulative dose limit should not exceed 450 mg /m² body surface area because fatal heart failure is more frequent beyond this concentration.  
**Side-effects:** see notes above; mucositis.

**Preparations**  
Doxorubicin hydrochloride injection, 10 mg vial  
Doxorubicin hydrochloride injection, 50 mg vial  
Pegylated Doxorubicin hydrochloride injection (encapsulated in liposomes), 2 mg/ml, 10 mL and 25 mL vials (for AIDS-related Kaposi’s
8: Malignant disease and immunosuppression

sarcoma, advanced breast and ovarian cancer)

Epirubicin
Indications: breast cancer, superficial bladder cancer by bladder instillation.
Cautions and side-effects: see notes above and doxorubicin; hepatic impairment.

Preparations
Epirubicin hydrochloride injection, powder for reconstitution, 10 mg vial

Idarubicin
Indications: breast cancer as a second line therapy; acute leukaemias.
Cautions: see notes above and doxorubicin; hepatic and renal impairment; caution in handling.
Side-effects: see notes above.

Preparations
Idarubicin tablets, 5 and 10 mg tabs.
Idarubicin injection, powder for reconstitution, 5 and 10 mg vials

8 A.4.3: Bleomycin group

Bleomycin
Indications: squamous cell carcinoma, solid tumour.
Cautions: see notes above; renal impairment, caution in handling.
Side-effects: see notes above; dermatological toxicity; mucositis; hypersensitivity reactions; dose related pulmonary fibrosis, more common with elderly.

Preparations
Bleomycin injection, powder for reconstitution, 15 mg vial

8 A.4.4: Mitomycin group

Mitomycin
Indications: upper gastro-intestinal cancer; breast cancer; by bladder instillation in superficial bladder cancer.
Cautions: see notes above; prolonged use may cause permanent bone marrow depression. Hepatic and renal impairment; caution in handling.
Side-effects: see notes above; lung fibrosis, renal damage.

Preparations
Mitomycin injection, powder for reconstitution, 10 mg vial

8 A.4.5: Antimetabolites

Azacitidine
Indications: Treatment of intermediate-2 and high-risk myelodysplastic syndromes, chronic myelomonocytic leukaemia, and acute myeloid leukaemia.
Contra-indications: Advanced malignant hepatic tumour.
Cautions: History of severe congestive heart failure; unstable cardiac disease (consider cardiopulmonary assessment before and during treatment); unstable pulmonary disease (consider cardiopulmonary
8: Malignant disease and immunosuppression

**Indications**: metastatic germ cell cancers; bladder, lung and upper gastrointestinal cancers.

**Cautions**: see notes above; keep patients well hydrated.

**Side-effects**: see notes above; nephrotoxicity, neurotoxicity, ototoxicity and hypomagnesaemia; severe nausea and vomiting.

**Preparations**
- Cisplatin injection, 1 mg/mL, 10 mL vial
- Cisplatin injection, 1 mg/mL, 50 mL vial

**Oxaliplatin**

**Indications**: used in combination with 5-Fluorouracil and Folinic acid in advanced colorectal cancer.

**Contra-indications**: see notes above; peripheral neuropathy.

**Cautions**: see notes above; renal impairment.

**Side-effects**: see notes above; neurotoxic side-effects, gastrointestinal disturbances, ototoxicity and myelosuppression.

**Preparations**
- Oxaliplatin injection, 50 mg vial
- Oxaliplatin injection, 100 mg vial

**Hydroxycarbamide (Hydroxyurea)**

**Indications**: chronic myeloid leukaemia; cancer of the cervix; polycythaemia; sickle cell disease.

**Cautions**: leg ulcers (review treatment if cutaneous vasculitic ulcers develop). Monitor renal and hepatic function before and during treatment, monitor full blood count and monitor for secondary malignancies. Patients should be advised to protect skin from sun exposure.

**Side-effects**: headache; myelosuppression; skin reactions, Alopecia; bleeding (in sickle-cell disease); bone-marrow suppression; dizziness; hyperuricaemia; hypomagnesaemia (in sickle-cell disease); nausea; oral mucositis; rash; reduced sperm count and activity; skin cancers (particularly in elderly patients); thromboembolism; tumour lysis syndrome; vomiting.

**Dose**: for chronic myeloid leukaemia; cancer of the cervix; polycythaemia: 20–30 mg/kg daily, alternatively 80 mg/kg every 3 days. For Sickle Cell Disease: Initially 15 mg/kg daily, increased in steps of 2.5-5 mg/kg daily every 12 weeks according to response; usual dose 15-30 mg/kg daily; maximum 35 mg/kg per day.

**Preparations**
- Hydroxycarbamide capsules, 500 mg cap

**Dacarbazine**

**Indications**: metastatic melanoma; in combination therapy of soft tissue sarcomas.

**Side-effects**: Abdominal pain; anorexia; anxiety; arthralgia; cerebral haemorrhage; constipation; diarrhoea; dizziness; drowsiness; dyspepsia; dyspnoea; gastro-intestinal disturbances; haematoma; haematuria; haemorrhage; headache; hypertension; hypokalaemia; hypotension; injection-site reactions; insomnia; myalgia; pneumonia; rash.

**Dose**: Consult local protocol.

**Preparations**
- Azacitidine injection, powder for reconstitution, 100 mg/ vial

**Mitoxantrone (Mitozantrone)**

**Indications**: breast cancer.

**Cautions**: see notes above; intrathecal administration not recommended; cardiac disease.

**Side-effects**: see notes above; cardiac toxicity.

**Preparations**
- Mitoxantrone hydrochloride injection, 2 mg/mL 10 mL, 12.5 mL and 15 mL vials

8 A.5: Miscellaneous cytotoxics

8 A.5.1: Platinum compounds

**Carboplatin**

**Indications**: advanced ovarian and lung cancers.

**Cautions**: see notes above; dose to be determined according to renal function; keep patients well hydrated.

**Side-effects**: see notes above; less severe nephrotoxicity, neurotoxicity, ototoxicity and hypomagnesaemia than with cisplatin; severe myelosuppression.

**Preparations**
- Carboplatin injection, 10 mg/mL, 5 mL vial

**Cisplatin**

**Indications**: Abdominal pain; anorexia; anxiety; arthralgia; cerebral haemorrhage; constipation; diarrhoea; dizziness; drowsiness; dyspepsia; dyspnoea; gastro-intestinal disturbances; haematoma; haematuria; haemorrhage; headache; hypertension; hypokalaemia; hypotension; injection-site reactions; insomnia; myalgia; pneumonia; rash.

**Dose**: Consult local protocol.

**Preparations**
- Clofarabine injection, 1 mg/ml, 20 mg vial

222
Indications: metastatic germ cell cancers; bladder, lung and upper gastro-intestinal cancers.  
Cautions: see notes above; keep patients well hydrated.  
Side-effects: see notes above; nephrotoxicity, neurotoxicity, ototoxicity and hypomagnesaemia; severe nausea and vomiting. 

Preparations  
Cisplatin injection, 1 mg/mL, 10 mL vial  
Cisplatin injection, 1 mg/mL, 50 mL vial  

**Oxaliplatin**  
Indications: used in combination with 5-Fluorouracil and Folinic acid in advanced colorectal cancer.  
Contra-indications: see notes above; peripheral neuropathy.  
Cautions: see notes above; renal impairment.  
Side-effects: see notes above; neurotoxic side-effects, gastrointestinal disturbances, ototoxicity and myelosuppression. 

Preparations  
Oxaliplatin injection, 50 mg vial  
Oxaliplatin injection, 100 mg vial  

8 A.5.2: Substituted urea  

**Hydroxycarbamide**  
(*Hydroxyurea*)  
Indications: chronic myeloid leukaemia; cancer of the cervix; polycythaemia; sickle cell disease  

Cautions: leg ulcers (review treatment if cutaneous vasculitic ulcerations develop). Monitor renal and hepatic function before and during treatment, monitor full blood count and monitor for secondary malignancies. Patients should be advised to protect skin from sun exposure  
Side-effects: headache; myelosuppression; skin reactions, Alopecia; bone-marrow suppression; dizziness; hyperuricaemia; hypomagnesaemia (in sickle-cell disease); nausea; oral mucositis; rash; reduced sperm count and activity; skin cancers (particularly in elderly patients); thromboembolism; tumour lysis syndrome; vomiting.  
Dose: for chronic myeloid leukaemia; cancer of the cervix; polycythaemia: 20–30 mg/kg daily, alternatively 80 mg/kg every 3 days. For Sickle Cell Disease: Initially 15 mg/ kg daily, increased in steps of 2.5-5 mg/kg daily every 12 weeks according to response; usual dose 15-30 mg/ kg daily; maximum 35 mg/ kg per day  

Preparations  
Hydroxyxycarbamide capsules, 500 mg cap.  

8 A.5.3: Methyl hydrazine derivatives  

**Dacarbazine**  
Indications: metastatic melanoma; in combination therapy of soft tissue sarcomas.
8: Malignant disease and immunosuppression

Side-effects: see notes above; nausea and vomiting are very severe, irritation to skin and tissues.

Preparations
Dacarbazine injection, powder for reconstitution, 100 mg vial

Procarbazine
Indications: Hodgkin’s disease.
Caution and side-effects: see Dacarbazine above
Dose: alone, initially 50 mg daily, increased by 50 mg daily to 250-300 mg daily in divided doses; maintenance (on remission) 50-150 mg daily to cumulative total of at least 6 g.
Preparations
Procarbazine hydrochloride capsules, 50 mg cap.

Temozolomide
Indications: is indicated for the treatment of adult patients with brain cancer, sometimes concomitantly with radiotherapy.
Contraindications: see notes above; hypersensitivity reaction to the drug.
Cautions: see notes above; severe hepatic or renal Impairment.
Side-effects: see notes above; rarely, erythema multiforme, opportunistic infections including Pneumocystis carinii pneumonia (PCP).

Preparations
Temozolomide capsules, 100 mg cap.

Temozolomide capsules, 250 mg cap.

8 A.5.4: Protein kinase inhibitors

Dasatinib
Indications: chronic myeloid leukaemia or acute lymphoblastic leukaemia in those who have resistance to or intolerance of previous therapy.
Contraindications: see notes above; breast-feeding.
Cautions: see notes above; susceptibility to QT-interval prolongation; hypokalaemia; hypomagnesaemia; hepatic impairment, pregnancy
Side-effects: see notes above; diarrhoea, anorexia, weight gain, abdominal pain, taste disturbance, constipation, dyspepsia, colitis, gastritis; arrhythmias, congestive cardiac failure, chest pain, flushing, haemorrhage (including gastrointestinal and CNS haemorrhage), palpitation; dyspnoea, cough, oedema (including pleural effusion); depression, dizziness, headache, insomnia, neuropathy; influenza-like symptoms; musculoskeletal pain; visual disturbances; acne, dry skin, sweating, pruritus, urticaria.
Dose: chronic phase chronic myeloid leukaemia, adult over 18 years 100 mg once daily, increased if necessary to max. 140 mg once daily. Accelerated and blast phase chronic myeloid leukaemia, adult over 18 years 70 mg twice daily, increased if necessary to max.
8: Malignant disease and immunosuppression

100 mg twice daily. Acute lymphoblastic leukaemia, adult over 18 years 70 mg twice daily increased if necessary to max. 100 mg twice daily.

Preparations
Dasatinib tablets, 50 mg tab.
Dasatinib tablets, 70 mg tab.

**Erlotinib**
**Indications:** for the treatment of patients with locally advanced non-small cell lung cancer after failure of at least one chemotherapy regimen, in combination with gemcitabine for metastatic pancreatic cancer.

Contra-indications: see notes above

**Cautions:** see notes above; hepatic and renal impairment, concomitant use with hepatotoxic drugs.

**Side-effects:** see notes above; diarrhoea, anorexia, depression, fatigue, rigor, conjunctivitis, dry skin.

Preparations
Erlotinib tablets, 150 mg tab.

**Everolimus**
**Indications:** Renal cell carcinoma, unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin, hormone-receptor-positive, human epidermal growth factor-2 (HER-2) negative advanced breast cancer, 10 mg once daily.

Subependymal giant cell astrocytoma associated with tuberous sclerosis complex and renal angiomyolipoma associated with tuberous sclerosis complex, consult product literature.

Preparations
Everolimus tablets, 0.75 mg tab.
Everolimus tablets, 5 mg tab.
Everolimus tablets, 10 mg tab.

**Gefitinib**
**Indications:** Treatment of locally advanced or metastatic non-small
**8: Malignant disease and immunosuppression**

cell lung cancer with activating mutations of epidermal growth factor receptor.

**Cautions:** Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed during therapy. Monitor for worsening of dyspnoea, cough and fever. Monitor liver function.

**Side-effects:** Acne; anorexia; asthenia; blepharitis; conjunctivitis; diarrhoea; dry eye; dry mouth; dry skin; epistaxis; haematuria; interstitial lung disease—discontinue if confirmed; nail disorder; proteinuria; pruritus; pyrexia; rash; skin reactions.

**Dose:** 250 mg once daily.

**Preparations**
Gefitinib tablets, 250 mg tab.

**Imatinib**

**Indications:** chronic myeloid leukaemia, acute lymphoblastic leukaemia, myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangement, hypereosinophilic syndrome and/or chronic eosinophilic leukaemia, dermatofibrosarcoma, gastrointestinal stromal tumours.

**Contra-indications:** pregnancy and breastfeeding.

**Cautions:** see notes above; renal and hepatic impairment, cardiac disease.

**Side-effects:** see notes above; gastrointestinal disorders, oedema and fluid retention, influenza like syndrome, visual disturbances, epistaxis, pruritus.

**Preparations**
Imatinib mesilate tablets, 100 mg tab.
Imatinib mesilate tablets, 400 mg tab.

**Lapatinib**

**Indications:** Treatment of advanced or metastatic breast cancer in patients with tumours that over-express human epidermal growth factor receptor-2 (HER2) with hormone-receptor-negative disease.

**Cautions:** Diarrhoea— withhold treatment if severe (consult product literature); low gastric pH (reduced absorption); susceptibility to QT-interval prolongation (including electrolyte disturbances).

**Side-effects:** Anorexia; cardiac failure (fatal cases reported); decreased left ventricular ejection fraction; diarrhoea (treat promptly); hepatotoxicity (discontinue permanently if severe); hyperbilirubinaemia; malaise; nail disorders; rash.

**Dose:** Hormone receptor negative disease with previous treatment with trastuzumab 1 g once daily. Previous treatment with anthracycline, a taxane and trastuzumab (incombination with capecitabine) 1.25 g once daily

Hormone receptor positive disease combination with an aromatase inhibitor 1.5 g once daily.
Consult product literature for more details.

Preparations
Lapatinib tablets, 250 mg tab.

Sorafenib
Indications: Advanced renal cell carcinoma. Treatment of progressive, locally advanced, or metastatic, differentiated thyroid carcinoma that is refractory to radioactive iodine. Treatment of hepatocellular carcinoma.

Cautions: Cardiac ischaemia; major surgical procedures; potential risk of bleeding—treat tracheal, bronchial, or oesophageal infiltration with localised therapy before initiating sorafenib in patients with differentiated thyroid carcinoma (DTC) and consider permanent withdrawal of sorafenib in any patient that requires medical intervention for bleeding; susceptibility to QT-interval prolongation.

Consider periodic monitoring of ECG and electrolytes in patients susceptible to QT-interval prolongation. Monitor blood pressure regularly and consider permanent discontinuation of sorafenib if resistant to antihypertensive therapy. Monitor plasma-calcium concentration (increased risk of hypocalcaemia if history of hypoparathyroid). Monitor thyroid stimulating hormone in patients with differentiated thyroid carcinoma.

Side-effects: Acne; anorexia; arthralgia; asthenia; congestive heart failure; constipation; depression; dermatitis; desquamation; diarrhoea; dry skin; dysgeusia; dyspepsia; dysphagia; dysphonia; electrolyte disturbances; erectile dysfunction; erythema; fatigue; fever; flushing; gastro-oesophageal reflux disease; haemorrhage; hand-foot skin reaction; hoarseness; hyperkeratosis; hypertension; hypophosphataemia; hypophosphataemia; keratoacanthoma; malaise; muscle spasms; myalgia; myocardial infarction; myocardial ischaemia; peripheral neuropathy; proteinuria; pruritus; rash; renal failure; rhinorrhoea; thyroid dysfunction; tinnitus.

Dose: 400 mg twice daily, for dose adjustments due to side-effects, consult product literature.

Preparations
Sorafenib tablets, 200 mg tab.

Sunitinib
Indications: Treatment of unresectable or metastatic malignant gastrointestinal stromal tumours, after failure of imatinib

Treatment of advanced or metastatic renal cell carcinoma. Treatment of unresectable or metastatic pancreatic neuroendocrine tumours

Cautions: Cardiovascular disease—discontinue if congestive heart failure develops; hypertension; increased risk of bleeding; susceptibility to QT-interval prolongation. Treatment with sunitinib may be a risk factor for the development of osteonecrosis of the jaw.

Side-effects: Abdominal pain; alopecia; anorexia; arthralgia; bone-
8: Malignant disease and immunosuppression

marrow suppression; constipation; cough; dehydration; diarrhoea; dizziness; dry skin; dyspnoea; epistaxis; fatigue; fistula formation (interrupt treatment if occurs); gastrointestinal perforation; hair discoloration; hand-foot syndrome; headache; hepatic failure; hypertension; hyperuricaemia; hypothyroidism; increased lacrimation; insomnia; myalgia; nausea; oedema; oral mucositis; osteonecrosis of the jaw; pancreatitis; paraesthesia; peripheral neuropathy; proteinuria; rash; seizures; skin discoloration; taste disturbance; thromboembolism; tumour lysis syndrome; urine discoloration; vomiting.

Dose: Unresectable or metastatic malignant gastro-intestinal stromal tumours and advanced or metastatic renal cell carcinoma 50 mg once daily for 4 weeks, followed by a 2-week treatment-free period to complete 6-week cycle, adjusted in steps of 12.5 mg, doses adjusted according to tolerability; usual dose 25–75 mg daily.
Unresectable or metastatic pancreatic neuroendocrine tumours 37.5 mg once daily without treatment-free period; adjusted in steps of 12.5 mg, doses adjusted according to tolerability; maximum 50 mg per day.

Preparations
Sunitinib capsules, 12.5 mg cap
Sunitinib capsules, 50 mg cap

8 A.5.5: Topoisomerase I inhibitors

Irinotecan hydrochloride

Indications: for colorectal carcinoma in combination with other antineoplastic drugs.
Contra-indications: see notes above; hypersensitivity to the drug, chronic inflammatory bowel disease, bowel obstruction.
Cautions: see notes above; raised plasma bilirubin concentration.
Side-effects: see notes above; acute cholinergic syndrome.

Preparations
Irinotecan hydrochloride injection, 20 mg/mL, 5 mL vial

Topotecan

Indications: as second line treatment for small cell lung cancer or ovarian cancer.
Contra-indications: see notes above; in patients with severe bone marrow depression.
Cautions: see notes above; hepatic and renal impairment.
Side-effects: see notes above; diarrhoea, febrile neutropoenia, abdominal pain, stomatitis, hypersensitivity, hyperbilirubinemia, malaise.

Preparations
Topotecan injection, powder for reconstitution, 1 mg vial
Topotecan injection, powder for reconstitution, 4 mg vial
8: Malignant disease and immunosuppression

8.A.5.6: Monoclonal antibodies

**Bevacizumab**

**Indications:** used along with chemotherapy to treat patients with metastatic colorectal and breast cancer.

**Contra-indications:** see notes above; untreated CNS metastases.

**Cautions:** see notes above; history of hypertension, cardiovascular diseases, intra-abdominal inflammation (risk of gastro-intestinal perforation), withhold prior and after elective operations.

**Side-effects:** see notes above; gastrointestinal perforation, impaired wound healing, mucocutaneous bleeding, arterial thromboembolism, congestive heart failure, proteinuria, tracheoesophageal fistula formation.

Preparations

Bevacizumab injection, 100 mg vial

Bevacizumab injection, 400 mg vial

**Cetuximab**

**Indications:** used along with chemotherapy to treat patients with metastatic colorectal, in combination with radiotherapy for the treatment of locally advanced squamous cell cancer of the head and neck.

**Contra-indications:** see notes above

**Cautions:** see notes above; cardiovascular disease.

**Side-effects:** see notes above; vomiting, headache, chills, fever, hypersensitivity reactions (patient must receive an antihistamine before infusion and resuscitation facilities should be available), acne, pruritus, nail disorders, conjunctivitis, hypomagnesaemia.

Preparations

Cetuximab injection, 100 mg vial

**Panitumumab**

**Indications:** Treatment of non-mutated RAS metastatic colorectal cancer.

**Contra-indications:** Interstitial pulmonary disease; the combination of panitumumab with oxaliplatin-containing chemotherapy is contra-indicated in patients with mutant RAS metastatic colorectal cancer or for whom RAS status is unknown.

**Cautions:** History of keratitis; history of severe dry eye; history of ulcerative keratitis; pulmonary disease—discontinue if interstitial lung disease develops; risk factors for keratitis; risk factors for severe dry eye; risk factors for ulcerative keratitis (including contact lens use).

**Side-effects:** Anorexia; anxiety; back pain; biochemical disturbances; cellulitis; chelitis; chills; cough; deep vein thrombosis; dyspepsia; dyspnoea; electrolyte disturbances; epistaxis; eyelash
8: Malignant disease and immunosuppression

Bicalutamide

**Indications:** Prostate Cancer

**Cautions:** Risk of photosensitivity—avoid excessive exposure to UV light and sunlight.

**Side-effects:** Abdominal pain; alopecia; anaemia; asthenia; breast tenderness; chest pain; cholestasis; constipation; decreased appetite; decreased libido; depression; dizziness; dry skin; dyspepsia; flatulence; gynaecomastia; haematuria; hepatotoxicity; hirsutism; hot flushes; impotence; jaundice; nausea; oedema; pruritus; rash; somnolence; weight gain.

**Preparations**
- Bicalutamide tablets, 150 mg tab.
- Amsacrine concentrate for intravenous infusion, 75 mg/1.5 mL, when reconstituted with 13.5 mL of diluent, a 5 mg/mL solution is obtained.

Amsacrine

**Indications:** acute myeloid leukaemia.

**Cautions:** electrolytes to be monitored to avoid hypokalaemia.

**Side-effects:** see note above; mucositis.

**Preparations**
- Amsacrine injection, 75 mg/mL, 10 mL vial
- Amsacrine concentrate for intravenous infusion, 75 mg/1.5 mL, when reconstituted with 13.5 mL of diluent, a 5 mg/mL solution is obtained.

Bortezomib

**Indications:** monotherapy for the treatment of multiple myeloma which has progressed despite the use of at least one therapy, and where the patient has already had bone-marrow transplantation or cannot have it.

**Contraindications:** see notes above; acute diffuse infiltrative pulmonary disease; pericardial disease; pregnancy; breast-feeding.

**Cautions:** see notes above; cardiovascular disease; pulmonary disease; history of seizures; amyloidosis; risk of neuropathy; monitor blood-glucose concentration in patients on oral antidiabetics; hepatic impairment; renal impairment.

**Side-effects:** see notes above; gastrointestinal disturbances including constipation, taste disturbance, dry mouth, decreased appetite; positional hypotension, hypertension, haematoma, phlebitis, chest pain, oedema; dyspnoea, cough; confusion, depression, insomnia, anxiety, peripheral neuropathy, paresthesia, headache, dizziness, tremor, asthenia, fatigue; influenza-like symptoms; renal impairment, dysuria; dehydration, hypokalaemia, hypoglycaemia; muscle cramps, arthralgia, bone pain; blurred vision, eye pain; epistaxis; urticaria, pruritus, erythema, dry skin, eczema, rash, increased sweating.

**Preparations**
- Bortezomib injection, powder for reconstitution, 3.5 mg vial
- Rituximab injection, 10 mg/mL, 10 mL vial
- Rituximab injection, 10 mg/mL, 50 mL vial
- Trastuzumab injection, 440 mg vial

Panitumumab

**Indications:** monoclonal antibody indicated in non-Hodgkin's lymphoma.

**Contra-indications:** see notes above; allergy to Rituximab.

**Cautions:** see notes above; cardiovascular diseases, antihypertensives (may need to be withheld for 12 hours before infusion), hepatitis B carriers (risk of reactivation of hepatitis), large tumour burden (increased risk of severe tumour lysis syndrome).

**Side-effects:** see notes above; infusion-related symptoms like chills, nausea, vomiting (consider premedication with corticosteroids).

**Preparations**
- Panitumumab injection, 100 mg vial
- Rituximab injection, 10 mg/mL, 10 mL vial
- Trastuzumab injection, 440 mg vial

8.A.5.7: Anti-androgens

Trastuzumab

**Indications:** as a single or adjuvant treatment of early breast cancer which over-expresses human epidermal growth factor receptor-2 (HER2).

**Contra-indications:** see notes above; severe dyspnoea at rest, breast-feeding.

**Cautions:** see notes above; hypertension, heart failure, uncontrolled arrhythmias, concomitant use with anthracyclines is associated with cardiotoxicity, pregnancy.

**Side-effects:** see notes above; fever, infusion reactions, cardiotoxicity, increased cough, headache, fatigue, shortness of breath, rash, low white and red blood cells, muscle pain.

**Preparations**
- Trastuzumab injection, 440 mg vial
Dose: 150 mg once daily.

Preparations
Bicalutamide tablets, 150 mg tab.

Amsacrine
Indications: acute myeloid leukaemia.
Cautions: electrolytes to be monitored to avoid hypokalaemia.
Side-effects: see note above; mucositis

Preparations
Amsacrine concentrate for intravenous infusion, 75 mg/1.5 mL, when reconstituted with 13.5 mL of diluent, a 5 mg/mL solution is obtained

Bortezomib
Bortezomib is a proteasome inhibitor
Indications: monotherapy for the treatment of multiple myeloma which has progressed despite the use of at least one therapy, and where the patient has already had bone-marrow transplantation or cannot have it. Contraindications: see notes above; acute diffuse infiltrative pulmonary disease; pericardial disease; pregnancy; breastfeeding.
Cautions: see notes above; cardiovascular disease; pulmonary disease; history of seizures; amyloidosis; risk of neuropathy; monitor blood-glucose concentration in patients on oral antidiabetics; hepatic impairment; renal impairment.
Side-effects: see notes above; gastrointestinal disturbances including constipation, taste disturbance, dry mouth, decreased appetite; postural hypotension, hypertension, haematoma, phlebitis, chest pain, oedema; dyspnkea, cough; confusion, depression, insomnia, anxiety, peripheral neuropathy, paraesthesia, headache, dizziness, tremor, asthenia, fatigue; influenza-like symptoms; renal impairment, dysuria; dehydration, hypokalaemia, hyperglycaemia; muscle cramps, arthralgia, bone pain; blurred vision, eye pain; epistaxis; urticaria, pruritus, erythema, dry skin, eczema, rash, increased sweating.

Preparations
Bortezomib injection, powder for reconstitution, 3.5 mg vial
8: Malignant disease and immunosuppression

8 A.7: Agents used to treat cytotoxic adverse reactions

8 A.7.1: Chelating agents

**MESNA**

**Indications**: haemorrhagic cystitis caused by cyclophosphamide and ifosfamide.

**Contra-indications**: hypersensitivity to thiol-containing drugs.

**Side-effects**: nausea and vomiting, abdominal cramp, diarrhoea, fatigue, tachycardia and hypotension, irritability.

**Dose**: by intravenous injection, with treatment with cytotoxic drugs repeated 4 and 8 hours after treatment. For dose calculation, consult product literature.

**Preparations**

MESNA injection, 100 mg/mL, 4 mL ampoule

8 A.7.2: Vitamins

**Folinic acid**

*(as calcium folinate)*

**Indications**: Folate rescue therapy, for counteracting folate-antagonist action of methotrexate to speed up recovery from mucositis and myelosuppression.

**Cautions**: avoid simultaneous administration of methotrexate.

**Side-effects**: hypersensitivity reactions.

**Dose**: as antidote to methotrexate, usually given 24 hours after methotrexate treatment. Intravenous or intramuscular injection, 120 mg in divided doses over 12-24 hours. Followed by 12-15 mg intramuscularly or 15 mg orally every 6 hours for the next 48-72 hours.

**Preparations**

Folinic acid (as calcium folinate) injection, 100 mg/10 mL, 10 mL ampoules

Folinic acid (as calcium folinate) tablets, 15 mg tab.

8 B: Drugs affecting the immune response

Drugs in this group are used to suppress rejection in organ transplants and in patients with chronic inflammatory and autoimmune diseases. Drugs such as corticosteroids, ciclosporin or azathioprine are used in solid organ transplant patients. The use of such drugs may cause a rapid spread of infections due to a suppressed immune system.

8 B.1: Cytotoxic immunosuppressants

Azathioprine is similar in structure, and is metabolised in the body to mercaptopurine. It is widely used for chronic management of transplant recipients and in treatment of a number of autoimmune conditions. Myelosuppression is the main adverse effect and blood test
and monitoring should be carried out regularly. Mycophenolate mofetil has more selective mode of action than azathioprine. It is used in acute rejection of renal transplantation. When used in combination with ciclosporin and corticosteroids, the risk of rejection is reduced; the risk of opportunistic viral infections and blood disorders may be higher.

**Azathioprine**

**Indications:** transplant rejection; autoimmune diseases.

**Contra-indications:** hypersensitivity to azathioprine or mercaptopurine.

**Cautions:** monitor blood count regularly; hepatic impairment; renal impairment; reduce dose in elderly.

**Side-effects:** hypersensitivity reactions; dose related bone marrow depression; alopecia; increase incidence of infections; nausea.

**Dose:** oral or by intravenous injection or infusion, for treatment of autoimmune diseases, 1-3 mg/kg daily adjusted according to response.

Suppression of transplant rejection, initially up to 5 mg/kg then 1-4 mg/kg daily according to response.

**Preparations**

Azathioprine tablets, 50 mg tab.

*Mycophenolate mofetil*

**Indications:** prophylaxis of acute rejection in renal transplantation.

**Contra-indications:** pregnancy, breast feeding.

**Cautions:** regularly monitor blood count; elderly; children.

**Side-effects:** nausea, diarrhoea, constipation, dyspepsia; hypertension, oedema; dyspnoea, cough; insomnia, headache; blood disorders; infections.

**Dose:** Mycophenolate mofetil renal transplantation, orally 1 g twice daily starting with 72 hours of transplantation. Mycophenolic acid (as Mycophenolate sodium/(CDL) ) 720 mg twice daily, to be started within 72 hours of transplantation.

**Preparations**

Mycophenolate mofetil capsules, 250 mg cap.

Mycophenolate mofetil capsules, 500 mg cap.

Mycophenolate mofetil suspension, 1 g/5 mL when reconstituted with water, 175 mL bottle

Mycophenolic acid tablets, 360 mg tab.\{gastro-resistant tablets\}.

**8 B.2: Corticosteroids and other immunosuppressants**

**8 B.2.1: Corticosteroids**

See section 6 C.2.

**Prednisolone**

**Indications and side-effects:** see section 6 C.2.

**Preparations**

Prednisolone tablets, 5 mg tab.

Prednisolone tablets, 20 mg tab.
8: Malignant disease and immunosuppression

8.2.2: Others

Antilymphocyte immunoglobulins
These are antibodies, raised in animals, which act against lymphocytes to produce suppression of cell mediated immunity. They may be used alone or added to other immunosuppressants to treat acute rejection episodes in patients who have undergone organ or tissue transplantation or they can be used routinely in multiple immunosuppressants therapy.

Indications: see notes above
Side-effects: hypersensitivity reactions.
Dose: by slow intravenous infusion, 10-30 mg/kg daily. The dose is diluted with normal saline solution.

Preparations
Antilymphocyte immunoglobulin injection, 50 mg/mL, 10 mL vial

Ciclosporin  (Cyclosporin)
Indications: prevention of graft rejection following tissue or organ transplantation; treatment and prophylaxis of graft-versus-host disease.
Contra-indications: uncontrolled hypertension; uncontrolled infections; malignancies.
Cautions: patients may be more prone to infection while being treated with ciclosporin; patients with nephrotic syndromes, impaired renal and hepatic functions; avoid concomitant use of other potent nephrotoxic drugs such as aminoglycosides.
Side-effects: dose-dependent increase in serum creatinine and urea during early stages of treatment; hypertension; tremor; gastrointestinal disturbances; burning sensation in hands and feet; gingival hypertrophy.
Dose: Organ transplantation, adult and child over 3 months, alone 10-15 mg/kg by mouth 4-12 hours before transplantation followed by 10-15 mg/kg daily 1-2 weeks postoperatively then reduced gradually to 2-6 mg/kg daily for maintenance. Dose is reduced if used concomitantly with other immunosuppressants.
Bone marrow transplantation, prevention of graft-versus-host disease, adult and child over 3 months, 3-5 mg/kg daily by intravenous infusion over 3-6 hours from day before transplantation to 2 weeks postoperatively (or by mouth 12.5-15 mg/kg daily) then 12.5 mg/kg daily by mouth for 3-6 months then tapered off, may take over a year after transplantation.

Preparations
Ciclosporin capsules, 25 mg cap.
Ciclosporin capsules, 50 mg cap.
Ciclosporin capsules, 100 mg cap.
Ciclosporin oral solution, 100 mg/mL; 50 mL/bottle
Ciclosporin injection, 50 mg/mL, 1 and 5 mL ampoule

Daclizumab
8: Malignant disease and immunosuppression

**Indications:** prophylaxis of acute rejection in allogenic renal transplantation with regimen including ciclosporin and corticosteroids.

**Contra-indications:** pregnancy and breast-feeding.

**Side-effects:** gastro-intestinal disturbances, hypersensitivity reactions.

**Dose:** by intravenous infusion, adult and child, 1 mg/kg within the 24-hour period before transplantation, then 1 mg/kg every 14 days for a total of 5 doses.

**Preparations**
Daclizumab injection, 5 mg/mL, 5 mL vial

**Sirolimus**

**Indications:** prophylaxis of organ rejection in kidney allograft recipients.

**Contra-indications:** pregnancy, breast-feeding.

**Cautions:** monitor kidney function when given with ciclosporin; Afro-Caribbean patients may require higher doses; hepatic impairment.

**Side-effects:** abdominal pain, diarrhoea, stomatitis; oedema, tachycardia, hypercholesterolaemia, hypertriglyceridaemia, venous thrombo-embolism; pneumonitis; pyrexia, increased susceptibility to infection, proteinuria, haemolytic uraemic syndrome; anaemia, thrombocytopenia, thrombotic thrombo-cytopenic purpura, leukopenia, neutropenia, hypokalaemia, hypophosphataemia, hyper-glycae-

**Dose:** Initially 6 mg, after surgery, then 2 mg once daily (dose adjusted according to blood - sirolimus concentration) in combination with ciclosporin and corticosteroid for 2–3 months (sirolimus given 4 hours after ciclosporin); ciclosporin should then be withdrawn over 4–8 weeks (if not possible, should be discontinued and an alternate immunosuppressive regimen used).

**Preparations**
Sirolimus tablets, 1 mg tab.

**Tacrolimus**

**Indications:** the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants. Also, in patients resistant to conventional immunosuppressive regimens.

**Contraindication:** hypersensitivity to tacrolimus.

**Cautions:** see under ciclosporin; also, monitor ECG (cases of cardiomyopathy have been reported),
8: Malignant disease and immunosuppression

should not be taken with ciclosporin (risk of nephrotoxicity).

Side-effects: gastro-intestinal disturbances, infections, nephrotoxicity, neurotoxicity, hyperglycaemia, hypertension, tremor.

Dose: In liver allograft recipient: by mouth 100-200 micrograms/kg/day in two divided doses or by intravenous infusion over 24 hours, 10-50 micrograms/kg daily for up to max.7 days. (Then transfer to oral therapy). Paediatric dose: orally: 300 micrograms/kg daily in two divided doses or by intravenous infusion over 24 hours, 50 micrograms/kg daily for up to max.7 days. (Then transfer to oral therapy). In kidney allograft recipient: by mouth 200-300 micrograms/kg/day in two divided doses or by intravenous infusion over 24 hours, 50-100 micrograms/kg daily for up to max.7 days. (Then transfer to oral therapy). Paediatric dose: orally: 300 micrograms/kg daily in two divided doses or by intravenous infusion over 24 hours, 75-100 micrograms/kg daily for up to max.7 days. (Then transfer to oral therapy).

Preparations:
Tacrolimus capsules, 500 micrograms cap.
Tacrolimus capsules, 1 mg cap.
Tacrolimus capsules, 5 mg cap.
Tacrolimus sachets, 200 micrograms per sachet
Tacrolimus sachets, 1 mg per sachet.

Thalidomide

Indications: multiple myeloma

Cautions: High tumour burden—risk of tumour lysis syndrome. Thromboembolism. Second primary malignancy. Peripheral neuropathy

Side-effects: Anaemia; asthenia; bradycardia; cardiac failure; confusion; constipation; deep vein thrombosis; depression; dizziness; drowsiness; dry mouth; dysesthesia; dyspepsia; dyspnoea; interstitial lung disease; leucopenia; lymphopenia; neutropenia; paraesthesia; peripheral neuropathy; peripheral oedema; pneumonia; pulmonary embolism; pyrexia; skin reactions; Stevens-Johnson syndrome; syncope; thrombocytopenia; tremor; vomiting

Dose: 200 mg once daily for 6–week cycle for a maximum of 12 cycles, dose to be taken at bedtime.

Preparations
Thalidomide tablets, 100 mg tab.
Thalidomide tablets, 200 mg tab.

Lenalidomide

Indications: Multiple myeloma. Treatment of transfusion-dependent anaemia

Cautions: High tumour burden—risk of tumour lysis syndrome; patients with risk factors for myocardial infarction. Risk factors for thromboembolism (such as smoking, hypertension, hyperlipidaemia)
should be minimised and thromboprophylaxis should be considered in patients with multiple risk factors. Patients should be carefully evaluated before and during treatment with lenalidomide using routine cancer screening for occurrence of second primary malignancy and treatment should be instituted as indicated.

**Side-effects:** Abdominal pain; anaemia; arthralgia; ataxia; atrial fibrillation; bacterial infections; bradycardia; cardiac failure; cataract; cerebrovascular events; chest pain; cholestasis; constipation; decreased appetite; deep vein thrombosis; dehydration; depression; diarrhoea; dizziness; dry mouth; dyspepsia; dysphagia; dyspnoea; electrolyte disturbances; falls; flu-like illness; fungal infections; haematomata; haematuria; haemorrhagic disorders; headache; hearing disturbances; hyperglycaemia; hyperhidrosis; hypotension; hypertensive urgency; insomnia; iron-overload; lethargy; leucopenia; malaise; mood changes; musculoskeletal disorders; myalgia; myocardial infarction; nausea; oedema; peripheral neuropathy; pneumonia; pruritus; pulmonary embolism; pyrexia; rash; renal failure; respiratory distress; respiratory tract infections; sepsis; severe neutropenia; sexual dysfunction; sinusitis; skin disorders; stomatitis; syncope; tachycardia; taste disturbance; thrombocytopenia; tremor; urinary incontinence; urinary retention; vasculitis; viral infections; visual disturbances; vomiting.

**Dose:** When given in combination with dexamethasone until disease progression 25 mg once daily for 21 consecutive days of repeated 28-day cycles

With melphalan and prednisone, 10 mg once daily for 21 consecutive days of repeated 28-day cycles for up to 9 cycles. For doses of melphalan and prednisone and cycle timings consult the product literature. Treatment of transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with an isolated deletion 5q cytogenetic abnormality when other treatment options are insufficient or inadequate, 10 mg once daily for 21 consecutive days of repeated 28-day cycles. Consult the product literature for more details

**Preparations**
Lenalidomide capsules, 10 mg cap.
Lenalidomide capsules, 25 mg cap.

### 8 B.3: Interferons

Human recombinant interferon alfa has shown to have several effects that result in immunostimulation, including activation of macrophages, T-lymphocytes and natural killer cells. Clinical benefits have been obtained with interferon alfa in some malignancies including hairy cell leukaemia, chronic myeloid leukaemia, solid tumors and...
lymphomas. Viral infections have also been treated with interferon alfa such as hepatitis.

**Interferon alfa**

**Indications:** see notes above  
**Contra-indications:** avoid benzyl alcohol containing injection in neonates.  
**Side-effects:** are dose related, including anorexia, nausea, flu like symptoms and lethargy.

**Preparations**

Interferon alfa injection, 6,000,000 units/mL, 0.5 mL ampoule (3,000,000 units/ampoule) Interferon alfa injection, 15,000,000 units/mL, 1.2 mL ampoule (18,000,000 units/ampoule)

**Peginterferon alfa**

It is a covalent conjugate of recombinant alfa-2a interferon with a single branched monomethoxy polyethylene glycol (PEG) chain. This pegylation increases the persistence of the interferon in the blood.

**Indications, contra-indications and side-effects:** see under interferon alfa

**Preparations:**

Peginterferon alfa-2a injection: 180 microgram in 0.5 mL prefilled syringe.

**Interferon beta**

**Indications:** treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations.  
**Contra-indications:** pregnancy and breast feeding, severe depression, decompensated liver disease.  
**Cautions:** renal and hepatic impairment, cardiac disorders, depressive disorders, seizures, myelosuppression.  
**Side-effects:** flu-like symptoms, injection site pain and inflammation, hypersensitivity reactions, alopecia, blood disorders, menstrual disorders, mood changes, hepatitis.

**Preparations**

Interferon beta-1a injection, powder for reconstitution, 30 microgram (6 million unit) vial  
Interferon beta-1b injection, powder for reconstitution, 300 microgram (9.6 million unit) vial

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**8 B.4: Immunomodulating drugs**

Fingolimod is an immunomodulating drug. It is known to cause transient bradycardias and heart block after the first dose. Fingolimod is not recommended in the following patient groups who are at high risk of cardiovascular events unless the anticipated benefits outweigh the potential risks, and advice from a cardiologist is sought before initiation:

**Patients with the following medical conditions:**

- 2nd degree Mobitz Type II or higher degree atrioventricular block, sick sinus syndrome, or sino-atrial heart block
- Significant QT prolongation (QT-interval greater than 470 milliseconds in women, or greater than 450 milliseconds in men)
- History of symptomatic bradycardia or recurrent syncope, known ischaemic heart disease, cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension, or severe sleep apnoea.

**Patients receiving the following antiarrhythmic or heart-rate lowering drugs:**

- class Ia or class III antiarrhythmics
- beta blockers
- heart rate-lowering calcium channel blockers
- other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic drugs or pilocarpine).

All patients receiving fingolimod should be monitored at treatment initiation, (first dose monitoring), and after treatment interruption (see note below); monitoring should include:

- Pre-treatment: a 12-lead ECG and blood pressure measurement before starting
- During the first 6 hours of treatment: continuous ECG monitoring for 6 hours, blood pressure and heart rate measurement every hour
- After 6 hours of treatment: a further 12-lead ECG and blood pressure measurement

If heart rate at the end of the 6 hour period is at its lowest since fingolimod was first administered, monitoring should be extended by at least 2 hours and until heart rate increases.

Extended monitoring, (at least overnight), should be performed in patients with evidence of clinically important cardiac effects during first dose monitoring. Monitoring in patients requiring pharmacological intervention for bradyarrhythmic-related symptoms during first dose monitoring should be extended at least overnight, and first dose monitoring should be repeated after the second dose.
cardiologist is sought before initiation:

Patients with the following medical conditions:

- 2nd degree Mobitz Type II or higher degree atrioventricular block, sick sinus syndrome, or sino-atrial heart block
- Significant QT prolongation (QT-interval greater than 470 milliseconds in women, or greater than 450 milliseconds in men)
- History of symptomatic bradycardia or recurrent syncope, known ischaemic heart disease, cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension, or severe sleep apnoea.

Patients receiving the following antiarrhythmic or heart-rate lowering drugs:

- class Ia or class III antiarrhythmics
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- other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic drugs or pilocarpine).

All patients receiving fingolimod should be monitored at treatment initiation, (first dose monitoring), and after treatment interruption (see note below); monitoring should include:

**Pre-treatment** - a 12-lead ECG and blood pressure measurement before starting

**During the first 6 hours of treatment** - continuous ECG monitoring for 6 hours blood pressure and heart rate measurement every hour

**After 6 hours of treatment** - a further 12-lead ECG and blood pressure measurement

If heart rate at the end of the 6 hour period is at its lowest since fingolimod was first administered, monitoring should be extended by at least 2 hours and until heart rate increases.

Extended monitoring, (at least overnight), should be performed in patients with evidence of clinically important cardiac effects during first dose monitoring. Monitoring in patients requiring pharmacological intervention for bradyarrhythmia-related symptoms during first dose monitoring should be extended at least overnight, and first dose monitoring should be repeated after the second dose.
8: Malignant disease and immunosuppression

Note
First dose monitoring as above should be repeated in all patients whose treatment is interrupted for:

- 1 day or more during the first 2 weeks of treatment
- more than 7 days during weeks 3 and 4 of treatment
- more than 2 weeks after one month of treatment

If the treatment interruption is of shorter duration than the above, repeated monitoring is not required and treatment should be continued with the next dose as planned.

Fingolimod
Indications: Multiple sclerosis
Contra-indications: Active infection; active malignancies (except cutaneous basal cell carcinoma); immunosuppression
Cautions: Check varicella zoster virus status—consult product literature for further information; chronic obstructive pulmonary disease; pulmonary fibrosis; risk of macular oedema; severe respiratory disease; susceptibility to QT-interval prolongation (including electrolyte disturbances. Effective contraception is needed two months after stopping treatment.
Side-effects: Alopecia; AV block; back pain; blurred vision; bradycardia; bronchitis; cough; depression; diarrhoea; dizziness; dyspnoea; eczema; gastroenteritis; headache; herpes; hypertension; influenza; leucopenia; lymphopenia; malaise; migraine; paraesthesia; pruritus; sinusitis; tinea versicolor; macular oedema; neutropenia; pneumonia; haemophagocytic syndrome; lymphoma; posterior reversible encephalopathy syndrome; progressive multifocal leukoencephalopathy
Dose: 500 micrograms daily.

Preparations
Fingolimod hydrochloride capsules, 500 microgram caps.

8 C: Sex hormones and hormone antagonists in malignant diseases.

8 C.1: Aromatase inhibitors

Anastrozole
Indications: adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer either as a sole therapy or following two to three years of tamoxifen, for the treatment of advanced breast cancer in postmenopausal women in whom disease has progressed following tamoxifen therapy.
Contra-indications: see notes above; severe renal and hepatic impairment, not indicated for premenopausal women.
8: Malignant disease and immunosuppression

**Cautions:** see notes above; assess bone mineral density (BMD) before and after treatment (risk of osteoporosis).

**Side-effects:** see notes above; hot flushes, vaginal bleeding and dryness, bone fractures, drowsiness, increased cholesterol levels, rash.

**Dose:** 1 mg daily.

**Preparations**

Anastrozole tablets, 1 mg tab.

**Exemestane**

**Indications:** adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen, for the treatment of advanced breast cancer in postmenopausal women in whom disease has progressed following tamoxifen therapy.

**Contra-indications:** see notes above; not indicated for premenopausal women.

**Cautions:** see notes above; hepatic and renal impairment.

**Side-effects:** see notes above; fatigue, depression, insomnia, hot flushes, sweating.

**Dose:** 25 mg daily.

**Preparations**

Exemestane tablets; 25 mg tab.

**Letrozole**

**Indications:** adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer, for the treatment of advanced breast cancer in postmenopausal women in whom disease has progressed following tamoxifen therapy.

**Contra-indications:** see notes above; severe hepatic impairment, not indicated for premenopausal women.

**Cautions:** see notes above; severe renal impairment.

**Side-effects:** see notes above; hot flushes, depression, bone fractures, drowsiness, increased appetite, rash.

**Dose:** 2.5 mg daily.

**Preparations**

Letrozole tablets, 2.5 mg tab.

**Fulvestrant**

**Indications:** Treatment of oestrogen-receptor-positive metastatic or locally advanced breast cancer in postmenopausal women in whom disease progresses or relapses while on, or after, other anti-oestrogen therapy.

**Contra-indications:** see notes above; hepatic and renal impairment.

**Side-effects:** Anorexia; asthenia; back pain; diarrhoea; headache; hot flushes; hypersensitivity reactions; injection-site reactions; nausea; rash; urinary-tract infections; venous thromboembolism; vomiting.

**Dose:** by deep intramuscular injection, 500 mg every 2 weeks for the first 3 doses, then 500 mg every 1 month, to be administered into the buttock.

**Preparations**

Fulvestrant injection, 250 mg/5 mL in prefilled syringe.
8: Malignant disease and immunosuppression

8 C.2: Gonadorelin analogues

Standard treatment of metastatic prostate cancer includes bilateral subcapsular orchidectomy or the use of gonadorelin analogues such as goserelin. They cause initial stimulation and then depression of luteinising hormone release by the pituitary. The initial effect (flare) will cause an increase in testosterone production and a progression of prostate cancer. Concomitant use of an anti-androgen such as flutamide may suppress this effect. In females, goserelin may be used in the treatment of breast cancer, endometriosis and infertility.

Goserelin (CDL)

**Indications:** prostate cancer; advanced breast cancer; see notes above.

**Contra-indications:** pregnancy; undiagnosed vaginal bleeding.

**Cautions:** caution is required in patients with metabolic bone disease; men at risk of ‘flare’ effects should be monitored closely; avoid pregnancy during treatment.

**Side-effects:** goserelin causes side-effects similar to menopause in women and orchidectomy in men; transient change in blood pressure, paraesthesia.

Preparations

Goserelin implant, 3.6 mg in syringe applicator

Flutamide

**Indications:** advanced prostate cancer; adjunct to goserelin (see above notes)

**Cautions:** cardiac disease; hepatic impairment.

**Side-effects:** gynaecomastia; nausea and vomiting, diarrhoea, increased appetite, insomnia.

**Dose:** 250 mg 3 times daily.

Preparations

Flutamide tablets, 250 mg tab.

8 C.3: Progestogens

Megestrol acetate

**Indications:** as appetite-enhancing agent in cachexia associated with AIDS or cystic fibrosis, palliative treatment of advanced breast cancer or endometrial carcinoma.

**Cautions:** diabetes, history of thromboembolic disease, not intended for prophylactic use to avoid weight loss, possibility of adrenal insufficiency in patients receiving or being withdrawn from chronic megestrol acetate therapy, use of megestrol in other types of neoplastic disease is not recommended.

**Side-effects:** sweating, hot flashes, weight gain, diarrhoea, dyspepsia, flatulence, nausea, vomiting, insomnia, mood swings, impotence, anaemia, deep venous thrombosis, thrombophlebitis, pulmonary embolism.
Preparations
Megestrol acetate suspension, 40 mg/mL
Section 9: Nutrition and blood

- Anaemias and some other blood disorders
- Electrolyte and water replacement
- Intravenous nutrition
- Oral nutrition
- Minerals
- Vitamins

9 A: Anaemias and some other blood disorders

The underlying cause should be determined before initiating therapy for anaemia. The use of iron in anaemias other than those due to iron deficiency may lead to a serious iron overload with harmful consequences.

9 A.1: Iron

9 A.1.1: Iron deficiency anaemias

The body recycles iron from the dead blood cells. The loss of iron is only seen when red blood cells are lost through bleeding. Iron deficiency is one of the most common causes of anaemia, and blood loss is virtually the only cause of anaemias in adult. A diet low in iron may lead to iron deficiency in infants and growing children. Normal dietary intake of iron is not sufficient to replace iron lost by chronic bleeding. Consequently an iron supplement must be given. Because a developing foetus uses iron, pregnant women also need iron supplements.

Orally administered iron salts are recommended for supplement therapy unless a good reason indicates the use of other routes. Ferrous salts are recommended for their good absorption in the gut. The oral dose of elemental iron for deficiency should be 100-200 mg daily. Different iron salts contain elemental iron as follows:

<table>
<thead>
<tr>
<th>Iron salt</th>
<th>Dose</th>
<th>Elemental iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous fumarate</td>
<td>200 mg</td>
<td>65 mg</td>
</tr>
<tr>
<td>Ferrous succinate</td>
<td>100 mg</td>
<td>35 mg</td>
</tr>
<tr>
<td>Ferrous sulphate</td>
<td>300 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>Ferrous sulphate, dried</td>
<td>200 mg</td>
<td>65 mg</td>
</tr>
</tbody>
</table>

Though rarely used, iron injections are reserved for patients who cannot tolerate oral iron or those who continue to lose large amount of haemoglobin from ongoing bleeding.

Iron salts may cause gastro-intestinal irritation, nausea and epigastric pain which are dose related. Constipation or diarrhoea, however are also common. In the elderly, the constipating effect may be very severe with oral iron preparations. Iron salts almost always turn stools
Iron Preparations

**Indications:** iron deficiency anaemia.

**Cautions:** other forms of anaemias; irritable bowel syndrome.

**Side-effects:** see notes above

**Dose:** see under preparation.

Iron preparations purchased and supplied by Ministry of Health will either be ferrous sulphate or ferrous fumarate depending on cost effectiveness.

Preparations

Dried ferrous sulphate tablets, 200 mg tab. (65 mg iron)

Dose: adult, prophylactic, 200 mg once daily; treatment, 200 mg 2-3 times daily.

Ferrous sulphate 150-200 mg/5 mL syrup (25 – 45) mg iron ; 100-150 mL/bottle

Dose: adult, prophylactic, 10 mL once daily; treatment, 10 mL 2-3 times daily.

Child, prophylactic, 1-6 years, 1.25 mL daily, 6-12 years 2.5 mL once daily.

Child, treatment, 1-6 years, 2.5 mL twice daily, 6-12 years, 5 mL 2-3 times daily.

Ferrous sulphate drops, 75 mg/0.6 mL (15 mg iron), 30 mL/bottle

Dose: infants and child under 1 year, prophylaxis, 0.6 mL once daily; treatment, 0.6 mL 2-3 times daily.

**Ferrous sulphate and Folic acid**

**Indications:** iron deficiency prophylaxis during pregnancy.

Caution and side-effects: see notes above

Preparations

Dried ferrous sulphate 150 mg (47 mg iron) + folic acid 500 micrograms spansule/tablets

Dose: one spansule/tablet daily.

**Iron injection**

**Indications:** iron deficiency anaemia in renal dialysis patient.

**Contra-indications:** pregnancy; allergic disorders; liver disease; infection.

**Cautions:** oral iron should not be given before five days of the last injection.

**Side-effects:** taste disturbances, nausea, vomiting, headache, hypotension.

**Dose:** by intravenous injection or infusion calculated according to patients need (consult manufacturer instruction).

Preparations

Iron (as iron sucrose) injection, 20 mg/mL, 5 mL ampoule

**9 A.1.2: Treatment of iron overload**

Iron overload may result from repeated blood transfusions in aplastic or refractory anaemias. Excessive iron absorption in the gut and
Deferoxamine mesilate (Desferrioxamine mesilate)

**Indications:** iron overload; emergency iron poisoning (see sec 17B)

**Cautions:** renal impairment; routine eye and ear examination during treatment; pregnancy, breast-feeding.

**Side-effects:** anaphylactic reaction and hypotension, more frequent with rapid intravenous infusion.

**Dose:** iron overload; consult product literature.

**Preparations**

Deferoxamine mesilate injection, 500 mg vial

Deferiprone

**Indications:** iron overload for patient intolerant to deferoxamine.

**Contra-indications:** pregnancy and breast feeding.

**Cautions:** neutropenia; renal and hepatic impairment, use with great caution in children 3-10 years of age.

**Side-effects:** agranulocytosis, neutropenia; gastro-intestinal disturbances; red colouration of urine.

**Dose:** adult and child over 6 years, 25 mg/kg 3 times daily; maximum 100 mg/kg daily.

**Preparations**

Deferiprone tablets, 500 mg tab.

Deferasirox (Restricted)

**Indications:** Chronic iron overload. Transfusion-related chronic iron overload.

**Cautions:** Elderly (increased risk of side-effects); history of liver cirrhosis; not recommended in conditions which may reduce life expectancy (e.g. high-risk myelodysplastic syndromes); platelet count less than 50x10⁹/litre; risk of gastro-intestinal ulceration and haemorrhage; renal impairment; hepatic impairment; eye and ear examination before and during treatment; unexplained cytopenia—consider treatment interruption.

**Side-effects:** Fatal gastro-intestinal haemorrhage; gastro-intestinal disturbances; gastro-intestinal ulceration; headache; proteinuria; pruritus; rash; elevated transaminases; earache; disturbances of hearing and vision.

**Dose:** Treatment of chronic iron overload: initially 10 mg/kg once daily; adjusted in steps of 5–10 mg/kg every 3–6 months, dose adjusted for maintenance according to serum-ferritin concentration and liver-iron concentration.
product literature); maximum 20 mg/kg per day. Transfusion-related chronic iron overload: initially 10–30 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood—consult product literature; adjusted in steps of 5–10 mg/kg every 3–6 months, dose adjusted for maintenance according to serum-ferritin concentration; usual dose up to 30 mg/kg daily, increased if necessary up to 40 mg/kg daily and reduced in steps of 5–10 mg/kg, dose to be reduced once control achieved.

Preparations
Deferasirox dispersible tablet 125 mg tab.
Deferasirox dispersible tablet 250 mg tab.
Deferasirox dispersible tablet 500 mg tab.

9 A.2 Platelet Disorders

**Romiplostim (Restricted)**

*Indications*: Chronic idiopathic thrombocytopenic purpura.

*Caution*: renal impairment; hepatic impairment; monitor full blood count and peripheral blood smears for morphological abnormalities before and during treatment. Monitor platelet count weekly until platelet count reaches 50 x 10⁹/litre or more for at least 4 weeks without dose adjustment, then monthly thereafter. Dizziness may affect performance of skilled tasks (driving)

*Side-effects*: Arthralgia; asthenia; bone pain; dizziness; ecchymosis; fatigue; flushing; gastro-intestinal disturbances; increased bone marrow reticulin; influenza-like symptoms; injection site reactions; insomnia; migraine; muscle spasm; myalgia; oedema; paraesthesia; rash.

*Dose*: by subcutaneous injection: initially 1 microgram/kg once weekly, adjusted in steps of 1 microgram/kg once weekly (max. per dose 10 micrograms/kg once weekly) until a stable platelet count of 50 x 10⁹/litre or more is reached, discontinue treatment if inadequate response after 4 weeks at maximum dose, consult product literature for dose adjustments.

Preparations
Romiplostim injection, powder for reconstitution, 250 micrograms vial

9 A.3 Megaloblastic anaemias

Vitamin B₁₂ and folic acid in addition to iron are needed by bone marrow to produce red blood cells. If any of these vitamins is lacking, megaloblastic anaemia will develop. Although megaloblastic anaemia results from lack of vitamin B₁₂ or folic acid in diet or inability to absorb them, it is some times caused
by drugs used for treatment of neoplastic diseases or antiepileptics.

**Folic acid deficiency** results from either low dietary supply or due to decreased absorption caused by drugs such as antiepileptics or contraceptive pills. Less commonly, pregnant and lactating women and people undergoing haemodialysis develop this deficiency due to their increased need for folic acid. In infants, folic acid deficiency may cause neurological abnormalities. In pregnant women, deficiency of folic acid can cause spinal cord defects and other malformation in the foetus. In folic acid deficiency anaemia, oral folic acid 5 mg daily for 4 months is administered to bring about a haematological remission and replenish body stores. Maintenance dose may be given once weekly depending on underlying disease. For prophylaxis in pregnancy the dose of folic acid is 200-500 microgram daily before conception and during the first 12 weeks of pregnancy. However, if there is a history of neural tube defect in a previous child, a higher dose of 5 mg daily is needed.

**Folic acid**

**Indications:** treatment and prophylaxis of folic acid deficiency anaemia.

**Cautions:** should not be given alone in pernicious anaemia or other vitamin B12 deficiencies.

**Dose:** *see* notes above

**Preparations**

Folic acid tablets, 5 mg tab.

**Vitamin B12 deficiency** causes pernicious anaemia, which is a megaloblastic anaemia. Vitamin B12, which is available in meat, is readily absorbed in the ileum. However, to be absorbed it must combine with gastric intrinsic factor. Without the intrinsic factor, vitamin B12 remains unabsorbed in the gut and excreted in the stool. Hydroxocobalamin and cyanocobalamin are the two forms of vitamin B12 for therapeutic use. Hydroxocobalamin is retained in the body longer than cyanocobalamin. Treatment is generally initiated with frequent administration of intramuscular injections to replenish the depleted body stores. Thereafter, maintenance therapy, which is for life, can be instituted. Oral doses of vitamin B12 are not recommended for treatment of megaloblastic anaemia. It could be added to supplementary vitamin preparations just to compensate for low dietary intake in otherwise normal people. Although vitamin B12 has been used in several other conditions like neuropathies, psychiatric illnesses, and as a general tonic in various chronic conditions, such use has not been shown to have any beneficial effects and lacks scientific validity.

**Cyanocobalamin**
9: Nutrition and blood

**Indications**: vitamin B₁₂ deficiency anaemia.

**Cautions**: should not be used unless diagnosis is fully established.

**Side-effects**: itching, fever, flushes, dizziness, exanthema.

**Dose**: intramuscularly, 1 mg repeated 10 times at intervals of 2-3 days. Maintenance, 1 mg monthly.

Preparations
Cyanocobalamin injection, 1 mg ampoule

9 A.4: Hypoblastic, haemolytic and renal anaemias

Recombinant human erythropoietin (epoetin) is used for anaemias associated with erythropoietin deficiency in chronic renal failure, to increase the yield of autologous blood in normal individuals and to shorten the period of anaemia in patients undergoing chemotherapy with platinum compounds. The use of erythropoietin reduces the requirement for blood transfusion. Other factors which contribute to anaemias such as iron or folate deficiency should be corrected before and during therapy.

**Recombinant human erythropoietin (Restricted)**

**Indications**: anaemias associated with chronic renal failure in patients on haemodialysis or peritoneal dialysis; anaemia in adult patients receiving platinum-containing chemotherapy.

**Contra-indications**: uncontrolled hypertension.

**Cautions**: uncontrolled blood pressure; exclude other causes of anaemia; chronic liver failure; malignancies; pregnancy and breast feeding.

**Dose**: initially, subcutaneous or slow intravenous injection, 50-100 unit/kg 3 times weekly adjusted according to patient need. Maintenance dose would be determined according to haemoglobin level and patient response.

Preparations
Human recombinant erythropoietin injection, 1,000 units vial
Human recombinant erythropoietin injection, 2,000 units vial
Human recombinant erythropoietin injection, 4,000 units vial
Human recombinant erythropoietin injection, 10,000 units vial

**Darbepoetin Alfa (Restricted)**

**Indications**: Symptomatic anaemia

**Contra-indications**: Patients unable to receive thromboprophylaxis; pure red cell aplasia following erythropoietin therapy; uncontrolled hypertension.

**Cautions**: Aluminium toxicity (can impair the response to erythropoietin).
etin); concurrent infection (can impair the response to erythropoietin); correct factors that contribute to the anaemia of chronic renal failure, such as iron or folate deficiency, before treatment.; during dialysis (increase in unfractionated or low molecular weight heparin dose may be needed); epilepsy; inadequately treated or poorly controlled blood pressure—interrupt treatment if blood pressure uncontrolled; ischaemic vascular disease; malignant disease; other inflammatory disease (can impair the response to erythropoietin); risk of thrombosis may be increased when used for anaemia before orthopaedic surgery—avoid in cardiovascular disease including recent myocardial infarction or cerebrovascular accident; risk of thrombosis may be increased when used for anaemia in adults receiving cancer chemotherapy; sickle-cell disease (lower target haemoglobin concentration may be appropriate); sudden stabbing migraine-like pain (warning of a hypertensive crisis); thrombocytosis (monitor platelet count for first 8 weeks).

**Side-effects:** Aggravation of hypertension (dose-dependent); cardiovascular events; diarrhoea; dose-dependent increase in platelet count regressing during treatment (but thrombocytosis rare); headache; hypertensive crisis (in isolated patients with normal or low blood pressure); increase in blood pressure (dose-dependent); influenza-like symptoms (may be reduced if intravenous injection given over 5 minutes); nausea; shunt thrombosis especially if tendency to hypotension or arteriovenous shunt complications; vomiting.

**Dose:** Symptomatic anaemia associated with chronic renal failure in patients on dialysis, by subcutaneous injection: initially 450 nanograms/kg once weekly, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose to be given once weekly or once every 2 weeks, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose, when changing route give same dose then adjust according to weekly or fortnightly haemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment.

Symptomatic anaemia associated with chronic renal failure in patients not on dialysis, by subcutaneous injection: initially 450 nanograms/kg once weekly, alternatively initially 750 nanograms/kg every 2 weeks, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose can be
given once weekly, every 2 weeks, or once a month, subcutaneous route preferred in patients not on haemodialysis, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose, when changing route give same dose then adjust according to weekly or fortnightly haemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment.

By intravenous injection: initially 450 nanograms/kg once weekly, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose given once weekly, subcutaneous route preferred in patients not on haemodialysis, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy.

Preparations
Darbepoetin Alfa, 10 micrograms prefilled syringes

9: Nutrition and blood

Symptomatic anaemia in adults with non-myeloid malignancies receiving chemotherapy, by subcutaneous injection: initially 6.75 micrograms/kg every 3 weeks, alternatively initially 2.25 micrograms/kg once weekly, if response inadequate after 9 weeks further treatment may not be effective; if adequate response obtained then reduce dose by 25–50%, reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy.

Preparations
Darbepoetin Alfa, 10 micrograms prefilled syringes
9: Nutrition and blood

9 A.5: Drugs used in neutropenia

Recombinant human granulocyte-colony stimulating factor stimulates the production of neutrophils and may reduce the duration of chemotherapy induced neutropenia and thereby reduce the incidence of associated sepsis. **Cautions:** should be used with caution in patients with pre-malignant or malignant myeloid conditions, patients with a history of pulmonary infiltrates or pneumonia and patients with sickle cell disease. (Full blood count and spleen size should be monitored). Recombinant human granulocyte-colony stimulating factors are not recommended in pregnancy or breast feeding. **Side-effects:** gastro-intestinal disturbances, musculoskeletal pain, alopecia, hypersensitivity reactions, pulmonary side-effects and splenic rupture.

**Filgrastim (Restricted)**
(Recombinant human granulocyte-colony stimulating factor)
**Indications:** (special use) severe neutropenia following autologous bone marrow transplantation and high dose chemotherapy; severe congenital neutropenia; cyclic neutropenia.
**Contra-indications:** sensitivity to the drug.
**Cautions:** see notes above; also leukaemic or preleukaemic conditions, patients with psoriasis and pre-existing cardiac conditions; monitor blood counts regularly.
**Side-effects:** see notes above; also musculoskeletal pain, disturbances in serum uric acid, urinary abnormalities, allergic reactions.
**Dose:** consult product literature.

**Preparations**
Filgrastim injection, 300 micrograms/mL (30 million units/mL), 1 mL vial

**Pegfilgrastim (Restricted)**
Is a covalent conjugate of recombinant methionyl human G-CSF (Filgrastim) and monomethoxypolyethylene glycol. This conjugation/Pegylation increases the duration of filgrastim activity.
**Indications:** is indicated for decreasing the risk of infection (as manifested by febrile neutropenia) associated with myelosuppressive treatment of non-myeloid malignancies
**Cautions:** see notes above
**Contraindications:** sensitivity to the drug.
**Side-effects:** see notes above
**Dose:** for adult, by subcutaneous injection of 6 mg (0.6 mL) administered once per chemotherapy. *(The 6 mg fixed-dose formulation should not be used in infants, children, and smaller adolescents weighing less than 45 kg)*

**Preparations**
Pegfilgrastim Injection, 10 mg/ml, available as 6 mg (0.6 mL) prefilled syringes
**Plerixafor (Restricted)**

**Indications:** Mobilise haematopoietic stem cells to peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma or multiple myeloma (specialist use only).

**Cautions:** monitor platelets and white blood cell count, pregnancy, renal impairment

**Side-effects:** Arthralgia; dizziness; dry mouth; erythema; fatigue; gastrointestinal disturbances; headache; injection-site reactions; insomnia; musculoskeletal pain; oral hypoesthesia; sweating

**Dose:** By subcutaneous injection: 240 micrograms/kg daily usually for 2–4 days (max 7 days), to be administered 6–11 hours before initiation of apheresis, dose to be given following 4 days treatment with a granulocyte-colony stimulating factor.

**Preparations**

Plerixafor injection, 24 mg in 1.2 mL vial

**Molgramostim (Restricted)**

(Recombinant human granulocyte macrophage – colony stimulating factor)

**Indications:** (special use) severe neutropenia following autologous bone marrow transplantation and high dose chemotherapy; severe congenital neutropenia; cyclic neutropenia.

**Contra-indications:** myeloid malignancies.

**Cautions:** monitor serum albumin, full blood counts, platelet and haemoglobin; not recommended for patients under 18 years.

**Side-effects:** nausea, diarrhoea, vomiting, anorexia; dyspnoea; asthenia, fatigue fever, rash musculoskeletal pain; local reaction after subcutaneous injection.

**Dose:** consult product literature.

**Preparations**

Molgramostim injection, 3.33 million unit (300 microgram) vial

Ministry of Health policy is that only one of the above colony stimulating factors will be purchased and made available for use depending on cost effectiveness

### 9 B: Electrolyte and water replacement

#### 9 B.1: Orally administered electrolytes

**9 B.1.1: Potassium supplement**

Potassium is a vital ion for the cell metabolism and the normal function of nerve and muscle cells. Most of the potassium body reserves are located intracellularly. The concentration of potassium in the blood is very critical and must be maintained within a narrow margin. Variation in plasma potassium level could have serious consequences on the heart. Intracellular
9: Nutrition and blood

Potassium helps maintaining the level in plasma. The plasma content of sodium is balanced between the intakes from dietary sources with the amount lost in the urine. A daily intake of 60-100 mmol is required. A balanced diet usually provides the body with its requirement of potassium.

Potassium supplement is needed in hypokalaemia associated with, chronic diarrhoea, intestinal malabsorption or laxative overuse. In patients using cardiac glycosides or antiarrhythmic agents, maintaining normal potassium level is mandatory.

Oral potassium supplement are better given in the liquid form to minimize irritation. Slow release preparations are also available to provide better prolonged absorption with anticipated less irritation.

**Potassium chloride**

*Indications:* potassium depletion.

*Contra-indications:* severe renal impairment.

*Cautions:* elderly, mild to moderate renal impairment, history of peptic ulceration, hiatus hernia; avoid with drugs that raise plasma potassium level such as potassium sparing diuretics or ACE inhibitors

*Side-effects:* nausea and vomiting, oesophageal or small bowel ulceration.

*Dose:* 1 sustained release tablets once or twice daily with plenty of water during meals while sitting or standing.

Preparations

Potassium chloride sustained release tablets, 600 mg tab.

Potassium Chloride syrup, 500 mL/bottle

9 B.1.2: Sodium bicarbonate supplement

**Sodium bicarbonate (Restricted)**

*Indications:* metabolic acidosis.

Preparations

Sodium bicarbonate tablets, 500 mg tab.

9 B.1.3: Drugs for potassium removal

**Calcium polystyrene sulphonate**

*Indications:* hyperkalaemia associated with renal impairment.

*Contra-indications:* obstructive bowel disease, malignancies, hyper-parathyroidism.

*Cautions:* children; monitor for electrolyte disturbances; pregnancy and breast feeding.

*Side-effects:* gastric irritation, anorexia, nausea and vomiting; constipation or diarrhoea.

*Dose:* by mouth, 15 g 3-4 times daily in water. Child, 0.5-1g/kg daily in divided doses.

Preparations

Calcium polystyrene sulphonate powder; 300 g/pack
9 B.2: Intravenous administration

Body water is distributed between intracellular and extracellular compartments; the distribution is solute dependent. Sodium is the main osmotically important ion in the extracellular compartment. Loss of water results in depletion of both extracellular and intracellular compartments, while loss of sodium leads to more severe depletion in the extracellular compartment. Electrolytes and water depletion can occur singly and in combination with or without disturbing the acid-base balance. In an individual patient the nature and severity of the electrolyte imbalance must be assessed from the history and clinical and biochemical examination.

9 B.2.1: Electrolyte preparations

Sodium chloride

**Indications:** electrolyte imbalance; sodium depletion.

**Cautions:** restrict intake in patients with renal failure, hypertension, cardiac failure, oedema, toxaemia of pregnancy.

**Side-effects:** large dose may cause sodium accumulation and oedema.

Preparations

Sodium chloride intravenous infusion, 0.9% solution, 500 mL pack
Sodium chloride injection, 0.9% solution, 5 mL vial/ampoule
Sodium chloride injection, 0.9% solution, 100 mL bottle
Sodium chloride injection, 14.6% solution, 40 mL vial (CDL)
Sodium chloride injection, 7% sterile (Hypertonic saline) (Restricted)

Potassium chloride solution (strong)

**Indications:** electrolyte imbalance.

**Cautions:** rapid infusion is toxic to the heart; specialist advice and ECG monitoring.

**Dose:** by slow intravenous infusion, the concentration should not usually exceed 3.2 g (43 mmol) / litre.

Preparations

Potassium chloride injection, 15% solution, 10 mL ampoule

Compound sodium lactate (Hartmann’s solution)

**Indications:** as a substitute to sodium chloride in surgery or in the initial management of the injured or wounded.

**Cautions and side-effects:** see sodium chloride

Preparations

Intravenous infusion containing, sodium chloride 0.6%, sodium lactate 0.25%, potassium chloride 0.04%, calcium chloride 0.027% is available as:
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Compound sodium lactate solution (Hartmann’s solution) full strength, 500 mL bag
Compound sodium lactate solution (Hartmann’s solution) half strength, 500 mL pack

Ringer’s solution (CDL)
Indications: electrolyte imbalance.
Cautions and side-effects: see sodium chloride

Preparations
Intravenous infusion containing, calcium chloride 0.032%, potassium chloride 0.03% and sodium chloride 0.86% available as :
Ringer’s solution for intravenous infusion, 500 mL pack

Sodium bicarbonate
Indications: metabolic acidosis.
Dose: by intravenous injection, a strong solution (up to 8.4%), or by intravenous infusion of a weaker solution, in an amount appropriate to body’s need for a base.

Preparations
Sodium bicarbonate injection, 8.4% solution, 50 mL vial
Sodium bicarbonate injection, 8.4% solution, 250 mL bottle
Sodium bicarbonate injection, 8.4% solution, 10 mL preloaded syringe
Sodium bicarbonate injection, 8.4% solution, 50 mL preloaded syringe

9 B.2.2: Electrolyte with dextrose preparations

Combined sodium chloride and glucose solutions are indicated when there is water and sodium depletion. Various strengths are available and the selection among them is usually determined by the degree of sodium depletion.

Dextrose + sodium chloride
Preparations
Dextrose 5% + sodium chloride 0.9% intravenous infusion, 500 mL pack
Dextrose 5% + sodium chloride 0.45% intravenous infusion, 500 mL pack
Dextrose 10% + sodium chloride 0.18% intravenous infusion, 500 mL pack
Dextrose 4.3% + sodium chloride 0.18% intravenous infusion, 500 mL pack

9 B.2.3: Dextrose preparations

Glucose solution is used to provide energy and to help replenish water deficit. It should be given alone when there is no significant loss of electrolytes. Treatment of severe hypoglycaemia may require high concentration glucose solution.
Dehydration may result from an imbalance between water intake and water loss through the skin, lung and urinary excretion. Excessive loss of water without loss of electrolyte is uncommon, occurring in
fevers, hyperthyroidism and in uncommon water-losing renal states such as diabetes insipidus or hypercalcaemia.
The volume of glucose solution needed to correct the deficit varies with the severity of the disorder, but usually lies within the range of 2-6 litres of 5% concentration. As a source of energy, glucose is given in higher concentrations.

*Dextrose*

**Indications:** see above

**Contra-indications:** diabetes mellitus.

**Caution and side-effects:** hypertonic glucose injection may cause venous irritation and thrombophlebitis.

**Dose:** water replacement, 2-6 litres of 5% glucose. Energy source, 1-3 litres of 20-50% glucose solution.

**Preparations**
- Dextrose 5% intravenous infusion, 500 mL pack
- Dextrose 10% intravenous infusion, 500 mL pack
- Dextrose 50% intravenous infusion, 500 mL pack
- Dextrose 50% injection, 20-50 mL ampoule

**9 B.2.4: Water for injection**

**Preparations**
- Water for injection, 5 mL ampoule
- Water for injection, 100 mL bottle

**9 B.3: Plasma and plasma substitutes**

*Concentrated Human Albumin*

A solution containing protein derived from plasma, serum or normal placenta. The concentrated solution contains 20-25% protein; mainly albumin. It can be given without regard to the recipient’s blood group.

**Indications:** severe hypovolaemia; plasma exchange.

**Contra-indications:** cardiac disease, severe anaemia.

**Cautions:** correct dehydration, avoid or administer very cautiously in patients with cardiac disease.

**Side-effects:** hypersensitivity reactions.

**Dose:** consult product literature.

**Preparations**
- Human albumin concentrated solution 20%; 50 mL vial
- Human plasma protein fraction

**Indications:** hypovolaemia due to burns, severe infections, and as protein replacement in hypoproteinaemia.

**Contra-indications:** hypersensitivity to albumin; severe anaemia, cardiac or circulatory disease.

**Cautions:** avoid rapid infusion; renal insufficiency.

**Side-effects:** hypersensitivity reactions.
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Dose: consult product literature.

Preparations
Human plasma protein fraction solution 5%, 50 mL vial
Human plasma protein fraction solution 5%, 250 mL vial

Gelatin (succinylated gelatin or polygeline)
Indications: low blood volume.
Cautions: used as immediate short-term measure to treat haemorrhage until blood is available. Rarely needed when hypovolaemia is due to water and sodium depletion. Avoid in cardiac disease.
Side-effects: hypersensitivity reactions.
Dose: consult product literature.

Preparations
Plasma volume replacement gelatin intravenous solution (succinylated gelatin) 3.5-4%, 500 mL bag

Hetastarch in sodium chloride solution
Indications: low blood volume.
Contra-indications: see gelatin above
Cautions: see gelatin above; children.
Side-effects: hypersensitivity reactions.
Dose: consult product literature.

Preparations
Hetastarch (average mol. weight 200,000) intravenous infusion, 6% in sodium chloride 0.9% solution, 500 mL bottle

9 C: Intravenous nutrition

Parenteral nutrition is indicated in malnourished patients who are unable to eat or absorb food, in comatose patients when tube feeding is not possible and other conditions when oral food intake is either impossible or hazardous. This may be in addition to oral or tube feeding and hence is called supplementary parenteral nutrition or may be the sole source of nutrition and then it is total parenteral nutrition (TPN). The nutrients solution should include amino acids for protein synthesis, glucose and lipids for energy supply as well as vitamins, trace elements and electrolytes.

The nutrient preparation is made according to the individual’s amino acid and energy requirements and should be freshly prepared by well trained personnel using aseptic techniques. The contents of the nutrient solution may vary in various clinical conditions such as diabetes, renal and hepatic failure, and electrolyte imbalance.

9 C.1: Electrolyte containing preparations

Amino acids + electrolytes
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Amino acids + electrolyte + carbohydrate

Electrolyte + trace elements

Consult manufacturer’s notes for contents and dose calculation.

9 C.2: Amino acid preparations

Essential amino acids plain

Essential amino acids + carbohydrate

Glutamine

Consult manufacturer’s notes for contents and dose calculation.

Preparations
Glutamine injection, 200 mg inj.

9 C.3: Fat preparations

Fractioned soya oil 100 g + glycerol 22g to give energy of 4600 kJ/litre
Fractioned soya oil 300 g + glycerol 16.7 g to give energy of 12600 kJ/litre

Consult manufacturer’s notes for contents and dose calculation.

9 C.4: Miscellaneous preparations

Fat-soluble vitamins in soya oil emulsion for infants

10 mL ampoule containing vitamin A, D, E and K

Vitamin B complex + vitamin C (Restricted)

Consult manufacturers notes for contents and dose calculation.

9 D: Oral nutrition

A special diet may be needed in certain clinical conditions. Foods are prepared for special diet to help eliminate or add certain common constituents of the complete food elements.

Enteral nutrition may, however, be needed in special cases where extra calories, protein, other nutrients and vitamins are given to supplement normal diet. There are many formulations of nutritionally complete foods available; selecting a preparation is determined by the patient’s need and the contents of the preparation.

9 D.1: Carbohydrate

Glucose powder

Used mainly for performance of the Oral Glucose Tolerance Test (OGTT).

This usually involves giving 75g of anhydrous glucose by mouth to the fasting patient and measuring the blood glucose concentration at appropriate intervals. The glucose
## 9: Nutrition and blood

should be given with at least 300 mL fluid.

### Note:
Anhydrous glucose powder 75g is equivalent to glucose monohydrate 82.5g

### Glucose polymer powder
Indicated for malnutrition and malabsorption states or other conditions requiring fortification with a high or dialysis available carbohydrate supplement.

**Preparation**
Glucose polymer powder; 350 g/can (providing 380 kcal/100 g of powder)

## 9 E: Minerals

### 9 E.1: Calcium and magnesium

#### 9 E.1.1: Calcium supplement

The requirement for calcium varies and is relatively greater in childhood, pregnancy, and lactation, due to increased demands, and in old age due to decreased absorption. In osteoporosis an increase in calcium daily intake would reduce the rate of bone loss. Calcium supplement are usually orally given. In hypocalcaemic tetany parenteral calcium is required. Calcium injections may also be needed in treatment of hyperkalaemia and cardiac resuscitation.

#### 9 D.2: Miscellaneous

### Medium chain triglycerides oil (CDL)

### Sodium benzoate tablets, 500 mg

## 9 D.3: Special feeding

### Protein + carbohydrate + fat + vitamins + minerals (energy 1674kJ)

Indicated as a sole source of nutrition or as nutritional supplement for patients with short-bowel syndrome, intractable malabsorption, following total gastrectomy. Available in liquid and powder forms.
Calcium chloride injection, 10% solution, 10 mL ampoule (27.3 mg calcium or 680 micromol Ca²⁺/mL)
Calcium gluconate injection, 10% solution, 10 mL ampoule (8.9 mg calcium or 220 micromol Ca²⁺/mL)
Calcium carbonate tablets, 500 mg tab.
Calcium carbonate + glycine tablets, 420 mg + 180 mg tab. (4.2 mmol Ca²⁺)
Calcium syrup, 100 mg / 5 ml

Potassium phosphate injection, 5-10 mL vial

**Cinacalcet (Restricted)**
**Indications:** Secondary hyperparathyroidism in patients with end-stage renal disease on dialysis. Treatment of hypercalcaemia in parathyroid carcinoma. Primary hyperparathyroidism in patients where parathyroidectomy is inappropriate.
**Cautions:** Treatment should not be initiated in patients with hypocalcaemia.
**Side-effects:** Anorexia; asthenia; dizziness; myalgia; nausea; paraesthesia; rash; reduced testosterone concentrations; vomiting.
**Dose:** Secondary hyperparathyroidism initially 30 mg once daily, dose to be adjusted every 2–4 weeks; maximum 180 mg per day. Hypercalcaemia and primary hyperparathyroidism. Initially 30 mg twice daily (max. per dose 90 mg 4 times a day), dose to be adjusted every 2–4 weeks according to response.

**Preparations**
Cinacalcet tablets, 30 mg tab.

**9 E.1.3: Magnesium**

**Magnesium sulphate**
**Indications:** hypomagnesaemia; prevention of seizure in severe pre-eclampsia or eclampsia.
**Cautions:** renal impairment; initial administration should be slow.
Nutrition and blood

Vitamins and minerals are an essential part of a healthy diet. If a person is eating a variety of foods, the likelihood of developing a deficiency of these nutrients is very small. Vitamins should only be used to treat or prevent a specific deficiency or to supplement otherwise inadequate diet.

People who follow strict diets may not get enough of certain vitamins or minerals. For example, strict vegetarians may develop vitamin B12 deficiency as this vitamin is only found in animal products. On the other hand, consuming large doses of vitamins and mineral supplements, without medical supervision, may lead to toxic effects.

Vitamins are in general classified into water-soluble vitamins (B group and vitamin C) and fat-soluble vitamins (A, D, E, and K).

The vitamin B group or sometimes called B complex includes vitamins that are essential for certain biological reactions in the body. Important members of this group are: thiamine (B1), riboflavin (B2), pyridoxine (B6), and nicotinamide (B7).

Folic acids and cyanocobalamin are mentioned in Section A.2. Others like biotin, choline, aminobenzoic acid, inositol, pantothenic acid do not seem to have any major importance.

Thiamine deficiency is manifested as anorexia, muscle cramps and in severe cases (beriberi) by neuropathy and cardiac failure. Alcoholics, due to deficient diet and the increased requirement for alcohol metabolism, manifest severe deficiency of thiamine and the development of neuropathy and beriberi. Treatment is initiated with parenteral administration of thiamine followed by oral administration over a long period.

Thiamine hydrochloride

Indications: deficiency of vitamin (B1).

Cautions: anaphylaxis may follow injection.

Dose: for mild to moderate deficiency, orally 10-25 mg daily. Severe deficiency 200-300 mg daily.

Preparations
- Thiamine hydrochloride tablets/capsules, 50 mg tab/cap.
- Thiamine hydrochloride tablets, 100 mg tab.
- Thiamine hydrochloride injection, 100 mg ampoule

Pyridoxine (B6)

Isolated deficiency is rare. It could occur during therapy with isoniazid and is characterized by peripheral neuritis. It has been applied in the treatment of cerebrovascular accidents.

Indications:

Cautions:

Dose:

Preparations
- Magnesium sulphate tablets, 100 mg tab. (CDL)
- Magnesium sulphate injection, 50% (500 mg/mL), 5 mL ampoule

9 E.2.1 Phosphate supplements

Supplement of phosphate is required in a minority of patients with hypophosphataemic, vitamin D resistant rickets. Diarrhoea is a common side effect that reflects overdosing and indicates a reduction in dosage.

Sodium acid phosphate (CDL)

Preparations
- Phosphate effervescent tablets containing, anhydrous sodium acid phosphate 1.936 g equivalent to 500 mg phosphorus

9 E.2.2 Phosphate binding agents

Sevelamer

Indications: hyperphosphataemia in patients on haemodialysis or peritoneal dialysis.

Cautions: pregnancy, breastfeeding, gastro-intestinal disorders.

Side-effects: gastrointestinal disturbances; hypotension, hypertension; headache; pruritus and rash; intestinal obstruction.

Dose: adult over 18 years, initially 2.4-4.8 g daily in 3 divided doses with meals, then adjusted according to plasma-phosphate concentration (usual dose range 2.4–12 g daily in 3 divided doses).

Preparations
- Sevelamer tablets, 800 mg, tab.
- Sevelamer powder, 800 mg per sachet

9 E.3. Zinc

Zinc (Restricted)

Indications: Zinc deficiency

Side-effects: gastrointestinal pain, nausea, vomiting and diarrhoea.

Dose: The dose beyond the RDA is not established. Dietary supplements contain 5–25 mg (elemental zinc) per daily dose.

Preparations
- Zinc syrup, 20 mg/5 ml
Vitamins and minerals are an essential part of a healthy diet. If a person is eating a variety of foods, the likelihood of developing a deficiency of these nutrients is very small.

Vitamins should only be used to treat or prevent a specific deficiency or to supplement otherwise inadequate diet. People who follow strict diet may not get enough of certain vitamins or minerals. For example, strict vegetarian may develop vitamin B₁₂ deficiency as this vitamin is only found in animal products. On the other hand consuming large doses of vitamin and mineral supplements, without medical supervision, may lead to toxic effects.

Vitamins are in general classified into water-soluble vitamins (B group and vitamin C) and fat-soluble vitamins (A, D, E and K).

9 F.1: Water soluble vitamins

9 F.1.1: Vitamin B group

The vitamin B group or sometimes called B complex includes vitamins that are essential for certain biological reaction in the body. Important members of this group are: thiamine (B₁), riboflavin (B₂), pyridoxine (B₆), and nicotinamide (B₁₂). Folic acids and cyanocobalamin are mentioned in sec 9 A.2. Others like biotin, choline, aminobenzoic acid, inositol, pantothenic acid do not seem to have any major importance.

Thiamine (B₁) deficiency is manifested as anorexia, muscle cramp and in severe cases (beriberi) by neuropathy and cardiac failure. Alcoholics, due to deficient diet and the increased requirement for alcohol metabolism, manifest severe deficiency of thiamine and the development of neuropathy and beri-beri. Treatment is initiated with parenteral administration of thiamine followed by oral administration over a long period.

Thiamine hydrochloride

Indications: deficiency of vitamin (B₁).

Cautions: anaphylaxis may follow injection.

Dose: for mild to moderate deficiency, orally 10-25 mg daily. Severe deficiency 200-300 mg daily.

Preparations
Thiamine hydrochloride tablets/capsules, 50 mg tab/cap.
Thiamine hydrochloride tablets, 100 mg tab.
Thiamine hydrochloride injection, 100 mg ampoule

Pyridoxine (B₆) isolated deficiency is rare. It could occur during therapy with isoniazid and is characterized by peripheral neuritis. It has been applied in the treatment of...
some metabolic disorders such as homocystinuria. Pyridoxine has been widely applied, though with a doubtful benefit, in the management of nausea and vomiting occurring during pregnancy.

**Pyridoxine Hydrochloride**

**Indications:** vitamin B6 deficiency; nausea and vomiting in pregnancy (see notes above), pre-menstrual syndrome, with isoniazid to prevent peripheral neuritis. **Cautions:** penicillamine antagonises pyridoxine effects and may precipitate clinical deficiency state. **Dose:** deficiency states, 20-50 mg up to 3 times daily. Isoniazid neuropathy, prophylaxis 10-20 mg daily; therapeutics 50 mg 3 times daily. Nausea and vomiting during pregnancy (see notes above), 50 mg at bed time.

**Preparations**

Pyridoxine hydrochloride tablets, 50 mg tab.

Pyridoxine hydrochloride injection, 100 mg ampoule (Restricted)

**Biotin (vitamin B7/ vitamin H)**

daily requirement is estimated to be 100-200 micrograms. Balanced diet provides 200-300 micrograms daily. However, part of the biotin synthesized by intestinal flora is available for absorption. Large dose of biotin (5-10 mg daily) are administered to babies with infantile seborrhoea and to individuals with genetic alteration of biotin-dependent enzymes. In adults it may be used as an adjuvant therapy in some cases of alopecia.

**Biotin**

**Indications and dose:** see notes above

**Preparations**

Biotin tablets, 5 mg tab.

**Vitamin B complex** is a combination of all vitamins of the B group. Oral as well as parenteral preparations are available with various strengths of each individual vitamin.

**Vitamin B complex and vitamin C injection (Restricted)**

**Preparations**

Vitamin B complex and vitamin C injection containing, biotin 60 microgram, B12 5 microgram, B1 3.2 mg, B6 4 mg, vitamin C 100 mg, nicotinamide 40 mg, folic acid 0.4 mg, pantothenic acid 15 mg/ampoule

**B9 F.1.2: Vitamin C**

Vitamin C is essential in the synthesis of connective tissues. Severe deficiency will lead to scurvy, which is rarely seen these days. The daily requirement for vitamin C is about 30-60 mg. Balanced diet usually provides the body with its need of the vitamin.
People, elderly in particular, who have been kept on very poor or restricted diet for a long time, may develop scurvy. Infants fed on formula that lacks vitamin C should be supplemented with vitamin C. Treatment of scurvy is achieved with oral or parenteral vitamin C doses of 500 mg daily in adults and 50-100 mg daily in infants and children, plus a balanced diet. Vitamin C has been indicated for a variety of clinical conditions with controversial benefits.

**Ascorbic acid (vitamin C)**

**Indications and dose:** see notes above

**Preparations**
- Ascorbic acid tablets, 50 mg tab.
- Ascorbic acid tablets, 100 mg tab.

**9 F.2: Fat soluble vitamins**

**9 F.2.1: Vitamin A**

Requirement for vitamin A is mainly derived from dietary sources. Vitamin A is essential for retinal function and epithelial cell structure and function. Deficiency results in development of night blindness as an early sign, dry skin and hyperkeratosis progressing to xerophthalmia and keratomalacia. Mild deficiency can be treated with 30,000 to 50,000 units daily, while severe cases need higher doses up to 100,000 units for 3 days and then 50,000 units daily for two weeks and the 10,000 –20,000 units daily for 2-3 months. Overdosage resulting from chronic un-recommended use may lead to hypervitaminosis A which is manifested clinically by dryness of the skin, brittle nails, hair loss, cheilosis, hyperostosis and bone pains, weight loss, hepatosplenomegaly, and benign intracranial hypertension. Vitamin A should be avoided during pregnancy unless otherwise indicated and should be strictly supervised.

**Vitamin A**

**Indications and side-effects and cautions:** see notes above

**Preparations**
- Vitamin A capsules, 50,000 units cap.
- Vitamin A capsules, 100,000 units cap.
- Vitamin A capsules, 200,000 units cap.

**9 F.2.2: Vitamin D**

Vitamin D is the term used to describe a range of compounds used for the prevention or curing of rickets. Alfacalcidol and calcitriol are new derivatives that are of a short duration of action. This makes them safer over chronic use since the resulting hypercalcaemia is short lived and easily treated.
9: Nutrition and blood

Vitamin D requires hydroxylation in the kidney, therefore the new hydroxylated derivatives alfacalcidol and calcitriol can be safely used in patients with renal impairment.

**Alfacalcidol**

**Indications:** vitamin D deficiency.

**Contra-indications:** hypercalcaemia, metastatic calcification.

**Cautions:** accurate dosing must be observed in infants; monitor calcium level in high doses of Vitamin D in adults and in renal impairment.

**Side-effects:** in overdose: anorexia, lassitude, nausea and vomiting, diarrhoea, weight loss.

**Dose:** orally or intravenously, adults and child over 20 kg, initially 1 microgram daily which should be reduced in elderly. Maintenance usually 0.25-1 microgram daily.

Neonates, premature infants and child under 20 kg, 50-100 nanograms/kg daily.

**Preparations**

Alfacalcidol oral drops, 2 micrograms/mL drops, 20 mL/bottle

Alfacalcidol capsules, 0.25 microgram cap.

Alfacalcidol capsules, 1 microgram cap.

Alfacalcidol injection, 2 micrograms/mL, 1 mL ampoule

**Calcitriol**

**Indication, cautions and side-effects:** see alfacalcidol above

**Dose:** initially 250 nanograms (0.25 micrograms) daily increased if necessary to 0.5-1 microgram daily.

**Preparations**

Calcitriol tablets, 250 nanograms (0.25 microgram) tab.

**Colecalciferol (Restricted)**

**Indications:** Prevention and treatment of vitamin D deficiency

**Contra-indications:** Hypercalcaemia; metastatic calcification

**Cautions:** Take care to ensure correct dose in infants

**Side-effects:** Symptoms of overdose include anorexia, lassitude, nausea and vomiting, diarrhoea, constipation, weight loss, polyuria, sweating, headache, thirst, vertigo, and raised concentrations of calcium and phosphate in plasma and urine.

**Dose:** Prevention of vitamin D deficiency 400 units daily.

Treatment of vitamin D deficiency 800 units daily, higher doses may be necessary for severe deficiency.

**Preparations**

Colecalciferol capsule, 50,000 IU cap.

Colecalciferol drops 400 IU / ml

Colecalciferol drops 10,000 IU / ml

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Ministry of Health policy is that only one of the above vitamin D preparations will be purchased and made available for use depending on cost.
Calcium with vitamin D

Preparations
Calcium lactate or carbonate + vitamin D tablets

9 F.2.3 Vitamin E

The daily requirement of vitamin E has not been well defined but is probably about 3 to 15 mg daily. There is little evidence that oral supplements of vitamin E are essential in adults, even where there is fat malabsorption secondary to cholestasis. In young children with congenital cholestasis, abnormally low vitamin E concentrations may be found in association with neuro-muscular abnormalities, which usually respond only to the parenteral administration of vitamin E. Vitamin E has been tried for various other conditions but there is little scientific evidence of its value.

Alpha tocopheryl acetate (Restricted)

Indications: see notes above; vitamin E deficiency, malabsorption in cystic fibrosis.

Cautions: predisposition to thrombosis; increased risk of necrotising enterocolitis in preterm neonates, pregnancy, breast-feeding.

Side-effects: diarrhoea and abdominal pain in high doses.

Dose: Malabsorption in cystic fibrosis, 100–200 mg daily; child 1 month–1 year 50 mg daily; 1–12 years, 100 mg daily.

9 F.3: Multivitamin preparations

It has been publicly promoted that the regular use of multivitamin preparations is beneficial to health, provides energy and protects against disease. This belief has no scientific validity, and of no therapeutic benefit in well fed people. Vitamins should only be prescribed to treat a specific vitamin deficiency or for prophylaxis in certain clinical states. The overuse of multivitamin preparations may damage health and cause serious adverse consequences in particular with those preparations containing high concentration of vitamin A and D.

Multivitamin preparations

Preparations
Multivitamin syrup; 90 - 120 mL/bottle
High potency Multivitamins tablet and suspension (Restricted)

9 G: Drugs used for metabolic disease

Breakdown of protein produces nitrogen compound such as ammonia. Hyperammonaemia may be the result of overloading with protein in total parenteral nutrition.
9: Nutrition and blood

**Carnitine (CDL)**
(carnitine is biosynthesized primarily in the liver and kidneys from the aminoacids and plays an important role in fatty acids metabolism)

**Indications:** carnitine deficiency due to inborn errors of metabolism or of secondary deficiency in haemodialysis patients.

**Cautions:** diabetes mellitus, renal impairment, pregnancy, breast feeding, monitoring of free and acyl carnitine in blood and urine recommended.

**Side-effects:** gastrointestinal disturbances, fishy body odour.

**Dose:** in primary deficiency, intravenously over 2-3 minutes, up to 100 mg/kg daily in 3-4 divided doses. In secondary deficiency, intravenously over 2-3 minutes, 20 mg/kg after each session of dialysis.

**Preparations**
Carnitine injection, 1 g vial

**Sodium Phenylbutyrate (CDL)**

**Indications:** used singly or in combination with sodium benzoate in the management of urea cycle disorders e.g. hyperammonaemia.

**Contra-indications:** pregnancy, breast feeding.

**Cautions:** hepatic and renal failure, congestive heart failure or any clinical conditions involving sodium retention with oedema.

**Side-effects:** menstrual cycle irregularities, body odour, decreased appetite, gastrointestinal and taste disturbances.

**Dose:** in acute hyperammonaemia, by intravenous infusion 250 mg/kg over 90 minutes followed by 20 mg/kg/hour adjusted according to response.

**Preparations**
Sodium Phenylbutyrate injection, 1g ampoule
Sodium phenylbutyrate tablets, 500 mg tab.

**Sodium benzoate and sodium phenylacetate (Controlled)**
are used orally or parenterally to treat hyperammonaemia (see sec 9 D.3)

**Preparations**
Sodium benzoate injection, 1 g/5 mL ampoule
sodium phenylacetate injection, 10% ampoule
Sodium phenylacetate and sodium benzoate injection, 100 mg/mL of each in vials for injection.

**Nitisinone (Restricted)**

**Indications:** Hereditary tyrosinaemia type I (in combination with dietary restriction of tyrosine and phenylalanine) (specialist use only)

**Side-effects:** Conjunctivitis; corneal opacity; eye pain; granulocytopenia; keratitis; leucopenia; photophobia; thrombocytopenia; blepharitis; erythematous rash; exfoliative dermatitis; leucocytosis; pruritus

**Dose:** Initially 500 micrograms/kg twice daily, adjusted according to
Nutrition and blood

Response; maximum 2 mg/kg per day.

Preparations
Nitisinone capsules 2 mg cap.

Carnitine (CDL)
(Carnitine is biosynthesized primarily in the liver and kidneys from the aminoacids and plays an important role in fatty acids metabolism)

Indications: carnitine deficiency due to inborn errors of metabolism or of secondary deficiency in haemodialysis patients.

Cautions: diabetes mellitus, renal impairment, pregnancy, breast feeding, monitoring of free and acyl carnitine in blood and urine recommended.

Side-effects: gastrointestinal disturbances, fishy body odour.

Dose: in primary deficiency, intravenously over 2-3 minutes, up to 100 mg/kg daily in 3-4 divided doses. In secondary deficiency, intravenously over 2-3 minutes, 20 mg/kg after each session of dialysis.

Preparations
Carnitine injection, 1 g vial
Sodium benzoate and sodium phenylacetate (Controlled)

Sodium benzoate and sodium phenylacetate (Controlled) are used orally or parenterally to treat hyperammonaemia (see sec 9 D.3)

Preparations
Sodium benzoate injection, 1 g/5 mL ampoule
Sodium phenylacetate injection, 10% ampoule
Sodium phenylacetate and sodium benzoate injection, 100 mg/mL of each in vials for injection.

Sodium Phenylbutyrate (CDL)
Indications: used singly or in combination with sodium benzoate in the management of urea cycle disorders e.g. hyperammonaemia.

Contra-indications: pregnancy, breast feeding.

Cautions: hepatic and renal failure, congestive heart failure or any clinical conditions involving sodium retention with oedema.

Side-effects: menstrual cycle irregularities, body odour, decreased appetite, gastrointestinal and taste disturbances.

Dose: in acute hyperammonaemia, by intravenous infusion 250 mg/kg over 90 minutes followed by 20 mg/kg/hour adjusted according to response.

Preparations
Sodium Phenylbutyrate injection, 1 g ampoule
Sodium phenylbutyrate tablets, 500 mg tab.

Nitisinone (Restricted)
Indications: Hereditary tyrosinaemia type I (in combination with dietary restriction of tyrosine and phenylalanine) (specialist use only)

Side-effects: Conjunctivitis; corneal opacity; eye pain; granulocytopenia; keratitis; leucopenia; phorophobia; thrombocytopenia; blepharitis; erythematous rash; exfoliative dermatitis; leucocytosis; pruritus

Dose: Initially 500 micrograms/kg twice daily, adjusted according to response; maximum 2 mg/kg per day.
10: Musculoskeletal and joint diseases

Section 10: Musculoskeletal and joint diseases

- Drugs used in rheumatic diseases and gout
- Drugs used in neuromuscular disorders

10 A: Drugs used in rheumatic diseases and gout

10 A.1: Non-steroidal anti-inflammatory drugs (NSAIDs)

All NSAIDs are antipyretic, analgesic and anti-inflammatory, but there are important differences in their activities. When employed as analgesics these drugs are effective only against pain of low to moderate intensity. Chronic postoperative pain or pain arising from inflammation is particularly well controlled by NSAIDs, whereas pain arising from hollow viscera is not relieved.

As antipyretics, NSAIDs reduce body temperature in febrile states. However, some NSAIDs are not suitable for either routine or prolonged use.

NSAIDs find their main clinical application as anti-inflammatory agents in the treatment of musculoskeletal disorders such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. They only provide symptomatic relief of pain and inflammation associated with the disease without actively interfering in the progression of the tissue damage associated with severe episodes of the disease.

NSAIDs have also been successfully used in the closure of the ductus arteriosus in neonates when it has remained patent. Dysmenorrhea, which might be caused by excessive release of prostaglandins by the endometrium, can be relieved by NSAIDs.

The choice among NSAIDS for an antipyretic or analgesic agent is seldom a problem. The choice of a NSAID for arthritides is largely empirical as there are individual patient variations in tolerance and response. The majority of patients respond to any NSAID, those who do not respond to one may well respond to another.

The main differences between NSAIDs are in the incidence and type of side-effects. Prescribers are advised always to weigh the efficacy of NSAIDs therapy against possible side-effects.

NSAIDs vary in their selectivity to inhibit the different types of cyclooxygenase enzymes (COX); the nonselective inhibition of the enzymes is thought to be the reason for the high incidences of GI adverse effects. Selective cyclooxygenase 2 (COX-2) enzyme inhibitors are claimed to be free from GI side-effects, a claim which needs to be further ratified.

In principle, one week is needed to show a maximal analgesic effect; while anti-inflammatory effect might not be seen before 3 weeks or
more. If appropriate responses are not obtained within these times another NSAID should be tried. The side-effects of NSAIDs vary in severity and frequency. GI disturbances, nausea, vomiting, occasional bleeding and ulceration; dyspepsia can be minimized by taking the drug with food and or milk. Other side-effects include hypersensitivity reactions (particularly angioedema, rashes and bronchospasm), headache, dizziness, vertigo, hearing disturbances such as tinnitus.

Cautions and contra-indications for the use of NSAIDs include:

- do not use more than one NSAID at a time
- NSAIDs with lower risk of GI toxicity (e.g. Ibuprofen) should be tried first in the lowest recommended dose.
- contraindicated in patients with peptic ulcer.
- should be used with caution in patients with infection since symptoms such as fever and inflammation may be masked.
- should be used with great caution in patients with asthma and allergic disorders. They are contraindicated in patients with a history of hypersensitivity reaction to such drugs.
- should be cautiously administered to patients with haemor-

rhagic disorders, hypertension, impaired renal, hepatic and cardiac functions.
- elderly patients may require dose reduction.
- regular use of NSAIDs during the third trimester of pregnancy may result in early closure of foetal ductus arteriosus in utero, and possibly in persistent pulmonary hypertension of the new born.
- There are concerns about the cardiovascular safety of selective COX-2 inhibitors (all are now withdrawn from use in Oman).

Ibuprofen

Indications: pain and inflammation in rheumatic disease and other musculoskeletal disorders (anti-inflammatory effects are weaker); mild to moderate pain including dysmenorrhea; post-operative analgesia, fever and pain in children.

Contra-indications: see notes above; not recommended for children under 7 kg.

Cautions: see notes above. Avoid concurrent use in patients on regular low dose aspirin.

Side-effects: fewer side-effects than other NSAIDs. See notes above.

Dose: 1.2-1.6 g daily dose in 3-4 divided doses preferably after food with adequate quantity of water. Maintenance, 0.8-1.2 g daily in divided doses (maximum 2.4 g daily).
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Child 20 mg/kg daily in divided doses. (Increase in juvenile arthritis up to 40 mg/kg daily).

Preparations
Ibuprofen tablets, 400 mg tab.
Ibuprofen syrup, 100 mg/5 mL syrup; 100 mL/bottle (Restricted)
Ibuprofen injection, 10 mg/mL (Restricted)

Celecoxib (Restricted)
Indications: Pain and inflammation in osteoarthritis. Pain and inflammation in rheumatoid arthritis. Ankylosing spondylitis
Contra-indications: Active gastrointestinal bleeding; active gastrointestinal ulceration; cerebrovascular disease; inflammatory bowel disease; ischaemic heart disease; mild to severe heart failure; peripheral arterial disease
Cautions: Allergic disorders; cardiac impairment (NSAIDs may impair renal function); coagulation defects; connective-tissue disorders; Crohn’s disease (may be exacerbated); elderly (risk of serious side-effects and fatalities); history of cardiac failure; hypertension; left ventricular dysfunction; oedema; risk factors for cardiovascular events; ulcerative colitis (may be exacerbated).
Side-effects: Dyspnoea; influenza-like symptoms; cerebral infarction; fatigue; muscle cramps; palpitation; paraesthesia; stomatitis; alopecia; alveolitis; aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible); hepatic damage; interstitial fibrosis associated with NSAIDs can lead to renal failure; pancreatitis; papillary necrosis associated with NSAIDs can lead to renal failure; pulmonary eosinophilia; Stevens-Johnson syndrome; taste disturbance; toxic epidermal necrolysis; visual disturbances
Dose: Pain and inflammation in osteoarthritis 200 mg daily in 1–2 divided doses, then increased if necessary up to 200 mg twice daily, discontinue if no improvement after 2 weeks on maximum dose.
Pain and inflammation in rheumatoid arthritis 100 mg twice daily, then increased if necessary to 200 mg twice daily, discontinue if no improvement after 2 weeks on maximum dose.
Ankylosing spondylitis 200 mg daily in 1–2 divided doses, then increased if necessary up to 400 mg daily in 1–2 divided doses, discontinue if no improvement after 2 weeks on maximum dose

Preparations
Celecoxib tablets, 200 mg tab.

Diclofenac
Indications: Pain and inflammation in rheumatic disease, other musculoskeletal disorders; post-operative pain; acute gout.
Contra-indications: see notes above; intravenous administration in patients on other NSAIDs or anticoagulants; history of confirmed
or suspected cerebrovascular bleeding; history of asthma.  
**Cautions:** see notes above; porphyria.  
**Side-effects:** see notes above; rectal irritation is common with suppositories.  
Dose: Maximum daily dose by any route 150 mg.  
Orally, 75-150 mg daily in divided doses after meal with adequate quantity of water.  
By deep intramuscular injection, for acute conditions, ureteric colic and post-operative pain, 75 mg once daily (maximum twice daily in severe case) for two days.  
By intravenous infusion, in hospital settings only, 75 mg may be repeated after 4–6 hour, maximum 2 days.  

**Preparations**  
*Diclofenac sodium tablets, 50 mg tab.*  
*Diclofenac sodium retard tablets, 100 mg tab. (Restricted)*  
*Diclofenac sodium injection, 25 mg/mL, 3 mL ampoule (Restricted)*  
*Diclofenac sodium suppositories, 25 mg tab. (Restricted)*  
*Diclofenac sodium suppositories, 100 mg tab. (Restricted)*  

**Etoricoxib (Restricted)**  
**Indications:** Pain and inflammation in osteoarthritis. Pain and inflammation in rheumatoid arthritis. Ankylosing spondylitis. Acute gout  
**Contra-indications:** Active gastrointestinal bleeding; active gastrointestinal ulceration; cerebrovascular disease; inflammatory bowel disease; ischaemic heart disease; mild to severe heart failure; peripheral arterial disease; uncontrolled hypertension (persistently above 140/90 mmHg).  
**Cautions:** Allergic disorders; cardiac impairment (NSAIDs may impair renal function); coagulation defects; connective-tissue disorders; Crohn’s disease (may be exacerbated); dehydration; history of cardiac failure; hypertension; left ventricular dysfunction; oedema; risk factors for cardiovascular events; ulcerative colitis (may be exacerbated), elderly (risk of serious side-effects and fatalities).  
**Side-effects:** Ecchymosis; fatigue; influenza-like symptoms; palpitation.  
**Dose:** Pain and inflammation in osteoarthritis. 30 mg once daily, then increased if necessary to 60 mg once daily. Pain and inflammation in rheumatoid arthritis/Ankylosing spondylitis 90 mg once daily. Acute gout 120 mg once daily for maximum 8 days.  

**Preparations**  
*Etoricoxib tablets, 90 mg tab.*  
*Etoricoxib tablets 120 mg tab.*
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**Indometacin (Indomethacin) (Restricted)**

**Indications:** indications are limited because of high incidences of adverse effects; prevention of heterotopic (ectopic) ossification in hip replacement.

**Contra-indications:** see notes above.

**Cautions:** see notes above; epilepsy, Parkinsonism, psychiatric disturbances; regularly examine the eye on chronic use, avoid during infection as it might mask the symptoms.

**Side-effects:** see notes above; more severe GI disturbances, morning headache, dizziness.

**Dose:** 75-150 mg daily after meal in 1-2 doses.

**Preparations**

Indometacin capsule, 75 mg cap.

**Mefenamic acid**

**Indications:** mild to moderate pain; rheumatoid arthritis, osteoarthritis; dysmenorrhoea and menorrhagia.

**Contra-indications:** see notes above; inflammatory bowel disease.

**Cautions:** see notes above; stop treatment if diarrhoea or rash develops; use for short course therapy (not exceeding 7 days).

**Side-effects:** see notes above; diarrhoea and rash; haemolytic anaemia; thrombocytopenia; convulsions in overdose.

**Dose:** 500 mg 3 times daily after food with adequate quantity of water.

Child, for a short course therapy, 25 mg /kg daily. Not recommended under 6 months.

**Preparations**

Mefenamic acid capsules/tablets, 500 mg cap/tab.

**Naproxen (Restricted)**

**Indications:** Pain and inflammation in rheumatic disease. Pain and inflammation in musculoskeletal disorders. Dysmenorrhoea. Acute gout

**Contra-indications:** Active gastrointestinal bleeding; active gastrointestinal ulceration; history of gastrointestinal bleeding related to previous NSAID therapy; history of gastrointestinal perforation related to previous NSAID therapy; history of recurrent gastrointestinal haemorrhage (two or more distinct episodes); history of recurrent gastrointestinal ulceration (two or more distinct episodes); severe heart failure.

**Cautions:** Allergic disorders; cardiac impairment (NSAIDs may impair renal function); cerebrovascular disease; coagulation defects; connective-tissue disorders; Crohn’s disease (may be exacerbated); elderly (risk of serious side-effects and fatalities); heart failure; ischaemic heart disease; peripheral arterial disease; risk factors for cardiovascular events; ulcerative colitis (may be exacerbated); uncontrolled hypertension.
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**Side-effects:** Alveolitis; aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible); hepatic damage; interstitial fibrosis associated with NSAIDs can lead to renal failure; pancreatitis; papillary necrosis associated with NSAIDs can lead to renal failure; pulmonary eosinophilia; Stevens-Johnson syndrome; toxic epidermal necrolysis; visual disturbances.

**Dose:** Pain and inflammation in rheumatic disease 0.5–1 g daily in 1–2 divided doses.

Pain and inflammation in musculoskeletal disorders/ Dysmenorrhoea initially 500 mg, then 250 mg every 6–8 hours as required, maximum dose after the first day 1.25 g daily. Acute gout Initially 750 mg, then 250 mg every 8 hours until attack has passed.

**Preparations**

Naproxen tablets, 250 mg tab.

**Tenoxicam (Restricted)**

**Indications:** pain and inflammation in rheumatoid arthritis and other musculoskeletal disorders.

**Contra-indications:** see notes above

**Cautions:** see notes above

**Side-effects:** see notes above

**Dose:** 20 mg daily in rheumatic disease. In acute conditions, 20 mg daily for 7 days (maximum 14 days).

Child, not recommended.

**Preparations**

Tenoxicam tablets, 20 mg tab.

10 A.2: Drugs which suppress the rheumatic disease process

A group of drugs including, penicillamine, gold, antimalarials, cytokine modulators and sulphasalazine may suppress the disease process in rheumatoid arthritis. They are known as disease modifying anti-rheumatic drugs (DMARDs). Unlike NSAIDs, these drugs need a longer time to show a therapeutic effect; 4-6 months may elapse before a full response is achieved.

Penicillamine is a chelating agent that has a similar action to gold in severe rheumatoid arthritis but is better tolerated. Treatment should be discontinued if there is no benefit within one year. Improvement is not expected before 6-12 weeks of treatment. If remission has been sustained for 6 months, reduction of dose by 125-250 mg every 12 weeks may be initiated.

Penicillamine has other therapeutic uses in Wilson’s disease, treatment of copper and lead poisoning and in cystinuria. Sulfasalazine is beneficial in suppressing the inflammatory process of rheumatoid arthritis. Side-effects such as gastrointestinal disturbances are frequent. Blood count should be closely monitored.
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**Adalimumab**

**Indications:** moderately to severely active rheumatoid arthritis, active psoriatic arthritis and ankylosing spondylitis in combination with methotrexate or used alone in patients who have had an inadequate response to one or more diseases modifying antirheumatic arthritis.

**Contra indications:** active infection, pregnancy and breast-feeding.

**Cautions:** congestive heart failure, history of active or chronic infections (tuberculosis should be excluded), demyelinating CNS disorders, renal and hepatic impairment.

**Side effects:** diarrhoea, dyspnoea, chest pain, hypertension, mouth ulceration, taste disturbances, drowsiness, menorrhagia, haematuria, proteinuria.

**Dose:** by subcutaneous injection, 40 mg on alternate weeks; if necessary increased to 40 mg weekly in patients receiving adalimumab alone, discontinue if no response after 12 weeks.

**Preparations**

Adalimumab injection, 40 mg in prefilled syringe

**Etanercept**

**Indications:** moderately to severely active rheumatoid arthritis, active psoriatic arthritis and ankylosing spondylitis in combination with methotrexate or used alone in patients who have had an inadequate response to one or more diseases modifying antirheumatic arthritis, also in polyarticular-course juvenile idiopathic arthritis.

**Contra indications:** active infection, pregnancy and breast-feeding, avoid injections containing benzyl alcohol in neonates.

**Cautions:** congestive heart failure, patients with a significant exposure to varicella virus, history of active or chronic infections (tuberculosis should be excluded), demyelinating CNS disorders, blood disorders.

**Side effects:** infections including tuberculosis and reactivation of hepatitis B, nausia, worsening of heart failure, hypersensitivity reactions, blood disorders, depression, diabetes, ulcerative colitis, malignancy, injection site reactions.

**Dose:** by subcutaneous injection, 25 mg twice weekly or 50 mg once weekly, child (4-17 years) with poly articular-course juvenile idiopathic arthritis, 400 micrograms/kg; maximum 25 mg twice weekly.

**Preparations**

Etanercept injection, powder for reconstitution, 25 mg vial

Etanercept injection, 50 mg in prefilled syringe

**Hydroxychloroquine**

**Indications:** rheumatoid arthritis, discoid and systemic lupus erythematosus, malaria.

**Contra indications:** long-term therapy in children and pregnant mothers, hypersensitivity to the drug.
**Cautions:** ophthalmologic examinations are recommended (irreversible retinal damage has been observed in some patients who had received long-term or high-dosage), hepatic and renal impairment, G6PD, pregnancy, breast-feeding, elderly, dangerous in overdose (doses above 8 g are usually fatal).

**Side-effects:** gastrointestinal complaints, headache, retinopathy, nystagmus, bleaching of hair, alopecia, pruritus, tinnitus, nystagmus, nerve deafness.

**Dose:** orally, initially 400 mg daily in divided doses, maintenance 200-400 mg daily; maximum 6.5 mg/kg daily (but not exceeding 400 mg daily).

**Preparations**

Hydroxychloroquine tablets, 200 mg tab.

**Infliximab**

**Indications:** moderately to severely active rheumatoid arthritis, active psoriatic arthritis andankylosing spondylitis in combination with methotrexate or used alone in patients who have had an inadequate response to one or more diseases modifying antirheumatic arthritis, also in inflammatory bowel disease.

**Contra-indications:** active infection, pregnancy and breast-feeding.

**Cautions:** congestive heart failure, history of active or chronic infections (tuberculosis should be excluded), demyelinating CNS disorders, history of malignancy, history of prolonged immunosuppressant or PUVA treatment in patient with psoriasis.

**Side-effects:** hypersensitivity reactions, diarrhoea, dyspnoea, dry skin, chest pain, cholecystitis, hypertension, oedema.

**Dose:** by intravenous infusion, in active rheumatoid arthritis, 3 mg/kg, repeated 2 weeks and six weeks after initial infusion, then every 8 weeks (discontinue if no response by 12 weeks), in active psoriatic arthritis and ankylosing spondylitis, increase the dose to 5 mg/kg with the same frequencies of infliximab in active rheumatoid arthritis.

**Preparations**

Infliximab injection, 100 mg vial

**Leflunomide (Restricted)**

**Indications:** Moderate to severe active rheumatoid arthritis. Active psoriatic arthritis.

**Contra-indications:** Serious infection; severe hypoproteinaemia; severe immunodeficiency.

**Cautions:** Anaemia (avoid if significant and due to causes other than rheumatoid arthritis); history of tuberculosis; impaired bone-marrow function (avoid if significant and due to causes other than rheumatoid arthritis); leucopenia (avoid if significant and due to causes other than rheumatoid arthritis); thrombocytopenia (avoid if significant and due to causes other than rheumatoid arthritis).
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**Side-effects:** Abdominal pain; alopecia; anorexia; asthenia; diarrhoea; dizziness; dry skin; headache; increased blood pressure; leucopenia; nausea; oral mucosal disorders; paraesthesia; pruritus; rash; tenosynovitis; vomiting

**Dose:** Moderate to severe active rheumatoid arthritis. Initially 100 mg once daily for 3 days, then reduced to 10–20 mg once daily. Active psoriatic arthritis. Initially 100 mg once daily for 3 days, then reduced to 20 mg once daily.

**Preparations**
Leflunomide tablets, 20 mg tab.

**Penicillamine (Restricted)**

**Indications:** severe active rheumatoid arthritis; Wilson’s disease; cystinuria; copper and lead poisoning.

**Contra-indications:** sensitivity to penicillamine, lupus erythematosus.

**Cautions:** see notes above; pregnancy and breast feeding; avoid concurrent use of other disease modifying antirheumatic drugs; watch carefully for the development of unusual side-effects during treatment.

**Side-effects:** nausea, vomiting, anorexia, taste disorders, myelosuppression, proteinuria, blood disorders.

**Dose:** severe active rheumatoid arthritis under strict specialist supervision. Adult, initially 125-250 mg daily before food for 1 month, increased gradually at one month intervals by 125-250 mg. The dose should not exceed 1.5 g daily. Elderly, initially less than 125 mg daily increase gradually to a maximum maintenance dose of 1g daily. Child, maintenance dose 15-20 mg / kg daily.

**Preparations**
Penicillamine tablets, 250 mg tab.

**Sulfasalzine (Sulphasalazine)**

**Indications:** active rheumatoid arthritis; ulcerative colitis, see sec 1D.3

**Contra-indications,** cautions and side-effects: see sec1D.3

**Dose:** orally as enteric coated tablets, initially 500 mg daily increased by 500 mg at intervals of 1 week to a maximum of 2-3 g daily in divided doses.

**Preparations**
Sulfasalazine tablets, 500 mg tab.

**Tocilizumab (Restricted)**

**Indications:** Moderate to severe active rheumatoid arthritis (in combination with methotrexate or alone if methotrexate inappropriate).

**Contra-indications:** Do not initiate if absolute neutrophil count less than 2 x 10⁹/litre; severe active infection

**Cautions:** History of diverticulitis; history of intestinal ulceration; history of recurrent or chronic infection (interrupt treatment if serious infection occurs); low absolute neutrophil count; low platelet count;
predisposition to infection (interrupt treatment if serious infection occurs)

**Side-effects:** Abdominal pain; antibody formation; dizziness; gastritis; headache; hypercholesterolaemia; hypersensitivity; hypertension; infection; leucopenia; mouth ulceration; neutropenia; peripheral oedema; pruritus; raised hepatic transaminases; rash; upper respiratory-tract infection

**Dose:** 8 mg/kg every 4 weeks (max. per dose 800 mg), for dose adjustments in patients with liver enzyme abnormalities, or low absolute neutrophil or platelet count, consult product literature.

Preparations
Tocilizumab injection 20 mg / ml, 10 ml vial

### 10 A. 3: Drugs used in the treatment of gout and hyperuricemia

Gout is an articular manifestation of hyperuricaemia. The acute attack is caused by deposition of urate crystals in the synovial fluids of the affected joint. This deposition will initiate inflammatory processes with phagocytosis of the urate crystals; these actively phagocytic leucocytes will produce lactic acid and this will promote further urate crystallization in the joint tissues.

Acute gout is best treated with high doses of NSAIDs. Colchicine is used as alternative especially in patients with heart disease since it does not cause fluid retention. The normal serum uric acid levels range from 1-7 mg / dL. It is important to note that hyperuricaemia and gout are not synonymous. It has been reported that 90% of hyperuricaemic patients with plasma uric acid above 9 mg / dL eventually develop gout. Hyperuricaemia must be corrected with drugs only when there is an acute attack of gout, soft tissue deposition, renal urate calculi or the serum uric acid level is markedly elevated. Long term prophylactic treatment of gout can be effectively achieved with allopurinol. Allopurinol, a xanthine oxidase inhibitor, reduces the formation of uric acid. It shows less adverse effects than uricosuric agents especially in patients with renal impairment or urate stones. Treatment with allopurinol should only be initiated after complete remission of an acute attack.

**Allopurinol**

**Indications:** prophylactic long term management of gout, renal urate stone, hyperuricemia associated with cancer therapy.

**Contra-indications:** Not a treatment for acute gout; sensitivity to the drug.

**Cautions:** ensure adequate water intake; pregnancy and breast feeding; start treatment with allopurinol
10: Musculoskeletal and joint diseases

before commencement of anti-neoplastic agents.

Side-effects: rashes, pruritus, nausea and vomiting, blood disorders.

Dose: initially, 100-300 mg daily as single dose, then adjusted according to plasma urate level. Maximum in severe conditions 900 mg daily.

Preparations
Allopurinol tablets, 100 mg tab.
Allopurinol tablets, 300 mg tab.

Colchicine (Restricted)

Indications: acute attack of gout; prophylaxis in initial therapy with allopurinol.

Contra-indications: pregnancy and breast feeding.

Cautions: elderly, GI disease, cardiac, renal and hepatic impairment.

Side-effects: nausea and vomiting, diarrhoea and abdominal pain. Large doses may cause rashes, GI bleeding and renal and hepatic damage.

Dose: treatment of gout; initially 1 mg, then 500 microgram every 2-3 hours until relief is obtained or vomiting or diarrhoea occurs or until a total of 6 mg has been reached. Do not repeat the course of therapy before three days. Prophylaxis therapy with allopurinol, 500 micrograms 2-3 times daily.

Preparations
Colchicine tablets, 500 microgram tab.

Rasburicase (Restricted)

Indications: Prophylaxis and treatment of acute hyperuricaemia, before and during initiation of chemotherapy, in patients with haematological malignancy and high tumour burden at risk of rapid lysis.

Contra-indications: G6PD deficiency.

Cautions: Atopic allergies.

Side-effects: Fever; anaphylaxis; bronchospasm; diarrhoea; haemolytic anaemia; headache; hypersensitivity reactions; methaemoglobinemia; nausea; rash; vomiting.

Dose: 200 micrograms/kg once daily for up to 7 days according to plasma-urate acid concentration.

Preparations
Rasburicase injection, powder for reconstitution, 1.5 mg / vial
Rasburicase injection, powder for reconstitution, 7.5 mg / vial

10 A.4: Topical NSAIDs and counter irritants

Pain whether superficial or deep seated may be relieved by any method that produces local inflammation associated with a feeling of warmth and comfort. Drugs which evoke such effects are termed counter-irritants. Preparations containing NSAIDs are also applied for the
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relief of pain in musculoskeletal conditions. Such preparations should be applied gently to the skin away from the eyes, mucous membranes, and broken or inflamed skin. Do not use with occlusive dressings.

Preparations
Analgesic balm cream tube

10 B: Drugs used in neuromuscular disorders

10 B.1: Drugs which enhance neuromuscular transmission

Anticholinesterase drugs prevent the degradation of acetylcholine and enhance transmission at the neuromuscular junctions. Excessive dosage of these drugs may impair neuromuscular transmission and cause depolarizing block. They are useful in myasthenia gravis, and as antagonists to the excessive effect of non-depolarizing neuromuscular blockers.

Edrophonium, neostigmine and pyridostigmine are anticholinesterase drugs which are used in the diagnosis and treatment of myasthenia gravis. Edrophonium is a short acting drug and is therefore more useful for diagnosis. Neostigmine is a potent anticholinesterase drug which may act for up to 4 hours. Its pronounced muscarinic action is a disadvantage.

Pyridostigmine is less powerful and slower in action than neostigmine. It is preferred for its smoother and longer action and less frequent GI side-effects.

Neostigmine
Indications: myasthenia gravis; for other indications see sec 15
Contra-indications: intestinal or urinary obstruction.
Cautions: asthma, bradycardia, hypotension, epilepsy, peptic ulceration, pregnancy and breast feeding.
Side-effects: muscarinic effects such as excessive salivation, gastrointestinal discomfort, bronchial secretion, miosis.
Dose: orally for myasthenia gravis, neostigmine bromide 15-30 mg at suitable intervals, total daily dose 75-300 mg in divided doses. Child, 1-6 years initially 7.5 mg, 6-12 years initially 15 mg, maximum daily dose 15-90 mg.
Intramuscular or subcutaneous injection, neostigmine methylsulphate, 1-2.5 mg at suitable intervals, total daily dose 5-20 mg; Child, 200-500 microgram as required.

Preparations
Neostigmine methylsulphate injection, 500 microgram/mL injection, 1 mL ampoule.
Neostigmine methylsulphate injection, 2.5 mg/mL injection, 5 mL ampoule
Neostigmine methylsulphate injection, 2.5 mg/mL, 1 mL ampoule
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*Edrophonium chloride (C.D.L)*

**Indications:** diagnosis of myasthenia gravis.

**Contra-indications, cautions and side-effects:** see under neostigmine

**Dose:** for diagnosis of myasthenia gravis, by intravenous injection, 2 mg followed after 30 seconds by 8 mg. Intramuscular injection, 10 mg.

**Preparations**
- Edrophonium chloride injection, 10 mg/mL, 1 mL ampoule

*Pyridostigmine bromide*

**Indications:** myasthenia gravis.

**Contra-indications, cautions and side-effects:** see under neostigmine

**Dose:** orally, 30-120 mg at suitable intervals, total daily dose 0.3-1.2 g.
- Child, up to 6 years, 30 mg, 6-12 years 60 mg, total daily dose 30-360 mg.

**Preparations**
- Pyridostigmine bromide tablets, 60 mg tab.

**Baclofen**

**Indications:** is useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis or in patients with spinal cord injuries.

**Contra-indications:** peptic ulceration.

**Cautions:** abrupt drug withdrawal, impaired renal function, stroke, epilepsy, Parkinson's disease, diabetes mellitus, pregnancy.

**Side-effects:** drowsiness, hypotension, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, urinary frequency, urinary retention, dysuria, sexual dysfunction, haematuria, nausea, constipation.

**Dose:** orally, 5 mg thrice daily, can be increased gradually up to 100 mg daily.

**Preparations**
- Baclofen tablet, 10 mg tab.
- Baclofen tablet, 25 mg tab.
- Baclofen oral solution, 5 mg/5 mL, 300 mL bottle

**Dantrolene sodium (Restricted)**

**Indications:** voluntary muscle spasticity, malignant hyperthermia.

**Contra-indications:** hepatic impairment, acute muscle spasm.

**Cautions:** history of liver disease or dysfunction, impaired pulmonary function or chronic obstructive pulmonary disease, impaired cardiac function secondary to myocardial disease, women over 30 years of age (greater likelihood of drug-induced, potentially fatal, hepato-cellular disease).

**Side-effects:** drowsiness, dizziness, photosensitivity, nausea and vomiting, abdominal cramps, hepatitis, malaise, fatigue, anorexia.

**Dose:** orally for muscle spasm, initially 25 mg daily may be increased at weekly intervals to a maximum 100 mg 4 times daily.

**Preparations**
- Dantrolene capsules, 25 mg cap.
- Dantrolene injection, 20 mg vial.
10: Musculoskeletal and joint diseases

induced, potentially fatal, hepato-cellular disease).

**Side-effects:** drowsiness, dizziness, photosensitivity, nausea and vomiting, abdominal cramps, hepatitis, malaise, fatigue, anorexia.

**Dose:** orally for muscle spasm, initially 25 mg daily may be increased at weekly intervals to a maximum 100 mg 4 times daily.

**Preparations**
Dantrolene capsules, 25 mg cap.
Dantrolene injection, 20 mg vial
Administration of eye drops to the eye will allow drugs to penetrate to the globe probably through the cornea. Systemic effects may result from eye drops, mostly through absorption from conjunctival blood vessels or from the nasal mucosa during drainage across the tear ducts. The extent of systemic absorption following ocular administration is highly variable. One drop, in most cases, is enough to produce the desired effect. Instillation should be properly done into the conjunctival sack that is formed by a gentle pulling outwards of the lower eyelid; the eye should be closed after application for as long as 1-2 minutes. In cases of more than one eye drops administration, an interval of 5 minutes should be kept between applications. Eye ointments are applied similarly; the ointment melts rapidly and blinking helps to spread it. A high degree of sterility should be maintained when eye drops are used. It is wise to use single-application containers during surgical procedures. Patients should be counselled to dispose of any unused eye drops after one month from opening.

### 11 A: Mydriatics and cycloplegics

#### 11 A.1: Antimuscarinics

Antimuscarinics dilate the pupil and paralyze the ciliary muscle. They are either short acting such as tropicamide, or long acting such as atropine.

**Atropine sulphate**

**Indications:** refraction procedures in children, anterior uveitis.

**Contra-indications:** glaucoma.

**Cautions:** systemic effects may follow topical application especially in children; patients should be advised not to drive immediately after instillation.

**Side-effects:** local irritation, increased intra-ocular pressure, systemic side-effects (see sec 1B).

**Preparations**

- Atropine sulphate eye drops, 1%; 5-10 mL/bottle
- Atropine sulphate eye ointment, 1%; 3-5 g/tube

**Cyclopentolate (Restricted)**

**Indications:** Cycloplegia. Uveitis. Anterior uveitis.
**Cautions**: Darkly pigmented iris is more resistant to pupillary dilatation and caution should be exercised to avoid overdosage; mydriasis can precipitate acute angle-closure glaucoma (usually in those aged over 60 years and hypermetropic (long-sighted), who are predisposed to the condition because of a shallow anterior chamber)

**Side-effects**: Conjunctivitis (on prolonged administration); contact dermatitis; eye oedema (on prolonged administration); hyperaemia (on prolonged administration); local irritation (on prolonged administration); raised intraocular pressure; transient stinging.

**Dose**: Cycloplegia. Child 3 months–11 years apply 1 drop, 30–60 minutes before examination, using 1% eye drops. Child 12–17 years apply 1 drop, 30–60 minutes before examination, using 0.5% eye drops.

Uveitis child 3 months–17 years apply 1 drop 2–4 times a day, using 0.5% eye drops (1% for deeply pigmented eyes).

Uveitis. Consult product literature.

**Preparations**
- Cyclopentolate eye drops 0.5%, 5 mL bottle
- Cyclopentolate eye drops 1.0%, 5 mL bottle
- Homatropine hydrobromide

**Indications**: see under atropine (shorter duration than atropine).

**Contra-indications, cautions and side-effects**: see under atropine.

**Preparations**
- Homatropine hydrobromide eye drops, 2%; 10-15 mL/bottle

**Tropicamide (Restricted)**

**Indications**: see under atropine (shorter duration than atropine).

**Contra-indications, cautions and side-effects**: see under atropine.

**Preparations**
- Tropicamide eye drops, 1%, 15 mL/bottle
- Tropicamide minims, 0.1% single use eye drops/0.5 mL
- Tropicamide minims, 0.5% single use eye drops/0.5 mL
- Tropicamide minims, 1% single use eye drops/0.5 mL

**11 A.2: Sympathomimetics**

**Phenylephrine hydrochloride (Restricted)**

**Indications**: mydriasis.

**Contra-indications**: angle-closure glaucoma.

**Cautions**: use low strength in children and elderly; caution in presence of cardiovascular disease.

**Side-effects**: eye pain and stinging; blurred vision, photophobia.

**Preparations**
- Phenylephrine HCl eye drops, 10%; 10 mL/bottle
11. Eye

Phenylephrine HCl minims, 1% single use eye drops/0.5 mL
Phenylephrine HCl minims, 10% single use eye drops/0.5 mL

11 B: Treatment of glaucoma

Glaucoma is a disorder in which the pressure in the eyeball increases, damaging the optic nerve and causing a loss of vision. Treatment of glaucoma is aimed at reducing the intra-ocular pressure which is more likely to be successful if started early; when vision is impaired, treatment may prevent further deterioration but it can not restore vision completely.

Medications that will increase the outflow from the anterior chamber are effective in reducing IOP in glaucoma. Topical therapy with beta blockers, pilocarpine can usually control glaucoma. Carbonic anhydrase inhibitors such as acetazolamide are orally effective. New approaches have been introduced in the management of glaucoma, such as topical prostaglandin analogues and carbonic anhydrase inhibitors.

11 B.1: Miotics

Pilocarpine

Indications: glaucoma.
Contra-indications: acute iritis, uveitis, acute inflammatory disease of the anterior segment.
Cautions: asthma, hypertension and other cardiac disease, peptic ulceration; darkly pigmented iris may require higher concentration or more frequent administration to achieve therapeutic effects, avoid overdosage.

Side-effects: headache and brow-ache, local irritation, blurred vision, conjunctival vascular congestion.

Dose: apply eye drops up to 4 times daily.

Preparations
Pilocarpine eye drops, 2%; 10 mL/bottle

11 B.2: Sympathomimetics

Brimonidine tartrate (Restricted)

Indications: ocular hypertension, open-angle glaucoma.
Contraindication: concomitant MAOI therapy.

Cautions: severe cardiovascular disease; cerebral or coronary insufficiency, Raynaud’s syndrome, postural hypotension, depression, hepatic or renal impairment; pregnancy, breast-feeding.

Driving: May cause drowsiness and affect performance of skilled tasks.

Side-effects: ocular reactions including conjunctival hyperaemia, stinging, pruritus, allergy, and conjunctival folliculosis, visual disturbances, blepharitis, epiphora, corneal erosion, superficial punctate keratitis, eye pain, discharge, dryness, and irritation, eyelid inflammation, oedema, pruritus con-
junctivitis, photophobia; also, hypotension, headache, depression, dry mouth, fatigue, drowsiness. **Dose:** Apply twice daily

**Preparations**
Brimonidine tartrate eye drops, 0.2%, 5 mL/bottle

11 B.3: Beta-adrenoceptor blockers

**Betaxolol (C.D.L)**
**Indications:** glaucoma.
**Cautions:** in asthmatic or patients with cardiovascular disorders.
Contraindications: bradycardia, overt heart failure.
**Side-effects:** local irritation, pain, dry eyes, erythema.
**Dose:** apply eye drops twice daily.

**Preparations**
Betaxolol eye drops, 0.5%; 5 mL/bottle

**Timolol maleate**
**Indications:** glaucoma.
Contra-indications: asthma.
**Cautions:** cardiac disease, angle-closure glaucoma.
**Side-effects:** local irritation, pain, dry eyes, erythema.
**Dose:** apply eye drops twice daily.

**Preparations**
Timolol maleate eye drops, 0.5%; 5 mL/bottle

11 B.4: Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors reduce the production of aqueous humor and hence reduce intra-ocular pressure. Orally (such as acetazolamide; see sec 2B.5) and topically applied preparations such as dorzolamide are available. Dorzolamide eye drops are used in patients resistant to or who can not use beta-blockers.

**Dorzolamide (Restricted)**
**Indications:** glaucoma uncontrolled with β-blockers.
**Contra-indications:** hyperchloremic acidosis; pregnancy and breast-feeding.
**Cautions:** hepatic impairment; systemic absorption follows topical administration; chronic corneal defects.
**Side-effects:** local ocular irritation, eyelid inflammation and crusting, corneal oedema, bitter taste, epistaxis, paraesthesia.
**Dose:** apply 3 times daily if used alone or twice daily if used with beta-blockers.

**Preparations**
Dorzolamide hydrochloride eye drops, 2%, 5 mL/bottle

11 B.5: Prostaglandin analogue

Prostaglandin analogues are capable of increasing uveoscleral outflow hence reduce intra-ocular pressure. They are used in open-an-
gle glaucoma and ocular hypertension in patients unresponsive to beta-blockers or when beta-blockers are contra-indicated. Darkening of eye coloration is a notable side effect with prostaglandin analogues. It is due to an increased brown pigmentation of the iris.

**Latanoprost (Restricted)**

**Indications:** glaucoma in patients unresponsive or intolerant to other drugs.

**Cautions:** monitor for changes in eye coloration; brittle or severe asthma; pregnancy and breast-feeding.

**Side-effects:** darkening of eye coloration, ocular irritation, exacerbation of asthma.

**Dose:** apply once daily preferably in the evening.

**Preparations**
Latanoprost eye drops, 0.005% (50 micrograms / mL) 2.5 mL/bottle

**Latanoprost with Timolol (Restricted)**

**Indications:** Raised intr-ocular pressure in patients with open-angle glaucoma and ocular hypertension when a beta-blocker or prostaglandin analogue alone not adequate

**Cautions:** see under individual drugs

**Side-effects:** see under individual drugs

**Dose:** apply once daily

**Preparations**
Latanoprost with Timolol eye drops, 50 microgram lanatanoprost and 5 mg timolol per mL

**11 B.6: Alpha2 adrenoceptor agonists**

**Apraclonidine (Restricted)**

**Indications:** Control or prevention of postoperative elevation of intr-ocular pressure after anterior segment laser surgery. Short-term adjunctive treatment of chronic glaucoma in patients not adequately controlled by another drug.

**Contra-indications:** History of severe or unstable and uncontrolled cardiovascular disease.

**Cautions:** Cerebrovascular disease; depression; heart failure; history of angina; hypertension; loss of effect may occur over time; Parkinson’s syndrome; Raynaud’s syndrome; recent myocardial infarction; reduction in vision in end-stage glaucoma (suspend treatment); severe coronary insufficiency; thromboangiitis obliterans; vasovagal attack.

**Side-effects:** Conjunctivitis; dry eye; ocular intolerance; rhinitis; taste disturbance.

**Dose:** Control or prevention of postoperative elevation of intr-ocular pressure after anterior segment laser surgery. Apply 1 drop, 1 hour before laser procedure, then 1 drop, immediately after completion of procedure, 1% eye drops to be administered.
Short-term adjunctive treatment of chronic glaucoma in patients not adequately controlled by another drug. Apply 1 drop 3 times a day usually for maximum 1 month, 0.5% eye drops to be administered, may not provide additional benefit if the patient is already using two drugs that suppress the production of aqueous humour.

Preparations
Apraclonidine eye drops, 0.5%
Apraclonidine eye drops, 1.0%

11 C: Anti-infective preparations

Acute infection of the eye should be promptly and intensively treated. Most acute infections respond to topically applied anti-infective agents. Blepharitis and conjunctivitis are often caused by staphylococci, while keratitis and endophthalmitis may be bacterial, viral or fungal. In severe infections systemic therapy may accompany topical applications as in gonococcal conjunctivitis in neonates. Subconjunctival injection may be required, as in keratitis and corneal ulcer, to increase the intraocular concentration of an appropriate anti-infective drug. Systemic treatment may occasionally be required and is usually undertaken after culturing organism from lid margin and determining their antibiotic sensitivity.

Chloramphenicol

**Indications**: superficial eye infections.

**Side-effects**: transient stinging.

**Dose**: apply one drop to the eye every 2-3 hours then reduce frequency when infection controlled; continue for 48 hours after healing.

**Preparations**
Chloramphenicol eye drops, 0.5%; 10 mL/bottle

Tetracycline hydrochloride

**Indications**: local treatment of infection including trachoma.

**Contra-indications**: sensitivity to tetracycline.

**Dose**: apply small quantity to the eye twice daily.

**Preparations**
Tetracycline HCl eye ointment, 1%; 3-5 g/tube
11. Eye

11 C. 2: Antivirals

Aciclovir
Indications: viral infections of the eye.
Side-effects: mild stinging and local inflammation.
Dose: apply 5 times daily and continue for 3 days after complete healing.
Preparations: Aciclovir eye ointment, 3%; 4.5 g/tube

Miconazole
Indications: fungal keratitis, endophthalmitis.
Dose: consult product literature.
Preparations: Miconazole eye drops, 1%

11 D: Corticosteroids, anti-allergy and anti-inflammatory preparations

Dexamethasone
Indications: short term treatment of local inflammation.
Contra-indications: undiagnosed red-eye.
Cautions: glaucoma, acute untreated infection, cataract.
Side-effects: thinning of the cornea and sclera.
Dose: apply 4-6 times daily. More frequent administration in severe inflammation.
Preparations: Dexamethasone eye drops, 0.1%; 5-10 mL/bottle
Dexamethasone eye ointment, 1%; 3-5 g/tube

11 C. 3: Miscellaneous

Gentamicin sulphate
Indications: ophthalmic infections, specifically with P. aeruginosa.
Contra-indications: sensitivity to gentamicin.
Side-effects: local irritation.
Dose: apply 3-6 times daily.
Preparations: Gentamicin sulphate eye/ear drops, 0.3%; 5-10 mL/bottle
Gentamicin eye ointment, 0.3%; 3-5 g/tube

Erythromycin
Indications: blepharitis; conjunctivitis.
Dose: apply small quantity to the eye twice daily.
Preparations: Erythromycin eye ointment, 0.5%; 3.5 g/tube

Fusidic acid
Indications: ophthalmic infections, specifically staphylococcal infections.
Dose: apply every 3-6 hours.
Preparations: Fusidic acid eye drops, 1%; 5 g/tube

Ofloxacin
Indications: conjunctivitis.
Cautions: pregnancy; not to be used for more than 10 days.
Side-effects: local irritation, photophobia
Dose: apply one drop to the eye every 2-3 hours then reduce frequency when infection controlled; continue for 48 hours after healing.
Preparations: Ofloxacin eye drops, 0.3%; 5-10 mL/bottle

Moxifloxacin (Restricted)
Indications: Local treatment of infections (MOH: only to be used in children under 1 year old)
Cautions: Not recommended for neonates
Side-effects: hyperaemia; ocular discomfort; ocular dryness; ocular irritation; ocular pain; taste disturbances.
Dose: Child. Apply 3 times a day continue treatment for 2-3 days after infection improves; review if no improvement within 5 days.
Preparations: Moxifloxacin eye drops, 0.5%
Aciclovir has been found very effective in treating herpes simplex infections such as dendritic corneal ulcer.

**Aciclovir**

**Indications:** viral infections of the eye.

**Side-effects:** mild stinging and local inflammation.

**Dose:** apply 5 times daily and continue for 3 days after complete healing.

**Preparations**

Aciclovir eye ointment, 3%; 4.5 g/tube

11 C.3: Antifungal preparations

Most of the ophthalmic fungal infections are caused by agricultural injuries. Specialists in specialized centres where antifungal preparations are made available invariably treat such infections.

Miconazole eye drops are made available in limited quantities at Al-Nahdha Ophthalmology Department

**Miconazole**

**Indications:** fungal keratitis, endophthalmitis.

**Dose:** consult product literature.

**Preparations**

Miconazole eye drop, 1%

11 D.1: Corticosteroids

It should be strongly emphasized that untreated bacterial or viral eye infections may be aggravated by topical application of corticosteroids. The use of steroids should be supervised by a specialist. Therapy with corticosteroids in bacterial infection should be accompanied by effective antibacterial drugs. Prolonged topical use of corticosteroids especially dexamethasone and prednisolone, may precipitate glaucoma in predisposed patients. Long term oral use of corticosteroids may cause lens opacity.

**Dexamethasone**

**Indications:** short term treatment of local inflammation.

**Contra-indications:** undiagnosed red-eye.

**Cautions:** glaucoma, acute untreated infection, cataract.

**Side-effects:** thinning of the cornea and sclera.

**Dose:** apply 4-6 times daily. More frequent administration in severe inflammation.

**Preparations**

Dexamethasone eye drops, 0.1%; 5-10 mL/bottle

Dexamethasone eye ointment, 1%
## 11. Eye

**Fluorometholone**  
**Indications:** short term treatment of local inflammation.  
**Contra-indications, cautions and side-effects:** see under dexamethasone.  
**Dose:** apply 2-4 times daily. Frequency may be increased in severe inflammation.  

**Preparations**  
Fluorometholone eye drops, 0.1%; 5 mL/bottle

**Prednisolone**  
**Indications:** short term treatment of local inflammation.  
**Contra-indications, cautions and side-effects:** see under dexamethasone.  
**Dose:** apply every 1-2 hours until inflammation is controlled then reduce frequency.  

**Preparations**  
Prednisolone eye drops, 1%; 5 mL/bottle (Restricted)  
Prednisolone minims, 0.5% single use eye drops/0.5 mL

## 11 D.2: Anti-inflammatory and anti-allergy preparations

**Lodoxamide 0.1% eye drops (Restricted)**  
**Indication:** vernal kerato-conjunctivitis, vernal conjunctivitis, and vernal keratitis.  
**Contraindication:** Hypersensitivity to the drug.  

**Side-effects:** burning, tingling, dizziness.  
**Dose:** from 4 years and onwards, 1-2 drops 4 times daily for up to 3 months.  

**Preparations**  
Lodoxamide eye drops 0.1%, 10 mL/bottle

**Sodium cromoglicate (Sodium cromoglycate)**  
**Indications:** allergic conjunctivitis, vernal keratoconjunctivitis.  
**Side-effects:** transient stinging and burning.  
**Dose:** apply 4 times daily.  

**Preparations**  
Sodium cromoglicate eye drops, 2%; 10 mL/bottle

**Antihistamine and astringent eye drops**  
Non-infective allergic conjunctivitis can be treated with topical application of antihistamine and decongestant eye drops such as antazoline, naphthazoline, zinc sulphate, phenylephrine etc.  

**Preparations**  
Antihistamine eye drops; 10 mL/bottle
**11 D.3: Non-steroidal anti-inflammatory drugs**

**Diclofenac or flurbiprofen**
They are used to inhibit intraoperative miosis during cataract surgery, or in postoperative inflammation in cataract surgery. They are also applied to relieve pain in trauma or in corneal epithelial defects.

**Preparations**
- Diclofenac eye drops, 0.1%; 5 mL/bottle
- Flurbiprofen eye drops, 0.03%; 5 mL/bottle

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**11 E: Miscellaneous preparations**

**11 E.1: Tear deficiency preparations**

Methyl cellulose and hypromellose are viscous preparations that are used to lubricate the eye. They are used as tear replacement to prevent the damage to the cornea in keratitis sicca or keratitis, and to lubricate artificial eyes. The choice is determined by the severity of the condition and patient preference.

**Hypromellose**
**Indications:** tear deficiency.

**Dose:** apply frequently to avoid dryness of the eye.
- Hypromellose eye drops, 0.5%; 10 mL/bottle
- Hypromellose (preservative free) eye drops, 0.5%; 10 mL/bottle

**Methyl cellulose**
**Indication:** tear deficiency
**Dose:** apply frequently to avoid dryness of the eye

**Preparations**
- Methyl cellulose eye drops, 2%; 10-15 mL/bottle

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**11 E. 2: Diagnostic ophthalmic preparations**

Fluorescein sodium is an indicator dyes used topically for the diagnosis of corneal and conjunctival abnormalities, and intravenously (fluorescein angiography) to evaluate retinal function and other ocular structures or conditions.

**Fluorescein sodium**
**Indications:** detection of lesions and foreign bodies; angiographies in ocular disorders.
**Side-effects:** nausea and vomiting, GI distress, bronchospasm, anaphylaxis, abnormal taste, hypotension.
11. Eye

Preparations
Fluorescein strips, individual sterile impregnated with fluorescein sodium; 1 mg/strip
Fluorescein injection, 20% solution, 5 mL ampoule (Restricted).
Fluorescein minims, 2% single application eye drops/0.3 mL (CDL)

11 E.3: Other ophthalmic preparations

**Acetylcholine chloride + Mannitol (Restricted)**
*Indications*: cataract surgery, penetrating keratoplasty, anterior segment surgery requiring complete rapid miosis.

Preparations
Acetylcholine chloride + Mannitol solution, 1% + 3% (upon reconstitution) sterile solution; 2 mL/ampoule

**Balanced salt solution (Restricted)**
*Indications*: ocular irrigation.

Preparations
Balanced salt solution, sodium chloride 0.64%, sodium acetate 0.39%, sodium citrate 0.17%, calcium chloride 0.048%, magnesium chloride 0.03%, potassium chloride 0.075%, sterile solution BSS, 15 mL bottle.

**Oxybuprocaine hydrochloride (Restricted)**
*Indications*: local anaesthetic.

**Contra-indications**: should not be used on infected area.
**Cautions**: frequent use may lead to tolerance.
**Side-effects**: corneal swelling, burning sensation.
**Dose**: apply 1-2 drops every 30-90 seconds.

Preparations
Oxybuprocaine HCL eye drops, 0.4% eye drops; 10-15 mL/bottle
Oxybuprocaine HCl minims, 0.4% single application eye drops/0.5 mL

**Silicone oil (Restricted)**
*Indications*: severe cases of retinal detachment e.g. severe detachment in massive proliferative vitreoretinopathy, traumatic detachments, which can not be treated with other forms of therapy.

**Contra-indications**: intraocular lenses made from silicon.
**Side-effects**: cataract, glaucoma.
**Dose**: Consult manufacturer literature

Preparations
Silicone oil, 10 mL/bottle

**Sodium hyaluronate (C.D.L)**
*Indications*: surgical aid in anterior segment procedures.
**Cautions**: overfilling the eye chambers,
warm the refrigerated solution before use.
**Side-effects**: postoperative increase in intra-ocular pressure.
**Dose**: as needed for the procedures.
Preparations
Sodium hyaluronate injection, 1% (10 mg/mL) 0.4-0.5 mL/ampoule
Sodium hyaluronate and sodium chondroitin sulphate injection, 3% (30 mg/mL) and 4% (40 mg/mL) respectively, 0.5 mL disposable syringe

Ranibizumab (Restricted)
Indications: Neovascular (wet) age-related macular degeneration (specialist use only). Diabetic macular oedema. Macular oedema secondary to retinal vein occlusion (specialist use only). Choroidal neovascularisation secondary to pathologic myopia (specialist use only). Concomitant treatment of diabetic macular oedema, or macular oedema secondary to branch retinal vein occlusion, with laser photocoagulation (specialist use only)
Contra-indications: Ocular or periocular infection; severe intraocular inflammation; signs of irreversible ischaemic visual function loss in patients with retinal vein occlusion.
Caution: Active systemic infection; diabetic macular oedema due to type 1 diabetes (limited information available); diabetic patients with HbA1c over 12%; history of stroke; history of transient ischaemic attack; patients at risk of retinal pigment epithelial tear; previous intravitreal injections; proliferative diabetic retinopathy; retinal detachment or macular hole (discontinue treatment if rhegmatogenous retinal detachment or stage 3 or 4 macular holes develop); uncontrolled hypertension. Ranibizumab is given by intravitreal injection by specialists. There is a potential risk of arterial thromboembolic events and non-ocular haemorrhage following the intravitreal injection of vascular endothelial growth factor inhibitors. Endophthalmitis can occur after intravitreal injections—patients should be advised to report any signs of infection immediately.
Pregnancy
Side-effects: Allergic skin reactions; anaemia; anterior chamber flare; anxiety; arthralgia; blepharitis; cataract; conjunctival disorders; conjunctivitis; cough; eye haemorrhage; eyelid oedema; headache; iridocyclitis; iritis; nasopharyngitis; nausea; ocular discomfort; photophobia; photopsia; posterior capsule opacification; punctuate keratits; raised intra-ocular pressure; retinal disorders; urinary tract infection; uveitis; visual disturbance; vitreous disorders.
Dose: Neovascular (wet) age-related macular degeneration (specialist use only). By intravitreal injection 500 micrograms once a month, to be administered into the affected eye, monitor visual acuity monthly, continue treatment until visual acuity is stable for 3 consecutive months, thereafter monitor visual acuity monthly, if necessary subsequent doses may be given at least 1 month apart.
Diabetic macular oedema. Macular oedema secondary to retinal vein occlusion (specialist use only)
Therapy of otitis externa involves thorough cleansing of the meatal skin and restoration of acidic surface pH, reduction of swelling, eradication of infection and avoidance of scratching. Before initiating therapy, an underlying chronic otitis media should be excluded.

Eczematous otitis externa is initially treated by dry mopping or careful cleansing by suction. If these measures fail, a cotton gauze wick soaked with corticosteroid is gently inserted into the meatus. Topical antibiotics are only applied when infection is present. Systemic antimicrobial is used in acute infection.

Acute oedematous otitis externa is treated as above for infected eczematous otitis externa. Otomycosis is treated with topical application of clotrimazole solution in addition to careful cleansing.

Acute furunculosis is caused by localized inflammation of the hair follicle in the cartilaginous part of the ear canal. It may follow abrasion or maceration in the ear canal. After cleansing, a cotton wick is saturated with a topical antibacterial ointment and inserted in the ear canal. An oral antimicrobial, which is effective against staphylococcus organism such as cloxacillin, is given in addition to analgesics. If furuncle bursts, aural cleansing and drainage are necessary.

Malignant otitis externa may occur in diabetics and in anaemic and malnourished children. It should be treated with systemic antimicrobial and local cleansing. Control of diabetes, if present, is essential.

Acetic acid 2% solution
- **Indications**: topical antibacterial and antifungal; acidifying agent.
- **Contra-indications**: perforated tympanic membrane.
- **Side-effects**: stinging or burning sensation
- **Dose**: 3-4 drops applied to the ear canal 4-5 times daily.
- **Preparations**: Acetic acid solution, 2% ear drops; 15 mL/bottle

Clotrimazole
- **Indications**: fungal infection in otitis externa.
- **Cautions**: causes staining of skin and clothing.
- **Side-effects**: local sensitivity.
- **Dose**: apply 2-3 times daily continuing for at least 14 days after disappearance of infection.

**Preparations**
- Ranibizumab injection, 10 mg/1 mL in prefilled syringe
Section 12: Ear, nose and oropharynx

- Drugs acting on the ear
- Drugs acting on the nose
- Drugs acting on the oropharynx

12 A: Drugs acting on the ear

12 A.1: Drugs for otitis externa

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**Contra-indications**: perforated tympanic membrane.

**Side-effects**: stinging or burning sensation

**Dose**: 3-4 drops applied to the ear canal 4-5 times daily.

**Preparations**

Acetic acid solution, 2% ear drops; 15 mL /bottle

**Clotrimazole**

**Indications**: fungal infection in otitis externa.

**Cautions**: causes staining of skin and clothing.

**Side-effects**: local sensitivity.

**Dose**: apply 2-3 times daily continuing for at least 14 days after disappearance of infection.
12: Ear, nose and oropharynx

Preparations
Clotrimazole solution, 1% ear drops; 15 mL/bottle

Dexamethasone + framycetin sulphate + gramicidin
Indications: eczematous inflammation in otitis externa with infection.
Contra-indications: acute infection.
Side-effects: local sensitivity.
Dose: 2-3 drops 3-4 times daily, reduce frequency upon relief.

Preparations
Dexamethasone + framycetin sulphate + gramicidin ear drops, 0.05% + 0.5% + 0.005% ear drops; 8 mL/bottle

Prednisolone
Indications: eczematous inflammation in otitis externa.
Contra-indications: untreated infection.
Cautions: avoid prolonged use.
Side-effects: local sensitivity.
Dose: 2-3 drops every 3-4 hours, reduce frequency when relief is obtained.

Preparations
Prednisolone sodium phosphate eye/ear drops, 0.5% eye/ear drops/bottle

Gentamicin
Indications: bacterial infection in otitis externa.
Contra-indications: perforated tympanic membrane.
Cautions: avoid prolonged use.

Acute otitis media is a bacterial or viral infection of the middle ear. Although this disorder can develop in people of all ages, it is more common in children between 3 months and 3 years of age. Usually this disorder develops as a complication of upper respiratory tract infection of viral origin but could also be secondary to the introduction of water through a perforation in eardrum. Otitis media with effusion (glue ear) is present in about 10% of the child population; it is a major cause of deafness in children with consequent delay in speech and language development.

Mild viral infections characterized by pinkness or infections of the eardrum often resolve spontaneously and require only analgesics and nasal decongestants. A bulging and inflamed eardrum indicates bacterial otitis media, which requires antimicrobial therapy. If discharge is present it should be examined to determine the causative organism. Local treatment in acute otitis media should be avoided, as it is ineffective.
Chronic otitis media may follow untreated or resistant acute otitis media. It is a longstanding infection characterized by perforated eardrum. Careful and adequate cleansing of the external canal and middle ear by the use of suction or mopping may control infection for long periods. Prolonged local antibacterial therapy with frequent cleansing usually dries up most chronic infections. Acute exacerbation of chronic otitis media should be treated with systemic antibiotics after identifying the causative organism.

_Acediasulfonum + cinchocaine + N,N-dihydroxymethyl carbamidum + glycerin_

**Indications**: chronic otitis media.

**Contra-indications**: acute otitis media.

**Side-effects**: local sensitivity.

**Dose**: 2-3 drops 2-3 times daily.

**Preparations**

_Acediasulfonum + cinchocaine + N,N-dihydroxymethyl carbamidum + glycerin ear drops, 0.84 g + 0.96 g + 0.42 g; 12 g/bottle_

**12 A.3: Agents for removal of wax**

Wax is a normal bodily secretion with a protective role, which needs only be removed if it impairs hearing or interferes with eardrum examination. Syringing with warm water may be sufficient; soaking

the ear with glycerol ear drops or almond oil ear drops could precede this procedure.

**Glycerol ear drop**

**Indications**: ear wax removal.

**Dose**: 2-3 drops 4-6 times daily for 2 days to soften hard wax and prepare the patient for syringing. If the wax is not very hard sufficient amount is applied on the same day of syringing.

**Preparations**

Glycerol ear drops; 10-15 mL/bottle

**12 B: Drugs acting on the nose**

**12 B.1: Topical nasal decongestants**

Nasal congestion associated with common cold, vasomotor rhinitis or nasal polyps may be symptomatically relieved by topical decongestants. Topical decongestants provide temporary relief, which might be followed by rebound congestion; their prolonged use may damage the nasal cilia and cause nasal obstruction. Normal saline nasal drops may relieve congestion associated with common cold by liquefying the mucous secretion. Inhaling moist warm air are useful in the treatment of symptoms of acute infective conditions, and the use of volatile compounds such as menthol or eucalyptus oil may encourage their use. There is no evidence
12: Ear, nose and oropharynx

that nasal preparations containing antihistamines and anti-infective agents have any therapeutic effect.

**Oxymetazoline hydrochloride**

**Indications**: nasal congestion.

**Cautions**: avoid excessive use.

**Side-effects**: local irritation, headache; tolerance with prolonged use; rebound congestion.

**Dose**: 1-2 sprays twice daily.

Preparations

Oxymetazoline HCl nasal spray, 0.05%; 20 mL/spray

**Sodium Chloride 0.9% Nasal Drops (Normal Saline Nasal Drops)**

**Indications**: nasal congestion by helping to liquefy mucous secretions.

**Dose**: 1-2 drops installed in each nostril 3-4 times daily when required.

Preparations

Sodium Chloride 0.9% Nasal Drops (Normal Saline Nasal Drops); 15 mL/bottle

**Chlorhexidine HCl 0.1% and Neomycin 0.5% cream**

For elimination of staphylococci from the nasal vestibule but re-colonisation frequently occurs. For eradication, apply to nostril 4 times daily for 10 days, for preventing nasal carriage of staphylococci apply to nostril twice daily.

Preparations

Chlorhexidine HCl 0.1% and Neomycin 0.5% cream, 15 g/tube

**Mupirocin (Restricted)**

A nasal ointment containing mupirocin is reserved for resistant cases of *Staphylococcal* infection of the nasal vestibules. The ointment should be applied 3 times daily for 5 days and a sample taken 2 days after treatment to confirm eradication. To avoid the development of resistance, the treatment course should not exceed 7 days and should only be repeated for one occasion.

Preparations

Mupirocin nasal ointment, 2% nasal ointment; 3 g/tube

12 B.3: Drugs used in nasal allergy

Mild nasal allergies can effectively be treated with oral antihistamines and decongestants. Antihistamines offer much relief from rhinorrhoea and sneezing but are less effective for the relief of nasal congestion. Severe allergies can be effectively controlled with topical application of corticosteroids or cromoglycate. In seasonal allergic rhinitis, treatment starts 2-3 weeks before the
season commences and may have to be continued for several months.

**Beclometasone dipropionate (Beclomethasone dipropionate)**

**Indications**: prophylaxis and treatment of allergic and vasomotor rhinitis.

**Cautions**: should be avoided in the presence of infections, and also after nasal surgery until healing has occurred; systemic absorption may take place after excessive and prolonged use leading to systemic effects (see sec 6C.).

**Side-effects**: dryness, irritation of the nose and throat, epistaxis.

**Dose**: adult and child over 6 years, apply 100 microgram (2 sprays) into each nostril twice daily, or 50 microgram (one spray) 3-4 times daily. Maximum 400 micrograms (8 sprays) daily.

**Preparations**

- Beclometasone dipropionate aqueous nasal spray, 50 microgram/metered spray, 200 doses/metered spray

**Budesonide Nasal Spray (Restricted)**

**Indications**: Prophylaxis and treatment of allergic and vasomotor rhinitis. Nasal polyps

**Cautions**: Avoid after nasal surgery (until healing has occurred); avoid in pulmonary tuberculosis; avoid in the presence of untreated nasal infections; patients transferred from systemic corticosteroids may experience exacerbation of some symptoms.

**Side-effects**: Glaucoma; raised intra-ocular pressure; Nasal septal perforation (usually following nasal surgery); Aggression (particularly in children); anxiety (particularly in children); bronchospasm; depression (particularly in children); dryness; epistaxis; headache; hyperactivity (particularly in children); hypersensitivity reactions; nasal irritation; nasal ulceration; sleep disturbances (particularly in children); smell disturbances; taste disturbances; throat irritation.

**Dose**: 128 micrograms once daily, dose to be administered into each nostril in the morning, alternatively 64 micrograms twice daily; reduced to 64 micrograms once daily when control achieved. Use for maximum 3 months, doses to be administered into each nostril.

Nasal polyps 64 micrograms twice daily for up to 3 months, dose to be administered into each nostril.

**Preparations**

- Budesonide nasal spray, 64 micrograms / spray

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### 12 C: Drugs acting on the oropharynx

#### 12 C.1: Drugs for oral ulceration and inflammation
Ulceration of the oral mucosa may be caused by trauma, recurrent aphthae, infections, gastrointestinal disease, carcinoma, drug therapy, blood disorders and nutritional deficiencies. The cause for ulceration of oral mucosa should be identified before commencement of treatment. In general, treatment is local and is aimed at protecting the ulcerated area, or to relieve pain or reduce inflammation.

Lidocaine (Lignocaine)
Indications: relief of pain in oral lesion.
Cautions: avoid prolonged use; care must be taken not to produce anaesthesia in the pharynx before a meal as this might lead to choking.
Dose: apply on need to the affected area in the oral cavity.

Preparations
Lidocaine topical solution, 4% solution; 30 mL/bottle

Triamcinolone acetonide
Indications: oral and perioral lesions.
Contra-indications: untreated oral infection.
Side-effects: occasional exacerbation of local infection.
Dose: apply a thin layer 2-4 times daily, do not rub; use to be limited to 5 days for children and elderly.

Preparations
Triamcinolone acetonide in orabase, 0.1% oral paste; 10 g/tube

Viral infection is a common cause of sore throat where anti-infective drugs are ineffective. Bacterial sore throats require systemic antibiotic therapy. Antifungal drugs such as amphotericin and miconazole are effective in the treatment of *candida albicans* and other fungal infections. Amphotericin is not absorbed from the GI tract and is applied locally in the mouth. Miconazole, though applied locally, is absorbed and therefore is more prone to cause adverse effects and interacts with other drugs.

Amphotericin
Amphotericin B
Indications: oral and perioral fungal infections
Side-effects: gastrointestinal disturbances
Dose: allow one lozenge to dissolve slowly in the mouth 4 times daily for 10-15 days. Increase up to 8 lozenges daily in severe infections.

Preparations
Amphotericin lozenges, 10 mg lozenge

Miconazole
Indications: prevention and treatment of oral fungal infections.
Contra-indications: hepatic impairment.
12: Ear, nose and oropharynx

**Cautions**: pregnancy and breast feeding.

**Side-effects**: nausea and vomiting, diarrhoea.

**Dose**: for generalized oral fungal infection, place 5-10 mL in the mouth after meal and retain near lesions 4 times daily.
For localized lesions, smear a small quantity of gel on affected area with clean finger 4 times daily.

**Preparations**

Miconazole oral gel, 20 mg/mL oral gel; 40 g/tube

12 C.3: Mouth washes, gargles and dentifrices

Mouth washes are used for the improvement of oral hygiene. Their cleansing effect is principally mechanical. Chlorhexidine is used as a mouth wash in oral infections and when tooth brushing is not possible. Mouth Gargles are of doubtful benefit

**Chlorhexidine Gluconate**

**Indications**: oral hygiene.

**Side-effects**: localized irritation, reversible brown staining of teeth.

**Dose**: rinse mouth with about 10 mL twice daily.

**Preparations**

Chlorhexidine Gluconate mouth wash, 0.2% mouth wash solution, 150–250 mL/bottle
13: Skin preparations

Section 13: Skin preparations

- Emollients and barrier preparations
- Local anaesthetics and antipruritics
- Topical corticosteroids
- Psoriasis and eczema preparations
- Preparations for acne
- Preparations for warts
- Anti-infective skin preparations
- Skin disinfectants
- Antiperspirants
- Depigmenting agents
- Pigmenting agents

Topical preparations

The active ingredients (virtually the medications) in a topical preparation are mixed with a vehicle, which is an inert carrier of the medications. Thus the formulation and consistency vary among topical preparations. The vehicle determines the consistency of the product and whether the active ingredients remain on the surface or penetrate the skin; whether the preparation is thick and greasy or light and watery. Depending on the vehicle used the preparation will be an ointment, cream, lotion, solution, powder or gel etc.

Applications are usually viscous solutions, emulsions, or suspensions for application to the skin.

Collodions are painted on the skin and allowed to dry to leave a flexible film over the site of application.

Creams are emulsion of oil in water, they are easy to apply and vanish when rubbed into the skin.

Lotions have more water content than creams. They are suitable for a cooling effect and for application on a hairy area. They may contain fine dispersed powder in a base of water or oil and water.

Ointments contain a lot of oil and very little water, feel greasy and are difficult to wash off. Ointments are more appropriate when the skin is scaly and dry. Some ointments have hydrophilic and lipophilic properties; they may have occlusive properties on the skin surface, enhance hydration, and be miscible with water.

Gels consist of active ingredients in suitable hydrophilic or hydrophobic bases; generally they have a high water content with very little absorption through the intact skin.

Pastes are stiff preparations containing a high proportion of finely powdered solids such as zinc oxide and starch suspended in ointment.

Solutions are liquids in which drugs are dissolved. They tend to dry rather than moisturize the skin.
13: Skin preparations

13 A: Emollients and barrier preparations

Emollients are used to soothe and hydrate the skin. Barrier preparations are used to protect the skin against hydration and irritation.

**Moisturizing cream**
A moisturizing cream with liquid paraffin or dimeticone base is available.
**Indications:** for dry skin conditions.

**Preparations**
- Moisturel® cream; 500 g/jar

**Zinc oxide cream**
A barrier preparation with zinc oxide.
**Indications:** napkin rash and eczema.

**Preparations**
- Zinc oxide + castor oil cream; 15-40%, 57 g/tube

**Lubricating jelly for gynaecological and surgical use**
A sterile water-soluble lubricating jelly.

**Preparations**
- K-Y® jelly; 82 g/tube

13 B: Topical local anaesthetics and antipruritics

Pruritus (itching) may be caused by systemic (jaundice, kidney failure, malignant disease and endocrine disorders) as well as skin disease (scabies, pediculosis, allergic and contact dermatitis). The underlying cause should be eliminated; treatment could be initiated with simple moisturising preparations. Systemic antihistamines may help but they tend to cause drowsiness. Calamine and crotamiton are used locally in pruritus and insect stings. Topical antihistamines and local anaesthetics should be avoided since they are of little value and may cause skin sensitisation.

13 B.1: Local anaesthetics

**Lidocaine (Lignocaine Hydrochloride)**

**Indications:** relief of local pain, (see sec 15.).
**Cautions:** occasional hypersensitivity, excessive absorption may occur specially from mucous surface, avoid in children.

**Preparations**
- Lidocaine HCl ointment, 5%; 15-35 g/tube
- Lidocaine HCl jelly, 2%; 20-30 g/tube

**Lidocaine + Prilocaine (Emla®)**

**Indications:** local anaesthesia.
**Contraindications:** infants under 1 year.
**Cautions:** not for wound, mucous membrane, or atopic dermatitis; avoid use near eyes or middle ear.
13: Skin preparations

Side-effects: transient paleness, redness and oedema.

Preparations
Lidocaine + Prilocaine cream, 2.5% + 2.5% cream; 5 g/tube

13 B.2: Antipruritics

Calamine
Indications: pruritus.

Preparations
Calamine lotion containing: Calamine 15% + zinc oxide 5% + glycerol 5% + bentonite 3% + sodium citrate 0.5% + liquefied phenol 0.5% in freshly boiled and cooled purified water, 100 mL/bottle

Crotamiton (Restricted)
Indications: pruritus including pruritus after scabies.
Contraindications: acute exudative dermatoses.
Cautions: avoid use on broken skin and near eyes; avoid use in children under 3 year.
Application: apply 2-3 times daily.

Preparations
Crotamiton cream, 10% cream, 20 g/tube

13 C: Topical Corticosteroids

13 C.1: Topical corticosteroids plain

Many skin inflammatory disorders respond to topical corticosteroids. Choice of a preparation depends on the severity of skin disease, the site of involvement and potency of the chosen steroid. Corticosteroids vary in their potency (see table). In severe skin disorders, a potent steroid preparation may be initially used followed by a less potent one. Twice a day application is mostly sufficient; more frequent application does not improve response. Steroids offer temporary relief and rebound inflammation may occur on withdrawal.

The extent of absorption through the skin varies with different steroids and formulations. It is greater when large areas are treated, duration of therapy is prolonged, large amount used, the surface of the skin is soft, and when occlusive dressing is applied. Extensive absorption leads to systemic toxicity, including suppression of hypothalamic-pituitary-adrenal axis and growth retardation, particularly in young children.

Prolonged application may cause local adverse effects especially when occlusive therapy is employed. These include, skin atrophy, striae, telangiectasias, purpura, acneiform eruptions, perioral dermatitis, overgrowth of fungus and bacteria, hypopigmentation and rosacea. Potent steroids should be avoided in children; mild preparations such as hydrocortisone are preferable.
### Skin preparations

<table>
<thead>
<tr>
<th>Potency of selected topical steroids:</th>
<th>Side-effects: see notes above.</th>
<th>Application: apply thinly to the skin 1-2 times daily for not more than 4 weeks.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild:</strong> Hydrocortisone 1%</td>
<td></td>
<td>Preparations</td>
</tr>
<tr>
<td><strong>Moderate:</strong> Clobetasone butyrate 0.05%; Fluocinolone acetonide 0.01%</td>
<td></td>
<td>Clobetasol propionate cream, 0.05% cream, 25 g/tube</td>
</tr>
<tr>
<td><strong>Potent:</strong> Betamethasone valerate 1%; Triamcinolone 0.1%</td>
<td></td>
<td>Clobetasol propionate ointment, 0.05% ointment, 25 – 30 g/tube</td>
</tr>
<tr>
<td><strong>Very Potent:</strong> Clobetasol propionate 0.05%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Betamethasone Valerate**

**Indications:** severe inflammatory skin disorders.

**Contraindications:** untreated bacterial, fungal or viral skin infections, acne vulgaris, rosacea.

**Cautions:** avoid prolonged use especially in children and infants; avoid prolonged use on the face.

**Side-effects:** see notes above

**Application:** apply topically 1-2 times daily.

**Preparations**

- Betamethasone valerate cream, 0.1% cream, 15 g/tube
- Betamethasone valerate ointment, 0.1% ointment, 15 g/tube
- Betamethasone valerate scalp application, 0.1% solution, 30 mL/bottle

**Clobetasol propionate (Restricted)**

**Indications:** short term therapy of severe resistant inflammatory skin disorders.

**Contraindications:** see under betamethasone.

**Cautions:** see notes above; not more than 50g of 0.05% should be applied per week.

**Indications:** eczema and dermatitis of all types; being moderate in potency it is applied between courses of potent steroids.

**Contraindications, cautions and side-effects:** see notes above.

**Application:** apply thinly 1-2 times daily.

**Preparations**

- Clobetasol butyrate cream, 0.05% cream; 25-30 g/tube
- Clobetasol butyrate ointment, 0.05% ointment; 25-30 g/tube

**Hydrocortisone**

**Indications:** mild inflammatory skin disorders.

**Contrainindications, cautions and side-effects:** see notes above.

**Application:** apply thinly 1-2 times daily.

**Preparations**

- Hydrocortisone cream, 1% cream, 15 g/tube
- Hydrocortisone ointment, 1% ointment; 15 g/tube
### 13: Skin preparations

#### 13 C.2: Topical corticosteroids with antimicrobials

**Antifungal + corticosteroids**
Preparations containing antifungal agents such as nystatin or econazole in combination with hydrocortisone are recommended for use in inflammation with fungal skin infections. Application to skin is 1-2 times daily.

Preparations
- Antifungal + steroid cream; 15 g/tube

#### 13 C.3: Topical corticosteroids with keratolytics

**Betamethasone dipropionate + salicylic acid (Restricted)**
*Indications*: psoriasis and seborrhea.
*Application*: apply thinly 1-2 times daily.

Preparations
- Betamethasone dipropionate + salicylic acid lotion, 0.05% + 2% lotion; 30 mL/bottle
- Betamethasone dipropionate + salicylic acid ointment, 0.05% + 3%; 30 g/tube

**Dexamethasone acetate + salicylic acid (Restricted)**
*Indications*: psoriasis and seborrhea.
*Application*: apply thinly 1-2 times daily.

Preparations
- Dexamethasone acetate + salicylic acid skin ointment, 0.12% + 3% ointment; 30 g/tube

#### 13 D: Psoriasis and eczema preparations

#### 13 D.1: Creams and ointments for psoriasis

**Calcipotriol with betamethasone (Restricted)**
*Indications*: Psoriasis
*Dose*: Scalp psoriasis: Apply 1–4 g once daily usual duration of therapy 4 weeks; if necessary, treatment may be continued beyond 4 weeks or repeated, on the advice of a specialist, shampoo off after leaving on scalp overnight or during day, when different preparations containing calcipotriol used together, maximum total calcipotriol 5 mg in any one week.
Mild to moderate plaque psoriasis: Apply once daily for 8 weeks; if necessary, treatment may be continued beyond 8 weeks or repeated, on the advice of a specialist, apply to maximum 30% of body surface, when different preparations containing calcipotriol used together, max. total calcipotriol 5 mg in any one week; maximum 15 g per day.
Stable plaque psoriasis: Apply once daily for 4 weeks; if necessary, treatment may be continued beyond 4 weeks or repeated, on the advice of a specialist, apply to a maximum
30% of body surface, when different preparations containing calcipotriol used together, max. total calcipotriol 5 mg in any one week; maximum 15 g per day.

Preparations
Calcipotriol with betamethasone cream containing betamethasone 500 microgram per 1 gram, calcipotriol 50 microgram per 1 gram
Calcipotriol with betamethasone gel containing betamethasone 500 microgram per 1 gram, calcipotriol 50 microgram per 1 gram

**13 D.3: Oral preparation for psoriasis**

*Acitretin (Restricted)*

**Indications:** severe extensive psoriasis, severe ichthyosis, palmoplantar pustular psoriasis.

**Contraindications:** hepatic and renal impairment; pregnancy and breast feeding.

**Cautions:** serious precautions must be taken to avoid pregnancy during therapy and at least 2 years after treatment; avoid high doses of vitamin A; regularly monitor hepatic and renal functions; not recommended for children except in very serious cases; avoid excessive exposure to sunlight.

**Side-effects:** dryness of mucous membranes, of skin and of conjunctiva; palmoplantar exfoliation, epidermal fragility, paronychia, reversible hair thinning and alopecia, myalgia and arthralgia, nausea, malaise, headache, drowsiness and sweating; photosensitivity, mood changes and blood disorders.

**Dose:** a specialist should strictly supervise administration and use. Initially, adult 25-30 mg daily for 2-4 weeks then adjust dose according to response, usually 25-50 mg daily.

Preparations
Acitretin capsules, 10 mg cap.
Acitretin capsules, 25 mg cap.

**13 E: Preparations for acne**

Acne results from excessive sebaceous gland secretion and colonization of glands by bacteria. The skin pores become clogged leading to pimples and inflamed, infected abscesses. Treatment of acne should be centred on early prevention of excessive scarring. Treatment choice depends on whether the acne is predominantly inflammatory or comedonal and its severity.

Topical treatment is useful in most mild to moderate acne. Systemic treatment with antibiotics is kept for moderate to severe cases or when topical treatment is not effective. Severe acne may be treated with oral retinoids under the supervision of specialist dermatologist. Comedonal and inflamed acne respond well to topical application of benzoyl peroxide. Alternatively, topical antibiotic preparations such as clindamycin may be effective.
13: Skin preparations

**Benzoyl peroxide**

**Indications:** acne vulgaris.

**Cautions:** avoid contact with eyes, mouth and mucous membrane; has a bleaching property.

**Side-effects:** initial skin irritation.

**Application:** initiate treatment with lower strength, apply 1-2 times daily; increase strength gradually.

**Preparations**

Benzoyl peroxide in clay base, 2.5%, 20 g/tube

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**Clindamycin phosphate (Restricted)**

**Indications:** acne vulgaris.

**Cautions:** should be immediately discontinued if severe skin reaction occurs.

**Side-effects:** rash and urticaria.

**Application:** apply twice daily.

**Preparations**

Clindamycin phosphate topical solution, 1% solution; 30-50 mL/bottle

---

**Erythromycin**

**Indications:** acne vulgaris.

**Side-effects:** irritation.

**Dose:** apply twice daily.

**Preparations**

Erythromycin topical solution, 2% solution, 50 mL/bottle

---

**Isotretinoin (Restricted)**

**Indications:** severe acne, which has not responded to other, forms of treatment; sever recalcitrant cystic and conglobate acne.

**Contraindications:** pregnancy and breast feeding; renal and hepatic impairment, hyperlipidaemia.

**Cautions:** pregnancy should be excluded before initiating therapy, and to be avoided during and one month after treatment. Hepatic function and plasma lipid are to be monitored before and during treatment.

**Side-effects:** see under Acitretin (sec.13 D.3).

**Dose:** initially 500 microgram/kg daily in 1-2 divided doses for 4 weeks; when good response is achieved, continue for 8-12 weeks; if response is not good, increase dose to 1 mg/kg daily.

**Preparations**

Isotretinoin capsules, 5 mg cap.
Isotretinoin capsules, 10 mg cap.
Isotretinoin capsules, 20 mg cap.

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**Tretinoin**

**Indications:** mild to moderate acne.

**Contra-indications:** pregnancy, cutaneous epithelioma.

**Cautions:** severe acne, exposure to UV, contact with mucous membranes, eczematous, broken or sunburned skin should be avoided.

**Side-effects:** redness, skin peeling, pruritus.

**Dose:** apply 1-2 times daily.

**Preparations**

Tretinoin cream, 0.025%, 60 g/tube
13 F: Preparations for warts

Warts are small skin growths caused by any of the human papilloma virus types. Warts can develop at any age and are more common at childhood and least common in the elderly. Although warts on the skin are easily spread from one area on the body to another, they are rarely contagious from one person to another. Genital warts however are contagious. The least destructive measures should be applied to remove warts, as they tend to be self-limiting and eventually disappear spontaneously. Strong salicylic acid, lactic acid or trichloro-acetic acids preparations are applied for the removal of warts. They tend to cause considerable irritation of the treated skin. Preparations containing silver nitrate are also applied for the removal of warts.

Salicylic acid + lactic acid (Restricted)
Indications: warts.
Contraindications: diabetes.
Cautions: avoid application on broken skin, ano-genital region, large surface areas or the face.
Application: apply daily.

Preparations
Salicylic acid + lactic acid in flexible collodion paint, 16.7% + 16.7% solution; 15 mL/bottle

Silver nitrate sticks
Indications: warts.
Cautions: avoid application to intact skin, open wound or the face. Not suitable for ano-genital region or large areas.
Side-effects: staining of skin and cloths.
Application: apply daily to affected skin for a maximum of 3 applications.

Preparations
Silver nitrate caustic pencil; 75% Silver Nitrate + 25% Potassium Nitrate/pencil

13 G: Anti-infective skin preparations

The skin can be infected by various aerobic and anaerobic bacteria, herpes viruses, dermatophytes, monilia and protozoa. Superficial and mild skin infections require only local cleansing with disinfectants. In severe widespread life threatening skin infections, it is prudent to initiate treatment promptly with suitable systemic anti-infective agents.

13 G. 1: Antibacterial agents

Staphylococcus and streptococcus microorganisms mostly cause bacterial skin infections. Infections from less common bacteria may develop in hospitals or while gardening or swimming in a lake, ocean or a pond. Some people are at special
risk of developing skin infections such as diabetics and the immunocompromised. Topical application of antibacterials may cause systemic toxicity if a large area of the skin is being treated. To minimize the emergence of resistance, it is preferable to use topically only those antibacterials that are not given systemically. The infecting microorganism and its sensitivity should be identified prior to treatment especially in patients residing in hospitals where resistant organisms are common. Deeply sited infections as in erysipelas and cellulites are treated with systemic antibacterials.

Fusidic acid
Indications: staphylococcal skin infections.
Cautions: avoid contact with eyes.
Application: apply 3-4 times daily.

Preparations
Fusidic acid skin cream, 2% cream; 15 g/ tube
Sodium fusidate skin ointment, 2% ointment; 15 g/tube

Mupirocin (Restricted)
Indications: bacterial skin infections.
Cautions: avoid over use to prevent the emergence of bacterial resistance.
Application: apply 3 times daily for not more than 10 days.

Preparations
Mupirocin skin ointment, 2% ointment, 15 g/tube

Silver Sulfadiazine (Silver Sulphadiazine)
Indications: prophylaxis and treatment of infection in burn.
Contraindications: sensitivity to sulphonamides; pregnancy and breast feedings.
Cautions: renal and hepatic impairment; G6PD deficiency.
Side-effects: blood disorders on prolonged use; allergic reactions, argyria (skin discolouration).
Application: apply daily until satisfactory healing of the burn is achieved.

Preparations
Silver Sulfadiazine cream, 1% ; 50 g/tube
Silver Sulphadiazine cream, 1% ;500 g/jar

Tetracycline
Indications: sensitive bacterial skin infections including acne vulgaris, prophylaxis of treatment of infections following skin abrasions, minor cuts, wounds or burns.
Caution: Avoid contact with skin around eyes; may stain clothing.
Application: apply 2 or 3 times a day.

Preparation
Tetracycline skin ointment 3%; 20 g/tube
13: Skin preparations

13 G.2: Antifungal agents

Correct diagnosis should be established before treatment with topical antifungal preparations begins. Most ringworm infections, including *tinea pedis*, can be treated with topical imidazole derivatives such as clotrimazole, econazole and miconazole, which are very effective. Widespread fungal skin infections should be treated systemically with fluconazole, itraconazole or ketoconazole (*see* sec 5 B.2)

Other preparations such as nystatin and compound benzoic acid (Whitfield’s ointment) are broad-spectrum antifungals.

Lotions and sprays are generally preferred when large or hairy areas are involved. Ointment is better avoided on moist surfaces because of its occlusive properties.

13 G.2.1: Imidazole derivatives

**Clotrimazole**

*Indications*: fungal skin infections.

*Side-effects*: skin irritation and some times sensitivity.

*Application*: apply 2-3 times daily. Continue treatment for further 2 weeks after lesions have healed.

**Econazole nitrate**

*Indications*: fungal skin infections.

*Side-effects*: skin irritation and some times sensitivity.

*Application*: apply 2-3 times daily. Continue treatment for further 2 weeks after lesions have healed.

Preparations
- Econazole nitrate cream, 1% cream; 15-20 g /tube
- Econazole nitrate lotion, 1% lotion; 30 mL/bottle

**Miconazole nitrate**

*Indications*: fungal skin infections.

*Side-effects*: skin irritation and some times sensitivity.

*Application*: apply 2 times daily. Continue treatment for further 10 days after lesions have healed. For nail infections, use tincture preparation daily.

Preparations
- Miconazole nitrate cream, 1% cream; 15-20 g/tube
- Miconazole nitrate lotion, 1% lotion
- Miconazole nitrate tincture, 2% solution; 30 mL/bottle (*Restricted*)
13: Skin preparations

13 G.2.2: Other antifungal preparations

**Nystatin**

**Indications**: fungal skin infection due to *candida* species.

**Application**: apply 2-4 times daily, continue treatment for a week after lesions have healed.

**Preparations**

Nystatin cream, 100,000 units/g cream; 15-20 g/tube

Salicylic acid + benzoic acid (Whitfield’s ointment)

**Indications**: fungal skin (ringworm) infections.

**Application**: apply twice daily.

**Preparations**

Benzoin acid + salicylic acid ointment, 6% + 3% ointment (Whitfield’s ointment); 25-40 g/tube

13 G.3: Parasiticidal preparations

**Antilice spray**

A suitable preparation should be available for general use

Antilice spray; 100-120 mL/spray

**Permethrin**

**Indications**: effective for scabies and crab lice.

**Cautions**: avoid contact with eyes; do not use on broken or secondarily infected skin; children under 6 months, medical supervision required for cream rinse (head lice); children aged 2 months–2 years, medical supervision required for dermal cream (scabies).

**Side-effects**: pruritus, erythema, stinging, rashes and oedema.

**Dose**: Scabies, apply 5% preparation over whole body and wash off after 8–12 hours; child apply over whole body including face, neck, scalp and ears; if hands washed with soap within 8 hours of application, they should be treated again with cream; repeat application after 7 days.

Crab lice, adult over 18 years, apply 5% cream over whole body, allow to dry naturally and wash off after 12 hours or after leaving on overnight; repeat application after 7 days.

**Preparations**

Permethrin cream, 5%, 30 g/tube
Permethrin lotion, 1%, 59 mL bottle

13 G.4: Antiviral agents

**Aciclovir (Acyclovir) (Restricted)**

**Indications**: herpes simplex and varicella zoster infections.

**Cautions**: avoid contact with eyes and mucous membranes.

**Side-effects**: transient stinging or burning, erythema, itching or drying of the skin.

**Dose**: apply to lesions five times daily for 5–10 days starting at first signs of attack.
Preparations
Aciclovir cream 5%, 2-10 g/tube

13 H: Skin disinfectants

13 H.1: Cationic surfactants and soaps

Cetrimide
Indications: skin disinfectant.
Cautions: avoid contact with eyes; avoid application on body cavities.
Side-effects: skin irritation.
Application: apply 1-2 times daily.

Preparations
Cetrimide cream, 0.5% cream; 30-50 g/tube

13 H.2: Astringents, oxidisers and dyes

Hydrogen peroxide solution
Indications: skin disinfectant, for cleansing and deodorizing wound and ulcers.
Cautions: bleaches fabrics and hair; avoid deep or large wounds.

Preparations
Hydrogen peroxide solution, 6% (20 vols); 150 mL/bottle

13 I: Antiperspirants

Aluminium chloride hexahydrate (Restricted)
Indications: hyperhidrosis.

Cautions: avoid contact with eyes or mucous membrane; avoid use on broken or irritated skin.
Application: apply at night and wash next morning. Initially daily and then less frequently as condition improves. Do not shave the area for the next 12 hours.

Preparations
Aluminium chloride hexahydrate in alcoholic basis lotion, 20% lotion; 60 mL/bottle

13 J: Depigmenting agents

Hydroquinone interferes with the formation of new melanin causing reversible depigmentation. It is indicated for the gradual bleaching of hyperpigmented skin in conditions such as melasma, freckles and senile lentigines.

Hydroquinone (Restricted)
Indications: skin hyperpigmentation.
Cautions: avoid exposure to sunlight.
Application: apply 1-2 times daily to the affected skin and rub well.

Preparations
Hydroquinone cream, 4%, 30 g/tube
### 13: Skin preparations

#### 13 K: Pigmenting agents

**Methoxsalen (Restricted)**  
**Indications:** photo chemotherapy of vitiligo, psoriasis.  
**Contraindications:** sensitivity to methoxsalen; aphakia; invasive squamous cell carcinoma or melanoma.  
**Cautions:** avoid extensive exposure to sun or ultraviolet light.  
**Side-effects:** nausea, pruritus, erythema, skin pain, nervousness, insomnia, psychological depression.  
**Dose:** vitiligo, orally 20 mg, 2-4 hours before UVA exposure. Psoriasis, 10-70 mg orally 2 hours before UVA radiation.  
**Application:** apply 1% lotion topically to area of vitiligo and expose to UVA source; once a week treatment intervals are generally recommended

**Preparations**  
Methoxsalen capsules, 10 mg cap.  
Methoxsalen lotion, 0.75-1%, 25 mL bottle

**Ammoidine + ammidine paint (Restricted)**  
**Indications:** topical therapy of vitiligo.  
**Contraindications:** sensitivity to the drug.  
**Cautions:** avoid excessive exposure to sunlight.  
**Side-effects:** local irritation.  
**Application:** cautiously apply to affected areas and expose to sun or ultraviolet light.

**Preparations**  
Ammoidine + ammidine paint, 0.75 mg + 0.25 mg/mL; 30 mL paint

### 13 L: Topical circulatory preparations

**Heparinoid (Restricted)**  
**Indications:** Superficial thrombophlebitis. Bruising. Haematoma  
**Cautions:** Should not be used on large areas of skin, broken or sensitive skin, or mucous membranes  
**Dose:** Apply up to 4 times a day

**Preparations**  
Heparinoid gel, 0.3%  
Heparinoid cream, 0.3%
Immunological Products and Vaccines

- Immunoglobulins
- Vaccines and antisera

14: Immunological Products and Vaccines

14 A: Immunoglobulins

Human immunoglobulin (Ig) preparations are commonly used now compared to the previously widely used animal types. Human immunoglobulins are of two types, normal immunoglobulin and specific immunoglobulins.

14 A.1: Normal immunoglobulin

Normal immunoglobulin (Ig) is prepared from pooled plasma obtained from at least 1,000 donors. It contains antibodies to measles, mumps, varicella, hepatitis A, and other viruses that are currently prevalent in normal individuals. Normal immunoglobulin is administered intramuscularly in certain clinical situations to prevent or modify some infectious diseases. It is indicated for the protection of susceptible contacts against hepatitis A virus, provided that the injection is given within 2 weeks of exposure. In susceptible contacts of patients with measles, especially those with immune deficiency states, the injection should be administered within 5 days of exposure. In pregnant women exposed to rubella and when therapeutic abortion is not feasible, immunoglobulin injection is given, although congenital foetal abnormalities might develop.

Normal immunoglobulin is also given in cases of hypogammaglobulinaemia.

Cautions and side-effects of immunoglobulins include malaise, chills, fever, back pain and anaphylactic reactions. Immunoglobulin contains varying quantities of IgA; it should be used with caution in patients with IgA antibodies or selective IgA deficiencies.

**Human normal immunoglobulin 16%**

**Dose**: consult manufacturer instructions.

**Preparations**
- Normal immunoglobulin injection, 16%; 2 mL ampoule

**Human immunoglobulin**

**Dose**: consult manufacturer instructions

**Preparations**
- Human immunoglobulin injection, 3 g vial
- Human immunoglobulin with IgM, IgA, and IgG injection, 5% preparation, 10 mL vial
- Human immunoglobulin with IgM, IgA, and IgG injection, 5% preparation, 50 mL vial
14: Immunological Products and Vaccines

14 A.2: Specific immunoglobulins

Specific immunoglobulins are meant to contain a high level of a specific antibody. They are prepared by pooling the plasma of selected donors.

Anti-D (RH0) immunoglobulin

**Indications**: in rhesus-negative women for prevention of Rh0 (D) sensitisation to foetal rhesus-positive cells which may pass into the maternal circulation.

**Cautions**: administer within 72 hours following any sensitising episodes e.g. due to miscarriage, abortion or birth. If more than 72 hours period has passed, some protection can still be achieved by giving the proper dose. The dose is determined by the level of exposure to rhesus-positive blood.

**Side-effects**: discomfort at site of injection, anaphylactic reaction, lethargy, myalgia, elevated bilirubin level.

**Dose**: 250-500 micrograms (1250-2500 units) by deep intramuscular injection during the first 72 hours after exposure.

Preparations

Anti-D (RH0) immunoglobulin injection, 250 microgram vial

Anti-varicella zoster human immunoglobulin (CDL)

**Indications**: Prophylaxis in high-risk individuals against infections with varicella.

**Cautions**: bleeding disorders; avoid intravenous administration; specific antibody (IgA) deficiency.

**Side-effects**: local pain and redness at the site of injection; malaise, headache and abdominal cramp.

**Dose**: by deep intramuscular injection, child up to 5 years 250 mg, 6-10 years 500 mg, 11-14 year 750 mg, adults 1g. A second dose required if further exposure occurs after 3 weeks.

Preparations

Varicella-zoster human immunoglobulin injection, 10%; 5 mL vial (500 mg injection)

Hepatitis B immunoglobulin (HBIG) (Restricted)

**Indications**: prophylaxis from infection with hepatitis B virus.

**Cautions**: individuals with a specific IgA deficiency; thrombocytopenia or bleeding disorders; should not be administered intravenously.

**Side-effects**: local pain, tenderness, angioedema, and urticaria.

**Dose**: intramuscular injection, adult 500 units, child under 5 years 200 units, 5-10 years 300 units

Preparations

Hepatitis immunoglobulin HBIG injection, 200-400 units/mL; 5 mL vial

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14: Immunological Products and Vaccines

**Human anti-cytomegalovirus immunoglobulin**

**Indications:** prophylaxis in patients receiving immunosuppressive therapy.

**Side-effects:** facial flushing, nausea and vomiting, muscle cramps, wheezing, diaphoresis.

**Dose:** intravenous infusion, 150 mg/kg as a first dose then 100 mg/kg/dose on weeks 2, 4, 6 and 8, then 50 mg/kg/dose on weeks 12 and 16.

**Preparations**

Human anti-cytomegalovirus immunoglobulin injection, 50 mL vial for intravenous infusion.

**Rabies immunoglobulin (human)**

**Indications:** following exposure of non-immunised individual to an infected animal. Adjunct to rabies vaccine in high-risk areas.

**Cautions:** avoid intravenous administration; allergy to avian protein or chicken eggs; allergy to specific immunoglobulins.

**Side-effects:** local pain at site of injection; fever, urticaria.

**Dose:** intramuscular injection of 10 units/kg and 10 units/kg by infiltration around the wound.

**Preparations**

Rabies immunoglobulin injection; 150 IU/mL; 2 and 5 mL vial

Consult pharmacy about available preparation.

**Tetanus immunoglobulin (human)**

**Indications:** management of proven or suspected tetanus in non-immunised patients or when less than 3 doses of tetanus vaccine have been received.

**Cautions:** should be used in addition to surgical toilet, prophylactic antibiotics and tetanus vaccine; avoid intravenous administration.

**Side-effects:** hypersensitivity, pain, tenderness, erythema, muscle stiffness; fever, hives, angioedema, local inflammation.

**Dose:** intramuscular injection, prophylaxis 250 units, increased to 500 units if there is a high risk or more than 24 hours have elapsed.

**Preparations**

Tetanus immunoglobulin (human) injection, 250 IU/mL, 1 mL pre-filled syringe

Consult pharmacy about available preparation.

14 B: Vaccines and antisera

14 B.1: Sera and antitoxins

**Anti-snake venom serum polyvalent (lyophilised)**

**Indications:** treatment of acute systemic envenoming from snakebite.

**Cautions:** sensitivity test should be conducted with diluted antivenom (intra-dermally, 0.02 mL of 1:100 dilution with normal saline).
14  B.2: Vaccines

Vaccines are antigenic materials that stimulate production of antibodies and other components of the immune mechanism. They may consist of live attenuated infective microorganism (virus or bacteria), inactivated forms of infective microorganism or bacterial toxoids. Live attenuated (e.g. OPV, rubella, measles, mumps or BCG) vaccines; produce immunity that is durable but may not be as long as that produced from natural infection. The vaccine causes sub clinical infection followed by antibody production. Inactivated (e.g. hepatitis B and influenza) vaccines provide immunogenicity without infectivity. They are administered parenterally, but repeated doses are required to produce adequate antibodies. Booster doses, in most cases, are required. The duration of immunity varies from months to years.

Toxoids are prepared from bacterial exotoxins. Inoculation with toxoids promotes the development of antibodies. Repeated administration and booster doses are required. 

Side-effects: Parenteral administration of vaccines may cause local reaction at the site of injection. Mild generalized reaction in the form of fever, malaise and headache may occur. Vaccines may contain some residual egg protein, additive antibacterials or animal serum, which could cause generalized allergic reaction.

Contra-indications: Prior allergic reactions to a specific vaccine or related vaccines are contraindication. Live attenuated vaccines are contraindicated in the following conditions: Immunosuppressive therapy. Immunodeficiency disorders. Leukaemia, lymphoma or generalized malignancy. Within three months of any injection of immunoglobulin.
14: Immunological Products and Vaccines

(Should be used cautiously during pregnancy because of a possible risk to the foetus.)

**Indications:** vaccines are indicated in the control of certain preventable infections, as is the case with the expanded programme on immunisation (EPI). Some vaccines may be used as a prophylactic measure in patients exposed to high risk of acquiring a disease (e.g. hepatitis B) or at high risk of developing complications (e.g. influenza in the elderly). Population exposed to localized outbreak of disease and those travelling to endemic areas should also be vaccinated.

14  B.2.1: Vaccines applied in the expanded programme on immunisation

The expanded programme on immunisation (EPI) was first launched in Oman in 1981 and has been repeatedly reviewed. Substantial progress has been made by EPI in the last two decades. Immunisation coverage levels have increased substantially from 10% in 1981 to near 100% in 1995 and maintained since. This has resulted in a marked decline in EPI targeted diseases. The followings are immunisation schedules effective in Oman. The EPI vaccines are available at the PHC levels.

14  B.2: Vaccines
## A. Childhood Immunisation schedule / 2016

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td>BCG</td>
</tr>
<tr>
<td></td>
<td>HBV</td>
</tr>
<tr>
<td>2 months</td>
<td>Hexa-1 (HBV, DTP, Hib, IPV)</td>
</tr>
<tr>
<td></td>
<td>PCV-1</td>
</tr>
<tr>
<td>4 months</td>
<td>OPV-1</td>
</tr>
<tr>
<td></td>
<td>Hexa-2 (HBV, DTP, Hib, IPV)</td>
</tr>
<tr>
<td></td>
<td>PCV-2</td>
</tr>
<tr>
<td>6 months</td>
<td>OPV-2</td>
</tr>
<tr>
<td></td>
<td>Hexa-3 (HBV, DTP, Hib, IPV)</td>
</tr>
<tr>
<td>9 months</td>
<td>Vitamin A 100, 000 IU</td>
</tr>
<tr>
<td>12 months</td>
<td>MMR-1</td>
</tr>
<tr>
<td></td>
<td>Varicella</td>
</tr>
<tr>
<td>13 months</td>
<td>PCV- Booster</td>
</tr>
<tr>
<td>18 months</td>
<td>OPV-Booster</td>
</tr>
<tr>
<td></td>
<td>DTP-Booster</td>
</tr>
<tr>
<td></td>
<td>MMR-2</td>
</tr>
<tr>
<td></td>
<td>Vitamin A 200,000 IU</td>
</tr>
</tbody>
</table>

## B. School immunisation schedules

### Class 1 (6-7 years)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Immunisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPV booster</td>
<td>One dose</td>
</tr>
<tr>
<td>DT booster</td>
<td>Give one dose to all children.</td>
</tr>
<tr>
<td>Or</td>
<td>(Booster dose)</td>
</tr>
<tr>
<td>DT (2 doses)</td>
<td>Give 2 doses at 6-8 weeks intervals if not vaccinated previously, or no</td>
</tr>
<tr>
<td></td>
<td>documentary evidence available, i.e. immunisation card</td>
</tr>
</tbody>
</table>
14: Immunological Products and Vaccines

Class 6 (12-13 years)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Immunisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Td booster</td>
<td>Give one booster dose for boys and girls fully immunised with DPT and/or DT.</td>
</tr>
<tr>
<td>Or</td>
<td>If not fully immunised as above or no record available, give two dose of Td</td>
</tr>
<tr>
<td>Td (2 doses)</td>
<td>at 6-8 weeks intervals.</td>
</tr>
</tbody>
</table>

Class 11 (17-18 years)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Immunisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPV booster</td>
<td>To be given to all students at this level</td>
</tr>
<tr>
<td>Td booster</td>
<td>Give one booster dose for students fully immunised with DPT and/or Td.</td>
</tr>
<tr>
<td>Or</td>
<td>If not fully immunised as above or no record available, give two dose of Td</td>
</tr>
<tr>
<td>Td (2 doses)</td>
<td>at 6-8 weeks intervals.</td>
</tr>
</tbody>
</table>

C. Females of childbearing age (15-49 years) and adult males (18 years or above)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Immunisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(TT)</td>
<td>- If immunised, give one booster of TT every 10 years</td>
</tr>
<tr>
<td></td>
<td>- If not immunised or immunisation status unknown, give 2 doses of TT at an</td>
</tr>
<tr>
<td></td>
<td>interval of 4-6 weeks apart</td>
</tr>
<tr>
<td></td>
<td>- Give 3rd dose of TT with a minimum of 6 months after the 2nd dose</td>
</tr>
<tr>
<td></td>
<td>- Give 4th dose with a minimum interval of one year after the 3rd dose</td>
</tr>
<tr>
<td></td>
<td>followed by a 5th dose after one year.</td>
</tr>
<tr>
<td></td>
<td>- Subsequently give one booster dose every 10 years.</td>
</tr>
</tbody>
</table>

Rubella  Administer a single dose to postpartum women within 40 days after delivery if no evidence of previous vaccination documentation

Route, site and dose of EPI vaccines
## 14: Immunological Products and Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Route</th>
<th>Site</th>
<th>dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>Intradermal</td>
<td>Lt.deltoid</td>
<td>0.05 mL</td>
</tr>
<tr>
<td>OPV</td>
<td>Oral</td>
<td>Mouth</td>
<td>2drops</td>
</tr>
<tr>
<td>DPT</td>
<td>Intramuscular (IM)</td>
<td>Antero lateral thigh muscle</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>HBV</td>
<td>IM</td>
<td>=</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>Hib</td>
<td>IM</td>
<td>=</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>Measles</td>
<td>IM</td>
<td>=</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>MMR</td>
<td>IM</td>
<td>=</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>DT</td>
<td>IM</td>
<td>Deltoid muscle</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>Td/TT</td>
<td>IM</td>
<td>=</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>TT</td>
<td>IM</td>
<td>=</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>Rubella</td>
<td>IM</td>
<td>=</td>
<td>0.5 mL</td>
</tr>
</tbody>
</table>

BCG: Bacillus Calmette-Guerin vaccine  
DPT: Diphtheria-pertussis-tetanus vaccine  
DT: Tetanus –diphtheria vaccine for children  
HBV: Hepatitis B vaccine  
Hib: Haemophilus influenzae type B vaccine  
IPV: Inactivated polio vaccine  
Td: Tetanus-diphtheria vaccine for adults  
OPV: Oral polio vaccine  
PCV7: Pneumococcal conjugate vaccine, 7-valent  
TT: Tetanus toxoid  
MMR: Measles, Mumps and Rubella (German measles)
Inactivated rabies vaccine

**Indications**: prophylaxis immunisation to high-risk individuals; for treatment after exposure in conjunction with rabies immunoglobulin.

**Dose**: for prophylaxis, 2 doses with a month interval, followed by a booster dose after 6-12 months with further doses every 2-3 years.

For post-exposure treatment, a dose on day 1 (2 injections at 2 sites intramuscular or subcutaneous), followed by reinforcing doses at days 7 and 28.

**Preparations**

- Inactivated rabies vaccine injection, single dose prefilled syringe

Hepatitis B vaccine for adults

**Indications**: vaccination of individuals at high risk of contracting hepatitis B.

**Dose**: intramuscularly, 3 doses of 20 microgram each, the 2nd dose 1 month and the 3rd dose 6 months after the first dose.

**Preparations**

- Hepatitis B vaccine for adult injection, 20 microgram/mL single dose injection

Inactivated influenza virus vaccine

**Indications**: prophylaxis against influenza in adults and children older than 6 months of age and who are at high risk (pilgrims (Omra/Hajj), health workers, ≥65 years and immunocompromised).

**Contraindications**: allergy to egg, chicken, drugs like gentamicin, formaldehyde and sodium deoxycholate.

**Side-effects**: mild fever, local swelling.

**Dose**: by intramuscular injection on annual basis, in adult and children from 36 months and above: single 0.5 mL dose, in children from 6 to 35 months: two doses of 0.25 mL each given 4 weeks apart.

**Preparations**

- Influenza vaccine injection, in prefilled syringe.

Note: the vaccine is manufactured every year with the strains of circulating influenza viruses.

Meningococcal (A, C, W135 and Y) vaccine

**Indications**: control of outbreak, routinely to pilgrims as protective measure and to individuals with high-risk exposure.

**Dose**: deep subcutaneous injection, 0.5 mL single dose. The dose is the same for child (>2 years) and adult.

**Preparations**

- Meningococcal (A, C, W 135 and Y) vaccine injection, 0.5 mL vial single dose.

Pneumococcal vaccine

**Indications**: immunisation of susceptible individuals over the age of
Section 15: Anaesthesia

15 A: General Anaesthesia

15 A.1: Intravenous anaesthetics

Etomidate
- Induction agent associated with rapid recovery without a hangover effect.
- Causes less hypotension than thiopental and propofol during induction.
- Produces a high incidence of extraneous muscle movement, which can be minimised by an opioid analgesic or a short-acting benzodiazepine given just before induction.
- Pain on injection can be reduced by injecting into a larger vein or by giving an opioid analgesic just before induction.
- Suppresses adrenocortical function, particularly during continuous administration.
- Should not be used for maintenance of anaesthesia.

Thiopental
- Most widely used intravenous anaesthetic that produces a pleasant induction.
- devoid of any analgesic effect.
- Acts rapidly (10-30 seconds), but it may take longer (up to 2 minutes) in patients with cardiac disease or shock.
- Redistribution to other parts of the body accounts for the short sleep and the re-awaking of patients.
- Repeated doses are cumulative.

14: Immunological Products and Vaccines

2 years with any of the following conditions: Homozygous sickle cell disease; Asplenia or severe dysfunction of the spleen; Chronic renal disease; Coeliac syndrome; Immunodeficiency or immunosuppression; Chronic heart disease; Chronic lung disease; Chronic liver disease; Diabetes mellitus.

**Dose:** 0.5 mL by subcutaneous or intramuscular injection

**Preparations**

Pneumococcal vaccine injection, 0.5 mL single dose injection

**14 B.2.3: Diagnostic agents**

**Tuberculin**

**Indications:** in the mantoux test as diagnostic agent for tuberculosis.  
**Dose:** various dilutions are available (10, 100 and 1000 units / mL). Follow manufacturer instructions very carefully.

**Preparations**

Tuberculin purified protein derivative (PPD) 2-3 IU (10 tests)/vial
Section 15: Anaesthesia

- General anaesthesia
- Local anaesthesia

15 A: General Anaesthesia

The state of general anaesthesia is a drug–induced total absence of perception of all sensations. The depth of anaesthesia required for surgical procedures can be achieved by a variety of drugs given alone, or more often in combinations. Intravenous anaesthetics are commonly used for induction followed by administration of inhalational anaesthetics. Specific drugs are often used to produce muscular relaxation. Such drugs may seriously interfere with spontaneous respiration. The choice of anaesthetic is determined by the understanding of the pharmacokinetic and pharmacodynamic properties of the various drugs and the influence of the underlying pathophysiological conditions.

15 A.1: Intravenous anaesthetics

Intravenous anaesthetics are used mainly for induction of anaesthesia and may be used alone to produce anaesthesia for short surgical procedures. They produce a rapid action that might be associated with hypotension and apnoea. Adequate resuscitation facilities should always be at hand. It should be noted that the elimination of these drugs could be delayed beyond the short anaesthetic effect.

It is important to remember that the requirements for intravenous anaesthetics vary among individuals and the recommended dose is only a guide. It could be decreased or increased according to the general conditions of the patient.

**Etomidate** is an induction agent associated with rapid recovery without a hangover effect. It causes less hypotension than thiopental and propofol during induction. It produces a high incidence of extraneous muscle movement, which can be minimised by an opioid analgesic or a short-acting benzodiazepine given just before induction. Pain on injection can be reduced by injecting into a larger vein or by giving an opioid analgesic just before induction. Etomidate can suppress adrenocortical function, particularly during continuous administration, and it should not be used for maintenance of anaesthesia.

**Thiopental** is the most widely used intravenous anaesthetic that produces a pleasant induction. It is devoid of any analgesic effect. It acts rapidly (10-30 seconds) but it may take longer (up to 2 minutes) in patients with cardiac disease or shock. Redistribution to other parts of the body accounts for the short sleep and the re-awakening of patient. Repeated doses are cumulative since

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14: Immunological Products and Vaccines

- 2 years with any of the following conditions: Homozygous sickle cell disease; Asplenia or severe dysfunction of the spleen; Chronic renal disease; Coeliac syndrome; Immunodeficiency or immunosuppression; Chronic heart disease; Chronic lung disease; Chronic liver disease; Diabetes mellitus.

**Dose**: 0.5 mL by subcutaneous or intramuscular injection

**Preparations**: Pneumococcal vaccine injection, 0.5 mL single dose injection

**Tuberculin**

- **Indications**: in the mantoux test as diagnostic agent for tuberculosis.
- **Dose**: various dilutions are available (10, 100 and 1000 units / mL). Follow manufacturer instructions very carefully.
- **Preparations**: Tuberculin purified protein derivative (PPD) 2 -3 IU (10 tests)/vial

14  B.2.3: Diagnostic agents
### 15: Anaesthesia

Metabolism is slow and distribution sites are saturable. Extravascular injections are painful and may cause local tissue necrosis. **Ketamine** can be given both intravenously and intramuscularly. It takes 1 minute to induce a state of sedation, amnesia, immobility and analgesia. It causes an increase in muscle tone, cardiac stimulation and hallucination. Hallucination and psychotic sequelae are disadvantages that might be reduced when drugs such as diazepam are also used. It is particularly suitable for children especially when repeated use is needed. Recovery is relatively slow. **Propofol** induces as rapid anaesthesia as thiopentone. Pain may be experienced at the site of injection, but rarely is followed by phlebitis or thrombosis. Anaesthesia may be maintained with continuous infusion of propofol combined with opioids and/or other inhalational anaesthetics. There have been some reports of seizure or involuntary movement during induction or emergence from propofol–induced anaesthesia. Emergence from propofol anaesthesia is more rapid than that with thiopental even following prolonged infusion.

<table>
<thead>
<tr>
<th><strong>Etomidate</strong></th>
<th><strong>Indications</strong>: induction of general anaesthesia. <strong>Contraindications, Cautions and Side-effects</strong>: see notes above; avoid in acute porphyria, pregnancy, breast-feeding. <strong>Dose</strong>: adult and child, by slow intravenous injection, 300 micrograms/kg max. total dose 60 mg; elderly 150–200 micrograms/kg; max. total dose 60 mg. <strong>Preparations</strong></th>
<th><strong>Thiopental sodium (Thiopentone sodium)</strong></th>
<th><strong>Indications</strong>: induction of general anaesthesia; general anaesthesia of short duration. <strong>Contraindications</strong>: porphyria; airway obstruction. <strong>Cautions and side-effects</strong>: see notes above; in oropharyngeal surgery; reduce dose in the elderly and in severe hepatic disease. <strong>Dose</strong>: by intravenous injection, as a 2.5% solution, initially 100-150 mg for a fit premedicated adult over a period of 10–15 second. Further doses may follow if necessary after 30-60 seconds; maximum 4 mg/kg. Child, for induction 2-7 mg/kg. <strong>Preparations</strong></th>
<th><strong>Ketamine hydrochloride</strong></th>
<th><strong>Indications</strong>: induction and maintenance of anaesthesia. <strong>Contraindications</strong>: hypertension; patients prone to hallucination.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preparations</strong></td>
<td><strong>Etomidate injection, 2 mg/mL, 10 mL ampoule</strong></td>
<td><strong>Thiopental sodium injection, Powder for reconstitution; 500 mg vial</strong></td>
<td><strong>Thiopental sodium (Thiopentone sodium)</strong></td>
<td><strong>Indications</strong>: induction of general anaesthesia; general anaesthesia of short duration. <strong>Contraindications</strong>: porphyria; airway obstruction. <strong>Cautions and side-effects</strong>: see notes above; in oropharyngeal surgery; reduce dose in the elderly and in severe hepatic disease. <strong>Dose</strong>: by intravenous injection, as a 2.5% solution, initially 100-150 mg for a fit premedicated adult over a period of 10–15 second. Further doses may follow if necessary after 30-60 seconds; maximum 4 mg/kg. Child, for induction 2-7 mg/kg. <strong>Preparations</strong></td>
<td><strong>Ketamine hydrochloride</strong></td>
</tr>
</tbody>
</table>
Cautions and side-effects: see notes above.

**Dose:** intramuscular injection, 4-10 mg/kg produces 10-25 minutes of surgical anaesthesia.

Intravenous injection, 2-4.5 mg/kg over 1 minute, produces 5-10 minutes of surgical anaesthesia.

Intravenous infusion for induction in longer procedures, total dose 0.5-2 mg/kg; maintenance, 10-45 micrograms/kg/minute.

**Preparations**

Ketamine hydrochloride injection, 50 mg/mL, 10 mL vial

**Propofol**

**Indications:** induction and maintenance of anaesthesia.

Contraindications, cautions and side-effects: see notes above.

**Dose:** induction of anaesthesia, by intravenous injection or infusion, 1.5-2.5 mg/kg at a rate of 20-40 mg every 10 seconds. Child, usual dose in over 8 years, 2.5 mg/kg slowly administered.

Maintenance of anaesthesia, by intravenous injection, 25-50 mg repeated according to response. Intravenous infusion, 4-12 mg/kg/hour.

**Preparations**

Propofol injection, 10 mg/mL, 20 mL vial

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**15 A.2: Inhalational anaesthetics**

Inhalational anaesthetics may be gases or volatile liquids. They are used for maintenance or induction of anaesthesia. Suitable instruments are needed to control the outflow rate and concentration. To avoid the occurrence of hypoxia, inhalational anaesthetics are administered with oxygen.

Halothane is a potent anaesthetic with smooth induction and very little irritation. Its association with hepatotoxicity is a main disadvantage. Muscle tone is reduced, but not enough for abdominal surgery.

Isoflurane is less potent than halothane, with good muscle relaxing effect. Its association with hepatotoxicity is less than with halothane.

Sevoflurane is a potent rapidly acting inhalational anaesthetic. Its low tissue and blood solubilities and high potency allow for better control of the anaesthesia depth and rapid recovery after discontinuing administration. It is rarely associated with hepatotoxicity.

In Oman, only isoflurane and sevoflurane are approved for use.

**Isoflurane**

**Indications:** general anaesthesia.

**Contraindications:** sensitivity to halogenated compounds.

**Side-effects:** respiratory depression, hypotension; see notes above.
15: Anaesthesia

**Dose:** induction, increase gradually from 0.5% to 3% in oxygen or nitrous oxide. Maintenance, 1-2.5% with nitrous oxide-oxygen. If oxygen is used alone an additional increase of 0.5-1% of isoflurane is needed.

**Preparation**
Isoflurane, 100 mL bottle

**Sevoflurane**

*Indications:* general anaesthesia.
*Contraindications and cautions:* sensitivity to halogenated compounds.
*Side-effects:* Nausea and vomiting, excitatory movements, respiratory depression, decreases in heart rate.

**Dose:** induction, up to 8% in oxygen or nitrous oxide-oxygen. Child, up to 7%.

**Preparation**
Sevoflurane, 250 mL bottle

15 A.3: Antimuscarinic premedication drugs

**Atropine sulphate**

*Indications:* drying of secretions, reversal of excessive bradycardia; adjunct to neostigmine for reversal of non-depolarizing neuromuscular block; other effects see sections 1, 2 and 11.

*Contraindications and cautions:* cardiac disease, see section 1

*Side-effects:* see section 1

**Dose:** premedication by intravenous injection, 300-600 micrograms immediately before induction. Intramuscular injection, 300-600 micrograms 30-60 minutes before induction; Child 20 micrograms/kg.

For management of muscarinic side-effects of neostigmine in the reversal of competitive neuromuscular block, intravenously 600-1200 micrograms. (0.6-1.2 mg).

**Preparations**

Atropine sulphate injection, 600 micrograms/mL ampoule

**Glycopyrronium bromide (CDL)**

*Indications,* contraindications, cautions and side-effects: see under atropine sulphate

**Dose:** premedication and intra-operative use, intravenous or intramuscular injection 200 microgram or 5 micrograms/kg to a maximum of 400 microgram; Child, 4-8 micrograms/kg preferably by intravenous injection, to a maximum of 200 micrograms.

For management of muscarinic side-effects of neostigmine in the reversal of competitive neuromuscular block, intravenously 10-15 micrograms/kg.

**Preparations**

Glycopyrronium bromide injection, 200 microgram/mL ampoule

15 A.4: Muscle relaxants
The muscle relaxants used in anaesthesia are also known as neuromuscular blocking agents. They differ from those acting on the spinal cord or brain and applied in musculoskeletal disorders. Muscle relaxants, by blocking the neuromuscular junction, allow light anaesthesia to be used with adequate relaxation of the abdomen and diaphragm. Tracheal intubation is also facilitated. Their use should always be accompanied by artificial respiration until the drug has been inactivated or antagonized.

Atracurium besylate

**Indications:** muscle relaxant for surgery (short to intermediate duration).

**Cautions:** may cause significant histamine release leading to cardiovascular effects.

**Side-effects:** skin flushing, hypotension, bronchospasm, anaphylactic reactions.

**Dose:** intravenous injection, for adults and child over 1 month, 300-600 micrograms/kg, then 100-200 micrograms/kg as required or by intravenous infusion, 5-10 micrograms/kg/minute.

**Preparations**

Atracurium besylate injection, 10 mg/mL, 2.5 mL ampoules
Atracurium besylate injection, 10 mg/mL, 5 mL ampoules

Cisatracurium

**Indications:** muscle relaxant for surgery (intermediate duration).

**Cautions:** hypersensitivity to other benzylisoquinolinium compounds.

**Side-effects:** less frequent hypotension and bradycardia than atracurium.
Preparations
Vecuronium bromide injection, 10 mg/vial

Vecuronium bromide

Indications: muscle relaxant for surgery (intermediate duration).
Cautions: dose adjustment in renal impairment, hepatic failure, obesity and elderly.
Side-effects: hypotension/hypertension, bronchospasm.

Dose: intravenous injection, initially 75-100 micrograms/kg, maintenance, 20-30 micrograms/kg according to response.
By intravenous infusion, 0.8-1.4 micrograms/kg/minute after an initial intravenous dose of 40-100 micrograms/kg.
Preparations
Vecuronium bromide injection, powder for reconstitution, 10 mg vial

15 A.4.2: Depolarising muscle relaxants

The depolarising agents such as suxamethonium depolarise the membrane by acting in a similar manner to acetylcholine. However, the effect is long lasting and results in blocking the transmission and neuromuscular paralysis. The degree of paralysis depends on many variables such as the type of anaesthetic used, the type of muscle affected and the intervals of drug administration.

Neostigmine dose not reverse the effects of depolarising neuromuscular blocking agents. Eliminating the depolarising drug mainly by plasma pseudo-cholinesterase terminates their effect. Deficiency in this enzyme will delay the recovery and could be very dangerous if artificial respiration is not mechanically maintained.

Suxamethonium has the most rapid onset and brief duration of action. It is an ideal muscle relaxant. It should be given after induction with anaesthetics because painful muscle fasciculation precedes the muscle paralysis. Atropine premedication reduces the excessive salivation and bradycardia caused by Suxamethonium.

Suxamethonium chloride

Indications: muscle relaxation (rapid onset and short duration).

Contraindications: history of malignant hyperthermia; deficiency of plasma cholinesterase; severe liver disease.

Cautions: neuromuscular disease, cardiac and respiratory disorders, raised intra-ocular pressure; pregnancy.

Side-effects: post-operative muscle pain, hyperkalaemia, tachycardia, arrhythmia, blood pressure changes, apnoea.

Dose: intravenous injection, adult 1 mg/kg (average 0.3-1.1 mg/kg), maximum 500 mg/hour. Child 1-2 mg/kg.

Intravenous infusion of a solution of 1-2 mg/mL at a rate of 2-5 mg/minute. Maximum, 500 mg/hour; in child reduce infusion rate according to body weight.

Preparations
Suxamethonium chloride injection, 50 mg/mL, 2 mL vial

15 A.5: Anti-cholinesterase used in anaesthesia

Neostigmine is used to reverse the effects of non-depolarising muscle relaxants. It is not effective in reversing the effects of depolarising muscle relaxants.

Neostigmine acts rapidly after intravenous injection. It is preferable to use atropine or glycopyrronium
with neostigmine in order to prevent its muscarinic effects such as bradycardia and excessive salivation.

**Neostigmine methyl sulphate**  
**Indications:** reversal of non-depolarising neuromuscular blockade. Contraindications, cautions and side-effects: see notes above and section 10.B.1.  
**Dose:** intravenous injection, 50-70 micrograms/kg, maximum 5 mg usually with atropine or glycopyrronium.

Preparations  
Neostigmine methyl sulphate injection, 500 micrograms/mL, 1 mL ampoule  
Neostigmine methyl sulphate injection, 500 micrograms/mL, 5 mL ampoule  
Neostigmine methyl sulphate injection, 2.5 mg/mL, 5 mL ampoule

**Doxapram hydrochloride**  
**Indications:** reversal of post-operative respiratory depression.  
**Contraindications, cautions and side-effects:** see section 3.E.  
**Dose and preparations:** see section 3.E

**Flumazenil**  
**Indications:** reversal of sedative effects of benzodiazepines in anaesthetic, intensive care and diagnostic procedures.  
**Contraindications:** life threatening conditions controlled by benzodiazepines (e.g. status asthmaticus, epilepsy).  
**Cautions:** repeated dose may be needed because of short duration; avoid rapid injection in high-risk patients; hepatic impairment; head injury (fear of convulsion).  
**Side-effects:** nausea, vomiting and flushing; with rapid recovery, agitation, anxiety and fear.  
**Dose:** intravenous injection, 200 micrograms over 15 seconds, then 100 micrograms at 60 seconds intervals if necessary, maximum dose 2 mg.

Preparations  
Flumazenil injection, 100 micrograms/mL, 5 mL ampoule

**Naloxone hydrochloride**  
**Indications:** reversal of opioid-induced respiratory depression.
Cautions: opioid physical dependence, cardiac disease.
Side-effects: precipitation of withdrawal syndrome.
Dose: intravenous injection, 100-200 micrograms; if response not adequate, 100 micrograms every 2 minutes.

Preparations
Naloxone hydrochloride injection, 400 micrograms/mL, 1 mL ampoule

15 B: Local anaesthesia

Local anaesthetics reversibly prevent the generation and conduction of nerve impulse. Their primary site of action is the nerve membrane. They affect all types of nerves and the small nerve fibres (sensory, autonomic) seem to be affected first; larger motor nerves are affected later. Local anaesthetics have the advantage of being applied by different routes. They can be used topically on mucous membranes, injected to produce infiltration, field block, nerve block, intravenous regional (Bier’s block), spinal and epidural anaesthesia.

Local anaesthetics vary widely in their potency, toxicity, duration, solubility in water and ability to penetrate mucous membranes. They are usually effective with a short onset of action (few seconds – few minutes) and act for a duration of 1-2 hours. The extent of circulation at the administration site is a major factor affecting duration. Absorption of local anaesthetics into circulation eliminates their local action. Simultaneous administration of vasoconstrictor may double the duration of action. Adrenaline is generally used in concentrations of 1-200,000 in general surgery and 1-80,000 in dentistry. However, vasoconstrictors are better avoided for nerve block of digits, nose or penis, in patients with cardiac disease, and in those receiving antidepressants. Felypressin is a safer vasoconstrictor since the concentrations used with local anaesthetics do not significantly affect the heart rate or blood pressure. Adverse effects usually occur within 20-30 minutes after regional anaesthetic procedure, since plasma peak concentration is attained within this time. These include, hypotension, bradycardia, respiratory depression, cardiac arrest, and convulsion. Great care should be taken to avoid accidental intravascular injection.

Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to traumatized urethra; the drug in these conditions may be extensively absorbed and causes systemic rather than local effects.
15: Anaesthesia

**Bupivacaine hydrochloride**

**Indications:** local anaesthetic (long duration and slow onset), suitable for epidural block.

**Contraindications:** intravenous regional anaesthesia (Bier’s block). Cautions and side-effects: see notes above.

**Dose:** adjust according to patient weight and nature of procedure.

- Local infiltration or peripheral nerve block, 0.25% (up to 60 mL). Epidural block;
- Surgery, lumbar, 0.5% (maximum 20 mL).
- Surgery, caudal, 0.5% (maximum 30 mL).
- Labour, lumbar, 0.25-0.5% (maximum 12 mL).

**Preparations**

- Bupivacaine hydrochloride injection, 0.25%, 20 mL ampoule
- Bupivacaine hydrochloride injection, 0.5%, 20 mL ampoule
- Bupivacaine hydrochloride + glucose injection, 0.5% (5 mg/mL) + 80 mg/mL, 4 mL (heavy) ampoule

**Levobupivacaine (Restricted)**

**Indications:** Surgical anaesthesia, acute postoperative pain, acute labour pain

**Contra-indications:** Application to the middle ear (can cause ototoxicity); avoid injection into infected tissues; avoid injection into inflamed tissues; complete heart block; preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block); should not be applied to damaged skin.

**Cautions:** The licensed doses stated may not be appropriate in some settings and expert advice should be sought. Cardiovascular disease; debilitated patients (consider dose reduction); elderly (consider dose reduction); epilepsy; hypovolaemia; impaired cardiac conduction; impaired respiratory function; myasthenia gravis; shock.

**Side-effects:** Anaemia; arrhythmias; blurred vision; cardiac arrest; convulsions; dizziness; drowsiness; feeling of inebriation; headache; lightheadedness; muscle twitching; myocardial depression (resulting in hypotension and bradycardia); nausea; numbness of the tongue and perioral region; paraesthesia (including sensations of hot and cold); peripheral vasodilatation (resulting in hypotension and bradycardia); pyrexia; restlessness; sweating; tinnitus; transient excitation (followed by depression with drowsiness, respiratory failure, unconsciousness, and coma); tremors; vomiting.

**Dose:** Surgical anaesthesia by peripheral nerve block 2.5–150 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution.

- Surgical anaesthesia by peribulbar nerve block: 37.5–112.5 mg, dose administered using a 7.5 mg/mL (0.75%) solution.
- Surgical anaesthesia by lumbar epidural: 50–150 mg, to be given over 5 minutes, dose administered using...
a 5 mg/mL (0.5%) or 7.5 mg/mL (0.75%) solution.
Surgical anaesthesia by intrathecal injection: 15 mg, dose administered using a 5 mg/mL (0.5%) solution.
Surgical anaesthesia by local infiltration: 2.5–150 mg, dose administered using a 2.5 mg/mL (0.25%) solution.
Acute postoperative pain by continuous epidural infusion: 12.5-18.75 mg/ hour, dose administered using a 2.5 mg/mL (0.25%) or 1.25 mg/mL (0.125%) solution; maximum 400 mg per day.
Acute labour pain: initially by lumbar epidural: 15-25 mg every 15 minutes as required, dose administered using a 2.5 mg/mL (0.25%) solution, alternatively (by continuous epidural infusion) 5-12.5 mg/hour, dose administered using a 1.25 mg/mL (0.125%) solution.

Preparations
Levobupivacaine injection, 25 mg / 10 ml ampoule
Levobupivacaine injection, 50 mg / 10 ml ampoule

**Lidocaine Hydrochloride** *(Lignocaine Hydrochloride)*

**Indications:** local anaesthesia, ventricular arrhythmias see section 2.C.

**Contraindications:** hypovolaemia, complete heart block.

**Cautions:** epilepsy, bradycardia, impaired cardiac conduction, porphyria, hepatic or respiratory impairment.

**Side-effects:** see notes above

**Dose:** infiltration anaesthesia, by injection, 200 mg plain and 500 mg when mixed with adrenaline.
Nerve block, epidural and caudal 1-2% with adrenaline.
Surface anaesthesia, 2-4%.

**Preparations**
Lidocaine hydrochloride plain injection, 1 %, 50 mL vial
Lidocaine hydrochloride plain injection, 2%, 25-50 mL vial
Lidocaine hydrochloride plain without preservative injection, 2%, 5 mL vial
Lidocaine hydrochloride heavy injection, 5 %, 10 mL vial
Lidocaine hydrochloride injection with adrenaline injection, 2% + 1:200,000, 20 mL vial
Lidocaine hydrochloride injection with adrenaline injection, 2% + 1:80,000, 1.8 mL dental cartridge
Lidocaine hydrochloride jelly, 2%, 20-30 g/tube
Lidocaine hydrochloride ointment, 5%, 15-35g/tube
Lidocaine hydrochloride spray, 10% preparation, 50 mL pump spray
Lidocaine hydrochloride viscous, 2% preparation
**15: Anaesthesia**

**Prilocaine + felypressin**

**Indications:** infiltration anaesthesia, intravenous regional anaesthesia, nerve block.

**Contraindications:** hypovolaemia, complete heart block, severe anaemia.

**Cautions:** epilepsy, bradycardia, impaired cardiac conduction, porphyria., hepatic or renal impairment.

**Side-effects:** see notes above

**Dose:** adjusted according to site of operation and response of the patient, to a maximum of 300 mg.

**Preparations**

Prilocaine hydrochloride + felypressin injection, 30 mg/mL + 0.54 mg/mL, 1.8 mL dental cartridge

**Ethyl chloride**

Ethyl chloride is applied in spray form for a rapid topical anaesthesia. Severe skin frosting may result from excessive application.

**Preparation**

Ethyl chloride spray; 50 – 100 mL

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15 C: Sedative and analgesic perioperative drugs

**Dexmedetomidine (Restricted)**

**Indications:** Maintenance of sedation during intensive care, adjunct for sedation and general anaesthesia for certain surgical procedures.

**Contra-indications:** Acute cerebrovascular disorders; second- or third-degree AV block (unless pacemaker fitted); uncontrolled hypotension.

**Cautions:** Abrupt withdrawal after prolonged use; bradycardia; ischaemic heart disease; malignant hyperthermia; severe cerebrovascular disease (especially at higher doses); severe neurological disorders; spinal cord injury, hepatic impairment, renal impairment, diabetes, patients on vasodilators

**Side-effects:** Agitation; blood pressure changes; bradycardia; changes in blood sugar; dry mouth; hyperthermia; myocardial infarction; myocardial ischaemia; nausea; tachycardia; vomiting, pleural effusion, pulmonary oedema

**Dose:** ICU sedation: loading dose one microgram/ kg over 10 minutes. Maintenance intravenous infusion: 0.2-1.4 microgram/ kg/hour.

Surgical procedure sedation: loading dose one microgram/ kg over 10 minutes. Maintenance intravenous infusion: 0.6 microgram/ kg/ hour.(titrate usually to 0.2-1 microgram/ kg/ hour)

**Preparations**

Dexmedetomidine injection, 100 micrograms/ ml

**Ketorolac (Restricted)**

**Indications:** Short-term management (≤ 5 days) of moderate to severe acute postoperative pain only. Prophylaxis and reduction of inflammation and associated symptoms following ocular surgery.
Contra-indications: With intramuscular use: active or history of gastro-intestinal bleeding; active or history of gastro-intestinal ulceration; coagulation disorders; complete or partial syndrome of nasal polyps; confirmed or suspected cerebrovascular bleeding; dehydration; following operations with high risk of haemorrhage or incomplete haemostasis; haemorrhagic diatheses; history of gastro-intestinal perforation; hypovolaemia; severe heart failure
With intravenous use: active or history of gastro-intestinal bleeding; active or history of gastro-intestinal ulceration; coagulation disorders; complete or partial syndrome of nasal polyps; confirmed or suspected cerebrovascular bleeding; dehydration; following operations with high risk of haemorrhage or incomplete haemostasis; haemorrhagic diatheses; history of gastro-intestinal perforation; hypovolaemia; severe heart failure, labour and delivery, intrathecal or epidural administration, advanced renal impairment, use as prophylactic analgesia before any major surgery, perioperative pain management in the setting of coronary artery bypass surgery
Cautions: With intramuscular use: allergic disorders; cardiac impairment (NSAIDs may impair renal function); cerebrovascular disease; coagulation defects; connective-tissue disorders; Crohn’s disease (may be exacerbated); elderly (risk of serious side-effects and fatalities); heart failure; ischaemic heart disease; peripheral arterial disease; risk factors for cardiovascular events; ulcerative colitis (may be exacerbated); uncontrolled hypertension
With intravenous use: allergic disorders; cardiac impairment (NSAIDs may impair renal function); cerebrovascular disease; coagulation defects; connective-tissue disorders; Crohn’s disease (may be exacerbated); elderly (risk of serious side-effects and fatalities); heart failure; ischaemic heart disease; peripheral arterial disease; risk factors for cardiovascular events; ulcerative colitis (may be exacerbated); uncontrolled hypertension
Side-effects: With intramuscular use: alveolitis; aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible); hepatic damage; interstitial fibrosis associated with NSAIDs can lead to renal failure; pancreatitis; papillary necrosis associated with NSAIDs can lead to renal failure; pulmonary eosinophilia; Stevens-Johnson syndrome; toxic epidermal necrolysis
With intravenous use: alveolitis; aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible); hepatic
Contrast media are agents used during visualization techniques such as X-ray including computed tomography (CT), some MRI examination or ultrasound imaging, to provide visual contrast in the pictures of different tissues and organs. They can be given orally or intravenously. Contrast media may increase the absorption of X-rays as they pass through the body and this is described as positive contrast. A gas may also be used (air, oxygen or carbon dioxide) for visualization, this will be referred to as negative contrast. When both gas and contrast medium are used concomitantly the procedure is called double contrast.

Contrast media contain elements with high atomic numbers that absorb X-rays. The most commonly used agents are iodinated organic compounds, whose degree of radiodensity is directly proportional to their iodine content. Barium sulphate is a metal salt with an established use as a contrast medium. The iodinated contrast media may be classified into ionic or non-ionic and additionally as monomeric or dimeric.

The ionic monomeric media such as diatrizoates (amidotrizoates) and iopodate have very high osmolality when given in concentrations suitable for radiographic visualization and this have been associated with a relatively high incidence of adverse effects. Since radiodensity depends solely on the iodine concentration, and osmolality solely upon the number of particles in a given weight of solvent, the osmolality of a particular contrast media can be reduced by using dimeric medium such as iotroxinate that contains twice the number of iodine atoms in each molecule or by the use of non-ionic medium. The non-ionic media may be monomeric such as iohexol, iopamidol and iopromide, or dimeric such as iotrolan.

Barium sulphate effectively coats and defines the mucous surface of the gastrointestinal tract. It is not absorbed but forms an even, homogeneous coat on the gastrointestinal mucosa without interacting with the gut secretion or producing misleading radiographic artefacts. Suitable formulations have been produced to improve its coating properties.

### 15: Anaesthesia

Dose: (consult product literature or use the hospital protocol).

Preparations
Ketorolac injection, 30 mg / ml ampoule
Section 16: Contrast media

- Positive contrast (radiopaque)
- Barium sulphate
- Iodinated organic compounds
- Double contrast
- Contrast media for MRI

Contrast media are agents used during visualization techniques such as X-ray including computed tomography (CT), some MRI examination or ultrasound imaging, to provide visual contrast in the pictures of different tissues and organs. They can be given orally or intravenously.

Contrast media may increase the absorption of X-rays as they pass through the body and this is described as positive contrast. A gas may also be used (air, oxygen or carbon dioxide) for visualization, this will be referred to as negative contrast. When both gas and contrast medium are used concomitantly the procedure is called double contrast.

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The non-ionic media may be monomeric such as iohexol, iopamidol and iopromide, or dimeric such as iotrolan.

16 A: Positive contrast (radiopaque)

16 A.1: Barium sulphate

Barium sulphate effectively coats and defines the mucous surface of the gastrointestinal tract. It is not absorbed but forms an even, homogeneous coat on the gastrointestinal mucosa without interacting with the gut secretion or producing misleading radiographic artefacts. Suitable formulations have been produced to improve its coating properties.
16: Contrast media

**Barium sulphate**

**Indications:** radiographic examination of the gastrointestinal tract.

**Contraindications:** should not be used in suspected GI perforation or leak.

**Cautions:** severely ill patients; in patients with intussusception for longer than 24 hours; history of food aspiration.

**Side-effects:** constipation after oral or rectal administration, obstruction and appendicitis have also been reported. Aspiration into the lung has led to pneumonitis or granuloma formation.

**Dose:** orally, 40 - 450 g. Rectally 150 - 750 g.

**Preparations**
- Barium sulphate enema disposable kit
- Barium sulphate suspension, 0.1%, 750 mL
- Barium sulphate cup to make suspension, 177-340 g
- E-Z Cat for CT scanning, 225 mL

16 A.2: Iodinated organic compounds

16 A.2.1: Monomeric ionic contrast media

**Sodium diatrizoate + meglumine diatrizoate**

**Indications:** visualization of the gastrointestinal tract.

**Contraindications:** sensitivity to diatrizoates; anuria; infection or open injury at the site to be examined.

**Cautions:** elderly, or debilitated patients. Iodine containing contrast media may interfere with thyroid function test.

**Side-effects:** nausea and vomiting, flushing and sensation of warmth, various degrees of allergic reactions. Extravasation may lead tissue damage. Renal failure has been reported after intravenous administration in dehydrated patients.

**Dose:** the dose is dependent on the procedures to be performed.

**Preparations**
- Sodium diatrizoate + meglumine diatrizoate injection, 10% + 66% injection

16 A.2.2: Non-ionic contrast media

**Iohexol**

Indications: myelography, angiography, urography, arthrography and visualization of the gastrointestinal tract and body cavities. Iohexol is also used to produce contrast enhancement during computed tomography.

**Contraindications:** see notes under diatrizoate

**Cautions:** elderly, or debilitated patients

**Side-effects:** see under diatrizoate; additionally when applied for myelography; severe headache, backache neck stiffness, and leg or sciatic-type pain. Mental confusion,
mild and transitory perceptual aberrations.

**Dose**: The choice of dose is dependent on the procedure of examination and route of administration. Iohexol is usually available as solutions containing 30.2–70.5% of iohexol which is equivalent to 140 – 350 mg iodine per mL.

**Preparations**
- Iohexol 240 injection, 240 mg/mL, 50 mL vial
- Iohexol 300 injection, 300 mg/mL, 10 mL vial
- Iohexol 300 injection, 300 mg/mL, 50 mL vial
- Iohexol 350 injection, 350 mg/mL, 50 mL vial
- Iohexol 350 injection, 350 mg/mL, 100 mL vial

**Iopromide**

**Indications**: angiography, urography, arthrography and visualization of body cavities.

**Contraindications, cautions and side-effects**: see under diatrizoate

**Dose**: The choice of dose is dependent on the procedure of examination and route of administration. Iopromide is usually available as solutions containing 31.2–76.9% of iopromide, which is equivalent to 150 – 370 mg iodine per mL.

**Preparations**
- Iopromide injection, 499 mg/mL, 50 mL ampoule
- Iopromide injection, 623 mg/mL, 50 and 100 mL ampoules

**Sodium bicarbonate + simethicone + citric acid**

**Indications**: adjunct preparation in double contrast radiography.

**Dose**: orally, 1 tablet 3 times daily and at bed time.

**Preparations**
- Sodium bicarbonate + simethicone + citric acid tablets or granules, 2.21 g + 1.53 g + 0.04 g tablets or granules

**Dimeglumine Gadopentetate**

**Indications**: diagnostic use in MRI.

**Contra-indications**: acute and severe renal insufficiency.

**Cautions**: hypersensitivity, bronchial asthma, cardiovascular disease, seizure disorders, pregnancy.

**Side-effects**: nausea, vomiting, headache, injection site reactions.
Poisoning is the harmful effect that occurs when a toxic substance is swallowed, is inhaled, or comes in contact with the skin, eyes, or mucous membranes. However, any substance ingested in high quantities can be toxic. Common sources of poisons include drugs, household products and chemicals, agricultural products, plants, industrial products and food substances.

Poisoning could be deliberate or accidental. In adults, the majority of cases are deliberate self-poisoning. However, accidental poisoning is more common among children. Substances used in self-poisoning include various categories of drugs, mainly CNS depressants, analgesics (paracetamol or aspirin), anticholinergic drugs, antidepressants, insecticides and others. Some patients use a combination of drugs. Accidental poisoning in children involves the use of household chemicals and drugs, such as petroleum products, disinfectants, detergents, paracetamol, iron tablets or CNS depressants.

Although many cases of drug poisoning present with a clear history of drug overdose ingestion, some patients may not willingly admit the fact or may be admitted unconscious. The diagnosis should be made through obtaining history from conscious patients or from relatives in unconscious ones. Characteristic clinical features remain the best guide to establish a correct diagnosis e.g. sweating, restlessness, and hyperventilation in salicylate poisoning; ulcerative lesions of the mouth in corrosive or pesticide poisoning; papillary dilatation and tachyarrhythmia in overdose with tricyclic antidepressants and anticholinergic drugs.

When the clinical examination or history fail to confirm the diagnosis, chemical analysis of blood or gastric content may be helpful. Blood level may also provide quantitative assessment of the degree of poisoning.

Time should not be wasted when it is difficult to reach a diagnosis; the treating doctor should make every effort to assess the clinical condition of the patient and to initiate effective measures to maintain vital physiological functions without any delay.

### 16: Contrast media

**Preparations**

Dimeglumine Gadopentetate injection, 469 mg/mL, 10 mL vial
Dimeglumine Gadopentetate injection, 469 mg/mL, 15 mL vial

**Gadoteric Acid**

**Indications:** diagnostic use in MRI.

**Cautions:** renal impairment.

**Side-effects:** nausea, paraesthesia, headache.

**Preparations**

Gadoteric Acid injection, 0.5 mmol/mL, 10-15 mL vial
Section 17: Emergency treatment of poisoning

- Removal of poisons from gastrointestinal tract
- Treatment by specific agents

General considerations

Poisoning is the harmful effect that occurs when a toxic substance is swallowed, is inhaled, or comes in contact with the skin, eyes, or mucous membranes. However, any substance ingested in high quantities can be toxic. Common source of poisons include drugs, household products and chemicals, agricultural products, plants, industrial products and food substances. Poisoning could be deliberate or accidental. In adult the majority of cases are deliberate self-poisoning. However, accidental poisoning is more common among children. Substances used in self-poisoning include various categories of drugs, mainly CNS depressants, analgesics (paracetamol or aspirin), anticholinergic drugs, antidepressants, insecticides and others. Some patients use a combination of drugs. Accidental poisoning in children involves the use of household chemicals and drugs, such as petroleum products, disinfectants, detergents, paracetamol, iron tablets or CNS depressants.

Diagnosis of poisoning

Although many cases of drug poisoning present with a clear history of drug overdosage ingestion, some patients may not willingly admit the fact or may be admitted unconscious. The diagnosis should be made through obtaining history from conscious patient or from relatives in unconscious ones. Characteristic clinical features remain the best guide to establish a correct diagnosis e.g. sweating, restlessness, and hyperventilation in salicylate poisoning; ulcerative lesions of the mouth in corrosive or pesticide poisoning; papillary dilatation and tachyarrhythmia in overdosage with tricyclic antidepressants and anticholinergic drugs.

When the clinical examination or history fail to confirm the diagnosis, chemical analysis of blood or gastric content may be helpful. Blood level may also provide quantitative assessment of the degree of poisoning. Time should not be wasted when it is difficult to reach a diagnosis; the treating doctor should make every effort to assess the clinical condition of the patient and to initiate effective measures to maintain vital physiological functions without any delay.
Section 17: Emergency treatment of poisoning

Treatment

Although specific therapy is very useful when available, the following are important general measures in the treatment of all cases of poisoning.

Maintenance of respiration. After assessing respiration, it is important to maintain an unobstructed airway. Pull the tongue forward, remove dentures and mucus, turn the patient to one side and keep head down to prevent aspiration. An oropharyngeal tube is placed in the unconscious patient. Assess ventilation through arterial gas analysis. High concentration of oxygen is given if signs of hypoxia develop. Bronchodilators and in some cases hydrocortisone may be given when there is a significant bronchospasm. If these measures prove inadequate, mechanical ventilation should be considered.

Avoid the use of respiratory stimulant drugs as they are mostly ineffective.

Maintenance of circulation. Cardiac conduction defects and arrhythmias usually result from tissue hypoxia, metabolic disturbances or the direct effect of the poison. Hypoxia and metabolic abnormalities should be corrected. If arrhythmia persists after correction of hypoxia and metabolic disturbances, an appropriate antiarrhythmic agent should be given.

Severe hypotension (systolic blood pressure below 70 mmHg) may lead to irreversible brain damage or renal tubular necrosis. Patients should be nursed while the head is kept downwards. Oxygen therapy should be given to correct hypoxia, and intravenous infusion should be set up whenever possible. Avoid using vasopressor agents, as they may tend to disturb the circulation to vital organs. They may be used in cases of severe hypotension resulting from an overdose of antihypertensive drugs.

Hypertension is less frequent in poisoning; it may be associated with sympathomimetic drugs.

Treatment of CNS effects. Unconscious patients need close observation and nursing. Transient short-lived convulsion does not require treatment. Protracted or recurring convulsion should be treated with intravenous injection of diazepam. Underlying causes such as hypoxia, brain oedema, hypoglycaemia and other metabolic disturbances have to be ruled out.

Maintenance of normal body temperature. Hypothermia may result from overdoses of barbiturates or phenothiazines. Patient with coma for few hours may develop hypothermia. Accurate assessment is necessary and when confirmed, the body should be warmed by wrapping to conserve body heat.

Hyperthermia can develop in patients taking CNS stimulants or antimuscarinic drugs. Body sponging with tepid tap water is usually sufficient. Avoid using iced water.
Section 17: Emergency treatment of poisoning

17 A: Elimination and removal of poison

Removal from stomach
Prevention of further absorption of poison is achieved by emesis or gastric lavage. The danger of gastric emptying should be balanced against the danger of the ingested poison as assessed by the quantity ingested, the toxicity of the poison and the duration of ingestion. Gastric emptying is clearly unnecessary if the risk of toxicity is minimal or the patient presents too late. Gastric lavage is of doubtful value if attempted more than 2 hour after ingestion of the poison. Emesis and gastric lavage is contraindicated in poisoning with corrosives because of the danger of perforating affected tissues and in the unconscious or drowsy for fear of aspiration. Gastric lavage is not recommended in poisoning with petroleum products as inhalation may cause severe chemical pneumonia. The gastric lavage fluid is either normal saline or tepid water given in a volume not exceeding 300 mL at a time. It should be repeated until the return fluid is clear. Emesis can be induced with ipecacuanha mixture or by pharyngeal stimulation in both adults and children. It should only be considered if the patient is fully conscious, if the poison is neither a corrosive nor a petroleum product, if it is not absorbed by activated charcoal, or if gastric lavage is inadvisable or refused by patient.

Ipecacuanha mixture (C.D.L.)
Indications: induction of emesis.
Contraindications: see notes above
Cautions: see notes above
Side-effects: excessive vomiting and mucosal damage; cardiac effects if absorbed.
Dose: adult, 30 mL of ipecacuanha mixture syrup. Child 6-18 months, 10 mL, older child 15 mL, the dose is followed by a 200 mL of water. Repeated if necessary after 30 minutes.

Preparations
Ipecacuanha emetic mixture syrup

Prevention of absorption and elimination after absorption

Many poisons are effectively adsorbed on activated charcoal and their absorption in the stomach is reduced. The sooner an oral activated charcoal is given the better and it could still be effective 1 hour after ingestion of the poison. Repeated oral doses of activated charcoal enhance the elimination of some drugs after being absorbed such as carbamazepine, phenobarbital, quinine, theophylline and dapsone. The usual dose is 50 g initially, followed by 50 g every 4 hours.
**Section 17: Emergency treatment of poisoning**

When the above measures are not effective and the poison is absorbed, other techniques have to be considered such as acidifying or alkalining the urine, peritoneal or haemodialysis for dialyzable toxins.

**Other techniques may be applied such as alkaline or acid diuresis, haemodialysis, or peritoneal dialysis**

*Activated charcoal*

**Indications**: prevention of absorption of toxic substances; selective active elimination *(see notes above).*

**Dose**: for reduction of absorption, orally, adult 50 g, child 25g.
For active elimination 50 g every 4 hours.

**Preparations**
Activated charcoal powder; 50 g/pack
Activated charcoal granules; 50 g/pack

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17 B: Treatment by specific agents

**Paracetamol poisoning**

Ingestion of 10-15 g (20-30 tablets) of paracetamol may cause serious hepatocellular necrosis. Liver damage is maximal 3-4 days after ingestion and may lead to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death.

**Antidotes** such as acetylcysteine may protect the liver if given within 24 hours of ingestion. Patient should be assessed at hospital for the level of serum paracetamol and further measures are considered accordingly.

**Acetylcysteine**

**Indications**: paracetamol overdose.

**Cautions**: asthma.

**Side-effects**: rashes, anaphylaxis.

**Dose**: by intravenous infusion, in 5% glucose intravenous infusion, initial dose 150 mg/kg in 200 mL over 15 minutes, followed by 50 mg/kg in 500 mL over 4 hours, then 100 mg/kg in 1000 mL over 16 hours.

**Preparations**
Acetylcysteine injection, 200 mg/mL, 10 mL ampoule

**Hypnotics and anxiolytics poisonings**

Overdose of benzodiazepines taken alone cause drowsiness, ataxia, dysarthria and occasionally minor and short-lived depression of consciousness and coma in severe cases. Serious sequelae of overdosage are rare because of the high safety index of benzodiazepines. Expert assessment is needed before the use of flumazenil. Special caution should be taken in patients dependent on benzodiazepine because of the possibility of convolution.
Section 17: Emergency treatment of poisoning

Flumazenil
Indications, side-effects and dose: see sec 15A.6.

Iron and heavy metals poisoning

Deferoxamine mesilate (Desferrioxamine mesilate)
Indications: iron poisoning.
Cautions: avoid Prochlorperazine (can cause coma due to a synergistic action between the two drugs).
Side-effects: anaphylactic reaction and hypotension, more frequent with rapid intravenous administration.
Dose: continuous intravenous infusion up to 15 mg/kg/hour; maximum 80 mg/kg in 24 hours.

Preparations
Deferoxamine mesilate injection, 500 mg vial

Dimercaprol (British Anti-Lewisite- BAL) (C.D.L)
Indications: poisoning with antimony, arsenic, bismuth, mercury, gold; adjunct to sodium calcium edetate in lead poisoning.
Contraindications: not indicated for iron, cadmium or selenium poisoning; hepatic impairment.
Cautions: hypertension, renal impairment, elderly, pregnancy and breast-feeding.
Side-effects: nausea and vomiting, headache, tremor, rhinorrhoea & lachrymation; hypertension and tachycardia.

Dose: intramuscularly, 2.5–3 mg/kg every 4 hours for 2 days, 2–4 times on the third day, then 1-2 times daily for 10 days or until recovery.

Preparations
Dimercaprol injection, 50 mg/mL, 2 mL ampoule

Sodium calcium edetate (C.D.L)
Indications: heavy metal poisoning especially lead.
Cautions: renal impairment.
Side-effects: nausea, cramp; renal impairment in overdosage.
Dose: intravenous infusion with sodium chloride 0.9% or dextrose 5% intravenous solutions, 40 mg/kg twice daily for up to 5 days, repeated if necessary.

Preparations
Sodium calcium edetate injection, 200 mg/mL, 5 mL ampoule

Pesticide poisoning

Poisoning with organophosphorus compound is very common. The insecticides are prepared with organic solvents that can be absorbed through intact skin, the bronchi and the gut. Their main effect is the inhibition of cholinesterase enzyme and hence prolonging the effects of acetylcholine. Atropine will help prevent the excessive muscarinic effects of acetylcholine and it can be given in a dose of 2 mg as atro-
Appendix 1: Drug interactions

The use of more than one drug to achieve therapeutic objective or treat co-existing diseases is a common and essential clinical practice. Such concurrent use increases the possibility of an interaction between drugs.

A potential drug interaction refers to the possibility that one drug may alter the intensity of pharmacological effects of another drug simultaneously used. The net result may be enhanced or diminished effects of one or both of the drugs or the appearance of a new effect that is not seen with either drug alone.

Interactions may be either pharmacokinetic (alteration of the absorption, distribution or elimination of one drug by another) or pharmaco-dynamic (such as the interaction between agonist and antagonist on the receptor site).

The most important drug interactions occur with drugs that have serious side-effects and a low therapeutic index, so that a small change in drug concentration can have significant adverse consequences.

**Pharmacokinetic drug-drug interaction**

Drugs may interact at any point during their absorption, distribution, metabolism or excretion. The result will be an increase or decrease in the concentration of drugs at the site of action. As individuals vary in their rates of disposition of any given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable but can be very significant.

**Interactions involving absorption**

Drug absorption can be impeded by an interaction with food or with other drugs. Antacids for example, may delay or even prevent the absorption of many drugs. Drugs altering gastric motility may delay absorption, though this is of little clinical significance unless a high peak plasma concentration is required.

**Interactions involving distribution**

Drugs bind to plasma protein with variable degree. The binding sites are non-specific and one drug can displace another on the same binding site. Such an interaction leads to a shift in plasma concentration of the unbound and effective fraction of the drug. This only produces a detectable effect if the drug is extensively bound to plasma protein and not very widely distributed throughout the body. Such an interaction rarely produces more than a transient potentiation because this increased concentration of the free drug results in an increased rate of elimination.

**Interactions involving metabolism**

Interactions involving drug metabolism can increase or decrease the amount of drug available for action.

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**Section 17: Emergency treatment of poisoning**

Pralidoxime mesilate

**Indications:** adjunct to atropine in the treatment of organophosphorus poisoning.

**Contraindications:** poisoning with neostigmine or other carbamate compounds

**Cautions:** renal impairment, myasthenia gravis.

**Side-effects:** drowsiness, dizziness, disturbances of vision, nausea, tachycardia, headache, hyperventilation, and muscular weakness, laryngospasm.

**Dose:** by slow intravenous injection, 30 mg/kg initially followed by 1-2 further doses if necessary; maximum 12 g in 24 hours.

**Preparations**

Pralidoxime mesilate injection, 200 mg/mL, 5 mL ampoule

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**Methylthioninium chloride (Methylene blue)**

**Indications:** poisoning with drugs or toxins inducing methaemoglobinaemia.

**Contraindications:** severe renal impairment.

**Cautions:** repeated injections may result in severe anaemia.

**Side-effects:** headache, dizziness, nausea and vomiting.

**Dose:** by intravenous injection of 1% solution, 1-4 mg/kg over 10 minutes.

**Preparations**

Methylthioninium chloride injection, 1% solution, 10 mL ampoule

**Sodium thiosulphate**

**Indications:** poisoning with cyanides adjunct to other therapies; poisoning with nitroprusside, cisplatin and bromate.

**Dose:** 12.5 grams given by slow intravenous route over 10 minutes.

**Preparations**

Sodium thiosulphate injection, 25% solution

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**Other poisoning**

**Pine sulphate** intravenously or intramuscularly every 20-30 minutes until signs of atropinisation are seen.

Pralidoxime helps to reactivate the cholinesterase enzyme and should be used in conjunction with atropine but it is only effective if given within 24 hours of exposure.

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Interactions involving metabolism:
Interactions involving drug metabolism can increase or decrease the amount of drug available for action
Appendix 1: Drug interactions

by inhibition or induction of metabolism, respectively. Interactions may occur among administered drugs or between drugs and dietary component (e.g. grapefruit juice) or other chemicals (cigarette smoking, alcohol). The effect of enzyme induction or inhibition is more obviously seen with drugs given orally; as such drugs undergo enterohepatic circulation.

**Interactions involving excretion:** Drugs eliminated through the kidney may interact at the active transport site at the distal tubules, where for example, probenecid inhibits the excretion of penicillin leading to a higher plasma concentration.

**Pharmacodynamic drug-drug inter-actions**
Due to the limitation in quantity of the receptor sites, drugs of similar or antagonistic pharmacological nature may interact on the same receptors. The interaction may be due to competition on the receptor sites or occur between drugs acting on the same physiological system. In general, such interactions are predictable due to the knowledge of pharmacological properties of the drug. Their occurrence is to a greater or lesser extent in most patients who use the interacting drugs.

The following is a list of drugs or therapeutic groups of drugs and their potentially significant interactions alphabetically arranged.

**Abacavir**
Methadone: abacavir possibly reduces plasma concentration of methadone
Phenobarbital: plasma concentration of abacavir possibly reduced by phenobarbital
Phenytoin: plasma concentration of abacavir possibly reduced by phenytoin
Rifampicin: plasma concentration of abacavir possibly reduced by rifampicin
Tipranavir: plasma concentration of abacavir reduced by tipranavir

**ACE Inhibitors**
Adrenergic Neurone Blockers: enhanced hypotensive effect
Alcohol: enhanced hypotensive effect
Alpha-blockers: enhanced hypotensive effect
Alprostadil: enhanced hypotensive effect
Angiotensin-II Receptor Antagonists: enhanced hypotensive effect
Anxiolytics and hypnotics: enhanced hypotensive effect
Beta-blockers: enhanced hypotensive effect
Calcium-channel Blockers: enhanced hypotensive effect
Ciclosporin: increased risk of hyperkalaemia
Corticosteroids: antagonism of hypotensive effect
### Appendix 1: Drug interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect/Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazoxide</td>
<td>enhanced hypotensive effect</td>
</tr>
<tr>
<td>Diuretics</td>
<td>enhanced hypotensive effect (can be extreme)</td>
</tr>
<tr>
<td>Diuretics, Potassium-sparing</td>
<td>risk of severe hyperkalaemia</td>
</tr>
<tr>
<td>Epoetin</td>
<td>antagonism of hypotensive effect and increased risk of hyperkalaemia</td>
</tr>
<tr>
<td>Heparins</td>
<td>increased risk of hyperkalaemia</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>enhanced hypotensive effect</td>
</tr>
<tr>
<td>Insulin</td>
<td>hypoglycaemic effect possibly enhanced</td>
</tr>
<tr>
<td>Lithium</td>
<td>ACE inhibitors reduce excretion of lithium (increased plasma-lithium concentration)</td>
</tr>
<tr>
<td>Metformin</td>
<td>hypoglycaemic effect possibly enhanced</td>
</tr>
<tr>
<td>Methyl dopa</td>
<td>enhanced hypotensive effect</td>
</tr>
<tr>
<td>Nitrates</td>
<td>enhanced hypotensive effect</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>enhanced hypotensive effect</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>antagonism of hypotensive effect, increased risk of renal impairment</td>
</tr>
<tr>
<td>Oestrogens</td>
<td>antagonism of hypotensive effect</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>enhanced hypotensive effect</td>
</tr>
<tr>
<td>Potassium Salts</td>
<td>risk of severe hyperkalaemia</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>hypoglycaemic effect possibly enhanced</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>See under diuretics</td>
</tr>
</tbody>
</table>

### Aciclovir
- Note: Interactions do not apply to topical aciclovir preparations
- Ciclosporin: increased risk of nephrotoxicity
- Mycophenolate: plasma concentration of aciclovir increased by mycophenolate, Also plasma concentration of inactive metabolite of mycophenolate increased
- Probenecid: excretion of aciclovir reduced by probenecid (increased plasma concentration)
- Tacrolimus: possible increased risk of nephrotoxicity when aciclovir given with tacrolimus

### Adalimumab
- Abatacept: increased risk of side-effects when adalimumab given with abatacept
- Anakinra: avoid concomitant use of adalimumab with anakinra
- Vaccines: avoid concomitant use of adalimumab with live vaccines

### Adefovir
- Tenofovir: avoidance of adefovir advised by manufacturer

### Adenosine
- Dipyridamole: effect of adenosine enhanced and extended by dipyridamole (important risk of toxicity)
- Theophylline: anti-arrhythmic effect of adenosine antagonised by theophylline
  - Also, see under Anti-arrhythmic
Appendix 1: Drug interactions

Adrenaline
See under sympathomimetics

Alendronic acid
See under bisphosphonates

Allopurinol
Amoxicillin: increased risk of rash
Ampicillin: increased risk of rash
Azathioprine: effects of azathioprine enhanced with increased toxicity, reduce dose when given with allopurinol
Captopril: increased risk of toxicity especially in renal impairment
Ciclosporin: plasma-ciclosporin concentration possibly increased (risk of nephrotoxicity)
Coumarins: anticoagulant effect possibly enhanced
Mercaptopurine: effects of mercaptopurine enhanced with increased toxicity, reduce dose when given with allopurinol
Theophylline: plasma-theophylline concentration possibly increased

Alpha-blockers
ACE Inhibitors: enhanced hypotensive effect
Adrenergic neurone blockers: enhanced hypotensive effect
Alcohol: enhanced hypotensive effect
Alprostadil: enhanced hypotensive effect
Anaesthetics, General: enhanced hypotensive effect
Angiotensin-II Receptor Antagonists: enhanced hypotensive effect
Antipsychotics: enhanced hypotensive effect
Anxiolytics and Hypnotics: enhanced hypotensive and sedative effects
Beta-blockers: enhanced hypotensive effect; increased risk of first-dose hypotensive effect of post-synaptic alpha-blockers such as prazosin
Calcium-channel Blockers: enhanced hypotensive effect; increased risk of first-dose hypotensive effect of post-synaptic alpha-blockers such as prazosin
Corticosteroids: antagonism of hypotensive effect
Diazoxide: enhanced hypotensive effect
Diuretics: enhanced hypotensive effect; increased risk of first-dose hypotensive effect of post-synaptic alpha-blockers such as prazosin
Hydralazine: enhanced hypotensive effect
Levodopa: enhanced hypotensive effect
Methyldopa: enhanced hypotensive effect
Nitrites: enhanced hypotensive effect
NSAIDs: antagonism of hypotensive effect
Oestrogens: antagonism of hypotensive effect

Alprostadil
Antihypertensives: enhanced hypotensive effects

Amantadine
Antimuscarinics: increased risk of antimuscarinic side-effects  
Antipsychotics: increased risk of extrapyramidal side-effects  
Bupropion: increased risk of side-effects  
Domperidone: increased risk of extrapyramidal side-effects  
Memantine: increased risk of CNS toxicity  
Methyldopa: increased risk of extrapyramidal side-effects  
Metoclopramide: increased risk of extrapyramidal side-effects  
Tetrabenazine: increased risk of extrapyramidal side-effects

Aminoglycosides  
Antibacterial: increased risk of nephrotoxicity with vancomycin  
Antifungals: increased risk of nephrotoxicity with amphotericin  
Bisphosphonates: increased risk of hypocalcaemia  
Ciclosporin: increased risk of nephrotoxicity  
Diuretics: increased risk of ototoxicity with loop diuretics  
Muscle relaxant: effects of non-depolarising muscle relaxant enhanced  

Aminosalicylates  
Azathioprine: possible increased risk of leucopenia  
Mercaptopurine: possible increased risk of leucopenia

Amiodarone  
Amiodarone has a long half-life and a possible interaction might take place with other drugs weeks after the treatment with it has stopped.  
Anti-arrhythmics: enhanced effects  
Anticoagulants: enhanced effects  
Antidepressants: increased risk of ventricular arrhythmias with tricyclic antidepressants  
Antipsychotics: increased risk of ventricular arrhythmias  
Beta-blockers: increased risk of bradycardia, AV block, and myocardial depression  
Calcium channel blockers: increased risk of bradycardia, AV block, and myocardial depression with diltiazem and verapamil  
Cardiac glycosides: increased plasma level of digoxin  
Diuretics: cardiac toxicity increased if hypokalaemia develops  
Ivabradine: increased risk of ventricular arrhythmias when amiodarone given with ivabradine

Amitriptyline  
See under antidepressants

Amoxicillin  
See under penicillin

Amphotericin  
Aminoglycosides: increased risk of nephrotoxicity when amphotericin given with aminoglycosides
Appendix 1: Drug interactions

**Antifungals:** Imidazole effects of amphotericin possibly antagonised by imidazoles
**Antifungals, Triazole effects of amphotericin possibly antagonised by triazoles**

**Cardiac Glycosides:** hypokalaemia caused by amphotericin increases cardiac toxicity with cardiac glycosides

**Ciclosporin:** increased risk of nephrotoxicity when amphotericin given with ciclosporin

**Corticosteroids:** increased risk of hypokalaemia when amphotericin given with corticosteroids — avoid concomitant use unless corticosteroids needed to control reactions

**Diuretics:** Loop or Thiazide increased risk of hypokalaemia

**Pentamidine Isetionate:** possible increased risk of nephrotoxicity

**Polymyxins:** increased risk of nephrotoxicity when amphotericin given with polymyxins

**Tacrolimus:** increased risk of nephrotoxicity when amphotericin given with tacrolimus

**Vancomycin** possible increased risk of nephrotoxicity

**Ampicillin**
*[See under penicillin]*

**Anaesthetics, General**

**Alpha-blockers:** enhanced hypotensive effect

**Antidepressants, Tricyclic:** increased risk of arrhythmias and hypotension

**Antipsychotics:** enhanced hypotensive effect when general anaesthetics given with antipsychotics

**Anxiolytics and Hypnotics:** enhanced sedative effect

**Antihypertensives:** enhanced hypotensive effect

**Argatroban:** increased risk of haemorrhage when anticoagulants given with intravenous diclofenac and ketorolac avoid concomitant use.

**Calcium-channel Blockers:** enhanced hypotensive effect

**Cytotoxics:** nitrous oxide increases antifolate effect of methotrexate

**Dopaminergics:** increased risk of arrhythmias when volatile liquid general anaesthetics given with levodopa

**MAOIs:** because of their hazardous interactions, MAOIs should normally be stopped 2 weeks before surgery

**Methylphenidate:** increased risk of hypertension when volatile liquid general anaesthetics given with methylphenidate

**Muscle Relaxants:** increased risk of myocardial depression and bradycardia when propofol given with suxamethonium; volatile liquid general anaesthetics enhance effects of non-depolarising muscle relaxants and suxamethonium; ketamine enhances effects of atracurium

**Nitrates:** enhanced hypotensive effect

**Nitroprusside:** enhanced hypotensive effect
Appendix 1: Drug interactions

Sympathomimetics: manufacturer of isoflurane advises avoid concomitant use with sympathomimetics (risk of ventricular arrhythmias); increased risk of arrhythmias when volatile liquid general anaesthetics given with adrenaline (epinephrine) or noradrenaline (norepinephrine); increased risk of hypertension when volatile liquid general anaesthetics given with methylphenidate

Vancomycin: hypersensitivity-like reactions can occur with concomitant intravenous vancomycin

Verapamil: enhanced hypotensive effect and AV delay

**Anaesthetics, Local**
Including lignocaine (lidocaine), bupivacaine & levobupivacaine
Anti-arrhythmics: increased risk of myocardial depression
Propranolol: increased risk of bupivacaine and lignocaine toxicity

**Analgesics**
See under individual drugs, aspirin, NSAIDs, opioids and paracetamol

**Angiotensin-II Receptor Antagonists**
ACE Inhibitors: increased risk of hyperkalaemia when
Adrenergic Neurone Blockers: enhanced hypotensive effect
Alcohol: enhanced hypotensive effect
Aldesleukin: enhanced hypotensive effect

Alpha-blockers: enhanced hypotensive effect
Alprostadil: enhanced hypotensive effect
Anaesthetics: General enhanced hypotensive effect
Antipsychotics: enhanced hypotensive effect
Anxiolytics and Hypnotics: enhanced hypotensive effect
Baclofen: enhanced hypotensive effect
Beta-blockers: enhanced hypotensive effect
Calcium-channel Blockers: enhanced hypotensive effect
Ciclosporin: increased risk of nephrotoxicity when amphotericin given with ciclosporin
Corticosteroids: increased risk of hypokalaemia when amphotericin given with corticosteroids—avoid concomitant use unless corticosteroids needed to control reactions

Diuretics: Loop or Thiazide increased risk of hypokalaemia
Pentamidine Isetionate: possible increased risk of nephrotoxicity
Polymyxins: increased risk of nephrotoxicity when amphotericin given with polymyxins
Tacrolimus: increased risk of nephrotoxicity when amphotericin given with tacrolimus
Vancomycin possible increased risk of nephrotoxicity
Ampicillin
See under penicillin

Antipsychotics: enhanced hypotensive effect when general anaesthetics given with antipsychotics
Anxiolytics and Hypnotics: enhanced sedative effect
Antihypertensives: enhanced hypotensive effect
Argatroban: increased risk of haemorrhage when anticoagulants given with intravenous diclofenac and ketorolac avoid concomitant use.
Calcium-channel Blockers: enhanced hypotensive effect
Cytotoxics: nitrous oxide increases antifolate effect of methotrexate
Dopaminergics: increased risk of arrhythmias when volatile liquid general anaesthetics given with levodopa
MAOIs: because of their hazardous interactions, MAOIs should normally be stopped 2 weeks before surgery
Methylphenidate: increased risk of hypertension when volatile liquid general anaesthetics given with methylphenidate
Muscle Relaxants: increased risk of myocardial depression and bradycardia when propofol given with suxamethonium; volatile liquid general anaesthetics enhance effects of non-depolarising muscle relaxants and suxamethonium; ketamine enhances effects of atracurium
Nitrates: enhanced hypotensive effect
Nitroprusside: enhanced hypotensive effect

Epoetin: antagonism of hypotensive effect and increased risk of hyperkalaemia
Epoetin: antagonism of hypotensive effect and increased risk of hyperkalaemia
Hydralazine: enhanced hypotensive effect
Levodopa: enhanced hypotensive effect
Lithium: angiotensin-II receptor antagonists reduce excretion of lithium (increased plasma concentration)
Appendix 1: Drug interactions

**MAOIs:** hypotensive effect of angiotensin-II receptor antagonists possibly enhanced by MAOIs

**Methyldopa:** enhanced hypotensive effect  
**Minoxidil:** enhanced hypotensive effect  
**Moxisylyte** (thymoxamine): enhanced hypotensive effect  
**Moxonidine:** enhanced hypotensive effect when angiotensin-II receptor antagonists given with moxonidine  
**NitrateS:** enhanced hypotensive effect  
**NSAIDs:** increased risk of renal impairment, Also hypotensive effect antagonised  
**Oestrogens:** hypotensive effect of angiotensin-II receptor antagonists antagonised by oestrogens  
**Potassium Salts:** increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with potassium salts Includes salt substitutes  
**Sodium Nitroprusside:** enhanced hypotensive effect  
**Tacrolimus:** increased risk of myocardial depression  
**Tropisetron:** caution with anti-arrhythmics advised by manufacturer of tropisetron (risk of ventricular arrhythmias)  
**Antimalarials:** avoidance of amiodarone advised by manufacturer of artemether with lumefantrine (risk of ventricular arrhythmias); avoidance of flecainide advised by manufacturer of artemether with lumefantrine (risk of ventricular arrhythmias)  
**Antipsychotics:** increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with antipsychotics that prolong the QT interval  
**Beta-blockers:** increased myocardial depression  
**Bupivacaine:** increased myocardial depression  
**Fingolimod:** possible increased risk of bradycardia when fingolimod given with amiodarone, disopyramide or dronedarone  
**Levobupivacaine:** increased myocardial depression  
**Prilocaine:** increased myocardial depression  
**Ropivacaine:** increased myocardial depression  
**Antidepressants (tricyclic):** plasma concentration of some tricyclics increased by SSRIs concentration of some tricyclics increased by SSRIs  
**Antiepileptics:** antagonism (convulsive effect increased by SSRIs)  
**Anticholinergics:** antagonism (concentration of some tricyclics increased by SSRIs)  
**Antibacterials:** ciprofloxacin inhibits metabolism of duloxetine  
**Adrenaline:** hypertension and arrhythmias  
**Barbiturates:** antagonism of antimuscarinic and sedative effects  
**Anxiolytics and hypnotics:** increased antimuscarinic and sedative effects  
**Antihistamines:** increased antimuscarinic side-effects  
**Antipsychotics:** increased plasma-threshold lowered); metabolism of tricyclics possibly accelerated (reduced plasma concentration)  
**Carbamazepine:** possibly accelerated (reduced plasma concentration)  
**Coumarins:** anticoagulant effect increased by MAOIs (risk of serious bleeding)  
**Diuretics:** increased risk of postural hypotension  
**Lithium:** increased risk of CNS toxicity  
**Methylthioninium:** risk of CNS toxicity  
**Lithium:** increased risk of CNS effects (lithium toxicity reported)  
**Coumarins:** anticoagulant effect increased by MAOIs (risk of serious bleeding)  

**Antacids**  
Generally, antacids should not be taken at the same time as other drugs. Impairment of absorption is likely to take place.

**Anti-arrhythmic**  
Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other anti-arrhythmics

**Antimalarials:** avoidance of amiodarone advised by manufacturer of artemether with lumefantrine (risk of ventricular arrhythmias); avoidance of flecainide advised by manufacturer of artemether with lumefantrine (risk of ventricular arrhythmias)

**Antipsychotics:** increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with antipsychotics that prolong the QT interval

**Beta-blockers:** increased myocardial depression

**Bupivacaine:** increased myocardial depression

**Fingolimod:** possible increased risk of bradycardia when fingolimod given with amiodarone, disopyramide or dronedarone

**Levobupivacaine:** increased myocardial depression

**Prilocaine:** increased myocardial depression

**Ropivacaine:** increased myocardial depression

**Antidepressants (tricyclic):** plasma concentration of some tricyclics increased by SSRIs

**Antiepileptics:** antagonism (convulsive effect increased by SSRIs)

**Anticholinergics:** antagonism (concentration of some tricyclics increased by SSRIs)

**Antibacterials:** ciprofloxacin inhibits metabolism of duloxetine

**Adrenaline:** hypertension and arrhythmias

**Barbiturates:** antagonism of antimuscarinic and sedative effects

**Anxiolytics and hypnotics:** increased antimuscarinic and sedative effects

**Antihistamines:** increased antimuscarinic side-effects

**Antipsychotics:** increased plasma-threshold lowered); metabolism of tricyclics possibly accelerated (reduced plasma concentration)

**Carbamazepine:** possibly accelerated (reduced plasma concentration)

**Coumarins:** anticoagulant effect increased by MAOIs (risk of serious bleeding)

**Diuretics:** increased risk of postural hypotension

**Lithium:** increased risk of CNS toxicity

**Methylthioninium:** risk of CNS toxicity

**Lithium:** increased risk of CNS effects (lithium toxicity reported)

**Coumarins:** anticoagulant effect increased by MAOIs (risk of serious bleeding)

**Alcohol:** possibly enhanced sedative effect
Appendix 1: Drug interactions

Antibacterials: ciprofloxacin inhibits metabolism of duloxetine—avoid concomitant use

Antidepressants (tricyclic): plasma concentration of some tricyclics increased by SSRI

Antiepileptics: antagonism (convulsive threshold lowered)

Antimalarials: avoidance of antidepressants advised by manufacturer of artemether with lumefantrine

Barbiturates: antagonism (convulsive threshold lowered)

Beta-blockers: plasma concentration of metoprolol increased by cital-opram; plasma concentration of metoprolol possibly increased by paroxetine, avoid concomitant use in cardiac insufficiency.

Coumarins: anticoagulant effect possibly enhanced

Lithium: increased risk of CNS effects (lithium toxicity reported)

MAOIs: CNS effects of SSRIs increased by MAOIs (risk of serious toxicity)

Methylthioninium: risk of CNS toxicity when SSRI-related antidepressants given with methylthioninium—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)

Tramadol: increased risk of CNS toxicity

Antidepressants, Tricyclic

Adrenaline: hypertension and arrhythmias (but local anaesthetics with adrenaline appear to be safe)

Alcohol: enhanced sedative effect

Amiodarone: increased risk of ventricular arrhythmias (avoid concomitant use)

Anaesthetics, (general): increased risk of arrhythmias and hypotension

Antidepressants, SSRI: plasma concentration of some tricyclics increased by SSRIs

Antiepileptics: antagonism (convulsive threshold lowered)

Antihistamines: increased antimuscarinic and sedative effects

Antimuscarinics: increased antimuscarinic side-effects

Antipsychotics: increased plasma-tricyclic concentrations; possibly increased risk of ventricular arrhythmias

Anxiolytics and hypnotics: enhanced sedative effect

Barbiturates: antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of tricyclics possibly accelerated (reduced plasma concentration)

Carbamazepine: possibly accelerated metabolism of tricyclics (reduced plasma concentration; reduced antidepressant effect)

Disopyramide: increased risk of ventricular arrhythmias

Diuretics: increased risk of postural hypotension

Flecainide: increased risk of ventricular arrhythmias
Appendix 1: Drug interactions

**MAOIs:** CNS excitation and hypertension with MAOIs; tricyclics should not be started until 2 weeks after stopping MAOI (3 weeks if starting clomipramine or imipramine); MAOI should not be started until at least 7-14 days after stopping tricyclic (3 weeks in the case of clomipramine or imipramine)

**Nitrates:** reduced effect of sublingual nitrates (owing to dry mouth)

**Noradrenaline (norepinephrine):** hypertension and arrhythmias

**Oestrogens:** antagonism of antidepressant effect but side-effects possibly increased due to increased plasma concentrations of tricyclics

**Opioid Analgesics:** possibly increased plasma-tricyclic concentration

**Phenothiazines:** increased antimuscarinic side-effects

**Phenytoin:** possibly reduced plasma-tricyclic concentration

**Procainamide:** increased risk of ventricular arrhythmias

**Quinidine:** increased risk of ventricular arrhythmias

**Rifampicin:** plasma concentrations of tricyclics possibly reduced (reduced antidepressant effect)

**Thioridazine:** increased risk of ventricular arrhythmias (avoid concomitant use)

**Tramadol:** increased risk of CNS toxicity

**Verapamil:** possibly increased plasma concentration of tricyclic

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**Anticoagulants**

*See under* individual drugs ar-gatroban, fondaparinux, ivaroxaban and warfarin

**Antidiabetics**

Include, insulins as well

**Alcohol:** enhanced hypoglycaemic effect; increased risk of lactic acidosis when metformin given with alcohol

**Analgesics:** effects of sulfonylureas possibly enhanced by NSAI Ds

**Anabolic Steroids:** hypoglycaemic effect possibly enhanced

**Beta-blockers:** masking of warning signs of hypoglycaemia such as tremor

**Antibacterials:** hypoglycaemic effect of acarbose possibly enhanced by neomycin; effects of sulfonylureas enhanced by chloramphenicol; metabolism of sulfonylureas possibly accelerated by rifamycins (reduced effect); effects of sulfonylureas rarely enhanced by sulfonamides and trimethoprim; hypoglycaemic effect of sulfonylureas possibly enhanced by tetracyclines;

**Anticoagulants:** exenatide possibly enhances anticoagulant effect of warfarin; hypoglycaemic effect of sulfonylureas possibly enhanced by coumarins,

**Antifungals:** plasma concentration of sulfonylureas increased by fluconazole and miconazole; hypoglycaemic effect of gliclazide enhanced by miconazole; plasma
Appendix 1: Drug interactions

concentration of sulfonylureas possibly increased by voriconazole

Corticosteroids: antagonism of hypoglycaemic effect

Diazoxide: hypoglycaemic effect antagonised by Diazoxide

Diuretics, Loop: antagonism of hypoglycaemic effect

Diuretics, Thiazide and related compounds: antagonism of hypoglycaemic effect

Lipid regulating Drugs: hypoglycaemic effect of acarbose possibly enhanced by colestyramine; plasma concentration of glibenclamide possibly increased by fluvastatin; may be improved glucose tolerance and an additive effect when insulin or sulfonylureas given with fibrates

Lithium: may occasionally impair glucose tolerance

MAOIs: possibly enhanced hypoglycaemic effect

Oestrogens: antagonism of hypoglycaemic effect

Progestogens: antagonism of hypoglycaemic effect

Testosterone: Hypoglycaemic effect possibly enhanced

Antiepileptics
See under individual drugs, carbamazepine, Clonazepam, chlorpromazine, lamotrigine, phenytoin, phenobarbitone, sodium valproate

Antifungals

Imidazole and triazole

**Imidazole antifungals include, clotrimazole, ketoconazole and miconazole; Triazole antifungals include fluconazole, voriconazole and itraconazole.**

Antacids: reduce absorption of itraconazole and ketoconazole

Anti-arrhythmics: plasma concentration of quinidine increased by itraconazole and miconazole

Antibacterials: rifampicin accelerates fluconazole, itraconazole, voriconazole and ketoconazole metabolism. Plasma concentration of ketoconazole may be reduced by isoniazid. Plasma concentration of itraconazole increased by clarithromycin. Triazoles possibly increase plasma concentration of rifabutin

Anticoagulants: warfarin effects enhanced by imidazole and Triazole antifungals; manufacturer of rivaroxaban advises avoid concomitant use with itraconazole; plasma concentration of rivaroxaban increased by ketoconazole—avoid concomitant use; manufacturer of rivaroxaban advises avoid concomitant use with voriconazole

Antidepressants: avoidance of triazoles advised by manufacturer of reboxetine; fluconazole possibly increases plasma concentration of amitriptyline and nortriptyline; plasma concentration of voriconazole reduced by St John’s wort avoid concomitant use

Antidiabetics: plasma concentration of sulphonylureas increased by
Appendix 1: Drug interactions

fluconazole, voriconazole and miconazole

Antiepileptics: effects of phenytoin enhanced by fluconazole and miconazole. Plasma concentration of itraconazole and ketoconazole reduced by phenytoin. Voriconazole increases plasma concentration of phenytoin, also phenytoin reduces plasma concentration of Voriconazole. Fluconazole possibly increases plasma concentration of carbamazepine; plasma concentration of voriconazole possibly reduced by carbamazepine and phenobarbital.

Antifungals, others: possible antagonism of amphotericin effect

Antihistamines: astizamole and terfenadine metabolism inhibited

Antimalarials: avoidance of imidazoles advised by manufacturer of arte-merther with lumefantrine; avoidance of triazoles advised by manufacturer of artemether with lumefantrine

Antimuscarinic: reduced absorption of ketoconazole

Antivirals: plasma concentration of zidovudine increased by fluconazole. Plasma concentration of voriconazole reduced by Ritonavir. Triazoles possibly increase plasma concentration of saquinavir. Fluconazole increases plasma concentration of zidovudine.

Anxiolytics and hypnotics: prolonged sedative effects of midazolam and diazepam

Calcium-channel blockers: plasma concentration of felodipine and other analogues increased

Cardiac glycosides: plasma concentration of digoxin increased by itraconazole

Ciclosporin: plasma concentration of ciclosporin increased

Clopidogrel: fluconazole, itraconazole and voriconazole possibly reduce antiplatelet effect of clopidogrel

Colchicine: itraconazole possibly increases risk of colchicine

Corticosteroids: itraconazole possibly inhibits metabolism of corticosteroids and methylprednisolone; itraconazole increases the plasma concentration of inhaled and oral budesonide; itraconazole increases plasma concentration of inhaled fluticasone

Cytotoxics: itraconazole may inhibit metabolism of vincristine

Diuretics: plasma concentration of fluconazole increased by hydrochlorothiazide

Domperidone: possible increased risk of ventricular arrhythmias when itraconazole or voriconazole

Everolimus: plasma concentration of everolimus possibly increased by voriconazole and itraconazole

Ivabradine: fluconazole increases plasma concentration of ivabradine—reduce initial dose of ivabradine; itraconazole possibly increases plasma concentration of ivabradine—avoid concomitant use; ketoconazole increases plasma concentration of ivabradine—reduce initial dose.
Appendix 1: Drug interactions

concentration of ivabradine—avoid concomitant use.
Lipid-regulating drugs: increased risk of myopathy with simvastatin and atorvastatin
Oestrogens and progestogens: possible contraceptive failure with imidazole and triazole antifungals
Opioids: Alfentanil metabolism inhibited by ketoconazole
Retinoids: fluconazole and voriconazole possibly increase risk of tretinoin toxicity
Sirolimus: fluconazole, itraconazole and voriconazole possibly increase plasma concentration of sirolimus
Tacrolimus: fluconazole, itraconazole and voriconazole increase plasma concentration of tacrolimus
Theophylline: plasma concentration increased by fluconazole
Ulcer-healing drugs: H2-receptor antagonists and proton pump inhibitors reduce absorption of ketoconazole and itraconazole. Sucralfate reduces absorption of ketoconazole. Voriconazole possibly increases plasma concentration of esomeprazole and omeprazole

Antihistamines
Non-sedating antihistamines show less sedative interactions; they do not potentiate the effects of alcohol
Alcohol: enhanced sedative effects
Antacids: reduced absorption
Anti-arrhythmics: avoid concomitant use

Antibacterials: possibility of increased plasma loratidine concentration with erythromycin
Antidepressants: MAOIs and tricyclics increase antimuscarinic and sedative effects
Antifungals: possibility of increased plasma loratidine concentration with ketoconazole
Antimuscarinics: increased antimuscarinic side-effects
Antipsychotics: avoid concomitant use with terfenadine - increased risk of ventricular arrhythmias
Antivirals: possibility of increased plasma loratidine concentration
Anxiolytics and hypnotics: enhanced sedative effects
Beta-blockers: sotalol may increase the risk of ventricular arrhythmias with non-sedating antihistamines
Betahistine: enhanced sedative effects

Antihypertensive drugs
See under individual drugs

Antimalarials
See under individual drugs

Antimuscarinics
Many drugs have antimuscarinic effects. Effects such as dry mouth, urine retention, constipation and blurred vision may be augmented when two drugs with antimuscarinic effects are used concomitantly. In the elderly, confusion is a notable interaction
Appendix 1: Drug interactions

**Alcohol:** sedative effect of hyoscine enhanced

**Anti-arrhythmics:** atropine delays absorption of mexiletine; increased antimuscarinic effects with disopyramide

**Antidepressants:** increased antimuscarinic side-effects with tricyclics and MAOIs

**Antifungals:** reduced absorption of ketoconazole

**Antihistamines:** increased antimuscarinic effects

**Antipsychotics:** increased antimuscarinic effects

**Antivirals:** plasma concentration of solifenacin possibly increased by ritonavir

**Dopaminergics:** absorption of levodopa possibly reduced

**Metoclopramide and domperidone:** antimuscarinics antagonize gastrointestinal effects

**Antiplatelet drugs**

*See under individual drugs*

**Antipsychotics**

Avoid concomitant use with drugs that may induce agranulocytosis such as carbamazepine, co-trimoxazole, chloramphenicol, sulphonamide, penicillamine or cytotoxics

**ACE inhibitors:** severe postural hypotension with chlorpromazine and possibly other phenothiazines

**Alcohol:** enhanced sedative effects

**Anaesthetics:** enhanced hypotensive effects

**Analgesics:** enhanced hypotensive and sedative effects with opioid analgesics

**Antacids:** reduced absorption

**Antarrhythmics:** increased risk of ventricular arrhythmias with thioridazine

**Antibacterials:** rifampicin enhances haloperidol metabolism (reduced plasma haloperidol concentration)

**Antidepressants:** increased plasma concentration and antimuscarinic effects on administration of tricyclics with phenothiazines and possibly with fluoxetine; fluoxetine increases plasma concentration of olanzapine and haloperidol

**Antiepileptics:** antagonism; carbamazepine accelerates the metabolism of haloperidol, olanzapine, and risperidone

**Antihypertensives:** enhanced hypotensive effects; increased risk of extrapyramidal effects with methyl-dopa

**Antimalarials:** manufacturer of artemether with lumefantrine advises avoid concomitant use with antipsychotics

**Antimuscarinics:** antimuscarinic side-effects of phenothiazines increased

**Antipsychotics (other):** increased risk of ventricular arrhythmias with thioridazine and other phenothiazines

**Antivirals:** plasma concentration of quetiapine possibly increased by darunavir—manufacturer of quetiapine advises avoid con-comitant use
Appendix 1: Drug interactions

Anxiolytics and hypnotics: enhanced sedative effects; buspirone increases plasma concentration of haloperidol
Beta-blockers: phenothiazines increases risk of ventricular arrhythmias with sotalol
Cabergoline: hypoprolactinaemic and antiparkinsonian effects of cabergoline antagonised by antipsychotics
Deferasirox: manufacturer of deferasirox advises avoid concomitant use with clozapine
Diuretics: hypokalaemia increases risk of ventricular arrhythmias with thioridazine
Dopaminergics: antagonism of effects
Everolimus: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Gefitinib: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Lapatinib: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Lithium: increased risk of neurotoxicity with phenothiazines, haloperidol and clozapine
Metoclopramide and domperidone: increased risk of extrapyramidal effects
Sorafenib: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Ulcer-healing drugs: cimetidine enhances effects of antipsychotics

Antivirals
See under individual drugs

Antioxylitics and Hypnotics
Alcohol: enhanced sedative effects
Anaesthetics, general: enhanced sedative
Analgesics: opioids enhance sedative effects
Antibacterials: clarithromycin and erythromycin
Inhibit metabolism of midazolam with profound sedation; rifampicin inhibit metabolism of diazepam and possibly other benzodiazepines
Antidepressants: enhanced sedative effects
Antiepileptics: plasma phenytoin concentrations fluctuate by diazepam, possibly other benzodiazepines
Antifungals: itraconazole, ketoconazole and fluconazole increase plasma concentration of midazolam
Antihistamines: enhanced sedative effects
Antihypertensives: enhanced hypotensive effects
Antipsychotics: enhanced sedative effects
Antivirals: increased risk of enhanced and prolonged sedative effects and respiratory depression
Calcium-channel blockers: enhanced effect of midazolam

Apraclonidine
Antidepressants: manufacturer of apraclonidine advises avoid con-
Appendix 1: Drug interactions

comitant use with MAOIs, tricyclic-related antidepressants and tricyclics

**Sympathomimetics:** manufacturer of apraclonidine advises avoid comitant use with sympathomimetics.

### Aprepitant

**Contraceptives:** aprepitant possibly causes contraceptive failure of hormonal contraceptives containing oestrogens (alternative contraception recommended); aprepitant possibly causes contraceptive failure of hormonal contraceptives containing progestogens (alternative contraception recommended)

### Argatroban

**Analgesics:** increased risk of haemorrhage when anticoagulants given with intravenous diclofenac and ketorolac avoid comitant use.

**Anticoagulants:** increase risk of haemorrhage when given with other anticoagulants including Rivaroxaban (avoid comitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)

### Artemether + lumefantrine

**Antidepressants:** avoidance of antidepressants advised by manufacturer of artemether with lumefantrine

**Antiarrhythmics:** avoidance of amiodarone advised by manufacturer of artemether with lumefantrine (risk of ventricular arrhythmias); avoidance of flecainide advised by manufacturer of artemether with lumefantrine (risk of ventricular arrhythmias)

**Antimalarials:** avoidance of antimalarials advised by manufacturer of artemether with lumefantrine

**Antipsychotics:** manufacturer of artemether with lumefantrine advises avoid comitant use with antipsychotics

**Antivirals:** plasma concentration of artemether with lumefantrine reduced by efavirenz

**Beta-blockers:** manufacturer of artemether with lumefantrine advises avoid comitant use with metoprolol; manufacturer of artemether with lumefantrine advises avoid comitant use with sotalol

**Antibacterial:** avoidance of macrolides advised by manufacturer of artemether with lumefantrine; avoidance of quinolones advised by manufacturer of artemether with lumefantrine

**Antifungals:** avoidance of imidazoles advised by manufacturer of artemether with lumefantrine; avoidance of triazoles advised by manufacturer of artemether with lumefantrine

### Aspirin

**Other analgesics:** increased risk of side-effects with other NSAIDs

**Antacids:** aspirin excretion increased in alkaline urine

**Anticoagulants:** increased risk of bleeding due to antiplatelet effect
Appendix 1: Drug interactions

Antidepressants: increased risk of bleeding when aspirin given with SSRIs
Antiplatelet: increased risk of bleeding
Corticosteroids: increased risk of gastro-intestinal bleeding and ulceration
Cytotoxic: increased risk of toxicity with methotrexate
Diuretics: antagonism of Spironolactone diuretic effect
Metoclopramide and domperidone: enhanced effect of aspirin
Uricosurics: effects of probenecid and sulphinpyrazone reduced

Atenolol
See Beta -blockers

Atomoxetine:
Amiodarone: increased risk of ventricular arrhythmias
Antidepressants: possible increased risk of convulsions
Antidepressants, Tricyclic: increased risk of ventricular arrhythmias
Antipsychotics: increased risk of ventricular arrhythmias when atomoxetine given with antipsychotics that prolong the QT interval
Bupropion: possible increased risk of convulsions
Disopyramide: increased risk of ventricular arrhythmias
Diuretics: risk of ventricular arrhythmias with atomoxetine increased by hypokalaemia caused by diuretics
Erythromycin: increased risk of ventricular arrhythmias when atomoxetine given with parenteral erythromycin
Fluoxetine: metabolism of atomoxetine possibly inhibited by fluoxetine
MAOs: atomoxetine should not be started until 2 weeks after stopping MAOIs, Also MAOIs should not be started until at least 2 weeks after stopping atomoxetine
Methadone: increased risk of ventricular arrhythmias
Moxifloxacin: increased risk of ventricular arrhythmias
Paroxetine: metabolism of atomoxetine possibly inhibited by paroxetine
Procainamide: increased risk of ventricular arrhythmias
Sotalol: increased risk of ventricular arrhythmias
Tramadol: possible increased risk of convulsions

Atorvastatin:
See under statins

Atracurium
See Muscle Relaxants

Atropine
See antimuscarinics

Azathioprine
Appendix 1: Drug interactions

**ACE Inhibitors**: increased risk of leucopenia

**Allopurinol**: increased risk of toxicity

**Antibacterials**: increased risk of haematological toxicity with co-trimoxazole

**Anticoagulants**: anticoagulant effect of warfarin possibly reduced

**Azithromycin**
See under erythromycin

**Baclofen**
See under muscle relaxants

**Barbiturates**

- Alcohol: enhances sedative effects
- Anti-arrhythmics: metabolism of disopyramide and quinidine increased

**Antibacterials**: metabolism of chloramphenicol, doxycycline and metronidazole increased

**Anticoagulants**: metabolism of warfarin accelerated; phenobarbital plasma concentration of rivaroxaban possibly reduced by phenobarbital—manufacturer of rivaroxaban advises monitor for signs of thrombosis

**Antidepressants**: antagonism of anti-convulsant effect

**Antiepileptics**: enhanced sedative and anti-convulsant effects

**Antipsychotics**: antagonism of anti-convulsant effect

**Calcium-channel blockers**: effect reduced

**Ciclosporin**: metabolism of ciclosporin accelerated

**Corticosteroids**: metabolism of corticosteroids accelerated

**Oestrogens and progestogens**: metabolism of gestrinone, Tibolone and oral contraceptives accelerated

**Bendamustine**

**Antipsychotics**: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

**Benzodiazepines**
See anxiolytics and hypnotics

**Benzylpenicillin**
See penicillins

**Beta-blockers**

Systemic absorption of topically applied preparation to the eye may take place.

**Alcohol**: enhanced hypotensive effect

**Alpha blockers**: enhanced hypotensive effect when beta-blockers are given with alpha-blockers, also increased chance of first dose hypotension with post-synaptic alpha blockers such as prazosin

**Alprostadil**: enhanced hypotensive effect

**Anaesthetics, local**: increased risk of bupivacaine toxicity with propranolol

**Analgesics**: NSAIDs antagonise hypotensive effect

**Anti-arrhythmics**: increased risk of myocardial depression and bradycardia
Appendix 1: Drug interactions

Antibacterials: metabolism of bisoprolol and accelerated by rifampicin. Plasma concentration of metoprolol reduced by rifampicin. 
Antidepressants: enhanced hypotensive effects with MAOIs; risk of ventricular arrhythmias associated with sotalol increased by tricyclics; plasma concentration of metoprolol increased by citalopram; Plasma concentration of metoprolol possibly increased by paroxetine, avoid concomitant use in cardiac insufficiency.
Antihypertensives: enhanced hypotensive effect
Antimalarials: manufacturer of artemether with lumefantrine advises avoid concomitant use with metoprolol or sotalol.
Antipsychotics: risk of ventricular arrhythmias associated with sotalol increased by phenothiazines
Anxiolytics and hypnotics: enhanced hypotensive effect
Calcium-channel blockers: increased risk of bradycardia and AV block with diltiazem; severe hypotension with nifedipine; asystole, severe hypotension and heart failure with verapamil
Cardiac glycosides: increased AV block and bradycardia
Corticosteroids: antagonise hypotensive effects
Diuretics: enhanced hypotensive effect
Fingolimod: possible increased risk of bradycardia when fingolimod given with beta-blockers
Ivabradine: increased risk of ventricular arrhythmias when sotalol given with ivabradine
Oestrogens and progestogens: oestrogens and combined oral contraceptives antagonize hypotensive effect
Sympathomimetics: severe hypertension with adrenaline, noradrenaline and possible with dobutamine

Betahistine
Antihistamines: antagonism (on theoretical basis)

Betamethasone
See corticosteroids

Bethanechol
See parasympathomimetics

Bezafibrate
See fibrates

Bicalutamide
Anticoagulants: bicalutamide possibly enhances anticoagulant effect of coumarins.

Biguanides:
See antidiabetics

Bile Acids:
Antacids: absorption of bile acids possibly reduced by antacids
Colestipol: absorption of bile acids possibly reduced by colestipol
Colestyramine: absorption of bile acids possibly reduced by colestyramine
Appendix 1: Drug interactions

Oestrogens: elimination of cholesterol in bile increased when bile acids given with oestrogens

**Bismuth chelate**
See tripotassium

**Bisoprolol**
See under beta-blockers

**Bisphosphonates**
Antacids: reduced absorption
Antibacterials: increased risk of hypocalcaemia with aminoglycosides
Calcium salt: reduced absorption
Iron: reduced absorption

**Bleomycin**
Cisplatin: increased pulmonary toxicity
*Also*, see cytotoxics

**Bortezomib:**
Ketoconazole: plasma concentration of bortezomib increased by ketoconazole
*Also, see under cytotoxics*

**Brimonidine**
Antidepressants, Tricyclic: manufacturer of brimonidine advises avoid concomitant use with tricyclics
MAOIs: manufacturer of brimonidine advises avoid concomitant use with MAOIs

**Bromazepam**
See anxiolytics and hypnotics

**Bromocriptine**
Alcohol: reduced tolerance to bromocriptine
Antibacterials: erythromycin increases risk of toxicity
Antipsychotics: antagonism of hypoprolactinaemic and antiparkinsonian effects
Metoclopramide and domperidone: antagonism of hypoprolactinaemic effect
Sympathomimetics: increased risk of toxicity with bromocriptine and phenylpropanolamine

**Budesonide**
See under corticosteroids

**Bupivacaine**
See local anaesthetics

**Buspirone**
See anxiolytics and hypnotics

**Busulfan**
Itraconazole: metabolism of busulfan inhibited by itraconazole (increased risk of toxicity)
Metronidazole: plasma concentration of busulfan increased by metronidazole (increased risk of toxicity)
Paracetamol: metabolism of intravenous busulfan possibly inhibited by paracetamol (manufacturer of
intravenous busulfan advises caution within 72 hours of paracetamol
Phenytoin: plasma concentration of busulfan possibly reduced by phenytoin
Tioguanine: increased risk of hepatotoxicity
Also, see cytotoxics

**Cabergoline**
- **Antibacterials:** plasma concentration of cabergoline increased by erythromycin; plasma concentration of cabergoline possibly increased by macrolides
- **Antipsychotics:** hypoprolactinaemic and antiparkinsonian effects of cabergoline antagonised by antipsychotics
- **Domperidone:** hypoprolactinaemic effect of cabergoline possibly antagonised by domperidone
- **Methyldopa:** antiparkinsonian effect of dopaminergics antagonised by methyldopa
- **Metoclopramide:** hypoprolactinaemic effect of cabergoline antagonised by metoclopramide

**Calcium salts**
- **Antibacterials:** reduced absorption of ciprofloxacin and tetracyclines
- **Cardiac glycosides:** large intravenous injection of calcium can precipitate arrhythmias.

**Calcium-channel blockers**
- **Grapefruit juice** significantly increases plasma concentration of dihydropyridine calcium-channel blockers and verapamil

**ACE Inhibitors:** enhanced hypotensive effect
- **Alcohol:** enhanced hypotensive effect
- **Alpha-blockers:** enhanced hypotensive effect; increased risk of first-dose hypotensive effect of post-synaptic alpha-blockers such as prazosin
- **Alprostadil:** enhanced hypotensive effect
- **Anaesthetics, General:** enhanced hypotensive effect; verapamil increases hypotensive effects and risk of AV delay
- **Anti-arrhythmics:** amiodarone-induced risk of AV Block, bradycardia and myocardial depression increased by diltiazem and verapamil
- **Antibacterials:** rifampicin increases metabolism; erythromycin inhibits metabolism of calcium channel blockers
- **Antidepressants:** diltiazem and verapamil increase plasma concentration of tricyclics
- **Antiepileptics:** effect of carbamazepine enhanced by diltiazem and verapamil
- **Antifungals:** possibly increased negative inotropic effects of itraconazole
- **Antihypertensives:** enhanced hypotensive effects
Appendix 1: Drug interactions

Antipsychotics: enhanced hypotensive effect

Anxiolytics and Hypnotics: enhanced hypotensive effect; diltiazem and verapamil inhibit metabolism of midazolam

Beta-blockers: enhanced hypotensive effect; increased risk of bradycardia and AV block with diltiazem; severe hypotension, asystole and heart failure with verapamil

Cardiac glycosides: plasma concentration of digoxin increased

Corticosteroids: antagonism of hypotensive effect

Diuretics: enhanced hypotensive effect

Everolimus: plasma concentration of both drugs may increase when everolimus given with verapamil

Fingolimod: possible increased risk of bradycardia when fingolimod given with diltiazem or verapamil

Ivabradine: diltiazem increases plasma concentration of ivabradine—avoid concomitant use; verapamil increases plasma concentration of ivabradine—avoid concomitant use

Lenalidomide: plasma concentration of lenalidomide possibly increased by verapamil

NSAIDs: antagonism of hypotensive effect

Theophylline: possibly enhanced theophylline effect (possibly increased plasma-theophylline concentration)

See Fluorouracil

Capreomycin

Other antibacterials: increased risk of nephrotoxicity and ototoxicity with aminoglycosides and vancomycin

Cytotoxics: increased risk of nephrotoxicity and ototoxicity with cisplatin

Captopril

See under ACE inhibitors

Carbamazepine

Acetazolamide: acetazolamide increases plasma-carbamazepine concentration

Alcohol: possibly enhanced CNS side-effects of carbamazepine

Antibacterials: effect of doxycycline reduced; clarithromycin and erythromycin increase plasma-carbamazepine concentration

Anticoagulants: accelerated metabolism of coumarins (reduced anticoagulant effect)

Antidepressants, Tricyclic: possibly accelerated metabolism of tricyclics (reduced plasma concentration; reduced antidepressant effect)

Antipsychotics: antagonism of anticonvulsant effect (convulsive threshold lowered)

Calcium-channel Blockers (dihydropyridines): probably reduced effect of dihydropyridine

Ciclosporin: accelerated metabolism (reduced plasma-ciclosporin concentration)
Corticosteroids: accelerated metabolism of corticosteroids (reduced effect)
Diuretics: increased risk of hypokalaemia
Hormone antagonists: danazol inhibits metabolism of carbamazepine
Oestrogens and progestogens: carbamazepine enhances metabolism of oral contraceptives
Rivaroxaban: plasma concentration possibly reduced by carbamazepine—manufacturer of rivaroxaban advises monitor for signs of thrombosis
Vitamins: carbamazepine possibly increases vitamin D requirements

**Carbonic anhydrase inhibitors**
See diuretics

**Cardiac glycosides**
ACE inhibitors: possibly increases plasma concentration of digoxin
Acetazolamide: Increased toxicity if hypokalaemia occurs
Anti-arrhythmics: plasma concentration of digoxin increased by amiodarone
Antifungals: increased toxicity if hypokalaemia occurs with amphoterin
Antimalarials: raise plasma concentration of digoxin
Beta-blockers: increased AV block and bradycardia
Calcium Channel blockers: plasma concentration of digoxin increased by diltiazem and verapamil

Calcium Salts: large intravenous doses of calcium can precipitate arrhythmias
Corticosteroids: increased risk of hypokalaemia
Diuretics: increased toxicity if hypokalaemia occurs
Lenalidomide: possibly increases plasma concentration of digoxin
NSAIDs: possibly exacerbation of heart failure, reduced GFR, and increased plasma-cardiac glycoside concentrations

**Carvedilol**
See beta-blockers

**Caspofungin**
Ciclosporin: plasma concentration of caspofungin increased by ciclosporin (manufacturer of caspofungin recommends monitoring liver enzymes)
Corticosteroids: plasma concentration of caspofungin possibly reduced by dexamethasone
Tacrolimus: caspofungin reduces plasma concentration of tacrolimus

**Cefaclor**
See cephalosporins

**Cefalaxin (cephalexin)**
See cephalosporins

**Cefixime**
See cephalosporins

**Cefotaxime**
See cephalosporins
Appendix 1: Drug interactions

### Cefradine
See cephalosporins

### Ceftazidime
See cephalosporins

### Ceftriaxone
See cephalosporins

### Cefuroxime
See cephalosporins

### Celecoxib
See under NSAIDs

### Cephalosporins
- **Antacids**: reduced absorption
- **Diuretics**: loop diuretics may increase nephrotoxicity
- **Uricosurics**: excretion of cephalosporins reduced by probenecid

### Cetirizine
See antihistamines

### Chloral hydrate
See anxiolytics and hypnotics

### Chloramphenicol
- **Anticoagulants**: anticoagulant effect enhanced
- **Antidiabetics**: effects of sulphonylureas enhanced
- **Antiepileptics**: increased plasma concentration of phenytoin
- **Ciclosporin**: plasma concentration of ciclosporin possibly increased

### Chloroquine and Hydroxychloroquine
- **Agalsidase Alfa and Beta**: chloroquine and hydroxychloroquine possibly inhibit effects of agalsidase alfa and beta
- **Amiodarone**: increased risk of ventricular arrhythmias
- **Antacids**: absorption of chloroquine and hydroxychloroquine reduced by antacids
- **Antiepileptics**: possible increased risk of convulsions
- **Ciclosporin**: chloroquine and hydroxychloroquine increase plasma concentration of ciclosporin (increased risk of toxicity)
- **Cimetidine**: metabolism of chloroquine and hydroxychloroquine inhibited by cimetidine (increased plasma concentration)
- **Digoxin**: chloroquine and hydroxychloroquine possibly increase plasma concentration of digoxin
- **Kaolin**: absorption of chloroquine and hydroxychloroquine reduced by kaolin
- **Lanthanum**: absorption of chloroquine and hydroxychloroquine possibly reduced by lanthanum (give at least 2 hours apart)
- **Laronidase**: chloroquine and hydroxychloroquine possibly inhibit effects of laronidase (manufacturer of laronidase advises avoid concomitant use)
- **Mefloquine**: increased risk of convulsions when chloroquine and hydroxychloroquine given with mefloquine
Appendix 1: Drug interactions

Moxifloxacin: increased risk of ventricular arrhythmias when chloroquine and hydroxychloroquine given with moxifloxacin
Neostigmine: chloroquine and hydroxychloroquine have potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine
Pyridostigmine: chloroquine and hydroxychloroquine have potential to increase symptoms of myasthenia gravis and thus diminish effect of pyridostigmine

Chlorpheniramine
See antihistamines

Chlorpromazine
See antipsychotics

Ciclosporin
ACE Inhibitors: Increased risk of hyperkalaemia
Allopurinol: plasma-ciclosporin concentration possibly increased (risk of nephrotoxicity)
Antibacterials: increased risk of nephrotoxicity with aminoglycosides and quinolones,
Anti-arrhythmics: amiodarone possibly increases plasma concentration of ciclosporin
Antidepressants: carbamazepine and phenytoin increase metabolism of ciclosporin
Antifungals: increased risk of nephrotoxicity with amphotericin

Antimalarials: chloroquine increases plasma ciclosporin concentration
Calcium-channel blockers: diltiazem, verapamil increase plasma-ciclosporin concentration
Caspofungin: plasma concentration of caspofungin increased by ciclosporin (manufacturer of caspofungin recommends monitoring liver enzymes)
Corticosteroids: high dose methylprednisolone increases plasma ciclosporin concentration (risk of convulsion)
Cytotoxics: increases risk of neurotoxicity, and nephrotoxicity
Diuretics, Potassium-sparing: increased risk of hyperkalaemia
Everolimus plasma concentration of everolimus increased by ciclosporin
Lenalidomide: plasma concentration of lenalidomide possibly increased by ciclosporin
Lipid regulating drugs: increased risk of myopathy with statins; possible increased risk of renal impairment with fibrates
NSAIDs: increased risk of nephrotoxicity
Oestrogens and progestogens: progestogens inhibits metabolism of ciclosporin
Potassium salts: increased risk of hyperkalaemia
Vaccines: avoid use of live vaccines with immunosuppressant drugs
Appendix 1: Drug interactions

**Cimetidine**
See H₂-antihistamines

**Cinacalcet**
Hormone Antagonists: cinacalcet possibly inhibits metabolism of tamoxifen to active metabolite

**Ciprofloxacin**
See quinolones

**Cisatracurium**
See muscle relaxants

**Cisplatin**
See platinum compounds

**Citalopram**
See antidepressants

**Clarithromycin**
See erythromycin

**Clindamycin**
Parasymptomimetics: antagonism of effects of neostigmine and pyridostigmine

**Clodronate**
See Bisphosphonates

**Clomethiazole**
See antiepileptics

**Clomipramine**
See antidepressants

**Clonazepam**
See anxiolytics and hypnotics

**Clonidine**
ACE Inhibitors: enhanced hypotensive effect
Adrenaline: (epinephrine) possible risk of hypertension
Adrenergic Neurone Blockers: enhanced hypotensive effect
Alcohol: enhanced hypotensive effect
Aldesleukin: enhanced hypotensive effect
Alpha-blockers: enhanced hypotensive effect
Alprostadil: enhanced hypotensive effect
Anaesthetics, General: enhanced hypotensive effect
Angiotensin-II Receptor Antagonists: enhanced hypotensive effect
Antidepressants, Tricyclic: hypotensive effect of clonidine antagonised by tricyclics, Also increased risk of hypertension on clonidine withdrawal
Anxiolytics and Hypnotics: enhanced hypotensive effect
Baclofen: enhanced hypotensive effect
Beta-blockers: increased risk of withdrawal hypertension when clonidine given with beta-blockers (withdraw beta-blockers several days before slowly withdrawing clonidine)
Calcium-channel Blockers: enhanced hypotensive effect
Captopril: previous treatment with clonidine possibly delays antihypertensive effect of captopril
Corticosteroids: hypotensive effect of clonidine antagonised by corticosteroids
Appendix 1: Drug interactions

Diazoxide: enhanced hypotensive effect
Diuretics: enhanced hypotensive effect
Hydralazine: enhanced hypotensive effect
Levodopa: enhanced hypotensive effect
MAOIs: enhanced hypotensive effect
Methyldopa: enhanced hypotensive effect
Methylphenidate: serious adverse events reported with concomitant use of clonidine and methylphenidate
Minoxidil: enhanced hypotensive effect
Moxisylyte (thymoxamine): enhanced hypotensive effect
Moxonidine: enhanced hypotensive effect
Nitrates: enhanced hypotensive effect
Noradrenaline (norepinephrine): possible risk of hypertension
Oestrogens: hypotensive effect of clonidine antagonised by oestrogens
Phenothiazines: enhanced hypotensive effect
Sodium Nitroprusside: enhanced hypotensive effect
Tizanidine: enhanced hypotensive effect

Clopidogrel
Analgesics: increased risk of bleeding when given with NSAIDs or aspirin
Anticoagulants: increased risk of bleeding
Proton pump inhibitors: esomeprazole and omeprazole reduce the antiplatelet effect of clopidogrel

Clotrimazole
See antifungals

Clozapine
Amprenavir: plasma concentration of clozapine possibly increased by amprenavir
Antidepressants, Tricyclic possibly increased antimuscarinic side-effects
Antimuscarinics: increased risk of antimuscarinic side-effects
Azapropazole: avoid concomitant use of clozapine with azapropazole (increased risk of agranulocytosis)
Carbamazepine: metabolism of clozapine accelerated by carbamazepine (reduced plasma concentration), also avoid concomitant use of drugs with substantial potential for causing agranulocytosis
Chloramphenicol: avoid concomitant use of clozapine with chloramphenicol (increased risk of agranulocytosis)
Cimetidine: effects of clozapine possibly enhanced by cimetidine
Ciprofloxacin: plasma concentration of clozapine increased by ciprofloxacin
Citalopram: plasma concentration of clozapine possibly increased by citalopram (increased risk of toxicity)
Appendix 1: Drug interactions

Cytotoxics: avoid concomitant use of clozapine with cytotoxics (increased risk of agranulocytosis)

Erythromycin: plasma concentration of clozapine possibly increased by erythromycin (possible increased risk of convulsions)

Flecainide: increased risk of arrhythmias when clozapine given with flecainide

Fluoxetine: plasma concentration of clozapine increased by fluoxetine

Flupentixol: avoid concomitant use of clozapine with depot formulation of flupentixol as cannot be withdrawn quickly if neutropenia occurs

Fluphenazine: avoid concomitant use of clozapine with depot formulation of fluphenazine as cannot be withdrawn quickly if neutropenia occurs

Fluvoxamine: plasma concentration of clozapine increased by fluvoxamine

Haloperidol: avoid concomitant use of clozapine with depot formulation of haloperidol as cannot be withdrawn quickly if neutropenia occurs

Lithium: increased risk of extrapyramidal side-effects and possibly neurotoxicity MAOIs: clozapine possibly increases CNS effects of MAOIs

Omeprazole: plasma concentration of clozapine possibly reduced by omeprazole

Paroxetine: plasma concentration of clozapine increased by paroxetine

Penicillamine: avoid concomitant use of clozapine with penicillamine (increased risk of agranulocytosis)

Phenytoin: metabolism of clozapine accelerated by phenytoin (reduced plasma concentration)

Pipotiazine: avoid concomitant use of clozapine with depot formulation of pipotiazine as cannot be withdrawn quickly if neutropenia occurs

Rifampicin: plasma concentration of clozapine possibly reduced by rifampicin

Risperidone: avoid concomitant use of clozapine with depot formulation of risperidone as cannot be withdrawn quickly if neutropenia occurs

Ritonavir: plasma concentration of clozapine increased by ritonavir (increased risk of toxicity)—avoid concomitant use

Sertraline: plasma concentration of clozapine increased by sertraline

Sulphonamides: avoid concomitant use of clozapine with sulphonamides (increased risk of agranulocytosis)

Venlafaxine: plasma concentration of clozapine increased by venlafaxine

Zuclopenthixol: avoid concomitant use of clozapine with depot formulation of zuclopenthixol as cannot be withdrawn quickly if neutropenia occurs
Appendix 1: Drug interactions

Also see antipsychotics

**Co-amoxiclav**
See penicillins

**Colchicine**
*Ciclosporin:* increased risk of nephrotoxicity and myotoxicity toxicity
*Clarithromycin:* increased risk of colchicine toxicity
*Erythromycin:* increased risk of colchicine toxicity

**Statins:** possible increased risk of myopathy

**Colecalciferol**
See under vitamins

**Colestyramine (cholestyramine)**
Absorption of other drugs will be affected if taken simultaneously with cholestyramine. It is advisable to take other drugs 1 hour before or 4-6 hours after cholestyramine.

**Colistin**
*Aminoglycosides:* increased risk of nephrotoxicity
*Capreomycin:* increased risk of nephrotoxicity
*Teicoplanin:* increased risk of nephrotoxicity and ototoxicity
*Vancomycin:* increased risk of nephrotoxicity and ototoxicity

Also, see under Polymyxins

**Contraceptives, oral**
*Antibacterials:* rifampicin enhances metabolism of oral combined or progestogen only contraceptive resulting in reduced contraceptive effect; broad-spectrum antibiotics possibly reduce contraceptive effects
*Anticoagulants:* antagonism of anticoagulant effects
*Antiepileptics:* carbamazepine and phenytoin accelerate metabolism of combined and progestogen only contraceptives
*Antifungals:* griseofulvin accelerates metabolism
*Aprepitant:* causes contraceptive failure of hormonal contraceptives containing oestrogens (alternative contraception recommended);
causes contraceptive failure of hormonal contraceptives containing progestogens (alternative contraception recommended)

**Corticosteroids**
The following interactions do not generally apply to topically applied corticosteroids
*Antibacterials:* rifampicin accelerates metabolism of corticosteroids;
erthromycin inhibits metabolism
*Anticoagulants:* corticosteroids may enhance or reduce anticoagulant effect of coumarins (warfarin)
*Antidiabetics:* antagonism of hypoglycaemic effects
*Antiepileptics:* accelerate metabolism of corticosteroids
*Antifungals:* increased risk of hypokalaemia when corticosteroids given with amphotericin; metabolism of corticosteroids and
Appendix 1: Drug interactions

methylprednisolone possibly inhibited by itraconazole; plasma concentration of inhaled and oral (and possibly also intranasal and rectal) budesonide increased by itraconazole; plasma concentration of inhaled fluticasone increased by itraconazole; dexamethasone possibly reduces plasma concentration of caspofungin

Antivirals: dexamethasone possibly reduces plasma concentration of indinavir, lopinavir, saquinavir and telaprevir; plasma concentration of inhaled and intranasal fluticasone increased by ritonavir—increased risk of adrenal suppression; plasma concentration of budesonide (including inhaled, intranasal, and rectal budesonide) possibly increased by ritonavir—increased risk of adrenal suppression; plasma concentration of corticosteroids possibly increased by ritonavir—increased risk of adrenal suppression

Antihypertensives: antagonism of hypotensive effect

Cardiac glycosides: increased risk of toxicity if hypokalaemia induced by corticosteroids

Caspofungin: plasma concentration of caspofungin possibly reduced by dexamethasone

Ciclosporin: plasma-ciclosporin concentration increased by prednisolone; ciclosporin increases plasma concentration of prednisolone.

Diuretics: antagonism of diuretic effect; increased risk of hypokalaemia

NSAIDs: increased risk of gastrointestinal bleeding and ulceration

Theophylline: increased risk of hypokalaemia

Co-trimoxazole and trimethoprim

Anti-arrhythmics: co-trimoxazole increases the risk of ventricular arrhythmias with amiodarone.

Anticoagulants: effect of coumarin and warfarin enhanced

Antidiabetics: effects of sulphonylurea compounds may be enhanced.

Antiepileptics: antifolate effect increased; plasma phenytoin concentration increased

Antimalarials: risk of antifolate effects increased with pyrimethamine

Ciclosporin: increased risk of nephrotoxicity

Cytotoxics: increased antifolate effect with methotrexate; methotrexate toxicity increased

Vaccines: high doses of corticosteroids impair immune response to vaccines, avoid concomitant use with live vaccines

Cyclopentolate

See under Antimuscarinics

Cyclophosphamide and ifosfamide

Anticoagulants: ifosfamide possible enhances effects of warfarin
Appendix 1: Drug interactions

Suxamethonium: possible enhancement of muscle relaxant effect

**Cycloserine**
- Alcohol: increased risk of seizure
- Antibacterials: increased risk of CNS toxicity with isoniazid
- Antiepileptics: increased risk of toxicity of phenytoin

**Cytotoxics**
- Clozapine: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis);
- Digoxin: cytotoxics reduce absorption of digoxin tablets
- Cytotoxics, others: plasma concentration of everolimus increased by imatinib; possible increased risk of neutropenia when lapatinib given with docetaxel; increased risk of neutropenia when lapatinib given with paclitaxel; sorafenib possibly increases plasma concentration of doxorubicin and irinotecan; sorafenib increases plasma concentration of docetaxel
- Phenytoin: cytotoxics possibly reduce absorption of phenytoin
- Also, see under individual drugs

**Danazol**
- Anticoagulants: effects of warfarin enhanced
- Antiepileptics: inhibits metabolism of carbamazepine
- Ciclosporin: increased plasma-ciclosporin concentration

**Dantrolene**
- See under muscle relaxants

**Dapsone**
- Antibacterials: plasma concentration reduced by rifampicin
- Probenecid: dapsone excretion reduced

**Darunavir**
- Antibacterials: plasma concentration of quinine possibly increased by darunavir (increased risk of toxicity)
- Antivirals: plasma concentration of darunavir reduced by efavirenz (adjust dose—consult product literature); plasma concentration of darunavir reduced by lopinavir—avoid concomitant use
- Antimalarials: rifampicin significantly reduces plasma concentration of darunavir—avoid concomitant use
- Antimaligants: darunavir possibly increases plasma concentration of everolimus—manufacturer of everolimus advises avoid concomitant use
- Antiphyscotics: plasma concentration of quetiapine possibly increased by darunavir—manufacturer of quetiapine advises avoid concomitant use

**Dasatinib**
- Famotidine: plasma concentration of dasatinib possibly reduced by famotidine
Appendix 1: Drug interactions

Rifampicin: metabolism of dasatinib accelerated by rifampicin
Simvastatin: dasatinib possibly increases plasma concentration of simvastatin
Also, see under cytotoxics

Deferasirox
Antacids: absorption of deferasirox possibly reduced by antacids containing aluminium
Antibacterials: plasma concentration of deferasirox reduced by rifampicin
Antidiabetics: deferasirox increases plasma concentration of repaglinide
Antipsychotics: manufacturer of deferasirox advises avoid concomitant use with clozapine.
Anxiolytics and Hypnotics: deferasirox possibly reduces plasma concentration of midazolam.
Muscle Relaxants: manufacturer of deferasirox advises avoid concomitant use with tizanidine.
Theophylline: deferasirox increases plasma concentration of theophylline (consider reducing dose of theophylline)

Desferrioxamine
Antipsychotics: avoid Prochlorperazine (on theoretical basis)

Desmopressin
Analgesics: effect of desmopressin is potentiated by Indomethacin

Dexamethasone
See under corticosteroids

Diazepam
See under anxiolytics and hypnotics

Diclofenac
See under NSAIDs

Didanosine
Allopurinol: plasma concentration of didanosine possibly increased by allopurinol
Ganciclovir: plasma concentration of didanosine possibly increased by ganciclovir
Hydroxyurea: increased risk of toxicity when didanosine given with hydroxyurea
Ribavirin: increased risk of side-effects
Stavudine: increased risk of side-effects
Tenofovir: plasma concentration of didanosine increased by tenofovir (increased risk of toxicity)
Tipranavir: plasma concentration of didanosine reduced by tipranavir

Digoxin
See under cardiac glycosides

Diltiazem
See under calcium-channel blockers

Dimenhydrinate
See under antihistamines

Diphenhydramine
See under antihistamines
Appendix 1: Drug interactions

**Dipyridamole**
*Antiarrhythmic*: effects of adenosine enhanced
*Anticoagulant*: effect enhanced due to antiplatelet action of dipyridamole
*Antiplatelets*: increased risk of bleeding

**Disodium etidronate**
*See under* bisphosphonates

**Disodium pamidronates**
*See under* bisphosphonates

**Disopyramide**
*Anti-arrhythmics (others)*: increased risk of myocardial depression; amiodarone increases risk of ventricular arrhythmias
*Antibacterials*: plasma concentration of disopyramide reduced by rifampicin but increased by erythromycin or clarithromycin
*Antidepressants*: increased risk of ventricular arrhythmias with tricyclics
*Antihistamines*: increased risk of ventricular arrhythmias
*Antipsychotics*: increased risk of hyponatraemia with carbamazepine
*Antihypertensives*: enhanced hypotensive effect
*Antipsychotics*
Cardiac glycosides: increased toxicity if hypokalaemia occurs with loop diuretics and thiazides; effect enhanced with spironolactone
*Ciclosporin*: increased risk of hyperkalaemia with potassium sparing diuretics
*Lithium*: lithium excretion reduced
*Potassium salts*: hyperkalaemia
*Theophylline*: increased risk of hypokalaemia

**Diuretics**
*ACE inhibitors and angiotensin II antagonists*: enhanced hypotensive effects; risk of severe hypokalaemia with potassium sparing diuretics
*Analgesics*: diuretics increase risk of NSAIDs nephrotoxicity; notably Indomethacin antagonises diuretic effect; Indomethacin and may be other NSAIDs increase risk of hyperkalaemia with potassium sparing diuretics
*Anti-arrhythmics*: cardiac toxicity of anti-arrhythmics increased if diuretics produce hypokalaemia
*Antibacterials*: loop diuretics increase the nephrotoxicity of and ototoxicity of aminoglycosides and
*Antidepressants*: increased risk of postural hypotension
*Antiepileptics*: increased risk of hyperkalaemia with carbamazepine
*Antihypertensives*: enhanced hypotensive effect
*Antipsychotics*
Cardiac glycosides: increased toxicity if hypokalaemia occurs with loop diuretics and thiazides; effect enhanced with spironolactone
*Ciclosporin*: increased risk of hyperkalaemia with potassium sparing diuretics
*Lithium*: lithium excretion reduced
*Potassium salts*: hyperkalaemia
*Theophylline*: increased risk of hypokalaemia

**Dobutamine**
*See under* sympathomimetics

**Docetaxel**
Appendix 1: Drug interactions

Ciclosporin: in vitro studies suggest a possible interaction between docetaxel and ciclosporin (consult docetaxel product literature)
Erythromycin: in vitro studies suggest a possible interaction between docetaxel and erythromycin (consult docetaxel product literature)
Ketoconazole: in vitro studies suggest a possible interaction between docetaxel and ketoconazole (consult docetaxel product literature)
Sorafenib: plasma concentration of docetaxel increased by sorafenib

Also, see cytotoxics

Domperidone
Antimuscarinics: antagonism of effects on gastrointestinal activity
Bromocriptine: possible antagonism of hypoprolactinaemic effect
Cabergoline: hypoprolactinaemic effect of cabergoline possibly antagonised by domperidone

Dopamine
See under sympathomimetics

Doxapram
Theophylline: possible increase in CNS stimulation

Doxazosin
See under alpha-blockers

Doxorubicin
Ciclosporin: increased risk of neurotoxicity

Doxycycline

See under tetracyclines

Drotrecogin Alfa
Heparin: manufacturer of drotrecogin alfa advises avoid concomitant use with high doses of heparin

Duloxetine
See under antidepressants SSRI

Dydrogesterone
See under progesterone

Efavirenz
Amprenavir: efavirenz reduces plasma concentration of amprenavir
Antimalarials: plasma concentration of arteether with lumefantrine reduced by efavirenz
Aripiprazole: efavirenz possibly reduces plasma concentration of aripiprazole — Atazanavir: efavirenz reduces plasma concentration of atazanavir
Atorvastatin: efavirenz reduces plasma concentration of atorvastatin
Carbamazepine: plasma concentration of both drugs reduced when efavirenz given with carbamazepine
Caspofungin: efavirenz possibly reduces plasma concentration of caspofungin — Clarithromycin: increased risk of rash
Darunavir: efavirenz reduces plasma concentration of darunavir
Diltiazem: efavirenz reduces plasma concentration of diltiazem

Also, see cytotoxics
Appendix 1: Drug interactions

**Ergot Alkaloids:** increased risk of ergotism

**Grapefruit Juice:** plasma concentration of efavirenz possibly increased by grapefruit juice

**Indinavir:** efavirenz reduces plasma concentration of indinavir

**Itraconazole:** efavirenz reduces plasma concentration of itraconazole

**Lopinavir:** efavirenz reduces plasma concentration of lopinavir

**Maraviroc:** efavirenz possibly reduces plasma concentration of maraviroc — Methadone: efavirenz reduces plasma concentration of methadone

**Midazolam:** increased risk of prolonged sedation

**Nevirapine:** plasma concentration of efavirenz reduced by nevirapine

**Oestrogens:** efavirenz possibly reduces contraceptive effect of oestrogens

**Pimozide:** efavirenz possibly increases plasma concentration of pimozide (increased risk of ventricular arrhythmias—avoid concomitant use)

**Posaconazole:** efavirenz reduces plasma concentration of posaconazole

**Pravastatin:** efavirenz reduces plasma concentration of pravastatin

**Rifabutin:** efavirenz reduces plasma concentration of rifabutin

**Rifampicin:** plasma concentration of efavirenz reduced by rifampicin

**Ritonavir:** toxicity of efavirenz increased by ritonavir, monitor liver function tests

**Saquinavir:** efavirenz significantly reduces plasma concentration of saquinavir

**Sertraline:** efavirenz reduces plasma concentration of sertraline

**Simvastatin:** efavirenz reduces plasma concentration of simvastatin

**St John's Wort:** plasma concentration of efavirenz reduced by St John's wort

**Voriconazole:** efavirenz reduces plasma concentration of voriconazole, Also plasma concentration of efavirenz increased

**Eformoterol (formoterol):**
See under sympathomimetics

**Enalapril:**
See under ACE inhibitors

**Enflurane:**
See under general anaesthetics

**Entacapone:**
Anticoagulants: anticoagulant effect of warfarin enhanced by entacapone

**Ephedrine:**
See under sympathomimetics

**Erlotinib:**
Capecitabine: plasma concentration of erlotinib possibly increased by capecitabine. (Capecitabine is a prodrug of fluorouracil)

**Coumarins:** increased risk of bleeding
Appendix 1: Drug interactions

Ketoconazole: metabolism of erlotinib inhibited by ketoconazole (increased plasma concentration)
NSAIDs: increased risk of bleeding
Rifampicin: metabolism of erlotinib accelerated by rifampicin (reduced plasma concentration)
Tobacco: plasma concentration of erlotinib reduced by tobacco smoking

Ertapenem
Antiepileptics: sodium valproate-carbapenems reduce plasma concentration of sodium valproate—avoid concomitant use

Erythromycin and other macrolides
Analgesics (opioid): plasma concentration of alfentanil increased by erythromycin
Anti-arrhythmics: plasma concentration of disopyramide increased by erythromycin
Anticoagulants: effects of warfarin enhanced by erythromycin and possibly by other macrolides
Antiepileptics: erythromycin and clarithromycin inhibit carbamazepine metabolism
Antihistamines: erythromycin possibly increases plasma-loratidine concentration
Antimalarials: avoidance of macrolides advised by manufacturer of arte-mether with lumefantrine
Anxiolytics and hypnotics: clarithromycin and erythromycin inhibit metabolism of midazolam resulting in profound sedation

Cabergoline: plasma concentration of cabergoline increased by erythromycin
Ciclosporin: macrolides inhibit ciclosporin metabolism
Everolimus: plasma concentration of everolimus possibly increased by clarithromycin; plasma concentration of everolimus increased by erythromycin
Ivabradine: clarithromycin possibly increases plasma concentration of ivabradine—avoid concomitant use; increased risk of ventricular arrhythmias when erythromycin given with ivabradine—avoid concomitant use
Lenalidomide: plasma concentration of lenalidomide possibly increased by clarithromycin (increased risk of toxicity)
Lipid-regulating drugs: erythromycin and clarithromycin increase risk of myopathy with simvastatin and atorvastatin; clarithromycin increases plasma concentration of atorvastatin
Theophylline: erythromycin and clarithromycin inhibit metabolism of Theophylline

Esmolol
See under beta-blockers

Esomeprazole
See under proton pump inhibitors

Estradiol
See under Oestrogens

Etanercept
Appendix 1: Drug interactions

Abatacept: increased risk of side-effects
Anakinra: increased risk of side-effects when etanercept given with anakinra
Vaccines: avoid concomitant use of etanercept with live vaccines

Ethinyloestradiol
See under contraceptives

Ethosuximide
Antibacterials: isoniazid increases plasma concentrations
Antidepressants: antagonism
Antiepileptics (other): potentiation of effects with excessive sedation
Antimalarials: mefloquine antagonises anticonvulsant effect; chloroquine reduces convulsive threshold
Antipsychotics: antagonism

Etidronate
See under bisphosphonates

Etomidate
See under Anaesthetics, General

Etonogestrel
See under Progestogens

Etoricoxib
See under NSAIDs

Everolimus
Antibacterials: plasma concentration of everolimus possibly increased by clarithromycin; plasma concentration of everolimus increased by erythromycin; plasma concentration of everolimus reduced by rifampicin
Antifungals: plasma concentration of everolimus possibly increased by voriconazole and itraconazole
Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Antivirals: plasma concentration of everolimus possibly increased by darunavir, indinavir, ritonavir, atazanavir and saquinavir
Calcium-channel Blockers: plasma concentration of both drugs may increase when everolimus given with verapamil
Ciclosporin: plasma concentration of everolimus increased by ciclosporin
Cytotoxics: plasma concentration of everolimus increased by imatinib (consider reducing the dose of everolimus)
Grapefruit Juice: manufacturer of everolimus advises avoid concomitant use with grapefruit juice

Exemestane
Rifampicin: plasma concentration of exemestane possibly reduced by rifampicin

Fenofibrate
See under fibrates

Fentanyl
See under opioid analgesics
Appendix 1: Drug interactions

**Ferrous salts**  
*See under Iron*

**Fibrates**  
*Anticoagulants: enhancement of effects of warfarin*  
*Ciclosporin: possible increased risk of renal impairment with fenofibrate*  
*Lipid-regulating drugs (other): increased risk of myopathy with statins*

**Filgrastim**  
*Fluorouracil: neutropenia possibly exacerbated when filgrastim given with fluorouracil*

**Finasteride**  
*No clinically important reaction reported*

**Fingolimod**  
*Anti-arrhythmics: possible increased risk of bradycardia when fingolimod given with amiodarone, disopyramide or dronedarone*  
*Antiepileptics: plasma concentration of fingolimod reduced by carbamazepine*  
*Beta-blockers: possible increased risk of bradycardia when fingolimod given with beta-blockers*  
*Calcium-channel Blockers: possible increased risk of bradycardia when fingolimod given with diltiazem or verapamil*

**Flecainide**  
*Anti-arrhythmics (other): amiodarone increases plasma-flecainide concentration (increased risk of ventricular arrhythmias); increased myocardial depression with any other anti-arrhythmics*  
*Antidepressants: fluoxetine increases plasma-flecainide concentration; increased risk of arrhythmias with tricyclics*  
*Antimalarials: increased plasma-flecainide concentration with quinine*  
*Beta-blockers: increased myocardial depression and bradycardia*  
*Calcium-channel blockers: increased myocardial depression and asystole with verapamil*  
*Diuretics: cardiac toxicity increased if hypokalaemia occurs*

**Flucloxacillin**  
*See penicillins*

**Fluconazole**  
*See under antifungals (imidazole and triazole)*

**Fludrocortisone**  
*See under corticosteroids*

**Flunarizine**  
*Alcohol: excessive sedation*  
*Anxiolytics and hypnotics: excessive sedation*

**Fluoroacil**  
*Anticoagulants: possible enhancement of warfarin effect*

**Fluoxetine**
Appendix 1: Drug interactions

See under antidepressants

Flupenthixol
See under antipsychotics

Fluphenazine
See under antipsychotics

Flutamide
Anticoagulants: effect of warfarin enhanced

Fluticasone
See under corticosteroids

Fluvastatin
See statins

Folates
Sulfasalazine: absorption of folic acid possibly reduced by sulfasalazine
Phenobarbital: folates possibly reduce plasma concentration of phenobarbital
Phenytoin: folates possibly reduce plasma concentration of phenytoin
Primidone: folates possibly reduce plasma concentration of primidone

Folic Acid
See folates

Fondaparinux
Analgesics: increased risk of haemorrhage when anticoagulants are given with intravenous diclofenac (avoid concomitant use); increased risk of harmorrrage when anticoagulants given with ketorolac (avoid concomitant use)

Formoterol (eformoterol)
See under sympathomimetics

Frusemide
See under diuretics

Fusidic Acid
Atorvastatin: possible increased risk of myopathy
Ritonavir: plasma concentration of both drugs increased
Simvastatin: increased risk of myopathy

Gabapentin
Antacids: absorption of gabapentin reduced by antacids Gabapentin belongs to Antiepileptics and will have the following interactions:
Antidepressants, SSRI: anticonvulsant effect of antiepileptics antagonised by SSRIs
Antidepressants, Tricyclic: anticonvulsant effect of antiepileptics antagonised by tricyclics
Chloroquine and Hydroxychloroquine: possible increased risk of convulsions
MAOIs: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs
Mefloquine: anticonvulsant effect of antiepileptics antagonised by mefloquine
St John's Wort: avoid concomitant use
Appendix 1: Drug interactions

Ganciclovir
Didanosine: ganciclovir possibly increases plasma concentration of didanosine
Imipenem with Cilastatin: increased risk of convulsions
Lamivudine: avoidance of intravenous ganciclovir advised by manufacturer of lamivudine
Mycophenolate: plasma concentration of ganciclovir possibly increased by mycophenolate, Also plasma concentration of inactive metabolite of mycophenolate possibly increased
Probencid: excretion of ganciclovir reduced by probenecid (increased plasma concentration and risk of toxicity)
Tacrolimus: possible increased risk of nephrotoxicity when ganciclovir given with tacrolimus
Zidovudine: profound myelosuppression

Gefitinib
Antibacterials: plasma concentration of gefitinib reduced by rifampicin
Anticoagulants: gefitinib possibly enhances anticoagulant effect of warfarin
Antiepileptics: manufacturer of gefitinib advises avoid concomitant use with carbamazepine, phenobarbital and phenytoin
Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Ulcerc-healing Drugs: plasma concentration of gefitinib reduced by ranitidine

Gentamicin
See under aminoglycosides

Glibenclamide
See under antidiabetics

Gliclazide
See under antidiabetics

Glimepiride
See under antidiabetics

Glyceryl trinitrate
See under nitrates

Griseofulvin
Contraceptives (oral): metabolism of oral contraceptives accelerated

Haloperidol
See under antipsychotics

Halothane
See under general anaesthetics

Heparin
ACE Inhibitors: increased risk of hyperkalaemia
Aliskiren: increased risk of hyperkalaemia Heparin has the following interaction information:
Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia
Aspirin: anticoagulant effect of heparins enhanced by aspirin
Appendix 1: Drug interactions

Clopidogrel: increased risk of bleeding

**Diclofenac**: increased risk of haemorrhage when heparins given with intravenous diclofenac (avoid concomitant use, including low-dose heparin)

**Dipyridamole**: anticoagulant effect of heparins enhanced by dipyridamole

**Drotrecogin Alfa**: avoidance of concomitant use of high doses of heparin with drotrecogin alfa advised by manufacturer of drotrecogin alfa literature

**Glyceryl Trinitrate**: anticoagulant effect of heparins reduced by infusion of glyceryl trinitrate

**Iloprost**: anticoagulant effect of heparins possibly enhanced by iloprost

**Ketorolac**: increased risk of haemorrhage when heparins given with ketorolac (avoid concomitant use, including low-dose heparin)

**NSAIDs**: possible increased risk of bleeding when heparins given with NSAIDs

**Histamine H\textsubscript{2}-antagonists**

*Cimetidine* inhibits activity of cytochrome P450 and thereby slows the metabolism of many drugs.

*Ranitidine* does not inhibit hepatic cytochrome P450 and therefore has little effect on drug metabolism

**5HT1 Agonists**

**Duloxetine**: possible increased serotonergic effects

**St John's Wort**: increased serotonergic effects

**Hydralazine**

**ACE inhibitors**: enhanced hypotensive effect

**Anaesthetics**: enhanced hypotensive effect

**Analgesics**: NSAIDs antagonise hypotensive effect

**Corticosteroids**: antagonise hypotensive effect

**Hydrochlorothiazide**

*See under diuretics*

**Hydrocortisone**

*See under corticosteroids*

**Hydromorphine**

*See under opioid analgesics*

**Hydroxycarbamide**

**Antipsychotics**: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

**Didanosine**: increased risk of toxicity

**Stavudine**: increased risk of toxicity

*Also, see under cytotoxics*

**Hydroxychloroquine**
### Appendix 1: Drug interactions

*See under* chloroquine and hydroxychloroquine

### Hydroxyprogesterone hexanoate
*See under* Progestogens

### Hydroxyzine
*See under* antihistamine

### Hyoscine
*See under* antimuscarinics

### Ibuprofen
*See under* NSAIDs

### Ifosfamide
*See under* cyclophosphamide

### Imatinib
- Carbamazepine: plasma concentration of imatinib reduced by carbamazepine
- Ciclosporin: imatinib possibly increases plasma concentration of ciclosporin
- Ketoconazole: plasma concentration of imatinib increased by ketoconazole
- Levothyroxine (thyroxine): imatinib possibly reduces plasma concentration of levothyroxine (thyroxine)
- Oxcarbazepine: plasma concentration of imatinib reduced by oxcarbazepine
- Phenytoin: plasma concentration of imatinib reduced by phenytoin
- Rifampicin: plasma concentration of imatinib reduced by rifampicin

### Simvastatin: imatinib increases plasma concentration of simvastatin
### St John's Wort: plasma concentration of imatinib reduced by St John's wort
### Warfarin: manufacturer of imatinib advises replacement of warfarin with a heparin (possibility of enhanced warfarin effect)
### Also, *see under* cytotoxics

### Imipramine
*See under* antidepressants

### Indinavir
- Alprazolam: increased risk of prolonged sedation
- Amiodarone: indinavir possibly increases plasma concentration of amiodarone
- Aripiprazole: indinavir possibly inhibits metabolism of aripiprazole
- Artemether with Lumefantrine: avoid concomitant use of indinavir with artemether/lumefantrine
- Atazanavir: avoid concomitant use of indinavir with atazanavir
- Atorvastatin: possible increased risk of myopathy
- Atovaquone: plasma concentration of indinavir possibly reduced by atovaquone
- Barbiturates: plasma concentration of indinavir possibly reduced by barbiturates
- Carbamazepine: plasma concentration of indinavir possibly reduced by carbamazepine
Appendix 1: Drug interactions

Cilostazol: indinavir possibly increases plasma concentration of cilostazol
Darifenacin: avoidance of indinavir advised by manufacturer of darifenacin
Darunavir: plasma concentration of both drugs increased
Dexamethasone: plasma concentration of indinavir possibly reduced by dexamethasone
Efavirenz: plasma concentration of indinavir reduced by efavirenz
Eletriptan: indinavir increases plasma concentration of eletriptan (risk of toxicity)
Methysergide: increased risk of ergotism when indinavir given with ergotamine and methysergide
Fesoterodine: manufacturer of fesoterodine advises dose reduction when indinavir given with fesoterodine
Flecainide: indinavir possibly increases plasma concentration of flecainide (increased risk of ventricular arrhythmias)
Itraconazole: plasma concentration of indinavir increased by itraconazole
Ketoconazole: metabolism of indinavir inhibited by ketoconazole
Maraviroc: indinavir increases plasma concentration of maraviroc
Midazolam: indinavir possibly increases plasma concentration of midazolam (risk of prolonged sedation)
Nelfinavir: combination of indinavir with nelfinavir may increase plasma concentration of either drug (or both)
Nevirapine: plasma concentration of indinavir reduced by nevirapine
Phenytoin: plasma concentration of indinavir possibly reduced by phenytoin
Pimozide: indinavir possibly increases plasma concentration of pimozide (increased risk of ventricular arrhythmias)
Primidone: plasma concentration of indinavir possibly reduced by primidone
Rifabutin: indinavir increases plasma concentration of rifabutin, Also plasma concentration of indinavir decreased (reduce dose of rifabutin and increase dose of indinavir)
Rivaroxaban: manufacturer of rivaroxaban advises avoid concomitant use with indinavir
Rifampicin: metabolism of indinavir accelerated by rifampicin (reduced plasma concentration)
Ritonavir: plasma concentration of indinavir increased by ritonavir
Rosuvastatin: possible increased risk of myopathy when indinavir given with rosuvastatin
Saquinavir: indinavir increases plasma concentration of saquinavir
Sertindole: indinavir increases plasma concentration of sertindole (increased risk of ventricular arrhythmias)
Sildenafil: indinavir increases plasma concentration of sildenafil
Appendix 1: Drug interactions

Simvastatin: increased risk of myopathy
St John's Wort: plasma concentration of indinavir reduced by St John's wort
Telithromycin: avoidance of concomitant indinavir in severe renal and hepatic impairment
Tolterodine: avoidance of indinavir advised by manufacturer of tolterodine
Vardenafil: indinavir increases plasma concentration of vardenafil

**Indomethacin**
*See under NSAIDs*

**Infliximab**
Abatacept: increased risk of side-effects
Anakinra: avoid concomitant use
Vaccines: avoid concomitant use of infliximab with live vaccines

**Insulins**
*See under antidiabetics*

**Interferons**
Vaccines: manufacturer of interferon gamma advises avoid concomitant use with vaccines
Telbivudine: increased risk of peripheral neuropathy when interferon alfa given with telbivudine
Theophylline: interferon alfa inhibits metabolism of theophylline (increased plasma concentration)

**Ipratropium**
*See under antimuscarinics*

**Irinotecan**
Atazanavir: metabolism of irinotecan possibly inhibited by atazanavir (increased risk of toxicity)
Carbamazepine: plasma concentration of irinotecan and its active metabolite reduced by carbamazepine
Ketoconazole: plasma concentration of irinotecan reduced by ketoconazole (but concentration of active metabolite of irinotecan increased)
Phenobarbital: plasma concentration of irinotecan and its active metabolite reduced by phenobarbital
Phenytoin: plasma concentration of irinotecan and its active metabolite reduced by phenytoin
Sorafenib: plasma concentration of irinotecan possibly increased by sorafenib
St John's Wort: metabolism of irinotecan accelerated by St John's wort (reduced plasma concentration)
*Also, see under cytotoxics*

**Iron**
Antacids: reduces absorption of oral iron salts
Antibacterials: tetracyclines reduce oral iron salt absorption; absorption of ciprofloxacin reduced by oral iron salts

**Isoflurane**
*See under anaesthesia*

**Isoniazid**
Anaesthesia: possible potentiation of hepatotoxicity with isoflurane
Appendix 1: Drug interactions

Antibacterials (other): increased CNS toxicity with cycloserine

Antiepileptics: metabolism of carbamazepine, ethosuximide and phenytoin inhibited; hepatotoxicity of isoniazid possibly increased with carbamazepine

Isoprenaline
See under sympathomimetics

Isosorbide
See under nitrates

Isotretinoin
See under retinoids

Itraconazole
See under antifungals (imidazole and triazole)

Ivabradine
Anti-arrhythmics: amiodarone increased risk of ventricular arrhythmias when amiodarone given with ivabradine
Antibacterials: clarithromycin possibly increases plasma concentration of ivabradine—avoid concomitant use; increased risk of ventricular arrhythmias when erythromycin given with ivabradine—avoid concomitant use
Antifungals: fluconazole increases plasma concentration of ivabradine—reduce initial dose of ivabradine; itraconazole possibly increases plasma concentration of ivabradine—avoid concomitant use; ketoconazole increases plasma concentration of ivabradine—avoid concomitant use.

Antimalrials: increased risk of ventricular arrhythmias when mefloquine given with ivabradine.

Antivirals: ritonavir possibly increases plasma concentration of ivabradine—avoid concomitant use.

Beta-blockers: increased risk of ventricular arrhythmias when sotalol given with ivabradine.

Calcium channel blockers: diltiazem increases plasma concentration of ivabradine—avoid concomitant use; verapamil increases plasma concentration of ivabradine—avoid concomitant use.

Ketamine
See under anaesthesia

Ketoconazole
See under antifungals (imidazole and triazole)

Labetalol
See under beta-blockers

Lamivudine
Emtricitabine: avoidance of lamivudine advised by manufacturer of emtricitabine
Foscarnet: manufacturer of lamivudine advises avoid concomitant use with foscarnet
Ganciclovir: manufacturer of lamivudine advises avoid concomitant use of intravenous ganciclovir
Appendix 1: Drug interactions

Trimethoprim: plasma concentration of lamivudine increased by trimethoprim (as co-trimoxazole)

Lamotrigine
Antidepressants: antagonism of anticonvulsant effect
Antiepileptics (other): potentiation of effects, increased sedation
Antimalarials: mefloquine antagonises anticonvulsant effect

Lapatinib
Antibacterials: manufacturer of lapatinib advises avoid concomitant use with rifabutin and rifampicin
Antiepileptics: plasma concentration of lapatinib reduced by carbamazepine; manufacturer of lapatinib advises avoid concomitant use with phenytoin
Antifungals: manufacturer of lapatinib advises avoid concomitant use with itraconazole and voriconazole
Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Antivirals: manufacturer of lapatinib advises avoid concomitant use with ritonavir and saquinavir
Cytotoxics: possible increased risk of neutropenia when lapatinib given with docetaxel; increased risk of neutropenia when lapatinib given with paclitaxel
Grapefruit Juice: manufacturer of lapatinib advises avoid concomitant use with grapefruit juice

Ulcer-healing Drugs: absorption of lapatinib possibly reduced by histamine H2-antagonists and proton pump inhibitors

Leflunomide
Note: Increased risk of toxicity with other haematotoxic and hepatotoxic drugs
Antibacterials: plasma concentration of active metabolite of leflunomide possibly increased by rifampicin
Anticoagulants: leflunomide possibly enhances anticoagulant effect of warfarin
Antidiabetics: leflunomide possibly enhances hypoglycaemic effect of tolbutamid
Antiepileptics: leflunomide possibly increases plasma concentration of phenytoin
Cytotoxics: risk of toxicity when leflunomide given with methotrexate.
Lipid-regulating Drugs: the effect of leflunomide is significantly decreased by colestyramine (enhanced elimination
Vaccines: avoid concomitant use of leflunomide with live vaccines.

Lenalidomide
Antibacterials: plasma concentration of lenalidomide possibly increased by clarithromycin (increased risk of toxicity)
Calcium-channel Blockers: plasma concentration of lenalidomide possibly increased by verapamil (increased risk of toxicity)
Cardiac Glycosides: lenalidomide possibly increases plasma concentration of digoxin  
Ciclosporin: plasma concentration of lenalidomide possibly increased by ciclosporin (increased risk of toxicity)

Levetiracetam  
Antidepressants, SSRI: anticonvulsant effect of antiepileptics antagonised by SSRIs  
Antidepressants, Tricyclic: anticonvulsant effect of antiepileptics antagonised by tricyclics  
Chloroquine and Hydroxychloroquine: possible increased risk of convulsions  
MAOIs: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs  
Mefloquine: anticonvulsant effect of antiepileptics antagonised by mefloquine  
St John's Wort: avoid concomitant use of antiepileptics with St John's wort

Levodopa  
Anaesthetics: risk of arrhythmias with halothane, isoflurane and other volatile anaesthetics  
Antidepressants: hypertensive crises with MAO inhibitors  
Antihypertensives: potentiation of hypotensive effect  
Antipsychotics: antagonism of effect  
Iron: absorption of levodopa may be reduced

Levofloxacin  
Amiodarone: increased risk of ventricular arrhythmias  
Antacids: absorption of levofloxacin reduced by antacids  
Coumarins: levofloxacin possibly enhances anticoagulant effect of coumarins  
Iron: absorption of levofloxacin reduced by oral iron  
Phenindione: levofloxacin possibly enhances anticoagulant effect of phenindione  
Sucralfate: absorption of levofloxacin reduced by sucralfate  
Zinc: absorption of levofloxacin reduced by zinc  
Also, see under quinolones

Levonorgestrel  
See under progesterone

Lignocaine (Lidocaine)  
Interactions are less likely when Lignocaine is used topically.  
Anti-arrhythmics (other): increased myocardial depression  
Beta-blockers: increased risk of myocardial depression; increased risk of lignocaine toxicity with propranolol

Lisinopril  
See under ACE inhibitors

Linezolid  
Antidepressants: MAOIs can cause increased risk of hypertension and CNS excitation when given with
Appendix 1: Drug interactions

other MAOIs (avoid for at least 2 weeks after stopping previous MAOIs and then start at a reduced dose);
Adrenaline: risk of hypertensive crisis when MAOIs given with adrenaline (epinephrine)
Atomoxetine: after stopping MAOIs do not start atomoxetine for 2 weeks, also MAOIs should not be started until at least 2 weeks after stopping atomoxetine
Antiepileptics: avoidance for 2 weeks after stopping MAOIs advised by manufacturer of carbamazepine, also antagonism of anti-convulsant effect
Antipsychotics: CNS effects of MAOIs possibly increased by clozapine
Dopaminergics: risk of hypertensive crisis when MAOIs given with co-careldopa, avoid co-careldopa for at least 2 weeks after stopping MAOIs; avoid concomitant use of non-selective MAOIs with entacapone
Ephedrine: risk of hypertensive crisis when MAOIs given with ephedrine, avoid ephedrine for at least 2 weeks after stopping MAOIs
Sympathomimetics: risk of hypertensive crisis when MAOIs given with dopamine

Liraglutide
See under Antidiabetics

Lithium
ACE inhibitors: lithium excretion reduced

Analgesics: NSAIDs reduce lithium excretion
Antidepressants: SSRI increase risk of CNS toxicity
Antihypertensives: neurotoxicity may occur with methyldopa
Antipsychotics: increased risk of extrapyramidal effects
Diuretics: lithium excretion reduced

Loperamide
Desmopressin: loperamide increases plasma concentration of oral desmopressin

Lopinavir
In combination with ritonavir as Kaletra® (ritonavir is present to inhibit lopinavir metabolism and increase plasma-lopinavir concentration)—see Also Ritonavir
Ampranavir: lopinavir reduces plasma concentration of ampranavir, effect on lopinavir plasma concentration not predictable
Aripiprazole: lopinavir possibly inhibits metabolism of aripiprazole
Artemether with Lumefantrine: avoid concomitant use of lopinavir with artemether/lumefantrine
Atorvastatin: possible increased risk of myopathy
Carbamazepine: plasma concentration of lopinavir possibly reduced by carbamazepine
Chlorphenamine (chlorpheniramine): lopinavir possibly increases plasma concentration of chlorpheniramine (chlorpheniramine)
Cilostazol: lopinavir possibly increases plasma concentration of cilostazol
Darifenacin: avoidance of lopinavir advised by manufacturer of darifenacin
Darunavir: plasma concentration of lopinavir increased by darunavir (Also plasma concentration of darunavir reduced)
Dexamethasone: plasma concentration of lopinavir possibly reduced by dexamethasone
Efavirenz: plasma concentration of lopinavir reduced by efavirenz
Flecainide: lopinavir possibly increases plasma concentration of flecainide (increased risk of ventricular arrhythmias)
Lidocaine (lignocaine): lopinavir possibly increases plasma concentration of lidocaine (lignocaine)
Maraviroc: lopinavir increases plasma concentration of maraviroc
Nelfinavir: plasma concentration of lopinavir reduced by nelfinavir, Also plasma concentration of active metabolite of nelfinavir increased
Nevirapine: plasma concentration of lopinavir possibly reduced by nevirapine
Phenobarbital: plasma concentration of lopinavir possibly reduced by phenobarbital
Phenytoin: plasma concentration of lopinavir possibly reduced by phenytoin
Primidone: plasma concentration of lopinavir possibly reduced by primidone
Rifampicin: plasma concentration of lopinavir reduced by rifampicin
Rivaroxaban: manufacturers advise avoid concomitant use of rivaroxaban with lopinavir
Rosuvastatin: possible increased risk of myopathy when lopinavir given with rosuvastatin
Saquinavir: lopinavir increases plasma concentration of saquinavir
Sertindole: lopinavir increases plasma concentration of sertindole (increased risk of ventricular arrhythmias)
Simvastatin: possible increased risk of myopathy when lopinavir given with simvastatin
Sirolimus: lopinavir possibly increases plasma concentration of sirolimus
St John's Wort: plasma concentration of lopinavir reduced by St John's wort —Telithromycin: avoidance of concomitant lopinavir in severe renal and hepatic impairment advised by manufacturer of telithromycin
Tenofovir: lopinavir increases plasma concentration of tenofovir
Tipranavir: plasma concentration of lopinavir reduced by tipranavir
Tolterodine: avoidance of lopinavir advised by manufacturer of tolterodine
Loratadine
See under antihistamines
Lorazepam
Valproate: plasma concentration of lorazepam possibly increased by valproate

**Lorazepam** belongs to Anxiolytics and Hypnotics and will have the following interactions:

Cimetidine: metabolism of benzodiazepines inhibited by cimetidine (increased plasma concentration) Disulfiram: metabolism of benzodiazepines inhibited by disulfiram (increased sedative effects) Fluvoxamine: plasma concentration of some benzodiazepines increased by fluvoxamine Levodopa: benzodiazepines possibly antagonise effects of levodopa Moxonidine: sedative effects possibly increased when benzodiazepines given with moxonidine Olanzapine: increased risk of hypotension, bradycardia and respiratory depression when parenteral benzodiazepines given with intramuscular olanzapine Phenytoin: benzodiazepines possibly increase or decrease plasma concentration of phenytoin Rifampicin: metabolism of benzodiazepines possibly accelerated by rifampicin (reduced plasma concentration) Sodium Oxybate: benzodiazepines enhance effects of sodium oxybate (avoid concomitant use) Theophylline: effects of benzodiazepines possibly reduced by theophylline

**Lorazepam** belongs to Anxiolytics and Hypnotics and will have the following interactions:

ACE Inhibitors: enhanced hypotensive effect when anxiolytics and hypnotics given with ACE inhibitors Adrenergic Neurone Blockers: enhanced hypotensive effect when anxiolytics and hypnotics given with adrenergic neurone blockers Alcohol: increased sedative effect when anxiolytics and hypnotics given with alcohol Alpha-blockers: enhanced hypotensive and sedative effects when anxiolytics and hypnotics given with alpha-blockers Anaesthetics, General: increased sedative effect when anxiolytics and hypnotics given with general anaesthetics Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when anxiolytics and hypnotics given with angiotensin-II receptor antagonists Antidepressants, Tricyclic: increased sedative effect when anxiolytics and hypnotics given with tricyclics Antidepressants, Tricyclic (related): increased sedative effect when anxiolytics and hypnotics given with tricyclic-related antidepressants Antihistamines: increased sedative effect when anxiolytics and hypnotics given with antihistamines
Appendix 1: Drug interactions

Antipsychotics: increased sedative effect when anxiolytics and hypnotics given with antipsychotics
Baclofen: increased sedative effect when anxiolytics and hypnotics given with baclofen
Beta-blockers: enhanced hypotensive effect when anxiolytics and hypnotics given with beta-blockers
Since systemic absorption may follow topical application of betablockers to the eye the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind
Calcium-channel Blockers: enhanced hypotensive effect when anxiolytics and hypnotics given with calcium-channel blockers
Dihydropyridine: calcium-channel blockers include amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, and nisoldipine
Clonidine: enhanced hypotensive effect when anxiolytics and hypnotics given with clonidine
Diazoxide: enhanced hypotensive effect when anxiolytics and hypnotics given with diazoxide
Diuretics: enhanced hypotensive effect when anxiolytics and hypnotics given with diuretics
Hydralazine: enhanced hypotensive effect when anxiolytics and hypnotics given with hydralazine
Lofexidine: increased sedative effect when anxiolytics and hypnotics given with lofexidine
Methyldopa: enhanced hypotensive effect when anxiolytics and hypnotics given with methyldopa
Minoxidil: enhanced hypotensive effect when anxiolytics and hypnotics given with minoxidil
Mirtazapine: increased sedative effect when anxiolytics and hypnotics given with mirtazapine
Moxonidine: enhanced hypotensive effect when anxiolytics and hypnotics given with moxonidine
Nabulone: increased sedative effect when anxiolytics and hypnotics given with nabulone
Nitrates: enhanced hypotensive effect when anxiolytics and hypnotics given with nitrates
Opioid Analgesics: increased sedative effect when anxiolytics and hypnotics given with opioid analgesics
Ritonavir: plasma concentration of anxiolytics and hypnotics possibly increased by ritonavir
Sodium Nitroprusside: enhanced hypotensive effect when anxiolytics and hypnotics given with sodium nitroprusside
Tizanidine: increased sedative effect when anxiolytics and hypnotics given with tizanidine
Losartan
See under ACE inhibitors and angiotensin II antagonists
Appendix 1: Drug interactions

Macrolides
See under erythromycin and other macrolides

Magnesium salts
Calcium-channel blockers: profound hypotension with nifedipine and intravenous magnesium sulphate in pre-eclampsia

Maprotiline
See under antidepressants

Medrosxyprogesterone
See under progesterone

Mefenamic acid
See under NSAIDs

Mefloquine
Anti-arrhythmics: increased risk of ventricular arrhythmias with amiodarone and quinidine
Antiepileptics: antagonism of anticonvulsant effect
Antipsychotics: increased risk of ventricular arrhythmias
Ivabradine: increased risk of ventricular arrhythmias when mefloquine given with ivabradine.

Megestrol
See under progestogens

Melphalan
Ciclosporin: increased risk of nephrotoxicity
Nalidixic Acid: increased risk of melphalan toxicity
Also, see under cytotoxics

Mercaptopurine
Allopurinol: enhancement of effect
Antibacterials: increased haematological toxicity with co-trimoxazole and trimethoprim

Meropenem
Probenecid: excretion of meropenem reduced by probenecid (manufacturers of meropenem advise avoid concomitant use)
Valproate: meropenem reduces plasma concentration of valproate

Mesalazine
See under aminosalicylates

Metoprolol
See under beta-blockers

Metformin
See under antidiabetics

Methadone
See under Opioid analgesics

Methotrexate
Anaesthetics: antifolate effect increased by N₂O
Analgesics: excretion reduced by aspirin and other NSAIDs
Antibacterials: antifolate effect increased by co-trimoxazole and trimethoprim; excretion reduced by penicillin
Ciclosporin: increased toxicity
Corticosteroids: increased risk of haematological toxicity
Proton pump inhibitors: decrease the excretion of methotrexate (increased risk of toxicity)
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Appendix 1: Drug interactions

**Montelukast**
- Phenobarbital: plasma concentration of montelukast reduced by phenobarbital
- Primidone: plasma concentration of montelukast reduced by primidone

**Morphine**
- See opioid analgesics

**Moxifloxacin**
- Amiodarone: increased risk of ventricular arrhythmias
- Antacids: absorption of moxifloxacin reduced by antacids
- Antidepressants, Tricyclic: increased risk of ventricular arrhythmias
- Atomoxetine: increased risk of ventricular arrhythmias
- Chloroquine and Hydroxychloroquine: increased risk of ventricular arrhythmias
- Disopyramide: increased risk of ventricular arrhythmias
- Erythromycin: increased risk of ventricular arrhythmias
- Haloperidol: increased risk of ventricular arrhythmias
- Iron: absorption of moxifloxacin reduced by oral iron
- Mefloquine: increased risk of ventricular arrhythmias
- Mizolastine: increased risk of ventricular arrhythmias
- Nilotinib: avoidance of moxifloxacin advised by manufacturer of nilotinib
- Pentamidine: Isetionate increased risk of ventricular arrhythmias

**Phenothiazines**: increased risk of ventricular arrhythmias
- Pimozide: increased risk of ventricular arrhythmias
- Procainamide: increased risk of ventricular arrhythmias
- Quinine: increased risk of ventricular arrhythmias
- Sertindole: increased risk of ventricular arrhythmias
- Sotalol: increased risk of ventricular arrhythmias
- Sucralfate: absorption of moxifloxacin reduced by sucralfate
- Zinc: absorption of moxifloxacin reduced by zinc

*Also, see under quinolones*

**Muscle relaxants**
- Anti-arrhythmics: lignocaine prolongs suxamethonium effect
- Antibacterials: effect of non-depolarising muscle relaxants enhanced by aminoglycosides
- Antiepileptics: effect of non-depolarising muscle relaxants antagonised by carbamazepine and phenytoin
- Calcium-channel blockers: nifedipine and verapamil enhance effect of non-depolarising muscle relaxant
- Parasympathomimetics: enhance effect of suxamethonium but antagonise effect of non-depolarising muscle relaxants
Appendix 1: Drug interactions

**Mycophenolate**

- **Aciclovir**: mycophenolate increases plasma concentration of aciclovir
- **Antacids**: absorption of mycophenolate reduced by antacids
- **Colestyramine**: absorption of mycophenolate reduced by colestyramine
- **Ganciclovir**: mycophenolate possibly increases plasma concentration of ganciclovir
- **Iron**: absorption of mycophenolate reduced by oral iron
- **Metronidazole**: bioavailability of mycophenolate possibly reduced by metronidazole
- **Norfloxacin**: bioavailability of mycophenolate possibly reduced by norfloxacin
- **Rifampicin**: plasma concentration of active metabolite of mycophenolate reduced by rifampicin
- **Sevelamer**: plasma concentration of mycophenolate possibly reduced by sevelamer

*Also, see under cytotoxics*

**Mycophenolate Mofetil**

*See under mycophenolate*

**Mycophenolate Sodium**

*See under mycophenolate*

**Mycophenolic Acid**

*See under mycophenolate*

**Nabumetone**

*See under NSAIDs*

**Nadolol**

*See under beta-blockers*

**Nalbuphine**

*See under opioid analgesics*

**Nalidixic acid**

*See under quinolones*

**Naproxen**

*See under NSAIDs*

**Naratriptan**

*See under 5HT1 Agonists*

**Neomycin**

*See under aminoglycosides*

**Neostigmine**

*See under parasympathomimetics*

**Netilmicin**

*See under aminoglycosides*

**Nevirapine**

- **Amprenavir**: nevirapine possibly reduces plasma concentration of amprenavir
- **Aripiprazole**: nevirapine possibly reduces plasma concentration of aripiprazole —**Atazanavir**: nevirapine possibly reduces plasma concentration of atazanavir
- **Caspofungin**: nevirapine possibly reduces plasma concentration of caspofungin —**Efavirenz**: nevirapine reduces plasma concentration of efavirenz
Appendix 1: Drug interactions

Fluconazole: plasma concentration of nevirapine increased by fluconazole

Indinavir: nevirapine reduces plasma concentration of indinavir

Ketoconazole: nevirapine reduces plasma concentration of ketoconazole

Lopinavir: nevirapine possibly reduces plasma concentration of lopinavir

Methadone: nevirapine possibly reduces plasma concentration of methadone

Oestrogens: nevirapine accelerates metabolism of oestrogens

Progestogens: nevirapine accelerates metabolism of progestogens (reduced contraceptive effect)

Rifabutin: nevirapine possibly increases plasma concentration of rifabutin

Rifampicin: plasma concentration of nevirapine reduced by rifampicin

St John's Wort: plasma concentration of nevirapine reduced by St John's wort

Warfarin: nevirapine may enhance or reduce anticoagulant effect of warfarin

Nifedipine
See under calcium-channel blockers

Nimodipine
See under calcium-channel blockers

Nitrates
Hypotensive interaction will be encountered with drugs that have the tendency to lower blood pressure

Anticoagulants: excretion of heparin increased by glyceryl trinitrate infusion

Antimuscarinics: dry mouth may cause a delay in absorption of sublingual glyceryl trinitrate

Sildenafil: hypotensive effect significantly enhanced

Nitrazepam
See under anxiolytics and hypnotics

Nitrofurantoin
Uricosurics: probenecid reduces excretion of nitrofurantoin

Nizatidine
See under histamine H2-antagonists

Noradrenaline
See under sympathomimetics

Norethisterone
See under progesterone

Norgestrel
See under progesterone

NSAIDs
ACE Inhibitors: antagonism of hypotensive effect; increased risk of renal impairment

Analgesics (other): avoid concomitant use of NSAIDs with
Appendix 1: Drug interactions

NSAIDs or aspirin (increased side-effects); avoid concomitant use of NSAIDs with ketorolac (increased side-effects and haemorrhage); ibuprofen possibly reduces antiplatelet effect of aspirin.

Antibacterials: indomethacin possibly increases plasma concentration of amikacin and gentamicin in neonates; plasma concentration of celecoxib and diclofenac reduced by rifampicin; possible increased risk of convulsions when NSAIDs given with quinolones

Anticoagulants: anticoagulant effect seriously enhanced by NSAIDs; increased risk of haemorrhage when anticoagulants are given with intravenous diclofenac (avoid concomitant use); increased risk of harmorrhage when anticoagulants given with ketorolac (avoid concomitant use); NSAIDs possibly enhance anticoagulant effect of coumarins; possible increased risk of bleeding when NSAIDs given with dabigatran or heparins

Antidepressants: increased risk of bleeding when NSAIDs given with SSRIs

Antidiabetics: effect of sulphonylureas possibly enhanced by NSAIDs

Antiepileptics: effect of phenytoin possibly enhanced by NSAIDs

Antihypertensives: antagonism of hypotensive effect

Antiplatelet drugs: increased risk of bleeding

Antivirals: increased risk of toxicity with zidovudine

Cardiac glycosides: NSAIDs may exacerbate heart failure, reduce GFR and increase plasma-glycoside concentration

Ciclosporin: increased risk of nephrotoxicity

Cytotoxics: NSAIDs probably reduce excretion of methotrexate (increased risk of toxicity); increased risk of bleeding when NSAIDs given with erlotinib

Diuretics: risk of nephrotoxicity of NSAIDs increased

Lithium: excretion of lithium reduced

Tacrolimus: possible increased risk of nephrotoxicity when NSAIDs given with tacrolimus; increased risk of nephrotoxicity when ibuprofen given with tacrolimus

Uricosurics: Probenecid delays NSAIDs excretion

Fluconazole: plasma concentration of nevirapine increased by fluconazole

Indinavir: nevirapine reduces plasma concentration of indinavir

Ketoconazole: nevirapine reduces plasma concentration of ketoconazole

Lopinavir: nevirapine possibly reduces plasma concentration of lopinavir

Methadone: nevirapine possibly reduces plasma concentration of methadone

Oestrogens: nevirapine accelerates metabolism of oestrogens

Progestogens: nevirapine accelerates metabolism of progestogens (reduced contraceptive effect)

Rifabutin: nevirapine possibly increases plasma concentration of rifabutin

Rifampicin: plasma concentration of nevirapine reduced by rifampicin

St John’s Wort: plasma concentration of nevirapine reduced by St John’s wort

Warfarin: nevirapine may enhance or reduce anticoagulant effect of warfarin

Nifedipine

See under calcium-channel blockers

Nimodipine

See under calcium-channel blockers

Nitrates

Hypotensive interaction will be encountered with drugs that have the tendency to lower blood pressure

Anticoagulants: excretion of heparin increased by glyceryl trinitrate infusion

Antimuscarinics: dry mouth may cause a delay in absorption of sublingual glyceryl trinitrate

Sildenafil: hypotensive effect significantly enhanced

Nitrazepam

See under anxiolytics and hypnotics

Nitrofurantoin

Uricosurics: probenecid reduces excretion of nitrofurantoin

Nizatidine

See under histamine H2-antagonists

Noradrenaline

See under sympathomimetics

Norethisterone

See under progesterone

Norgestrel

See under progesterone

NSAIDs

ACE Inhibitors: antagonism of hypotensive effect; increased risk of renal impairment

Analgesics (other): avoid concomitant use of NSAIDs with...
Appendix 1: Drug interactions

Octreotide
Bromocriptine: octreotide increases plasma concentration of bromocriptine
Ciclosporin: octreotide reduces plasma concentration of ciclosporin
Cimetidine: octreotide possibly delays absorption of cimetidine
Insulin: octreotide possibly reduces requirements for insulin
Metformin: octreotide possibly reduces requirements for metformin
Repaglinide: octreotide possibly reduces requirements for repaglinide
Sulphonylureas: octreotide possibly reduces requirements for sulphonylureas

Oestrogens
See under contraceptives

Olanzapine
See under antipsychotics

Olsalazine
See under aminosalicylates

Omeprazole
See under proton pump inhibitors

Opioid analgesics
Anti-arrhythmics: delay absorption of mexiletine
Antidepressants: CNS excitation or depression if opioids are used with MAO inhibitors; tramadol increases risk of CNS toxicity with SSRIs and tricyclics; possibly increased sedation with tricyclics

Antiepileptics: effect of tramadol and methadone decreased by carbamazepine
Antipsychotics: enhanced sedative and hypotensive effect
Metoclopramide and domperidone: antagonism of gastro-intestinal effects

Orphenadrine
See under antimuscarinics

Oxaliplatin
See under platinum compounds
See under cytotoxics

Oxymetazoline
See under sympathomimetics

Oxytocin
Anaesthetics: inhalational anaesthetics possibly reduce oxytocin effect
Prostaglandins: enhanced uterotonic effect

Pancreatin
Antidiabetics: hypoglycaemic effect of acarbose reduced

Pancuronium
See under muscle relaxants

Panitumumab
Antipsychotics: avoid concomitant use of cytotoxic with clozapine (increased risk of agranulocytosis)
Vaccine: risk of generalized infection when monoclonal antibodies given with live vaccine
Appendix 1: Drug interactions

Paracetamol
Anticoagulants: prolonged use of paracetamol possibly enhances warfarin effect
Metoclopramide and domperidone: paracetamol absorption accelerated

Parasympathomimetics
Antibacterials: aminoglycosides and clindamycin antagonize the effect of neostigmine
Antimuscarinics: antagonism
Beta-blockers: propranolol antagonizes effects of neostigmine and pyridostigmine
Muscle relaxants: effect of suxamethonium enhanced

Paroxetine
See under antidepressants

Pegfilgrastim:
See under filgrastim

Peginterferon alfa
See under interferons

Penicillamine
Antacids: reduce absorption of penicillamine
Iron: reduce absorption of penicillamine

Penicillins
Allopurinol: increased risk of rash with concomitant use of penicillins
Uricosurics: excretion of penicillins reduced with probenecid

Pentamidine isethionate
Anti-arrhythmics: increased risk of ventricular arrhythmias
Antipsychotics: increased risk of ventricular arrhythmias with thioridazine

Pethidine
See under opioid analgesics

Phenobarbitone
See under barbiturates

Phenoxybenzamine
See alpha-blockers

Phenoxyethylpenicillin
See under penicillins

Phentolamine
See under alpha-blockers

Phenytoin
Analgesics: plasma-phenytoin concentration increased by aspirin
Anti-arrhythmics: amiodarone increases plasma-phenytoin concentration; phenytoin decreases plasma concentration of disopyramide, mexiletine and quinidine
Antibacterials: plasma-phenytoin concentration increased by chloramphenicol, clarithromycin, isoniazid and metronidazole; plasma-phenytoin concentration reduced by rifampicin
Anticoagulants: metabolism of warfarin accelerated; plasma concentration of rivaroxaban possibly
Appendix 1: Drug interactions

Reduced by phenytoin—manufacturer of rivaroxaban advises monitor for signs of thrombosis
Antidepressants: antagonism of anticonvulsant effect; fluoxetine increases plasma-phenytoin concentration
Antiepileptics (other): potentiation of sedative effect
Antimalarials: mefloquine antagonises anticonvulsant effect; chloroquine reduced convulsive threshold
Antipsychotics: antagonism of anticonvulsant effect
Calcium-channel blockers: diltiazem and nifedipine increase plasma-phenytoin concentration
Ciclosporin: metabolism of ciclosporin accelerated
Corticosteroids: metabolism of corticosteroids accelerated
Oestrogens: metabolism of oestrogens, tibolone and oral contraceptives, accelerated
Proton pump inhibitors: effect of phenytoin enhanced by omeprazole and esomeprazole

Physostigmine
See under parasympathomimetics

Phytomenadione
See under vitamins

Pilocarpine
See under parasympathomimetics

Piperacillin
See under penicillins

Pirenidone

Antibacterials: ciprofloxacin increases plasma concentration of pirfenidone

Platinum Compounds
Aminoglycosides: increased risk of nephrotoxicity and possibly of ototoxicity
Capreomycin: increased risk of nephrotoxicity and ototoxicity
Diuretics: increased risk of nephrotoxicity and ototoxicity
Polymyxins: increased risk of nephrotoxicity and possibly of ototoxicity

Polymyxins
Aminoglycosides: increased risk of nephrotoxicity
Amphotericin: increased risk of nephrotoxicity
Capreomycin: increased risk of nephrotoxicity
Ciclosporin: increased risk of nephrotoxicity
Diuretics, Loop: increased risk of ototoxicity
Muscle Relaxants, non-depolarising: polymyxins enhance effects of non-depolarising muscle relaxants
Neostigmine: polymyxins antagonise effects of neostigmine
Platinum Compounds: increased risk of nephrotoxicity and possibly
Appendix 1: Drug interactions

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Appendix 1: Drug interactions

Pyrimethamine: increased antifolate effect
Warfarin: isolated reports that proguanil may enhance anticoagulant effect of warfarin

Promethazine
See under antihistamines

Propofol
See under anaesthetics

Propranolol
See under beta-blockers

Proton pump inhibitors
Anticoagulants: effect of warfarin possibly enhanced by omeprazole and esomeprazole
Antiepileptics: effect of phenytoin enhanced by omeprazole and esomeprazole
Clopidogrel: esomeprazole and omeprazole reduce the antiplatelet effect of clopidogrel
Cytotoxics: proton pump inhibitors possible reduce the excretion of methotrexate (increased risk of toxicity).

Quetiapine
Antiepileptics: increased antifolate effect and antagonism of anticonvulsant effect of phenytoin
Cytotoxics: increased antifolate effect with methotrexate

Quinidine
Anti-arrhythmics (other): avoid concomitant use of amiodarone
Antibacterials: rifampicin accelerates metabolism
Antidepressants: increased risk of ventricular arrhythmias with tricyclics
Antifungal: plasma concentration increased by itraconazole and miconazole
Antimalarials: increased risk of ventricular arrhythmias with mefloquine
Appendix 1: Drug interactions

Antipsychotics: increased risk of ventricular arrhythmias
Calcium-channel blockers: nifedipine reduces plasma-quinidine concentration; verapamil increases plasma-quinidine concentration
Cardiac glycosides: plasma concentration of digoxin increased
Diuretics: quinidine toxicity increased if hypokalaemia occurs with diuretics
Muscle relaxants: muscle relaxant effect enhanced

Quinidine
Anti-arrhythmics: plasma-concentration of flecainide increased; increased risk of ventricular arrhythmias with amiodarone increased
Antipsychotics: increased risk of ventricular arrhythmias
Antivirals: plasma concentration of quinine possibly increased by darunavir (increased risk of toxicity)
Cardiac glycosides: plasma concentration of digoxin increased

Quinolones
Analgesics: possible increased risk of convulsion with NSAIDs
Anticoagulants: anticoagulant effect of warfarin enhanced by ciprofloxacin and nalidixic acid
Antidepressants: ciprofloxacin inhibits metabolism of duloxetine—avoid concomitant use
Antimalarials: avoidance of quinolones advised by manufacturer of arte-mether with lumefantrine

Ciclosporin: increased risk of nephrotoxicity
Pirfenidone: ciprofloxacin increases plasma concentration of pirfenidone
Theophylline: possible increased risk of convulsion

Ranitidine
See under Histamine H₂-antagonists

Remifentanil
See under opioid analgesics

Retinoids
Antibacterials: possible increased risk of benign intracranial hypertension with acitretin and tretinoin
Anticoagulants: acitretin possibly reduces the effect of warfarin
Antifungals: fluconazole and voriconazole possibly increase risk of tretinoin toxicity
Cytotoxic: acitretin increases plasma concentration of methotrexate
Oral contraceptives: acitretin possibly reduces the efficacy of low oestrogen oral contraceptives

Ribavirin
Didanosine: increased risk of side-effects
Stavudine: ribavirin possibly inhibits effects of stavudine
Zidovudine: increased risk of anaemia

Rifabutin
See under Rifamycins

Pyrimethamine: increased antifolate effect
Warfarin: isolated reports that proguanil may enhance anticoagulant effect of warfarin
Promethazine
See under antihistamines
Propofol
See under anaesthetics
Propranolol
See under beta-blockers
Proton pump inhibitors
Anticoagulants: effect of warfarin possibly enhanced by omeprazole and esomeprazole
Antiepileptics: effect of phenytoin enhanced by omeprazole and esomeprazole
Clopidogrel: esomeprazole and omeprazole reduce the antiplatelet effect of clopidogrel
Cytotoxics: proton pump inhibitors possibly reduce the excretion of methotrexate (increased risk of toxicity.
Pseudoephedrine
See under sympathomimetics
Pyridostigmine
See under parasympathomimetics
Pyridoxine
See under vitamins
Pyrimethamine
Antibacterials: increased antifolate effect with sulphonamides
Antiepileptics; increased antifolate effect and antagonism of anticonvulsant effect of phenytoin
Cytotoxics: increased antifolate effect with methotrexate
Quetiapine
Antifungals, Imidazole: plasma concentration of quetiapine possibly increased by imidazoles (reduce dose of quetiapine)
Antifungals, Triazole: plasma concentration of quetiapine possibly increased by triazoles (reduce dose of quetiapine)
Carbamazepine: metabolism of quetiapine accelerated by carbamazepine (reduced plasma concentration)
Macrolides: plasma concentration of quetiapine possibly increased by macrolides
Phenytoin: metabolism of quetiapine accelerated by phenytoin (reduced plasma concentration)
Also, see under antipsychotics
Quinidine
Anti-arrhythmics (other): avoid concomitant use of amiodarone
Antibacterials: rifampicin accelerates metabolism
Antidepressants: increased risk of ventricular arrhythmias with tricyclics
Antifungal: plasma concentration increased by itraconazole and miconazole
Antimalarials: increased risk of ventricular arrhythmias with mefloquine
Ranitidine
See under Histamine H₂-antagonists
Remifentanil
See under opioid analgesics
Retinoids
Antibacterials: possible increased risk of benign intracranial hypertension with acitretin and tretinoin
Anticoagulants: acitretin possibly reduces the effect of warfarin
Antifungals: fluconazole and voriconazole possibly increase risk of tretinoin toxicity
Cytotoxic: acitretin increases plasma concentration of methotrexate
Oral contraceptives: acitretin possibly reduces the efficacy of low oestrogen oral contraceptives
Ribavirin
Didanosine: increased risk of side-effects
Stavudine: ribavirin possibly inhibits effects of stavudine
Zidovudine: increased risk of anaemia
Rifabutin
See under Rifamycins

Pyrimethamine: increased antifolate effect
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Antiepileptics; increased antifolate effect and antagonism of anticonvulsant effect of phenytoin
Cytotoxics: increased antifolate effect with methotrexate
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Phenytoin: metabolism of quetiapine accelerated by phenytoin (reduced plasma concentration)
Also, see under antipsychotics
Quinidine
Anti-arrhythmics (other): avoid concomitant use of amiodarone
Antibacterials: rifampicin accelerates metabolism
Antidepressants: increased risk of ventricular arrhythmias with tricyclics
Antifungal: plasma concentration increased by itraconazole and miconazole
Antimalarials: increased risk of ventricular arrhythmias with mefloquine
Appendix 1: Drug interactions

Rifampicin
See under Rifamycins

Rifamycins
Anti-arrhythmics: reduced plasma concentration of disopyramide, mexiletine and quinidine
Antibacterials (other): plasma concentration of chloramphenicol reduced; plasma concentration of dapsone reduced increased risk of side-effects including neutropenia when rifabutin given with azithromycin; rifamycins reduce plasma concentration of clarithromycin and dapsone; plasma concentration of rifabutin increased by clarithromycin; plasma concentration of rifabutin possibly increased by erythromycin; rifampicin possibly reduces plasma concentration of tinidazole and trimethoprim; rifampicin reduces plasma concentration of doxycycline; rifampicin accelerates metabolism of chl ramphnenicol; increased risk of hepatotoxicity when rifampicin given with isoniazid; rifampicin reduces plasma concentration of linezolid; metabolism of sunitinib accelerated by rifampicin
Anticoagulants: metabolism of warfarin accelerated; rifampicin reduces plasma concentration of rivaroxaban—manufacturer of rivaroxaban advises monitor for signs of thrombosis. Antidiabetics: metabolism of sulphonylureas possibly accelerated

Antiepileptics: metabolism of phenytoin accelerated; plasma concentration of carbamazepine reduced. Rifabutin reduces plasma concentration of carbamazepine; rifampicin reduces plasma concentration of lamotrigine; plasma concentration of rifampicin possibly reduced by phenobarbital; rifamycins accelerate metabolism of phenytoin
Antifungals: plasma concentration of rifabutin increased by fluconazole; rifampicin accelerates metabolism of fluconazole; rifabutin and rifampicin reduce plasma concentration of itraconazole; plasma concentration of rifabutin increased by voriconazole, also rifabutin reduces plasma concentration of voriconazole; rifampicin reduces plasma concentration of voriconazole; rifampicin initially increases and then reduces plasma concentration of caspofungin
Antimalarials: avoidance of rifampicin advised by manufacturer of piperaquine with artemimol; rifampicin reduces plasma concentration of mefloquine avoid concomitant use; rifampicin reduces plasma concentration of quinine
Antipsychotics: rifampicin accelerates metabolism of haloperidol
Antivirals: rifampicin significantly reduces plasma concentration of da-runavir—avoid concomitant use; plasma concentration of rifabutin reduced by efavirenz
Appendix 1: Drug interactions

; rifampicin reduces plasma concentration of efavirenz; rifampicin reduces plasma concentration of ritonavir; plasma concentration of rifabutin increased by ritonavir

Beta blockers: metabolism of bisoprolol accelerated by rifampicin; plasma concentration of metoprolol reduced by rifampicin.

Calcium-channel blockers: metabolism of most calcium-channel blockers accelerated

Ciclosporin: metabolism accelerated

Corticosteroids: rifamycins accelerate metabolism of corticosteroids

Deferasirox: plasma concentration of deferasirox reduced by rifampicin

Everolimus: plasma concentration of everolimus reduced by rifampicin

Gefitinib: plasma concentration of gefitinib reduced by rifampicin

Lapatinib: manufacturer of lapatinib advises avoid concomitant use with rifabutin and rifampicin

Lipid regulating drugs: metabolism of fluvastatin accelerated

Oestrogens and progestogens: metabolism accelerated (reduced effect of oral contraceptives)

Sirolimus: rifabutin and rifampicin reduce plasma concentration of sirolimus

Sorafenib: plasma concentration of sorafenib reduced by rifampicin

Tacrolimus: rifabutin possibly reduces plasma concentration of tacrolimus; rifampicin reduces plasma concentration of tacrolimus

Risperidone

See under antipsychotics

Ritodrine

See under sympathomimetics, Beta2

Ritonavir

Alfuzosin: ritonavir possibly increases plasma concentration of alfuzosin

Alprazolam: ritonavir possibly increases plasma concentration of alprazolam (risk of extreme sedation and respiratory depression)

Amiodarone: ritonavir increases plasma concentration of amiodarone (increased risk of ventricular arrhythmias)

Amprenavir: ritonavir increases plasma concentration of amprenavir

Antidepressants, SSRI: ritonavir possibly increases plasma concentration of SSRIs

Antidepressants, Tricyclic: ritonavir possibly increases plasma concentration of tricyclics

Antihistamines, Non-sedating: ritonavir possibly increases plasma concentration of non-sedating antihistamines

Antipsychotics: ritonavir possibly increases plasma concentration of antipsychotics

Anxiolytics and Hypnotics: ritonavir possibly increases plasma concentration of...
Appendix 1: Drug interactions

concentration of anxiolytics and hypnotics
Aprepitant: ritonavir possibly increases plasma concentration of aprepitant
Aripiprazole: ritonavir possibly inhibits metabolism of aripiprazole
Artemether with Lumefantrine: avoid concomitant use of ritonavir with artemether/lumefantrine
Atorvastatin: possible increased risk of myopathy
Azithromycin: ritonavir possibly increases plasma concentration of azithromycin
Bosentan: ritonavir possibly increases plasma concentration of bosentan
Budesonide: ritonavir increases plasma concentration of inhaled and intranasal budesonide
Buprenorphine: ritonavir possibly increases plasma concentration of buprenorphine
Bupropion: ritonavir increases plasma concentration of bupropion (risk of toxicity)
Buspirone: ritonavir increases plasma concentration of buspirone (increased risk of toxicity)
Calcium-channel Blockers: ritonavir possibly increases plasma concentration of calcium-channel blockers
Carbamazepine: ritonavir possibly increases plasma concentration of carbamazepine
Ciclosporin: ritonavir possibly increases plasma concentration of ciclosporin

Cilostazol: ritonavir possibly increases plasma concentration of cilostazol
Clarithromycin: ritonavir increases plasma concentration of clarithromycin
Clozapine: ritonavir increases plasma concentration of clozapine (increased risk of toxicity)
Corticosteroids: ritonavir possibly increases plasma concentration of corticosteroids
Coumarins: ritonavir possibly enhances anticoagulant effect of coumarins
Darifenacin: avoidance of ritonavir advised by manufacturer of darifenacin
Dexamethasone: ritonavir possibly increases plasma concentration of dexamethasone
Dexamfetamine: ritonavir possibly increases plasma concentration of dexamfetamine
Dextropropoxyphene: ritonavir increases plasma concentration of dextropropoxyphene (risk of toxicity)
Diazepam: ritonavir possibly increases plasma concentration of diazepam (risk of extreme sedation and respiratory depression)
Digoxin: ritonavir possibly increases plasma concentration of digoxin
Disopyramide: ritonavir possibly increases plasma concentration of disopyramide (increased risk of toxicity)
Efavirenz: ritonavir increases toxicity of efavirenz, monitor liver function tests
Appendix 1: Drug interactions

Eletriptan: ritonavir increases plasma concentration of eletriptan (risk of toxicity)
Eplerenone: ritonavir increases plasma concentration of eplerenone
Erythromycin: ritonavir possibly increases plasma concentration of erythromycin
Fentanyl: ritonavir increases plasma concentration of fentanyl
Fesoterodine: manufacturer of fesoterodine advises dose reduction when ritonavir given with fesoterodine
Flecainide: ritonavir possibly increases plasma concentration of flecainide (increased risk of ventricular arrhythmias)
Fluconazole: plasma concentration of ritonavir increased by fluconazole
Flurazepam: ritonavir possibly increases plasma concentration of flurazepam (risk of extreme sedation and respiratory depression)
Fluticasone: ritonavir increases plasma concentration of inhaled and intranasal fluticasone
Fusidic Acid: plasma concentration of both drugs increased when ritonavir given with fusidic acid
Indinavir: ritonavir increases plasma concentration of indinavir
Itraconazole: combination of ritonavir with itraconazole may increase plasma concentration of either drug (or both)
Ivabradine: ritonavir possibly increases plasma concentration of ivabradine
Ketoconazole: combination of ritonavir with ketoconazole may increase plasma concentration of either drug (or both)
Lercanidipine: avoidance of ritonavir advised by manufacturer of lercanidipine
Methadone: ritonavir reduces plasma concentration of methadone
Midazolam: ritonavir possibly increases plasma concentration of midazolam (risk of prolonged sedation)
Morphine: ritonavir possibly reduces plasma concentration of morphine
Nelfinavir: combination of ritonavir with nelfinavir may increase plasma concentration of either drug (or both)
Nilotinib: avoidance of ritonavir advised by manufacturer of nilotinib
NSAIDs: ritonavir possibly increases plasma concentration of NSAIDs
Oestrogens: ritonavir accelerates metabolism of oestrogens (reduced contraceptive effect)
Olanzapine: ritonavir reduces plasma concentration of olanzapine
Paclitaxel: ritonavir increases plasma concentration of paclitaxel
Paroxetine: ritonavir possibly reduces plasma concentration of paroxetine
Pethidine: ritonavir reduces plasma concentration of pethidine, but increases plasma concentration of toxic metabolite of pethidine
**Appendix 1: Drug interactions**

**Phenindione**: ritonavir possibly enhances anticoagulant effect of phenindione

**Phenytoin**: plasma concentration of ritonavir possibly reduced by phenytoin, *Also* plasma concentration of phenytoin possibly affected

**Pimozide**: ritonavir increases plasma concentration of pimozide (increased risk of ventricular arrhythmias)

**Piroxicam**: ritonavir increases plasma concentration of piroxicam (risk of toxicity)

**Prednisolone**: ritonavir possibly increases plasma concentration of prednisolone

**Propafenone**: ritonavir increases plasma concentration of propafenone (increased risk of ventricular arrhythmias)

**Rifabutin**: ritonavir increases plasma concentration of rifabutin (increased risk of toxicity)

**Rifampicin**: plasma concentration of ritonavir possibly reduced by rifampicin

**Rivaroxaban**: plasma concentration of rivaroxaban increased by ritonavir—avoid concomitant use

**Rosuvastatin**: possible increased risk of myopathy when ritonavir given with simvastatin

**Sildenafil**: ritonavir increases plasma concentration of solifenacin

**Solifenacin**: ritonavir increases plasma concentration of solifenacin

**St John's Wort**: plasma concentration of ritonavir reduced by St John’s wort

**Tacrolimus**: ritonavir possibly increases plasma concentration of tacrolimus

**Tadalafil**: ritonavir increases plasma concentration of tadalafil

**Telithromycin**: avoidance of concomitant ritonavir in severe renal and hepatic impairment advised by manufacturer of telithromycin

**Theophylline**: ritonavir accelerates metabolism of theophylline (reduced plasma concentration)

**Tolbutamide**: ritonavir possibly increases plasma concentration of tolbutamide

**Tolterodine**: avoidance of ritonavir advised by manufacturer of tolterodine

**Trazodone**: side-effects possibly increased when ritonavir given with trazodone

**Vardenafil**: ritonavir possibly increases plasma concentration of vardenafil

**Voriconazole**: ritonavir reduces plasma concentration of voriconazole

**Warfarin**: ritonavir may enhance or reduce anticoagulant effect of warfarin

**Zolpidem**: ritonavir possibly increases plasma concentration of zolpidem (risk of extreme sedation and respiratory depression)
Appendix 1: Drug interactions

**Rivaroxaban**

*Analgesics:* increased risk of haemorrhage when intravenous diclofenac given with anticoagulants (avoid concomitant use, including low-dose heparins)

*Antibacterials:* rifampicin reduces plasma concentration of rivaroxaban—manufacturer of rivaroxaban advises monitor for signs of thrombosis

*Anticoagulants:* increased risk of haemorrhage when other anticoagulants given with rivaroxaban (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency); increased risk of haemorrhage when ketorolac given with anticoagulants (avoid concomitant use, including low-dose heparins).

*Antiepileptics:* plasma concentration of rivaroxaban possibly reduced by carbamazepine—manufacturer of rivaroxaban advises monitor for signs of thrombosis; plasma concentration of rivaroxaban possibly reduced by phenytoin—manufacturer of rivaroxaban advises monitor for signs of thrombosis; phenobarbital plasma concentration of rivaroxaban possibly reduced by phenobarbital—manufacturer of rivaroxaban advises monitor for signs of thrombosis

*Antifungals:* manufacturer of rivaroxaban advises avoid concomitant use with itraconazole; plasma concentration of rivaroxaban increased by ketoconazole—avoid concomitant use; manufacturer of rivaroxaban advises avoid concomitant use with voriconazole

*Antivirals:* manufacturer of rivaroxaban advises avoid concomitant use with indinavir; manufacturers advise avoid concomitant use of rivaroxaban with lopinavir. Note: In combination with ritonavir as Kaletra® (ritonavir is present to inhibit lopinavir metabolism and increase plasma-lopinavir concentration)—see also Ritonavir; plasma concentration of rivaroxaban increased by ritonavir—avoid concomitant use

**Rizatriptan**

*Methysergide:* increased risk of vasospasm

*MAOIs:* risk of CNS toxicity

*Moclobemide:* risk of CNS toxicity

*Propranolol:* plasma concentration of rizatriptan increased by propranolol

*Also, see under 5HT1 agonists*

**Salbutamol**

*See under sympathomimetics, (β2-agonists)*

**Salmeterol**

*See under sympathomimetics, (β2-agonists)*

**Selegiline**

*Antidepressants: increase CNS toxicity*
Appendix 1: Drug interactions

Methyldopa: antiparkinsonian effect antagonised by methyldopa
Moclobemide: avoid concomitant use
Oestrogens: plasma concentration of selegiline increased by oestrogens (increased risk of toxicity)
Paroxetine: increased risk of selegiline given with citalopram (especially if dose of selegiline exceeds 10 mg daily)
Dopamine: risk of hypertensive crisis
Entacapone: max. dose of 10 mg selegiline advised by manufacturer of entacapone if used concomitantly
Escitalopram: caution with selegiline advised by manufacturer
Fluoxetine: increased risk of hypertension and CNS excitation
Fluvoxamine: increased risk of hypertension and CNS excitation
Levodopa: selegiline enhances effects and increases toxicity of hypertension and CNS excitation
Pethidine: hyperpyrexia and CNS toxicity
Progestogens: plasma concentration of selegiline increased by progestogens (increased risk of toxicity)
Sertraline: increased risk of hypertension and CNS excitation

Sevelamer
Ciclosporin: sevelamer possibly reduces plasma concentration of ciclosporin
Ciprofloxacin: sevelamer reduces bioavailability of ciprofloxacin
Mycophenolate: sevelamer possibly reduces plasma concentration of mycophenolate
Tacrolimus: sevelamer possibly reduces plasma concentration of tacrolimus
Thyroid Hormones: sevelamer possibly reduces absorption of levothyroxine
Vitamins: sevelamer reduces absorption of calcitriol (give at least I
Appendix 1: Drug interactions

hour before or 3 hours after sevelamer)

**Sildenafil**

*Alpha-blockers*: enhanced hypotensive effect

*Amlodipine*: enhanced hypotensive effect when sildenafil given with amlodipine

*Amprenavir*: plasma concentration of sildenafil possibly increased by amprenavir

*Atazanavir*: side-effects of sildenafil possibly increased by atazanavir

*Bosentan*: plasma concentration of sildenafil reduced by bosentan

*Cimetidine*: plasma concentration of sildenafil increased by cimetidine

*Clarithromycin*: plasma concentration of sildenafil possibly increased by clarithromycin

*Erythromycin*: plasma concentration of sildenafil increased by erythromycin

*Grapefruit Juice*: plasma concentration of sildenafil possibly increased by grapefruit juice

*Indinavir*: plasma concentration of sildenafil increased by indinavir

*Itraconazole*: plasma concentration of sildenafil increased by itraconazole

*Ketoconazole*: plasma concentration of sildenafil increased by ketoconazole

*Nelfinavir*: plasma concentration of sildenafil possibly increased by nelfinav

*Nicorandil*: sildenafil significantly enhances hypotensive effect of nicorandil

*Nitrates*: sildenafil significantly enhances hypotensive effect of nitrates

*Ritonavir*: plasma concentration of sildenafil significantly increased by ritonavir

*Saquinavir*: plasma concentration of sildenafil possibly increased by saquinavir

*Telithromycin*: plasma concentration of sildenafil possibly increased by telithromycin

**Simvastatin**

*See under statins*

**Sirolimus**

*Atazanavir*: plasma concentration of sirolimus possibly increased by atazanavir

*Ciclosporin*: plasma concentration of sirolimus increased by ciclosporin

*Clarithromycin*: plasma concentration of sirolimus increased by clarithromycin

—*Diltiazem*: plasma concentration of sirolimus increased by diltiazem

*Erythromycin*: plasma concentration of both drugs increased when sirolimus given with erythromycin

*Grapefruit Juice*: plasma concentration of sirolimus increased by grapefruit juice

*Itraconazole*: plasma concentration of sirolimus increased by itraconazole
Appendix 1: Drug interactions

Ketoconazole: plasma concentration of sirolimus increased by ketoconazole
Lopinavir: plasma concentration of sirolimus possibly increased by lopinavir
Miconazole: plasma concentration of sirolimus increased by miconazole
Posaconazole: plasma concentration of sirolimus possibly increased by posaconazole
Rifabutin: plasma concentration of sirolimus reduced by rifabutin
Rifampicin: plasma concentration of sirolimus reduced by rifampicin
Telithromycin: plasma concentration of sirolimus increased by telithromycin
Verapamil: plasma concentration of both drugs increased when sirolimus given with verapamil
Voriconazole: plasma concentration of sirolimus increased by voriconazole

Sitagliptin
*See under Antidiabetics*

Sodium phenylbutyrate
Corticosteroids: effects of sodium phenylbutyrate possibly reduced by corticosteroids
Haloperidol: effects of sodium phenylbutyrate possibly reduced by haloperidol
Probenecid: excretion of conjugate formed by sodium phenylbutyrate possibly reduced by probenecid
Valproate: effects of sodium phenylbutyrate possibly reduced by valproate

Sodium valproate
Antidepressants: antagonism of anticonvulsant effect
Antibacterials: carbapenems reduce plasma concentration of sodium valproate—avoid concomitant use
Antimalarials: mefloquine antagonises anticonvulsant effect; chloroquine reduces convulsive threshold
Antipsychotics: antagonism of anticonvulsant effect

Solifenacin
*See under Antimuscarinics*

Sorafenib
Antibacterials: bioavailability of sorafenib reduced by neomycin; plasma concentration of sorafenib reduced by rifampicin
Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Cytotoxics: sorafenib possibly increases plasma concentration
Appendix 1: Drug interactions

of doxorubicin and irinotecan; sorafenib increases plasma concentration of docetaxel

**Spironolactone**  
*See under diuretics*

**Statins**  
*Grapefruit juice increases plasma concentration of simvastatin*

**Antibacterials:** metabolism of fluvastatin accelerated by rifampicin; clarithromycin and erythromycin increase risk of myopathy with simvastatin; clarithromycin increases plasma concentration of atorvastatin.

**Anticoagulants:** effect of warfarin enhanced by simvastatin; atorvastatin may transiently reduce the effect of warfarin.

**Antifungals:** imidazole and triazole derivatives increase the risk of myopathy with simvastatin and atorvastatin; avoid atorvastatin with ketoconazole.

**Ciclosporin:** increased risk of myopathy with simvastatin (avoid concomitant use)

**Lipid-regulating drugs (other):** increased risk of myopathy with fibrates and nicotinic acid

**Stavudine**  
*Didanosine: increased risk of side-effects*  
*Doxorubicin: effects of stavudine possibly inhibited by doxorubicin*

**Hydroxycarbamide:** increased risk of toxicity

**Ribavirin:** effects of stavudine possibly inhibited by ribavirin

**Zidovudine:** effects of stavudine possibly inhibited by zidovudine

**Streptomycin**  
*See under aminoglycosides*

**Sucralfate**  
*Anticoagulants:** absorption of warfarin possibly reduced

**Antiepileptics:** reduced absorption of phenytoin

**Sulfadoxine**  
*See under co-trimoxazole and trimethoprim*

**Sulfasalazine (Sulphasalazine)**  
*See under aminosalicylates*

**Sulphonylureas**  
*See under antidiabetics*

**Sumatriptan**  
*See under 5HT1 Agonists*

**Sunitinib**  
*Antibacterials:** metabolism of sunitinib accelerated by rifampicin (reduced plasma concentration)

**Antipsychotics:** avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

**Antivirals:** avoidance of sunitinib advised by manufacturer
Appendix 1: Drug interactions

of boceprevir.

**Suxamethonium**
*See under muscle relaxants*

**Sympathomimetics**
*Anaesthetics:* risk of arrhythmias if adrenaline is given with inhalational liquid anaesthetics such as halothane and isoflurane
*Antidepressants:* risk of hypertension with tricyclics
*Beta-blockers:* severe hypertension with adrenaline and noradrenaline, possible with dobutamine
*Corticosteroids:* ephedrine accelerates metabolism dexamethasone
*Oxytocin:* risk of hypertension

**Sympathomimetics (β2-agonists)**
*Antihypertensives:* acute hypertension reported with salbutamol infusion and methyldopa
*Corticosteroids:* increased risk of hypokalaemia if high doses of corticosteroids are used with β2-agonists
*Diuretics:* increased risk of hypokalaemia when used with high doses of β2-agonists

**Tacrolimus**
*Aciclovir:* possible increased risk of nephrotoxicity
*Aminoglycosides:* increased risk of nephrotoxicity
*Amphotericin:* increased risk of nephrotoxicity

**Angiotensin-II Receptor Antagonists:** increased risk of hyperkalaemia
**Antifungals, Imidazole:** plasma concentration of tacrolimus possibly increased by imidazoles
**Antifungals, Triazole:** plasma concentration of tacrolimus possibly increased by triazoles
**Atazanavir:** plasma concentration of tacrolimus possibly increased by atazanavir
**Caspofungin:** plasma concentration of tacrolimus reduced by caspofungin
**Chloramphenicol:** plasma concentration of tacrolimus possibly increased by chloramphenicol
**Ciclosporin:** tacrolimus increases plasma concentration of ciclosporin (increased risk of nephrotoxicity)
**Clarithromycin:** plasma concentration of tacrolimus increased by clarithromycin
**Danazol:** plasma concentration of tacrolimus possibly increased by danazol
**Diltiazem:** plasma concentration of tacrolimus increased by diltiazem
**Diuretics, Potassium-sparing and Aldosterone Antagonists:** increased risk of hyperkalaemia
**Erythromycin:** plasma concentration of tacrolimus increased by erythromycin
**Ethinylestradiol:** plasma concentration of tacrolimus possibly increased by ethinylestradiol
**Felodipine:** plasma concentration of tacrolimus possibly increased by felodipine
Appendix 1: Drug interactions

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<td>Phenobarbital</td>
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<tr>
<td>Phenytoin</td>
<td>Plasma concentration of tacrolimus reduced by phenytoin, Also plasma concentration of phenytoin possibly increased</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Plasma concentration of tacrolimus increased by posaconazole</td>
</tr>
<tr>
<td>Potassium Salts</td>
<td>Increased risk of hyperkalaemia</td>
</tr>
<tr>
<td>Progestogens</td>
<td>Tacrolimus possibly inhibits metabolism of progestogens</td>
</tr>
<tr>
<td>Quinupristin</td>
<td>With Dalfopristin plasma concentration of tacrolimus increased by quinupristin/dalfopristin</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Plasma concentration of tacrolimus reduced by rifampicin</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Plasma concentration of tacrolimus possibly increased by ritonavir</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Plasma concentration of tacrolimus increased by saquinavir</td>
</tr>
<tr>
<td>Sevelamer</td>
<td>Plasma concentration of tacrolimus possibly reduced by sevelamer</td>
</tr>
<tr>
<td>St John's Wort</td>
<td>Plasma concentration of tacrolimus reduced by St John's wort —Telithromycin: Plasma concentration of tacrolimus possibly increased by telithromycin</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Plasma concentration of tacrolimus possibly increased by verapamil</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Plasma concentration of tacrolimus increased by voriconazole</td>
</tr>
</tbody>
</table>

**Tamoxifen**

Anticoagulants: Effect of warfarin enhanced
Appendix 1: Drug interactions

Cinacalcet: possibly inhibits metabolism of tamoxifen to active metabolite (avoid concomitant use)

Tamsulosin
See under alpha-blockers

Teicoplanin
Antibacterials: increased risk of ototoxicity and nephrotoxicity with aminoglycosides

Temozolomide
Valproate: plasma concentration of temozolomide increased by valproate
Also, see under cytotoxics

Tenofovir
Adefovir: avoid concomitant use with adefovir
Atazanavir: tenofovir reduces plasma concentration of atazanavir, Also plasma concentration of tenofovir possibly increased
Cidofovir: combination of tenofovir with cidofovir may increase plasma concentration of either drug (or both)
Didanosine: tenofovir increases plasma concentration of didanosine (increased risk of toxicity)
Antacids: in tablet formulation may affect absorption of other drugs
Lopinavir: plasma concentration of tenofovir increased by lopinavir

Tenoxicam
See under NSAIDs

Terazosin
See under alpha-blockers

Terbinafine
Antibacterials: enhanced metabolism by rifampicin
Oral contraceptives: reports of breakthrough bleeding

Terbutaline
See under sympathomimetics, β₂

Testosterone
Anticoagulants: effect of warfarin enhanced
Antidiabetics: hypoglycaemic effect possibly enhanced

Tetracosactrin
See under corticosteroids

Tetracyclines
Antacids: reduced absorption
Antiepileptics: metabolism of doxycycline enhanced by carbamazepine and phenytoin
Calcium salts: reduced absorption of tetracyclines
Ciclosporin: doxycycline possibly increases plasma-ciclosporin concentration
Dairy products: reduce absorption (except for doxycycline and minocycline)
Retinoids: possible increased risk of benign intracranial hypertension with tetracyclines
Appendix 1: Drug interactions

**Theophylline**
- Anaesthetics: increased risk of arrhythmias with halothane; increased risk of convulsion with Ketamine
- Antibacterials: increased risk of convulsion with ciprofloxacin; plasma concentration of theophylline increased by ciprofloxacin, clarithromycin, erythromycin and isoniazid; rifampicin reduces plasma-theophylline concentration
- Antifungals: plasma-theophylline possible increased by fluconazole and ketoconazole
- Antiplatelets: ticlopidine increases plasma-theophylline concentration
- Calcium channel blockers: plasma-theophylline concentration increased
- Corticosteroids: increased risk of hypokalaemia
- Deferasirox: increases plasma concentration of theophylline
- Diuretics: increased risk of hypokalaemia
- Lithium salts: lithium excretion accelerated
- Anticoagulants: effect of warfarin enhanced
- Antiepileptics: carbamazepine, phenobarbitone and phenytoin enhanced metabolism of thyroid hormones

**Tiaprofenic acid**
*See under NSAIDs*

**Tibolone**
- Antibacterials: rifampicin accelerates metabolism
- Antiepileptics: carbamazepine, phenobarbitone and phenytoin accelerate metabolism

**Ticlopidine**
- Analgesics: increased risk of bleeding with NSAIDs
- Anticoagulants: increased risk of bleeding
- Ciclosporin: reduced plasma-ciclosporin concentration

**Tigecycline**
- Anticoagulants: tigecycline possibly enhances anticoagulant effect of coumarins

**Timolol**
*See under beta-blockers*

**Tiotropium**
*See under antimuscarinics*

**Tirofiban**
- Illoprost: increased risk of bleeding when tirofiban given with illoprost
Appendix 1: Drug interactions

**Tobramycin**
*See under* aminoglycosides

**Tocilizumab**
Vaccines: avoid concomitant use of tocilizumab with live vaccines

**Tolterodine**
Amiodarone: increased risk of ventricular arrhythmias
Amprenavir: manufacturer of tolterodine advises avoid concomitant use
Clarithromycin: manufacturer of tolterodine advises avoid concomitant use
Disopyramide: increased risk of ventricular arrhythmias
Erythromycin: manufacturer of tolterodine advises avoid concomitant use
Flecainide: increased risk of ventricular arrhythmias
Indinavir: manufacturer of tolterodine advises avoid concomitant use
Itraconazole: manufacturer of tolterodine advises avoid concomitant use
Ketoconazole: manufacturer of tolterodine advises avoid concomitant use
Lopinavir: manufacturer of tolterodine advises avoid concomitant use
Nelfinavir: manufacturer of tolterodine advises avoid concomitant use
Procainamide: increased risk of ventricular arrhythmias
Ritonavir: manufacturer of tolterodine advises avoid concomitant use
Saqunavir: manufacturer of tolterodine advises avoid concomitant use
Sotalol: increased risk of ventricular arrhythmias
*Also, see under* antimuscarinics

**Topiramate**
Carbamazepine: plasma concentration of topiramate often reduced by carbamazepine
Glibenclamide: topiramate possibly reduces plasma concentration of glibenclamide
Lithium: topiramate possibly affects plasma concentration of lithium
Oestrogens: topiramate accelerates metabolism of oestrogens
Phenytoin: topiramate increases plasma concentration of phenytoin (*Also plasma concentration of topiramate reduced*)
Progestogens: topiramate accelerates metabolism of progestogens
*Also, see under* antiepileptics

**Tramadol**
*See under* opioid analgesics

**Tretinoin**
*See under* retinoids

**Triamcinolone**
*See under* corticosteroids

**Trifluoperazine**
*See under* antipsychotics

**Trimethoprim**
Antimalarials: increased risk of antifolate effect with pyrimethamine
Ciclosporin: increased risk of nephrotoxicity
Cytotoxics: increased risk of haematological toxicity with azathioprine and mercaptopurine; antifolate effect of methotrexate increased

**Tripolidine**
*See under* antihistamines

**Tropicamide**
*See under* antimuscarinics

**Ursodeoxycholic Acid**
Ciclosporin: ursodeoxycholic acid increases absorption of ciclosporin
*Also, see under* bile Acids

**Vaccines**
Abatacept: avoid concomitant use
Adalimumab: avoid concomitant use
Anakinra: avoid concomitant use
Corticosteroids: immune response to vaccines impaired by high doses of corticosteroids
Efalizumab: live or live-attenuated vaccines should be given 2 weeks before efalizumab or withheld until 8 weeks after discontinuation
Etanercept: avoid concomitant use
Infliximab: avoid concomitant use
Interferon Gamma: avoidance of vaccines advised by manufacturer of interferon gamma
Leflunomide: avoid concomitant use

**Phenytoin**
influenza vaccine enhances effects of phenytoin

**Theophylline**
influenza vaccine possibly increases plasma concentration of theophylline

**Warfarin**
influenza vaccine possibly enhances anticoagulant effect of warfarin

**Valaciclovir**
*See under* aciclovir

**Valganciclovir**
*See under* ganciclovir

**Valsartan**
*See under* Angiotensin-II Receptor Antagonists

**Vancomycin**
Antibacterials (other): increased of ototoxicity and nephrotoxicity with aminoglycosides
Cytotoxics: increased risk of ototoxicity and nephrotoxicity with cisplatin
Diuretics: increased risk of ototoxicity with loop diuretics

**Vecuronium**
*See under* muscle relaxants

**Verapamil**
*See under* calcium-channel blockers

**Vigabatrin**
Antiepileptics (other): enhanced effects, increased sedation and reduction in plasma concentration

**Appendix 1: Drug interactions**
Appendix 1: Drug interactions

Antimalarials: antagonism of anticonvulsant effect with mefloquine

Vildagliptin
See under Antidiabetics

Vinblastine
Erythromycin: toxicity of vinblastine increased by erythromycin
Posaconazole: metabolism of vinblastine possibly inhibited by posaconazole (increased risk of neurotoxicity)
Also, see under cytotoxics

Vincristine
Itraconazole: metabolism of vincristine possibly inhibited by itraconazole (increased risk of neurotoxicity)
Nifedipine: metabolism of vincristine possibly inhibited by nifedipine
Posaconazole: metabolism of vincristine possibly inhibited by posaconazole (increased risk of neurotoxicity)
Also, see under cytotoxics

Vitamins
Anticoagulants: warfarin effect antagonised by vitamin K
Antiepileptics: vitamin D requirement increased
Diuretics: increased risk of hypercalcaemia if vitamin D and thiazides are given together
Retinoids: risk of hypervitaminosis A with vitamin A given concomitantly with retinoids
Sevelamer: reduces absorption of calcitriol (give at least 1 hour before or 3 hours after sevelamer)

Voriconazole
See under Antifungals

Warfarin
Alcohol: enhanced anticoagulant effect with large amounts of alcohol
Analgesics: enhanced anticoagulant effect
Anion-exchange resins: may enhance or reduce anticoagulant effects
Anti-arrhythmics: amiodarone and quinidine enhance anticoagulant effect
Antibacterials: rifampicin reduced anticoagulant effect; anticoagulant effect enhanced by chloramphenicol, ciprofloxacin, co-trimoxazole, erythromycin, metronidazole and sulphonamides; anticoagulant effect possibly enhanced by clarithromycin, nalidixic acid, neomycin and trimethoprim. Tigecycline possibly enhances anticoagulant effect of coumarins

Antidepressants: SSRIs possibly enhance anticoagulant effect
Antiepileptics: anticoagulant effect reduced by carbamazepine and phenobarbitone; anticoagulant effect increased by valproate; phenytoin may increase or decrease the anticoagulant effect
Antifungals: anticoagulant effect reduced by griseofulvin; anticoagulant effect enhanced by fluconazole, itraconazole, ketoconazole and miconazole

Antiplatelets: increased risk of bleeding

Barbiturates: anticoagulant effect reduced

Corticosteroids: anticoagulant effect possibly altered

Cytotoxics: anticoagulant effect possibly enhanced by ifosfamide and fluorouracil; azathioprine possibly enhances the anticoagulant effect; gefitinib possibly enhances anticoagulant effect of warfarin

Entacapone: anticoagulant effect of warfarin enhanced by entacapone

Hormone antagonists: danazol, tamoxifen and flutamide possibly enhance anticoagulant effect

Lipid-regulating drugs: fibrates and simvastatin enhance anticoagulant effect, atorvastatin reduced the anticoagulant effect transiently

Oral contraceptives: anticoagulant effect reduced testosterone: anticoagulant effect enhanced

Rivaroxaban: increased risk of haemorrhage when other anticoagulants given with rivaroxaban (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency).

Thyroid hormones: anticoagulant effect enhanced

Ulceter healing drugs: omeprazole enhances anticoagulant effect

Vitamins: vitamin K reduces warfarin anticoagulant effect

Zidovudine

Analgesics: increased risk of haematological toxicity with NSAIDs

Antibacterials: clarithromycin tablets reduces absorption of zidovudine

Antivirals (other): profound myelosuppression with Ganciclovir

Uricosurics: probenecid increases plasma-zidovudine concentration and risk of toxicity

Zinc

Antibacterials: zinc reduces absorption of ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin, norfloxacin; tetracyclines (give at least 2 hours apart)

Calcium Salts: absorption of zinc reduced by calcium salts.

Iron: absorption of zinc reduced by oral iron, also absorption of oral iron reduced by zinc

Penicillamine: absorption of zinc reduced by penicillamine, also absorption of penicillamine reduced by zinc

Zoledronic Acid

See under bisphosphonates

Zolmitriptan

Cimetidine: metabolism of zolmitriptan inhibited by cimetidine
Appendix 2: Drug Induced Hepatotoxicity

Drugs are an important cause of liver injury. This is the most common reason cited for withdrawal of an approved drug. Risk factors for drug-induced hepatotoxicity include age (common in elderly), sex (common in females), liver disease, alcohol ingestion, genetic factors, the presence of other comorbidities and drug formulations (long acting drugs may cause more injury than short acting drugs).

Some drugs are directly toxic: with these, injury is generally characteristic for the drug, begins within hours of exposure, and is dose-related. E.g. Acetaminophen (Paracetamol).

Other drugs produce damage only rarely and only in susceptible people; the injury generally first occurs within a few weeks but occasionally may be delayed for several months after drug exposure. This injury is not dose-related. These reactions are rarely allergic; they are more accurately described as idiosyncratic. E.g. Halothane, Isoniazid and Methyldopa.

Metabolic drug interactions:

Cytochrome P-450 enzymes are haemoproteins located in the smooth endoplasmic reticulum of the liver. At least 50 enzymes have been identified, and based on structure; they are categorized into 10 groups, with groups 1, 2, and 3 being the most important in drug metabolism. Each P-450 enzyme can metabolize many drugs. Drugs that share the same P-450 specificity for biotransformation may competitively inhibit each other, resulting in drug interactions. Several drugs can induce and inhibit the P-450 enzyme (see table)

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</tr>
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</tr>
<tr>
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<td>Erythromycin</td>
</tr>
<tr>
<td>Primidone</td>
<td>Grapefruit</td>
</tr>
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<td>Ethanol/ Alcohol</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Ketoconazole</td>
</tr>
<tr>
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<td>Metronidazole</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Quinine</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Omeprazole</td>
</tr>
</tbody>
</table>

Appendix 1: Drug interactions

Ergotamine and Methysergide: increased risk of vasospasm
Fluvoxamine: metabolism of zolmitriptan possibly inhibited by fluvoxamine
Moclobemide: risk of CNS toxicity
Quinolones: metabolism of zolmitriptan possibly inhibited by quinolones
Also, see under 5HT1

Zuclopenthixol
See under antipsychotics
**Appendix 2: Drug Induced Hepatotoxicity**

**Drug induced hepatotoxicity:**

Drugs are an important cause of liver injury. This is the most common reason cited for withdrawal of an approved drug. Risk factors for drug induced hepatotoxicity include age (common in elderly), sex (common in females), liver disease, alcohol ingestion, genetic factors, the presence of other comorbidities and drug formulations (long acting drugs may cause more injury than short acting drugs).

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<td>Quinine</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Omeprazole -Induces</td>
<td>Omeprazole - Inhibits</td>
</tr>
<tr>
<td>P-450 1A2</td>
<td>P-450 2C8</td>
</tr>
</tbody>
</table>
Appendix 3: Kidney and Drugs

Creatinine clearance provides a measure of renal function and can be used to classify renal insufficiency. For some medications doses are adjusted according to severity of renal impairment.

Creatinine clearance (CrCl) calculation for adult:
From 24 hour urine collection:

- Cockroft and Gault formula:

\[ \text{Creatinine clearance (mL/min)} = \frac{\text{Serum creatinine (µmol/L) x time (min)}}{(140 - \text{age in years}) \times \text{body weight in kg} \times F} \]

- F = 1.04 for women, 1.23 for men

Creatinine clearance (CrCl) calculation for a child over 1 year:

- Approximate Creatinine clearance (mL/minute/1.73 m²) = \( \frac{\text{Serum creatinine (µmol/L) x time (min)}}{(140 - \text{age in years}) \times \text{body weight in kg} \times F} \) x 1.73

Creatinine clearance (CrCl) calculation for a neonate:

- Approximate Creatinine clearance (mL/minute/1.73 m²) = \( \frac{30 \times \text{height (cm)}}{\text{Serum creatinine (µmol/L)}} \)

Appendix 2: Drug Induced Hepatotoxicity

The majority of drugs are metabolised by the liver and under normal circumstances there is considerable reserve. If, however, the metabolic capacity of the liver is markedly reduced (e.g. in different liver diseases), the metabolism of the drug will be reduced.

Hepatic insufficiency also affects the action of different drugs through other mechanisms, see the diagram.

- **Reduced clotting**
  Reduced hepatic synthesis of clotting factors, increases the sensitivity to certain drugs e.g.
  - Warfarin

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

- **Hypoalbuminemia**
  It will reduce protein binding and increase toxicity of some highly protein bound drugs e.g.
  - Phenytoin
  - Prednisolone

- **Hepatic encephalopathy**
  Many drugs can precipitate hepatic encephalopathy e.g.
  - Sedative drugs
  - Drugs that cause constipation
  - Diuretics

- **Biliary obstruction**
  It will prevent the excretion of some drugs e.g.
  - Fusidic acid
  - Rifampicin
Creatinine clearance provides a measure of renal function and can be used to classify renal insufficiency. For some medications doses are adjusted according to severity of renal impairment.

Creatinine clearance (CrCl) calculation for adult:

From 24 hour urine collection:

- Creatinine clearance (mL/min) = \( \frac{\text{Urine creatinine (µmol/L) x Urine volume (mL)}}{\text{Serum creatinine (µmol/L) x time (min)}} \)

Cockroft and Gault formula:

- Creatinine clearance (mL/min) = \( \frac{(140-\text{age in years}) \times \text{body weight in kg} \times F}{\text{Serum creatinine (µmol/L)}} \)

\( F = 1.04 \) for women, 1.23 for men

Creatinine clearance (CrCl) calculation for a child over 1 year:

- \( \text{Approximate Creatinine clearance} \)

\( (mL/\text{minute}/1.73\ m^2) = \frac{40 \times \text{height (cm)}}{\text{Serum creatinine (µmol/L)}} \)

Creatinine clearance (CrCl) calculation for a neonate:

- \( \text{Approximate Creatinine clearance} \)

\( (mL/\text{minute}/1.73\ m^2) = \frac{30 \times \text{height (cm)}}{\text{Serum creatinine (µmol/L)}} \)
Appendix 3: Kidney and Drugs

The definitions of mild, moderate and severe renal impairment are as follows:

<table>
<thead>
<tr>
<th>Severity of renal impairment</th>
<th>CrCl (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>20-50</td>
</tr>
<tr>
<td>Moderate</td>
<td>10-20</td>
</tr>
<tr>
<td>Severe</td>
<td>Less than 10</td>
</tr>
</tbody>
</table>
Renal dysfunction secondary to medications is common. Renal toxicity can be classified into three:

Pre-renal toxicity: this occurs when drugs alter renal blood flow.

Intrarenal toxicity: medications can have direct injury to cells and tissues through different mechanisms e.g.  
- Acute Tubular Necrosis  
- Glomerulonephropathies  
- Interstitial Nephritis  
- Renal tubular acidosis  
- Myoglobinuria.

Postrenal toxicity: occurs by obstruction of renal excretion by drugs inducing crystalluria or nephrolithiasis.

As it is impossible to list all drugs associated with nephrotoxicity, the diagram next page will summarize the mechanisms of injury associated with particularly common drugs.

Note: this illustration modified from Oxford handbook of practical drug therapy. Duncan Richards, Jeffry Aronson (Ed). Oxford University Press. UK. 20
Appendix 4: Drugs and Blood Donation

Blood donation is extremely important because it is the only way to maintain sufficient blood supplies for medical treatment. Certain drugs (primarily Non-Steroidal Anti-Inflammatory Drugs ‘NSAIDs’ which affect platelets function) should be stopped for some days prior blood donation. See the table below for more details.

<table>
<thead>
<tr>
<th>Medications affect platelet function for 48 hours</th>
<th>Medications affect platelet function for 5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aceclofenac</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>Acematacin</td>
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<tr>
<td>Azapropazone</td>
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<tr>
<td>Diclofenac</td>
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<tr>
<td>Diflunisal</td>
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<tr>
<td>Fenoprofen</td>
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<tr>
<td>Fenbufen</td>
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<td>Flurbiprofen</td>
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<tr>
<td>Nabumetone</td>
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<tr>
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<tr>
<td>Naproxen</td>
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<tr>
<td>Indometacin (Indomethacin)</td>
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<tr>
<td>Phenylbutazone</td>
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<tr>
<td>Sodium salicylate</td>
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Note: Other medicines which are used in various conditions are not mentioned as these conditions might themselves disqualify a person from donating blood permanently or temporarily. E.g. Atenolol in poorly controlled high blood pressure.

Some of the above NSAIDs are not available from or approved for use by Ministry of Health.

Appendix 3: Kidney and Drugs

Nephron of the kidney

**Glomerulonephropathies**
- Captopril (high doses)
- Gold salts
- Heavy metals
- NSAIDs
- Penicillamine
- Penicillins
- Phenytin

**Myoglobinuria**
- Dapsone
- Drugs given to patient with G6PD deficiency
- Methyldopa
- Quinine
- Statins

**Acute tubular necrosis**
- Aminoglycosides
- Amphotericin
- Cisplatin
- NSAIDs
- Radiocontrast media
- Paracetamol in overdose

**Altered renal blood flow**
- ACE inhibitors in patients with renovascular disease
- Anaphylaxis
- Amphotericin
- Nitrates
- Penicillins
- Sulfonamides
- Thiazide diuretics

**Renal tubular acidosis**
- Acetazolamide
- Amphotericin
- Lithium

**Crystalluria**
- Methotrexate
- Quinolones
- Sulfonamides

**Interstitial nephritis**
- Allopurinol
- Azathioprine
- Furosemide
- NSAIDs
- Penicillins
- Sulfonamides
- Thiazide diuretics
- Vancomycin (iv)
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<tr>
<td>Ketoprofen</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Sodium salicylate</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>Tenoxicam</td>
</tr>
<tr>
<td>Tiaprofenic acid</td>
<td></td>
</tr>
<tr>
<td>Tolmetin</td>
<td></td>
</tr>
</tbody>
</table>

Note:
Other medicines which are used in varies conditions are not mentioned as these conditions might themselves disqualify a person from donating blood permanently or temporarily. E.g. Atenolol in poorly controlled high blood pressure.

Some of the above NSAIDs are not available from or approved for use by Ministry of Health.
Below is a list for the common drugs and agents known to cause oxidative reactions and should be avoided in patients with G6PD deficiency.

### Note:

- **Not all the drugs are approved by MOH.**
- **Susceptibility to the hemolytic risk from drugs varies; thus, a drug found to be safe in some G6PD deficiency individuals may not be equally safe in others.**
- **List of other agents that can lead to hemolysis in patients with G6PD deficiency could be found in the following link:** [http://www.g6pd.org/favism/english/index.mv?pgid=avoid](http://www.g6pd.org/favism/english/index.mv?pgid=avoid)

<table>
<thead>
<tr>
<th>Name of the medicine in alphabetical order</th>
<th>Risk Level (Definite/ Possible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Possible ( acceptable up to a dose at least 1 g daily)</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Possible ( acceptable in acute malaria)</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Definite</td>
</tr>
<tr>
<td>Menadiol Sodium Sulfate</td>
<td>Possible</td>
</tr>
<tr>
<td>Tetramethylthionine Chloride (methylene blue)</td>
<td>Definite</td>
</tr>
<tr>
<td>Niridazole</td>
<td>Definite</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Definite</td>
</tr>
<tr>
<td>Pamaquine</td>
<td>Definite</td>
</tr>
<tr>
<td>Primaquine</td>
<td>Definite</td>
</tr>
<tr>
<td>Probenecid</td>
<td>Possible</td>
</tr>
<tr>
<td>Quinolones&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Definite</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Possible ( acceptable in acute malaria)</td>
</tr>
<tr>
<td>Quinine</td>
<td>Possible ( acceptable in acute malaria)</td>
</tr>
<tr>
<td>Rasburicase</td>
<td>Possible</td>
</tr>
<tr>
<td>Sulphonamides&lt;sup&gt;3&lt;/sup&gt; (including co-trimoxazole)</td>
<td>Definite</td>
</tr>
</tbody>
</table>

<sup>1</sup> Not all the drugs are approved by MOH.

<sup>2</sup> Susceptibility to the hemolytic risk from drugs varies; thus, a drug found to be safe in some G6PD deficiency individuals may not be equally safe in others.

<sup>3</sup> List of other agents that can lead to hemolysis in patients with G6PD deficiency could be found in the following link: [http://www.g6pd.org/favism/english/index.mv?pgid=avoid](http://www.g6pd.org/favism/english/index.mv?pgid=avoid)
Appendix 5: Drugs and G6PD Deficiency

### Name of some foods and chemicals associated with haemolysis in patients with G6PD deficiency

<table>
<thead>
<tr>
<th>Name of Chemicals/ Foods</th>
<th>Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blueberries</td>
<td></td>
</tr>
<tr>
<td>Fava beans</td>
<td></td>
</tr>
<tr>
<td>Henna application</td>
<td></td>
</tr>
<tr>
<td>Lentils</td>
<td></td>
</tr>
<tr>
<td>Naphthalene</td>
<td></td>
</tr>
<tr>
<td>Red wine</td>
<td></td>
</tr>
<tr>
<td>Soya products</td>
<td></td>
</tr>
<tr>
<td>Tonic water</td>
<td></td>
</tr>
<tr>
<td>Vitamin K</td>
<td></td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td></td>
</tr>
</tbody>
</table>

1. **Other Antipyretics and analgesics with susceptibility to hemolytic risk include:**

   - Acetanilide
   - Acetophenetidin
   - Antipyrine
   - Aminopyrine

2. **Quinolones:**

   - Ciprofloxacin
   - Moxifloxacin
   - Nalidixic acid
   - Norfloxacin
   - Ofloxacin
Appendix 6: Body Surface Area (BSA)

Body surface area (BSA): Body surface area is recommended as the principle basis for drug dosages in paediatric age group than body weight since many physiological phenomena correlate better with body surface area.

BSA calculation by using child-BSA-nomogram:
- Get the child weight and height.
- Find the weight in the right column and the height in the left column.
- Place a straightedge on the nomogram so the weight and height are connected.
- The point where the straightedge crosses the centre column denotes the body’s surface area in square meters.

Appendix 5: Drugs and G6PD Deficiency

3 Sulphonamides

- Furaltadone
- Furazolidone
- N-Acetylsulfanilamide
- Nitofurantoin
- Nitrofurazone
- Salicylazosulfapyridine
- Sulfacetamide
- Sulfamethoxypyridazine
- Sulfanilamide
- Sulfapyridine
- Sulfisoxazole

Fava beans
Body surface area (BSA):

Body surface area is recommended as the principle basis for drug dosages in paediatric age group than body weight since many physiological phenomena correlate better with body surface area.

BSA calculation by using child-BSA-nomogram:

- Get the child weight and height.
- Find the weight in the right column and the height in the left column.
- Place a straightedge on the nomogram so the weight and height are connected.
- The point where the straightedge crosses the centre column denotes the body's surface area in square meters.
Therapeutic drug monitoring (TDM) is defined as the use of drug measurements in body fluids as an aid to the management of patients receiving specific drugs. It plays an important role in facilitating optimization of therapy where the pharmacological response cannot be established easily by clinical means or by laboratory markers, and so drug efficacy or toxicity is difficult or impossible to be assessed.

Criteria for valid TDM:
- For drugs with poor correlation between dose and clinical response
- For drugs with narrow concentration interval between toxic and therapeutic effect
- Where there are no good clinical markers of effects (e.g., BP, blood glucose, INR, and lipid profile)
- There is a good correlation between plasma concentration and effect

Generally, the list of drugs which fulfill these criteria is small, and only those drugs which are frequently monitored will be mentioned in this appendix.

1. Analgesics

**Indications for TDM**
- Paracetamol (Acetaminophen) poisoning: see section 17 B
- Acetylsalicylic acid (Aspirin) poisoning

**Paracetamol (Acetaminophen)**

**Clinical use:**
- see section 4 D

**Recommended sampling time:**
- 1 hour after a dose for a peak

**Target therapeutic range:**
- no age limit, 10 to 20 mg/L (66-132 µmol/L)

**Toxic levels:**
- ≥ 200 mg/L (1320 µmol/L) 4 hour post ingestion
- ≥ 50 mg/L (330 µmol/L) 12 hour post ingestion

---

**Appendix 6: Body Surface Area (BSA)**

**NOMOGRAM**

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>Weight (lb)</th>
<th>Surface area (square meters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>240</td>
<td>50</td>
<td>2.0</td>
</tr>
<tr>
<td>220</td>
<td>40</td>
<td>1.9</td>
</tr>
<tr>
<td>200</td>
<td>35</td>
<td>1.8</td>
</tr>
<tr>
<td>190</td>
<td>30</td>
<td>1.7</td>
</tr>
<tr>
<td>180</td>
<td>25</td>
<td>1.6</td>
</tr>
<tr>
<td>170</td>
<td>20</td>
<td>1.5</td>
</tr>
<tr>
<td>160</td>
<td>15</td>
<td>1.4</td>
</tr>
<tr>
<td>150</td>
<td>15</td>
<td>1.3</td>
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<td>140</td>
<td>10</td>
<td>1.2</td>
</tr>
<tr>
<td>130</td>
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<tr>
<td>120</td>
<td>10</td>
<td>1.0</td>
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<tr>
<td>110</td>
<td>10</td>
<td>0.9</td>
</tr>
<tr>
<td>100</td>
<td>9</td>
<td>0.8</td>
</tr>
<tr>
<td>90</td>
<td>8</td>
<td>0.7</td>
</tr>
<tr>
<td>80</td>
<td>7</td>
<td>0.6</td>
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<td>70</td>
<td>6</td>
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<td>0.1</td>
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<td>0.1</td>
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<tr>
<td>8</td>
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<td>7</td>
<td>1</td>
<td>0.1</td>
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<tr>
<td>6</td>
<td>1</td>
<td>0.1</td>
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<tr>
<td>5</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Therapeutic drug monitoring (TDM)

Therapeutic drug monitoring (TDM) is defined as the use of drug measurements in body fluids as an aid to the management of patients receiving specific drugs. It plays an important role in facilitating optimization of therapy where the pharmacological response can not be established easily by clinical means or by laboratory markers, and so drug efficacy or toxicity is difficult or impossible to be assessed.

Criteria for valid TDM:

- For drugs with poor correlation between dose and clinical response
- For drugs with narrow concentration interval between toxic and therapeutic effect
- Where there are no good clinical markers of effects (e.g. BP, blood glucose, INR and lipid profile)
- There is a good correlation between plasma concentration and effect

Generally the list of drugs which fulfill these criteria is small and only those drugs which are frequently monitored will be mentioned in this appendix.

1. Analgesics

   Indications for TDM

   - Paracetamol (Acetaminophen) poisoning: see section 17 B
   - Acetylsalicylic acid (Aspirin) poisoning

Paracetamol (Acetaminophen)

Clinical use: see section 4 D
Recommended sampling time: 1 hour after a dose for a peak
Target therapeutic range: no age limit, 10 to 20 mg/L (66-132 µmol/L)
Toxic levels: ≥ 200 mg/L (1320 µmol/L) 4 hour post ingestion
            ≥ 50 mg/L (330 µmol/L) 12 hour post ingestion
Appendix 7: Therapeutic drug monitoring

The diagram shows when the treatment with an antidote such as N-Acetyl-cysteine should be started in relation to plasma-paracetamol concentration and time of ingestion.

[Diagram showing plasma paracetamol concentration over time, with treatment lines for normal and enhanced risk patients.]
Appendix 7: Therapeutic drug monitoring

Acetylsalicylic acid (Aspirin)

Clinical use: see section 4D
Recommended sampling time: 1 to 3 hours after an oral dose (formulation dependent)
Target therapeutic range: no age limit, 150 -300 mg/L(1085-2170 µmol/L) (for anti-inflammatory dose)
N.B. therapeutic range is usually lower if the drug is used for analgesia
Toxic levels: > 300 mg/L(2170 µmol/L)

2. Antibiotics

Indications for TDM
- Patients on long term therapy
- Patients with renal impairment
- Monitoring is essential in infants, the elderly, in obesity, in cystic fibrosis or if high doses are being used

Amikacin

Clinical uses: see section 5 A
Recommended sampling time: peak 0.5-1 hour after the end of 30 minute infusion (1 hour after IM dose), trough level is measured, immediately before next dose
Target therapeutic range: peak is (20-30 mg/L) and trough is (<5 mg/L)

Gentamicin:

Clinical uses: see section 5 A
Recommended sampling time: peak 0.5-1 hour after the end of 30 minute infusion (1 hour after IM dose), trough level is measured, immediately before next dose
Target therapeutic range: peak is (5-10 mg/L) and trough is (<2 mg/L)

Once daily Gentamicin:

The rational for pulse dosing of gentamicin is based on the following factors:
Appendix 7: Therapeutic drug monitoring

- Relatively easy, straightforward initial dosing
- Enhanced efficacy due to higher peak levels
- Enhanced safety due to shorter effective exposure time
- Convenience for both patients and doctors/nurses
- Likely on-time administration
- A much reduced need for serum aminoglycoside levels (reduced cost)

Exclusion criteria for once daily aminoglycoside dosing:

1. Pregnancy
2. Patients with extensive burn (>20% of body surface area)
3. Patients with severe liver disease (e.g. ascites)
4. Patients with severe renal disease (CrCl < 30 mL/min)
5. Patients with neutropenia
6. Patients with enterococcal endocarditis
7. Patients with Gram positive infections (when the aminoglycoside is used for synergy).
8. Children < 12 years

Guidelines for the pulse dosing of gentamicin:

1. First determine the creatinine clearance (CrCl): for (CrCl) calculation see appendix 3
2. Usually dosage is 5-7 mg/kg, unless the patient is more than 20% of ideal body weight (morbid obesity), the dosing weight should be calculated as follows:

\[
\text{Dosing weight (Adjusted Body Weight)} = \text{Ideal body weight in kg} + 0.4 \times (\text{Actual body weight} - \text{Ideal body weight})
\]

\[
\text{Ideal Body Weight (men)} = 50 + 2.3 \times (\text{Height (inches)} - 60)
\]

\[
\text{Ideal Body Weight (women)} = 45.5 + 2.3 \times (\text{Height (inches)} - 60)
\]

\[
\text{1 inch} = 2.54 \text{ cm}
\]

\[
\text{The calculated dose is diluted in 100 ml of isotonic saline and infused over 0.5-1 hour}
\]

4. The initial dosing interval is determined by the creatinine clearance (CrCl):

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Dosing interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>24 hrs</td>
</tr>
<tr>
<td>40 - 60</td>
<td>36 hrs</td>
</tr>
<tr>
<td>20 - 40</td>
<td>48 hrs</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Consultation is needed</td>
</tr>
</tbody>
</table>

5. To determine the proper dosing interval, the reported level is plotted on a special graph (Hartford nomogram), which is applicable to gentamicin.

6. Obtain a single serum level after first dose, 8 hrs after start of infusion

7. Evaluate on the nomogram, if the level falls in area 24hrs, 36hrs or 48hrs, the interval should be every 24, 36 or 48 hrs respectively

8. If the point is on the line, choose the longer interval

9. If the point is above the nomogram, stop scheduled treatment. Do serial levels to determine the time of next dose (< 2 mg/L)

Laboratory analytical limit of detection is 2 mg/L
Appendix 7: Therapeutic drug monitoring

Dosing weight (Adjusted Body Weight) = Ideal body weight in kg + 0.4 (Actual body weight-Ideal body weight)

Ideal Body Weight (men) = 50 + 2.3 (Height (inches) - 60)

Ideal Body Weight (women) = 45.5 + 2.3 (Height (inches) - 60)

* 1 inch = 2.54 cm

3. The calculated dose is diluted in 100 ml of isotonic saline and infused over 0.5-1 hour

4. The initial dosing interval is determined by the creatinine clearance (CrCl):

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>&gt; 60</th>
<th>40-60</th>
<th>20-40</th>
<th>&lt; 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing interval</td>
<td>24 hrs</td>
<td>36 hrs</td>
<td>48 hrs</td>
<td>Consultation is needed</td>
</tr>
</tbody>
</table>

5. To determine the proper dosing interval, the reported level is plotted on a special graph (Hartford nomogram), which is applicable to gentamicin. See next page

6. Obtain a single serum level after first dose, 8 hrs after start of infusion

7. Evaluate on the nomogram, if the level falls in area 24hrs, 36hrs or 48hrs, the interval should be every 24, 36 or 48 hrs respectively

8. If the point is on the line, choose the longer interval

9. If the point is above the nomogram, stop scheduled treatment. Do serial levels to determine the time of next dose (< 2 mg/L)

* Laboratory analytical limit of detection is 2 mg/L
Appendix 7: Therapeutic drug monitoring

**Indications for TDM**
- On initial therapy to check if the desired dose is achieved
- During intravenous therapy in status epileptics
- Unexpected deterioration in seizure control
- As an adjunct to the diagnosis of toxicity
- When interacting drugs are added or withdrawn
- During pregnancy

**Carbamazepine**
- **Clinical use:** see section 4.E
- **Recommended sampling time:** usually trough levels
- **Target therapeutic range:** no age limit, 4-10 mg/L (17-42 µmol/L)

**Phenobarbital (Phenobarbitone)**
- **Clinical use:** see section 4.E
- **Recommended sampling time:** trough or peak due to long half life
- **Target therapeutic range:**
  - Age ≤12 yrs: 15-20 mg/L (65-85 µmol/L)
  - Age >12 yrs: 15-40 mg/L (65-170 µmol/L)

**Phenytoin**
- **Clinical use:** see section 4.E
- **Recommended sampling time:** usually trough levels
- **Target therapeutic range:**
  - Age ≤3 months: 6-14 mg/L (24-56 µmol/L)
  - Age >3 months: 10-20 mg/L (40-80 µmol/L)

**Valproic acid (Sodium valproate)**
- **Clinical use:** see section 4.E
- **Recommended sampling time:** usually trough levels
- **Target therapeutic range:** no age limit, 50-100 mg/L (350-700 µmol/L)

**4. Antineoplastics**

**Methotrexate**

**Vancomycin**

**Clinical uses:** *see* section 5 A

**Recommended sampling time:** trough level is usually measured, immediately prior to next dose

**Target therapeutic range:** (5-10 mg/L)

**N.B:** trough level is higher for less sensitive strains of methicillin resistant staphylococcus aureus

3. **Antiepileptics (Anticonvulsants)**

450
Appendix 7: Therapeutic drug monitoring

Indications for TDM
- On initial therapy to check if the desired dose is achieved
- During intravenous therapy in status epilepticus
- Unexpected deterioration in seizure control
- As an adjacent to the diagnosis of toxicity
- When interacting drugs are added or withdrawn
- During pregnancy

Carbamazepine

Clinical use: see section 4.E
Recommended sampling time: usually trough levels
Target therapeutic range: no age limit, 4-10 mg/L (17-42 μmol/L)

Phenobarbital (Phenobarbitone)

Clinical use: see section 4.E
Recommended sampling time: trough or peak due to long half life
Target therapeutic range:
Age ≤12 yrs 15 - 20 mg/L (65-85 μmol/L)
Age >12 yrs 15 - 40 mg/L (65-170 μmol/L)

Phenytoin

Clinical use: see section 4.E
Recommended sampling time: usually trough levels
Target therapeutic range:
Age ≤3 months 6-14 mg/L (24-56 μmol/L)
Age >3 months 10-20 mg/L (40-80 μmol/L)

Valproic acid (Sodium valproate)

Clinical use: see section 4.E
Recommended sampling time: usually trough levels
Target therapeutic range: no age limit, 50-100 mg/L (350-700 μmol/L)

4. Antineoplastics

Methotrexate
Appendix 7: Therapeutic drug monitoring

Indications for TDM
- Only required for high dose therapy to identify patients at risk of toxicity and as a guide to the dose and timing of Leucovorin (Calcium folinate) rescue

Clinical use: see section 8 A
Recommended sampling time: initial sample (in the first 24 hours) to calculate half life, 24 hours post-infusion and 48 hours post-infusion

If the levels are found to be high (see toxic levels below) or in the presence of clinical risk factors (e.g. renal impairment, pleural effusion or ascites), methotrexate levels should be monitored daily to achieve concentration < 0.01 μmol/L

Target therapeutic range: a recommended therapeutic range for methotrexate has not been well defined. The minimum cytotoxic concentration (threshold level) is 4.5 μg/L (0.01 μmol/L)

Toxic levels:
- 24 hours post-infusion ≥ 2250 μg/L (≥ 5 μmol/L)
- 48 hours post-infusion ≥ 225 μg/L (≥ 0.5 μmol/L)

5. Bronchodilators

Indications for TDM
- Optimizing dosage
- Diagnosis of Theophylline toxicity

Theophylline

Clinical use: see section 3 A
Recommended sampling time: both peak and trough are useful.

For intravenous infusion:
Prior to intravenous infusion
30 minutes after loading dose
4-6 hours after beginning of continuous infusion therapy or before next infusion

For oral product with rapid release properties:
Peak: 2 hours after administration
Trough: immediately before next dose
Appendix 7: Therapeutic drug monitoring

For oral product with sustained release properties:
Peak: 4-8 hours after administration
Trough: immediately before next dose

Target therapeutic range: 8-20 mg/L (45-110 µmol/L)

6. Cardiac agents

Indications for TDM
- When there is an initial poor response to treatment
- In helping to confirm digoxin toxicity (careful clinical examination remains the most important tool)
- To decide if continued therapy is justified

Digoxin

Clinical use: see section 2 A
Recommended sampling time: peak level (8-24 hours) after dose
Target therapeutic range: no age limit, 0.8-2.0 µg/L (1.0-2.6 nmol/L)
Toxic levels: > 3.0 µg/L (> 3.8 nmol/L)

N.B: it is recommended to measure both plasma digoxin and potassium. Hypokalaemia sensitizes the myocardium to the action of digoxin and so can precipitate or aggravate toxicity.

7. Immunosuppressants:

Indications for TDM
- Solid organ transplantation to predict toxicity or rejection

Ciclosporin:

Clinical use: see section 8 B
Recommended sampling time: 2 hours post dose
Target therapeutic range: 100-400 µg/L (83-332 nmol/L) Therapeutic range varies depending upon organ transplant type, the length of period post transplantation and concomitant drug therapy

Post renal transplant
Appendix 7: Therapeutic drug monitoring

<table>
<thead>
<tr>
<th>Period</th>
<th>Therapeutic range (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>1500-2000</td>
</tr>
<tr>
<td>2 months</td>
<td>≤ 1500</td>
</tr>
<tr>
<td>3 months</td>
<td>≤ 1300</td>
</tr>
<tr>
<td>4-6 months</td>
<td>≤ 1100</td>
</tr>
<tr>
<td>7-12 months</td>
<td>≤ 900</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>≤ 300</td>
</tr>
</tbody>
</table>

**Post liver transplant**

<table>
<thead>
<tr>
<th>Period</th>
<th>Therapeutic range (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 months</td>
<td>≤ 1000</td>
</tr>
<tr>
<td>4-6 months</td>
<td>≤ 800</td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>≤ 600</td>
</tr>
</tbody>
</table>

**Sirolimus**

Clinical use: see section 8 B  
Recommended sampling time: trough concentration  
Target therapeutic range:  
When given with ciclosporin, during the three months following transplantation, target level is 4-12 µg/L  
When ciclosporin is discontinued, target level is recommended to be increased to 12-20 µg/L

**Tacrolimus**

Clinical use: see section 8 B  
Recommended sampling time: trough concentration  
Target therapeutic range: no age limit  
Trough level: 8-15 µg/L  
Long term Rx: 3-8 µg/L

8. Psychoactive agents

Indications for TDM
- Optimizing dosage  
- Diagnosis of lithium toxicity
Appendix 7: Therapeutic drug monitoring

**Lithium**

**Clinical use:** see section 4. B  
**Recommended sampling time:** trough (12 hours after evening dose)  
**Target therapeutic range:**  
In acutely manic patients: 0.9-1.4 mmol/L  
In patients on maintenance therapy: 0.6-1.2 mmol/L  
**Toxic levels:** > 2.0 mmol/L

**Conversion factors:**

*To convert from (mg/L to µmol/L)*  
Multiply the number of mg/L by the conversion factor

<table>
<thead>
<tr>
<th>Drug</th>
<th>Conversion Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen / Paracetamol</td>
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*To convert from (µg/L to nmol/L)*  
Multiply number of micrograms per mL by the conversion factor

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<td>Digoxin:</td>
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Appendix 8: Drug Administration

Guide to use metered dose inhaler (MDI):

- Remove MDI cap.
- Hold inhaler upright.
- Shake the inhaler vigorously.
- Breathe out slowly and completely.
- Put the inhaler in your mouth between closed lips (held vertically) and tilt head back slightly.
- Start to breathe in slowly.
- While starting to breathe in, immediately depress canister once.
- Breathe in slowly and deeply until your lungs are full.
- Remove inhaler with mouth closed.
- Hold your breath for 10 seconds.
- Breathe out / relax.
- For a 2nd inhalation wait 20-30 seconds and repeat the same steps.
- Clean the mouthpiece with dry and clean tissue.

Appendix 7: Therapeutic drug monitoring

References:

Appendix 8: Drug Administration

Guide to use metered dose inhaler (MDI):

- Remove MDI cap.
- Hold inhaler upright.
- Shake the inhaler vigorously.
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- Hold your breath for 10 seconds.
- Breathe out / relax.
- For a 2nd inhalation wait 20-30 seconds and repeat the same steps.
- Clean the mouthpiece with dry and clean tissue.

References:

Appendix 8: Drug Administration

- Put the cap back to the inhaler.

    A spacer can be used with an MDI; it requires less hand-breath coordination and decreases oral candidiasis with inhaled corticosteroids.

Steps:
- Shake inhaler and insert it in one side of the spacer, insert the mouthpiece in the opposite side.
- Place mouthpiece in mouth and exhale gently.
- Depress canister once.
- Breathe in slowly and deeply and hold breath for 10 seconds or
- Breathe in and out normally through the spacer for 4 breaths.
- Remove spacer from mouth.
- Relax.
- For a 2nd inhalation wait 20-30 seconds and repeat the same steps.
- Wash spacer but drip dry, DO NOT dry with a cloth (causes static electricity build up which can attract drug droplets)

N.B: for children, a face mask is attached to the spacer instead of the mouth piece and it should be placed over mouth and nose.

Other common inhaler devises:

*Dry powder inhalers:*
These types of inhaler do not have a gas propellant to push the drug out of a canister. Instead, each dose contains a tiny amount of drug in a powder form that the patient can suck in. Various devices are made by different companies. Each has a different method of providing the correct amount of powder for each dose. Some types are shown below.
Appendix 8: Drug Administration

Eye drops:

1. Wash your hands and remove any contact lenses.
2. Do not touch the dropper opening.
3. Look upward.
4. Pull the lower eyelid down to make a gutter.
5. Bring the dropper as close to the gutter as possible without touching it or the eye.
6. Apply the prescribed amount of drops in the gutter.
7. Close the eye for about two minutes. Do not shut eye too tight.
8. Excess fluid can be removed with a tissue.
9. If more than one drop is prescribed or another kind of eye drop is used wait at least five minutes before applying the next drops.
10. Eye-drops may cause a burning feeling but this should not last for more than a few minutes. If it does last longer consult a doctor or pharmacist.

In children:

1. Wash your hands thoroughly.
2. Do not touch the edge of the dropper to keep it clean.
3. Let the child lie straight on his back.
4. The child's eye should be closed.
5. Drip the prescribed dose at the eye angle close to the nose.
6. Keep the head straight for one minute.
7. Always keep the droppers clean and closed.
8. Do not use any type of droppers after four weeks from the date the dropper was opened.
Appendix 8: Drug Administration

Eye ointment:

1. Wash your hands thoroughly.
2. Do not touch the edge of the tube to avoid contamination.
3. Look upward and move your head slightly backward.
4. Hold the tube and pull the lower eyelid downward with your other hand.
5. Put the upper end of the tube near the opened eyelid and apply the prescribed amount of ointment.
6. Close the eye gently for two minutes.
7. Wipe the excessive amount of ointment with a clean tissue.
8. Clean the upper end of the tube with a clean tissue and keep it tightly closed.
9. Do not use the ointment after four weeks from the date the tube was opened.
Ear drops:

1. Warm up the ear dropper for two minutes by grasping it with hand. Do not use hot water tap as there is no way to control temperature.
2. Move the head aside or lie it down on any side.
3. Pull the earlobe gently to widen the ear opening.
4. Apply the prescribed amount of drops in the ear.
5. Wait for five minutes before you apply drops in the other ear.
6. Clean the upper end of the dropper with a clean tissue.
7. Always keep the dropper clean and closed.
8. Do not use any type of droppers after four weeks from the date the dropper was opened.
9. Do not use gauze to close ear canal after applying the drops unless recommended by doctor.
10. Ear-drops should not burn or sting longer than a few minutes.
Appendix 8: Drug Administration

Nasal drops:

1. Blow the nose.
2. Sit down and gently tilt head backward as far as possible or lie down with a pillow under the shoulders; keep head straight.
3. Insert the dropper one centimetre into the nostril.
4. Apply the number of drops prescribed.
5. Pinch nose and immediately afterward tilt head forward as far as possible. (The rational behind this position is to get the liquid to spread over all the inside surface including the upper surface of the nose.)

N.B: if this position is inconvenient e.g. patient is obese, lying on a bed with head hanging back over the edge for two minutes is an alternative.

6. Sit up after a few seconds, the drops will then drip into the pharynx.
7. Repeat the procedure for the other nostril, if necessary.
8. Rinse the dropper with boiled water.

Nasal spray:

1. Blow your nose.
2. Sit down with the head slightly moved forward.
3. Shake the nasal spray.
4. Insert the upper end of the nebulizer inside the nostril.
5. Close the other nostril and mouth.
6. Press the nasal spray and inhale slowly.
7. Keep the upper end away from the nose and put your head between your knees.
8. Breathe through the mouth.
9. Repeat the same steps in the other nostril, if necessary.
10. Clean the upper end of the nasal spray and keep it closed.
Appendix 8: Drug Administration

Rectal suppository:

1. If necessary, go the toilet to empty your bowels.
2. Wash your hands.
3. Remove any foil or plastic wrapping from the suppository.
4. If the suppository is too soft let it harden first by cooling it (fridge) then remove covering.
5. Moist the suppository with cold water.
6. Lie on one side with one leg straight and the other is bent.
7. Gently insert the suppository, tapered end first, into the back passage (the rectum).
8. Remain lying down for several minutes.
9. Wash your hands.
10. Try not to have a bowel movement during the first hour (unless suppository is a laxative).

Nasal drops:

1. Blow the nose.
2. Sit down and gently tilt head backward as far as possible or lie down with a pillow under the shoulders; keep head straight.
3. Insert the dropper one centimetre into the nostril.
4. Apply the number of drops prescribed.
5. Pinch nose and immediately afterward tilt head forward as far as possible. (The rational behind this position is to get the liquid to spread over all the inside surface including the upper surface of the nose.)
6. Sit up after a few seconds, the drops will then drip into the pharynx.
7. Repeat the procedure for the other nostril, if necessary.
8. Rinse the dropper with boiled water.

Nasal spray:

1. Blow your nose.
2. Sit down with the head slightly moved forward.
3. Shake the nasal spray.
4. Insert the upper end of the nebulizer inside the nostril.
5. Close the other nostril and mouth.
6. Press the nasal spray and inhale slowly.
7. Keep the upper end away from the nose and put your head between your knees.
8. Breathe through the mouth.
9. Repeat the same steps in the other nostril, if necessary.
10. Clean the upper end of the nasal spray and keep it closed.
Appendix 8: Drug Administration

**Rational application of topical treatments:**

Unlike many other creams and ointments, it is important to get the dose right when using topical steroids. This is why a standard measure is often used, a fingertip unit. One fingertip unit (FTU) is the amount of topical steroid that is squeezed out from a standard tube along an adults fingertip. (This assumes the tube has a standard 5 mm nozzle.) A finger tip is from the very end of the finger to the first crease in the finger. One FTU is enough to treat an area of skin twice the size of the flat of an adult's hand with the fingers together.

Two FTUs are about the same as 1 g of topical steroid. Therefore, for example, say you treat an area of skin the size of eight adult hands. You will need four FTUs for each dose (This is 2 g per dose). If the dose is once a day, then a 30 g tube should last about 15 days of treatment.
The following gives a rough guide:

N.B: for more details, refer to Pharmaco-logical newsletter volume 1, No. 2, issued by Directorate of Rational Use of Medicines
Insulin injection techniques

1- Wash your hands

2- If you are taking cloudy insulin, roll the bottle between your hands until it is uniformly cloudy. *Never* shake a bottle.

3- Wipe the top of the insulin bottle with alcohol swab

4- Draw air into the syringe by pulling out one the plunger to the approximate dose.
5-Push the needle through the centre of the rubber top of the insulin bottle.

- Push the air into the insulin bottle.

- Turn the insulin bottle and syringe upside down.

- Pull the plunger down about 5 units past your dose. If there are no bubbles, push the top of the plunger tip up to the line which marks your exact dose.

- If there are air bubbles, tap the syringe until they float to the top, then eliminate them out as you push the plunger tip to your exact dose.

6-Clean the injection site with an alcohol swab. Move the swab in a circular motion. Start from the centre and move outward. Allow the alcohol to dry for a few seconds.
Appendix 8: Drug Administration

7-Carefully pick up the syringe without allowing the needle to touch anything. Gently pinch up a two inch fold of skin. With one quick motion, inject the needle into the skin. The usual injection angle is between 45 and 90 degrees.

8-Release the fold of skin. Use one hand to hold the barrel of the syringe steady, and with the other hand push on the plunger to inject the insulin. The injection of the insulin should be completed in 3 to 5 seconds.

9-When finished with the injection, hold an alcohol swab at the injection site. Pull the needle straight out of the skin and gently wipe the site with the alcohol swab. Do not massage the area.

10-Destroy the syringe by clipping off the needle with an insulin needle clipper, or very carefully break off the needle. Drop the unusable syringe into an empty re-sealable household container such as a coffee can or bleach bottle. When the container is full, seal the lid securely and deposit in the trash.
Appendix 8: Drug Administration

It is essential to rotate the site of insulin injection. DO NOT use the same site repeatedly.

This illustration shows the common sites for insulin injections:

a- The abdomen
b- The upper buttocks or hips, and the outer side of the thighs
c- The back of the upper arms
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Glossary of Scientific Terms and Abbreviations

(Most of the following acronyms, words or symbols appear in the ONF text. Only a few recurrent medical words appear here. For further assistance consult a good medical dictionary.)

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® Signifies a commercial or brand name product e.g. Actifed® see also TM

3TC Lamivudine – an antiviral drug – a nucleoside reverse transcriptase inhibitor - NRTI

5-HT 5-Hydroxytryptamine or Serotonin

Ab Antibody

ac before food or meals

ACE Angiotensin-converting enzyme

ACTH Adrenocorticotropic hormone

ADH Antidiuretic hormone (vasopressin)

ADR(s) Adverse drug reaction(s)

AF Atrial Fibrillation

Ag Antigen

AIDS Acquired immunodeficiency syndrome

APTT Activated partial thromboplastin time (used for heparin monitoring)

ARB Angiotensin receptor blocker

ARI Acute respiratory infections

ATPase Adenosine triphosphatase enzyme

AV Atrio-ventricular

BAL British anti Lewisite or dimercaprol

BCG Bacillus Calmette Guérin (attenuated strain of TB bacillus - Mycobacterium bovis)

bd twice a day

BMI Body mass index (ratio of weight to height)

BSA Body surface area
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<td>cAMP</td>
<td>Cyclic Adenosine Monophosphate</td>
</tr>
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<td>Continuous ambulatory peritoneal dialysis</td>
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<td>CAT</td>
<td>Computerised axial tomography</td>
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<tr>
<td>CAT scan</td>
<td>Computerised axial tomography scan (multiple X-rays turned into images)</td>
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<td>CCF</td>
<td>Congestive cardiac failure</td>
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<td>CDC</td>
<td>Central Drug Committee</td>
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<td>CDL</td>
<td>Complimentary Drug List</td>
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<td>CFC</td>
<td>Chlorofluorocarbon</td>
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<tr>
<td>EP</td>
<td>Extra pyramidal</td>
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<td>Expanded programme on immunisation</td>
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<td>film coated</td>
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<td>FEV1</td>
<td>Forced expiratory volume in first second</td>
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<td>Follicle stimulating hormone</td>
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<td>fingertip unit</td>
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<td>G6PD</td>
<td>Glucose-6-phosphate dehydrogenase</td>
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<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<td>GI</td>
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<td>Gastro-oesophageal reflux disease (or GERD in US)</td>
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<td>Glucagon-Like Peptide 1 Receptor Agonists</td>
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<td>Glyceryl trinitrate</td>
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<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
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<td>Hepatitis B Immunoglobulin</td>
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<td>HBV</td>
<td>Hepatitis B vaccine</td>
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<td>HCG</td>
<td>Human chorionic gonadotrophin</td>
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<td>HCV</td>
<td>Hepatitis C vaccine</td>
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<td>High density lipoprotein</td>
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<td>Hydrofluoroalkane</td>
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<td>Human immunodeficiency virus</td>
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<td>HRT</td>
<td>Hormone Replacement Therapy</td>
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<td>HTN</td>
<td>Hypertension</td>
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<td>IA i/a</td>
<td>Intra-articular – injection into a joint</td>
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<td>Drug induced</td>
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<td>Cyclic Guanosine Monophosphate</td>
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<td>chronotropic</td>
<td>rate of cardiac contraction</td>
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<td>CI</td>
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<td>COAD</td>
<td>Chronic obstructive airways disease</td>
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<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<td>COX</td>
<td>Cyclo-oxygenase enzyme e.g. COX-1 or COX-2</td>
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<td>CrCl</td>
<td>Creatinine clearance</td>
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<td>CRF</td>
<td>Chronic renal failure</td>
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<td>C-reactive protein (blood marker for inflammation)</td>
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<td>CS</td>
<td>Cephalosporins</td>
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<td>CSF</td>
<td>Cerebro-spinal fluid</td>
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<td>CT</td>
<td>Computerized tomography</td>
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<td>DI</td>
<td>Drug Information</td>
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<td>DMARDs</td>
<td>Disease Modifying Antirheumatic Drugs</td>
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<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<td>DPP-4 inhibitors</td>
<td>Dipeptidyl peptidase 4 inhibitors</td>
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<td>DPT or DTP</td>
<td>Diphtheria Pertussis Tetanus</td>
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<td>DVT</td>
<td>Deep vein thrombosis</td>
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<td>EC or ec</td>
<td>Enteric coated (or gastric acid-resistant)</td>
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<td>Description</td>
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<td>Electro-cardiogram (EKG in US)</td>
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<td>EEG</td>
<td>Electro-encephalogram</td>
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<tr>
<td>eGFR</td>
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<tr>
<td>FEV₁</td>
<td>Forced expiratory volume in first second</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
</tr>
<tr>
<td>FTU</td>
<td>Fingertip unit</td>
</tr>
<tr>
<td>G6PD</td>
<td>Glucose-6-phosphate dehydrogenase</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>GI</td>
<td>Gastro-intestinal</td>
</tr>
<tr>
<td>GORD</td>
<td>Gastro-oesophageal reflux disease (or GERD in US)</td>
</tr>
<tr>
<td>GLP-1 Receptor Agonists</td>
<td>Glucagon-Like Peptide 1 Receptor Agonists</td>
</tr>
<tr>
<td>GTN</td>
<td>Glyceryl trinitrate</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
</tr>
<tr>
<td>HBIG</td>
<td>Hepatitis B Immunoglobulin</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B vaccine</td>
</tr>
<tr>
<td>HCG</td>
<td>Human chorionic gonadotrophin</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C vaccine</td>
</tr>
<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
</tr>
<tr>
<td>HFA</td>
<td>Hydrofluoroalkane</td>
</tr>
<tr>
<td>Hib</td>
<td><em>Haemophilus influenzae</em> type B</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone Replacement Therapy</td>
</tr>
<tr>
<td>HTN</td>
<td>Hypertension</td>
</tr>
<tr>
<td>IA i/a</td>
<td>Intra-articular – injection into a joint</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Drug induced</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>------</td>
<td>------------</td>
</tr>
<tr>
<td>IBS</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>IDDM</td>
<td>Insulin Dependent Diabetes Mellitus</td>
</tr>
<tr>
<td>Ig</td>
<td>Immunoglobulin e.g. IgE or IgG or IgM, etc</td>
</tr>
<tr>
<td>IGT</td>
<td>Impaired glucose tolerance</td>
</tr>
<tr>
<td>IM, im or i/m</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>IMCI</td>
<td>Integrated management of childhood illnesses (guidelines)</td>
</tr>
<tr>
<td>INCB</td>
<td>International Narcotic Control Board</td>
</tr>
<tr>
<td>INH</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>inotropic</td>
<td>force of cardiac contraction</td>
</tr>
<tr>
<td>INR</td>
<td>International normalised ratio (prothrombin time {PT} ratio in blood-coagulation)</td>
</tr>
<tr>
<td>IOP</td>
<td>Intra-ocular pressure</td>
</tr>
<tr>
<td>ISA</td>
<td>Intrinsic sympathomimetic activity</td>
</tr>
<tr>
<td>IV, iv or i/v</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LA</td>
<td>Long acting</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>LH</td>
<td>Luteinising hormone</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low molecular weight heparins (fractionated heparin)</td>
</tr>
<tr>
<td>mAB</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>MAOI</td>
<td>Mono Amine Oxidase Inhibitors</td>
</tr>
<tr>
<td>MCT</td>
<td>Medium chain triglycerides</td>
</tr>
<tr>
<td>MDI</td>
<td>Metered dose inhaler</td>
</tr>
<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>MMR</td>
<td>Mumps Measles Rubella</td>
</tr>
<tr>
<td>MR or m/r</td>
<td>Modified Release</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin Resistant Staphylococcus aureus</td>
</tr>
<tr>
<td>MSA</td>
<td>Membrane stabilising activity</td>
</tr>
<tr>
<td><strong>Abbreviation</strong></td>
<td><strong>Explanation</strong></td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------</td>
</tr>
<tr>
<td><strong>NIDDM</strong></td>
<td>Non Insulin Dependent Diabetes Mellitus</td>
</tr>
<tr>
<td><strong>NNRTI</strong></td>
<td>Non-nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td><strong>NPH</strong></td>
<td>Isophane Insulin (Neutral Protamine Hagedorn)</td>
</tr>
<tr>
<td><strong>NRTI</strong></td>
<td>Nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>Non Steroidal Anti-Inflammatory Drugs</td>
</tr>
<tr>
<td><strong>OCP</strong></td>
<td>Oral Contraceptive Pills</td>
</tr>
<tr>
<td><strong>od</strong></td>
<td>each day</td>
</tr>
<tr>
<td><strong>OPV</strong></td>
<td>Oral polio vaccine</td>
</tr>
<tr>
<td><strong>ORS</strong></td>
<td>Oral Rehydration Salts</td>
</tr>
<tr>
<td><strong>ORT</strong></td>
<td>Oral Rehydration Therapy</td>
</tr>
<tr>
<td><strong>OTC</strong></td>
<td>Over the counter</td>
</tr>
<tr>
<td><strong>PaCO₂</strong></td>
<td>Arterial carbon dioxide tension</td>
</tr>
<tr>
<td><strong>PaO₂</strong></td>
<td>Arterial oxygen tension</td>
</tr>
<tr>
<td><strong>pc</strong></td>
<td>after food or meals</td>
</tr>
<tr>
<td><strong>PEG</strong></td>
<td>Polyethylene Glycol</td>
</tr>
<tr>
<td><strong>PET</strong></td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td><strong>PI</strong></td>
<td>Protease inhibitor</td>
</tr>
<tr>
<td><strong>po</strong></td>
<td>Orally or by mouth</td>
</tr>
<tr>
<td><strong>PPI</strong></td>
<td>Proton Pump Inhibitors</td>
</tr>
<tr>
<td><strong>PRN</strong></td>
<td>as required or as necessary</td>
</tr>
<tr>
<td><strong>PSVT</strong></td>
<td>Paroxysmal supraventricular tachycardia</td>
</tr>
<tr>
<td><strong>PT</strong></td>
<td>Prothrombin time</td>
</tr>
<tr>
<td><strong>PUD</strong></td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td><strong>qid or qds</strong></td>
<td>four times a day</td>
</tr>
<tr>
<td><strong>qnh</strong></td>
<td>every n hours (n represents any number e.g. usually 4, 6, 8 or 12)</td>
</tr>
<tr>
<td><strong>QRST interval</strong></td>
<td>electrocardiographic period of ventricular electrical activity</td>
</tr>
<tr>
<td><strong>rINN</strong></td>
<td>Recommended International Non-proprietary Name</td>
</tr>
<tr>
<td><strong>RBS</strong></td>
<td>Random blood sugar (level)</td>
</tr>
</tbody>
</table>
# Glossary of Terms and Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>SA</td>
<td>Sustained action</td>
</tr>
<tr>
<td>SC or sc</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>SOS</td>
<td>if necessary</td>
</tr>
<tr>
<td>spp</td>
<td>species</td>
</tr>
<tr>
<td>SR or S/R</td>
<td>Sustained release</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Selective Serotonin Re-uptake Inhibitors</td>
</tr>
<tr>
<td>Stat</td>
<td>At once</td>
</tr>
<tr>
<td>STD</td>
<td>Sexually transmitted disease</td>
</tr>
<tr>
<td>STG</td>
<td>Standard Treatment Guidelines</td>
</tr>
<tr>
<td>T₃</td>
<td>Tri-iodothyronine</td>
</tr>
<tr>
<td>T₄</td>
<td>Thyroxine or Tetra-iodothyronine</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TCA</td>
<td>Tricyclic antidepressant drug</td>
</tr>
<tr>
<td>TD or Td</td>
<td>Tetanus and Diphtheria (vaccine)</td>
</tr>
<tr>
<td>TDM</td>
<td>Therapeutic drug monitoring</td>
</tr>
<tr>
<td>TENS</td>
<td>Transcutaneous electrical nerve stimulator (electrically controlled pain relief)</td>
</tr>
<tr>
<td>TGs</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischaemic attack</td>
</tr>
<tr>
<td>tid or tds</td>
<td>three times a day</td>
</tr>
<tr>
<td>™</td>
<td>Signifies a trade mark for a commercial/brand name product</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumour necrosis factor</td>
</tr>
<tr>
<td>TPA</td>
<td>Tissue plasminogen activator</td>
</tr>
<tr>
<td>TPN</td>
<td>Total Parenteral Nutrition</td>
</tr>
<tr>
<td>TRH</td>
<td>Thyrotrophin releasing hormone</td>
</tr>
<tr>
<td>TT</td>
<td>Tetanus Toxoid</td>
</tr>
<tr>
<td>TTS</td>
<td>Transdermal therapeutic system</td>
</tr>
<tr>
<td>UF-heparin</td>
<td>Unfractionated heparin</td>
</tr>
<tr>
<td>URTI</td>
<td>Upper respiratory tract infection</td>
</tr>
</tbody>
</table>
### Glossary of Terms and Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Term/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>UVA</td>
<td>Ultraviolet light in the A range of frequency (long-wavelength)</td>
</tr>
<tr>
<td>VIP</td>
<td>Vaso-active intestinal polypeptide</td>
</tr>
<tr>
<td>VLDL</td>
<td>Very low density lipoprotein</td>
</tr>
<tr>
<td>VRE</td>
<td>Vancomycin resistant enterococcae</td>
</tr>
<tr>
<td>VRSA</td>
<td>Vancomycin resistant Staphylococcus aureus</td>
</tr>
<tr>
<td>VT</td>
<td>Ventricular tachycardia</td>
</tr>
</tbody>
</table>

### Useful Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNF</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>DGMS</td>
<td>Directorate General of Medical Supplies</td>
</tr>
<tr>
<td>DGPA&amp;DC</td>
<td>Directorate General of Pharmaceutical Affairs and Drug Control</td>
</tr>
<tr>
<td>DRUM</td>
<td>Directorate of Rational Use of Medicine</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drugs Administration</td>
</tr>
<tr>
<td>INRUD</td>
<td>International Network for the Rational Use of Drugs</td>
</tr>
<tr>
<td>MoH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>ONF</td>
<td>Oman National Formulary</td>
</tr>
<tr>
<td>OR or RO</td>
<td>Omani Rials</td>
</tr>
<tr>
<td>RDU</td>
<td>Rational Drug Use</td>
</tr>
<tr>
<td>RUM</td>
<td>Rational Use of Medicines</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
**CONFIDENTIAL**

Suspected Adverse Drug Reactions (ADRs) & Drug Related Problems Reporting Form
Drugs / Herbal Medicines / Health Products / Biological Products

1 Patient Details

<table>
<thead>
<tr>
<th>Patient initials:</th>
<th>Date of Birth/Age:</th>
<th>Sex: M [ ] F [ ]</th>
<th>Weight (Kg):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nationality:</td>
<td>M.R.No:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2 Suspected Medicine/ Herbal/ Health Product/ Biological

<table>
<thead>
<tr>
<th>Trade</th>
<th>Date started</th>
<th>End Date</th>
<th>Daily Dose</th>
<th>Dosage form</th>
<th>Route</th>
<th>BN</th>
<th>MF</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3 Suspected Reaction(s)/ Error/ Quality Problem

<table>
<thead>
<tr>
<th>Description of Reaction(s) / Error(s) / Quality Problem(s):</th>
<th>Date of Onset: / / 20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Date Stopped: / / 20</td>
</tr>
<tr>
<td>Outcome of Reaction:</td>
<td></td>
</tr>
<tr>
<td>Recovered ☐       Recovering ☐   No Improvement ☐   Fatal ☐   Unknown ☐</td>
<td></td>
</tr>
<tr>
<td>Seriousness of reaction:</td>
<td></td>
</tr>
<tr>
<td>Patient died ☐    Life-threatening ☐   Permanently Disability ☐   Hospitalization ☐   Congenital Abnormality ☐</td>
<td></td>
</tr>
<tr>
<td>Other ☐  ..........................................................................................................................</td>
<td></td>
</tr>
<tr>
<td>Additional Notes (medical history, test results, allergies, dechallenge, rechallenge, pregnancy etc. Attach papers if necessary)</td>
<td></td>
</tr>
</tbody>
</table>

4 Reporter Details

<table>
<thead>
<tr>
<th>Name:</th>
<th>Specialty:</th>
<th>Address:</th>
<th>Tel No:</th>
<th>Email:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature:</td>
<td>Date:</td>
<td>Kindly submit the report to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacovigilance &amp; Drug Information Department</td>
<td>Director of Pharmaceutical Affairs &amp; Drug Control, Ministry of Health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P.O.BOX: 393, Muscat, PC: 100, Sultanate of Oman</td>
<td>Phone: 24602177, Ext: 7688/7689/7690, Fax: 24602287; Email: <a href="mailto:moh.phar@omantel.net.om">moh.phar@omantel.net.om</a></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Guidelines for Reporting

<table>
<thead>
<tr>
<th>This form can be used by:</th>
<th>Use this form to report adverse drug reactions, medication errors &amp; quality problems from:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Physician</td>
<td>• Drugs</td>
</tr>
<tr>
<td>• Pharmacist</td>
<td>• Herbal Medicines</td>
</tr>
<tr>
<td>• Dentist</td>
<td>• Health Products</td>
</tr>
<tr>
<td>• Nurses</td>
<td>• Biological Products (e.g. Vaccines)</td>
</tr>
<tr>
<td>• Other healthcare providers</td>
<td></td>
</tr>
</tbody>
</table>

Confidentiality: Reporter’s and patient’s identity are held in strict confidence by Pharmacovigilance & Drug Information Department, information provided by the reporter will be strictly protected and will not be used in any way against him / her.

Adverse Drug Reaction (ADR) is a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

Medication Error: is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient (prescribing, dispensing, storing, preparation and administration of a medicine).

### Quality Problems:

- [ ] Suspected counterfeit product.
- [ ] Suspected contamination.
- [ ] Suspected pharmaceutical defects
- [ ] Product non-compliant with specification (chemical/ physical/ microbial)
- [ ] Poor packaging or labeling.
- [ ] Therapeutic failure.
- [ ] Others........................

Number of samples affected in the batch  

Please provide sample
Regestration No: 493 / 2016
ISBN No: 978-99969-0-816-3