

# NFI

**National Formulary of India**

**2011**



सत्यमेव जयते

**Government of India  
Ministry of Health & Family Welfare**

**INDIAN PHARMACOPOEIA COMMISSION**  
Ministry of Health & Family Welfare  
Government of India

# NFI

National Formulary of India  
4<sup>th</sup> Edition  
2011



Government of India  
Ministry of Health & Family Welfare

**INDIAN PHARMACOPOEIA COMMISSION**  
Ministry of Health & Family Welfare  
Government of India

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# Preface

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The first, second and third editions of National Formulary of India (NFI) were published in 1960, 1966 and 1979 respectively by the Ministry of Health, Govt. of India. In the past 3 decades there has been vast expansion in the range of new drugs and their formulations. To address the need of publication of an updated version of NFI, Ministry of Health and Family Welfare, Govt. of India vide their Notification No. F.No.X.11035/2/06-DFQC dated 8th May, 2008 assigned this mandatory responsibility to the Indian Pharmacopoeia Commission (IPC), Ghaziabad and hence the NFI is being published by the IPC on behalf of the Govt. of India, Ministry of Health and Family Welfare. For this purpose, an Apex Body and a Core Group with the following composition were constituted:

**Chairman:** Secretary, Ministry of Health and Family Welfare, Govt. of India

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9. Dr Surinder Singh, Drugs Controller General of India, New Delhi
10. Prof. B. Suresh, Chairman, Scientific Body, Indian Pharmacopoeia Commission, Ghaziabad

## Core Group (in alphabetical order)

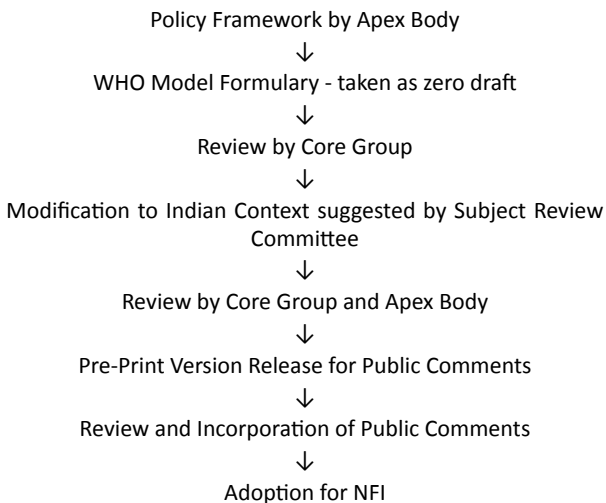
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9. Dr G. N. Singh, Secretary-cum-Scientific Director, Indian Pharmacopoeia Commission, Ghaziabad
10. Prof. Pramil Tiwari, Head, Department of Pharmacy Practice, National Institute of Pharmaceutical Education & Research, Mohali, Punjab, India

## The Criteria for Inclusion of Drugs in NFI:

- Drugs in National List of Essential Medicines 2011, India
- Drugs used in National Health Programmes
- Drugs listed in Indian Pharmacopoeia
- Drugs not covered but recommended by panel of experts
- Any drug (s) considered appropriate by the IPC

## NFI Review Process

To fulfil the mandate of publishing the NFI, the following process has been adopted:



## Subject Review Committee (in alphabetical order)

The manuscript was reviewed and the contents updated to suit Indian context by the Subject Review Committee.

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21. Dr Rakesh Yadav, Cardiology, All India Institute of Medical Sciences, New Delhi

NFI is not a regulatory document. Physicians are supposed to use their professional judgement. Inclusion/Exclusion of monographs in NFI is a dynamic process. The drugs contained in NFI have been chosen for rational and economic prescribing. NFI would serve as a guidance document to medical practitioners, pharmacists, nurses, medical and pharmacy students, and other healthcare professionals and stakeholders in healthcare system. The feedback from stakeholders is invited

# Acknowledgements

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We are pleased to present the 4th Edition of National Formulary of India. It has materialized after a gap of 3 decades. During this period, there have been tremendous advancements in therapeutic strategies and newly available drugs. This edition incorporates the changes based on the current knowledge.

Valuable inputs that emerged during the meetings of the Core Group and the inputs received in response to the pre-print version circulated have given this edition a unique feature by incorporating value added informations. The Commission is greatly indebted to the Members of the Core Group and the Subject Review Experts from diverse fields who consented to review the manuscript of the Formulary. The services of all these experts are appreciated.

The inspiration and the historical perspective were made available by Dr Nitya Anand, Dr Harkishan Singh, and Dr B. D. Miglani with close involvement of Mr P. D. Sheth, Vice-President, FIP. The initial inputs in the form of list of drugs to be incorporated was compiled based on drugs available in IP and NLEM at a short notice by Dr Pramil Tiwari and his team.

The Commission is especially indebted to Mr P. D. Sheth for providing the infrastructural facilities required to carry out this work uninterrupted. During the preparation of pre-print version, important guidance was received from Mr Duncan Enright of BNF. We are thankful to Dr Richard Laing and Dr Suzanne Hill at WHO Geneva and Dr Krisantha Weerasuria at WHO-SEARO for their suggestions, support and encouragement. Thanks are due to Dr P. Venugopal for his participation and guidance. Mr P. D. Sheth engaged a technical team consisting of Mr S. C. Bhasin, Mr M. Ahmed Khan and Mr Syed Jalal Q. Rahman in the initial compilation of the NFI.

Dr Jai Prakash, Principal Scientific Officer, Indian Pharmacopoeia Commission played a major role in every step in bringing out the NFI. He was ably supported by other members mainly Dr V. Kalaiselvan, Mr S. Prabu, Ms Sreeja PV, Mrs Puja Rajput and Mr Munesh Bindal in coordinating and contributing in updating the manuscript of NFI.

Special thanks go to the members who prepared Appendices which have added value to this fourth edition of NFI.

Prof. Y. K. Gupta deserves a special mention for his crucial role in preparing and enriching the contents of the formulary by closely coordinating with his colleagues throughout the course of preparation of this Formulary.

This National Formulary has been adopted from the WHO Model Formulary and thoroughly updated for its content, especially keeping in view the end user in India for which we wish to thank profusely Dr Y. K. Gupta, Dr Praveen Aggarwal, Dr Sheffali Gulati and the Resident Clinicians team of Dr Y. K. Gupta of the Department of Pharmacology – Dr Pooja Gupta, Dr Biswa Mohan Padhy, Dr Ashish Kakkar, Dr Aarohan Pruthi, Dr Arun Kumar Dahiya, Dr Aman Goyal and Dr Hemant Singh Bhadauria at the All India Institute of Medical Sciences, New Delhi.

We are grateful to Dr B. D. Miglani and Mr S. L. Nasa for their strong recommendation to bring out the National Formulary containing the much needed information for physicians, nurses and pharmacists on the uses and doses of drugs.

The Commission is highly appreciative of the encouragement and support received from Mr L. C. Goyal, Additional Secretary & DG (CGHS), Mr Debasish Panda, Joint Secretary (HR), Dr A. K. Panda, Joint Secretary (Regulation), Mr Sanjay Prasad, Director (Drugs) and Dr Surinder Singh, DCG (I) and other officials of Ministry of Health & Family Welfare.

The Commission appreciates the comments offered on the pre-print version of NFI by the stakeholders. The inputs received from the institutions, state governments and stakeholders have helped to shape the 4th Edition. Their names figure on website of the Commission ([www.ipc.gov.in](http://www.ipc.gov.in)).

The Commission acknowledges the significant contribution of Prof. Y. K. Gupta and his team in critically analysing the comments received on pre-print version of NFI from stakeholders.

Last but not the least, IPC also places on record thanks to the services of IPC employees, its scientific body members and other subject experts who from time to time provided their valuable inputs.

**Dr G. N. Singh**

Secretary-cum-Scientific Director  
Indian Pharmacopoeia Commission

## List of Medicines in NFI

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2	Abciximab	317
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4	Acetylsalicylic Acid	4
5	Actinomycin D	248
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40	Beclomethasone	448
41	Benzathine Benzyl Penicillin	119
42	Benzyl Benzoate	365
43	Benzyl Penicillin	120
44	Betamethasone	354
45	Betaxolol	546
46	Biperiden	45
47	Bisacodyl	75
48	Bleaching Powder	276
49	Bleomycin	249
50	Bromocriptine	46
51	Budesonide	449
52	Bupivacaine	417
53	Busulphan	250
54	Calamine	355
55	Calcium Disodium Edetate	84
56	Calcium Gluconate	607
57	Capreomycin	196
58	Carbamazepine	55
59	Carbimazole	505
60	Cefazolin	121
61	Cefixime	122
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64	Ceftazidime	124
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83	Clomifene	495
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376	Zolpidem	569
377	Zonisamide	67

#### **FIXED DOSE COMBINATIONS**

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1	Amoxicillin + Clavulanic acid	116
2	Benzoic Acid + Salicylic Acid	351
3	Calcium Carbonate + Vitamin D <sub>3</sub>	606
4	Cotrimoxazole (Trimethoprim and Sulphamethoxazole)	133
5	'Ethinylestradiol + Levonorgestrel' and 'Ethinylestradiol + Norethisterone'	462
6	Formoterol + Fluticasone propionate	449
7	Glucose + Sodium Chloride	596
8	Imipenem + Cilastatin	138
9	Lamivudine + Nevirapine + Stavudine	221
10	Lamivudine + Zidovudine	221
11	Levodopa + Carbidopa	47
12	Lopinavir + Ritonavir	223
13	Mifepristone + Misoprostol	501
14	Neomycin + Bacitracin	348
15	Piperacillin + Tazobactam	146
16	Rifampicin + Isoniazid	201
17	Rifampicin + Isoniazid + Ethambutol	202
18	Rifampicin + Isoniazid + Pyrazinamide	202
19	Rifampicin + Isoniazid + Pyrazinamide + Ethambutol	203
20	Sulfadoxine + Pyrimethamine	185
21	Thiacetazone + Isoniazid	204
22	Zidovudine + Lamivudine + Nevirapine	221

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2	Antitetanus Immunoglobulin (Human)	512
3	Antivenom Sera	514
4	BCG Vaccine	524
5	Diphtheria Antitoxin	512
6	Diphtheria, Pertussis and Tetanus (DPT) Vaccine	524
7	Haemophilus Influenza Type B Vaccine	525
8	Hepatitis A Vaccine	525
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10	Influenza Vaccine	526
11	Measles Vaccine	527
12	Polio Vaccine (OPV/IPV)	528
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18	Typhoid Vaccine	531
19	Varicella Vaccine	531
20	Yellow Fever Vaccine	532

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2	Cyanocobalamin (Vitamin B <sub>12</sub> )	616
3	Ergocalciferol (Vitamin D <sub>2</sub> )	607
4	Folic Acid	619
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6	Methylcobalamin	609
7	Nicotinamide	610
8	Phytomenadione	332
9	Pyridoxine	610
10	Riboflavin	611
11	Thiamine	612
12	Vitamin A	612

# Common Abbreviations

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ACE	Angiotensin Converting Enzyme
ACE Inhibitors	Angiotensin Converting Enzyme Inhibitors
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immuno Deficiency Syndrome
ARB	Angiotension Receptor Blocker
BCG	Bacillus Calmette Guerin
BNF	British National Formulary
BP	British Pharmacopoeia
BSA	Body Surface Area
CAPD	Continuous Ambulatory Peritoneal Dialysis
CD4	Cluster of Differentiation 4
CDSCO	Central Drugs Standards Control Organization
CIOMS	Council for International Organization of Medical Sciences
CMV	Cytomegalo Virus
COPD	Chronic Obstructive Pulmonary Disease
COLD	Chronic Obstructive Lung Disease
CR	Controlled Release
CSF	Cerebrospinal Fluid
DCGI	Drugs Controller General (India)
DMARDs	Disease Modifying Anti-Rheumatic Drugs
DOTS	Directly Observed Treatment Shortcourse
DT	Dispersible Tablet/Diphtheria Tetanus
DPT	Diphtheria Pertussis Tetanus
EMEA	European Medicines Evaluation Agency
ER	Extended Release
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease
GFR	Glomerular Filtration Rate
G-6-PD	Glucose-6-Phosphate Dehydrogenase



HAART	Highly Active Anti-Retroviral Therapy
HD	Hemodialysis
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic Pituitary Adrenal Axis
HT	Hormone Therapy
ICMR	Indian Council of Medical Research
INR	International Normalized Ratio
IP	Indian Pharmacopoeia
IPC	Indian Pharmacopoeia Commission
IPV	Inactivated Poliomyelitis Vaccine
IU	International Units
LFT	Liver Function Test
MAO	Mono Amine Oxidase
MD	Mouth Dissolving
MDR	Multi Drug Resistance
mEq	MilliEquivalent
MI	Myocardial Infarction
mMol	Millimole
MMR	Measles, Mumps and Rubella
MOHFW	Ministry of Health and Family Welfare
MR	Modified Release
NLEM	National List of Essential Medicines
NFI	National Formulary of India
NRHM	National Rural Health Mission
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NS	Normal Saline
ODT	Oral Dispersible Tablet
OPV	Oral Polio Vaccine
PFS	Pre-Filled Syringes
PK/PD	Pharmacokinetic/Pharmacodynamic
PD	Peritoneal Dialysis
PvPI	Pharmacovigilance Programme of India
SC	Subcutaneous
SL	Sublingual
SLE	Systemic Lupus Erythematosus
SR	Sustained Release
SWI	Sterile Water for Injection

SSRI	Selective Serotonin Reuptake Inhibitor
TDM	Therapeutic Drug Monitoring
USP	United States Pharmacopoeia
WHO	World Health Organization
W/V	Weight/Volume
W/W	Weight/Weight
*	Drugs listed in National List of Essential Medicines 2011, India
Schedule H:	List of substances that could be sold by retail on the prescription of a Registered Medical Practitioner only (Prescription Drugs).
Schedule X:	List of drugs for which the retailer is to preserve prescription for a period of two years.
Schedule G:	List of drugs that could be dangerous to take except under medical supervision.

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**Notes:**

- 1. Wherever Schedule H and X are stated it means that the drug is specified in that Schedule of Drugs and Cosmetics Rules, 1945.*
  - 2. Substances specified in Schedule H or Schedule X shall not be sold by retail except on and in accordance with the prescription of a Registered Medical Practitioner and in the case of substances specified in Schedule X, the prescriptions shall be in duplicate, one copy of which shall be retained by the licensee for a period of two years.*
  - 3. The supply of drugs specified in Schedule H or Schedule X to Registered Medical Practitioners, Hospitals, Dispensaries and Nursing Homes shall be made only against the signed order in writing which shall be preserved by the licensee for a period of two years.*
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# General Advice to Prescribers

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## 1. Rational Approach to Therapeutics

Drugs should only be prescribed when they are necessary, and in all cases the benefit of administering the medicine should be considered in relation to the risks involved. Bad prescribing habits lead to ineffective and unsafe treatment, exacerbation or prolongation of illness, distress and harm to the patient, and higher cost. The Guide to Good Prescribing (WHO, Geneva; 1994) provides important tools for training in the process of rational prescribing.

The following steps will help prescribers to follow the rational approach to therapeutics.

### 1 Define the Patient's Problem

Whenever possible, making the right diagnosis is based on integrating many pieces of information: the complaint as described by the patient; a detailed history; physical examination; laboratory tests; X-rays and other investigations. This will help in rational prescribing, always bearing in mind that diseases are evolutionary processes.

### 2 Specify the Therapeutic Objective

Doctors must clearly state their therapeutic objectives based on the pathophysiology underlying the clinical situation. Very often physicians are required to select more than one therapeutic goal for each patient.

### 3 Selecting Therapeutic Strategies

The selected strategy should be agreed with the patient; this agreement on outcome, and how it may be achieved, is termed concordance.

The selected treatment can be non-pharmacological and/or pharmacological; it also needs to take into account the total cost of all therapeutic options.

#### a. Non-Pharmacological Treatment

It is very important to bear in mind that the patient does not always need a medicine for treatment of the condition. Very often, health problems can be resolved by a change in lifestyle or diet, use of physiotherapy or exercise, provision of adequate psychological support, and other non-pharmacological treatments; these have the same importance as a prescription medicine, and instructions must be written, explained and

monitored in the same way.

## **b. Pharmacological Treatment**

### **Selecting the Correct Group of Drugs**

Knowledge about the pathophysiology involved in the clinical situation of each patient, pharmacokinetics and pharmacodynamics of the chosen group of drugs, are fundamental principles for rational therapeutics.

### **Selecting the Medicine from the Chosen Group**

The selection process must consider benefit/risk/cost information. This step is based on evidence about maximal clinical benefits of the medicine (efficacy) for a given indication with the minimum production of adverse effects (safety).

It must be remembered that each medicine has adverse effects and it is estimated that up to 10% of hospital admissions in industrialized countries are due to adverse effects. Not all medicine-induced injury can be prevented but much of it is caused by inappropriate selection of drugs.

In cost comparison between drugs, the cost of the total treatment and not only the unit cost of the medicine must be considered.

### **Verifying the Suitability of the Chosen Pharmaceutical Treatment for Each Patient**

The prescriber must check whether the active substance chosen, its dosage form, standard dosage schedule and standard duration of treatment are suitable for each patient. Medicine treatment should be individualized to the needs of each patient.

### **Prescription Writing**

The prescription is the link between the prescriber, the pharmacist (or dispenser) and the patient so it is important for the successful management of the presenting medical condition.

### **Giving Information, Instructions and Warnings**

This step is important to ensure patient compliance and is covered in detail in the following chapter (Refer 2.11. Adherence (compliance) with medicine treatment).

### **Monitoring Treatment**

Evaluation of the follow up and the outcome of treatment allow the stopping of it (if the patient's problem is solved) or to reformulate it when necessary. This step gives rise to important information about the effects of

drugs contributing to building up the body of knowledge of pharmacovigilance, needed to promote the rational use of drugs.

## 2. Factors Affecting Medicine Response

### 2.1. Variation in Dose

Success and effectiveness of medicine therapy depends not only on the correct choice of medicine but also on the correct dose regimen. Unfortunately, treatment frequently fails because either the dose is too small or it is too large that it produces adverse effects amongst other factors. The concept of a standard or 'average' adult dose for every medicine is firmly rooted in the mind of most prescribers. After the initial 'dose ranging studies on new drugs', manufacturers recommend a dosage that appears to produce the desired response in the majority of subjects. These studies are usually done on healthy, young male volunteers, rather than on older men and women with illnesses and of different ethnic and environmental backgrounds. The use of standard doses in the marketing literature suggests that standard responses are the rule, but in reality there is considerable variation in medicine response. There are many reasons for this variation such as medicine formulation, body weight and age, variation in pharmacokinetics (absorption, distribution, metabolism and excretion), variation in pharmacodynamics, disease variables, environmental and genetic variables, adherence to instructions and adverse effects and interactions etc. Some of them are described below.

### 2.2. Formulation

The type of drug formulation is an important factor affecting its response, apart from its lipid solubility and so many other factors. Pharmaceutical dosage forms such as tablets, capsules, emulsions, ointments, injectables, liposomes etc provide a mechanism for safe, effective, accurate, and convenient delivery of drugs to the target site. Poorly formulated drugs may fail to disintegrate or dissolve. Enteric-coated drugs are particularly problematic, and have been known to pass through the gastrointestinal tract intact. Some drugs like digoxin or phenytoin have a track record of formulation problems, and dissolution profiles can vary not only from manufacturer to manufacturer but also from batch to batch manufactured by the same manufacturer. Lately, biogeneric products (off patent biopharmaceuticals) have also been available in the pharmaceutical market. The production of biogenerics involves complex processes.

### 2.3. Body Weight and Age

Although the concept of varying the dose with the body weight or age of children has a long tradition, adult doses have been

assumed to be the same irrespective of size or shape. Yet adult weights vary two to threefold, while a large fat mass can store large excess of highly lipid soluble drugs compared to lean patients of the same weight. Age changes are also important. Adolescents may oxidize some drugs relatively more rapidly than adults, while the elderly may have reduced renal function and eliminate some drugs more slowly.

## 2.4. Sex

Females usually require smaller doses than males. Iron preparations and other haematinics are exceptions to this rule because of the blood lost by women during menstruation. There is a possibility that males metabolize benzodiazepines, estrogen containing preparations and salicylate at a faster rate than females.

## 2.5. Route of Administration

It governs the speed and intensity of drug response. The indications for a drug may vary when route of administration varies.

Example: Magnesium sulphate when administered orally- acts as a purgative, when administered topically- decreases swelling on sprained joints, and when administered intravenously- CNS depression and hypotension occur.

## 2.6. Tolerance

The therapeutic effects of some medications are lessened in individuals over a prolonged period of use. Thus, a patient who has been using a drug for longer time, requires a higher dose so as to obtain the same therapeutic effect as produced by the drug when taken for the first time. This is called tolerance. Opioids, benzodiazepines,  $\beta_2$  agonists, caffeine, cocaine, amphetamines, and barbiturates fall into this category. Cross-tolerance develops when the use of one drug causes a tolerance to another. Alcoholics, barbiturate and narcotic addicts develop a cross-tolerance to sedatives and anaesthetics. These individuals require very large amounts of anaesthetics before surgical anaesthesia can be attained.

## 2.7. Synergistic Effect

Several drugs when combined may show synergistic action in the form of either additive or supraadditive action or potentiation. A few examples are:

- a) Trimethoprim + Sulphamethoxazole.
- b) ACE inhibitor + Angiotensin Receptor blocker + Diuretic.
- c) Long acting  $\beta_2$  agonists + Inhaled steroids (Example- Salmeterol + Fluticasone)

## 2.8. Resistance

Development of resistance to drugs is a common problem with antimicrobial agents (antituberculosis drugs, antileprotic drugs, antimalarial drugs etc). Rational prescribing and in turn compliance by the user will prevent the emergence of resistance.

## 2.9. Pharmacokinetic Variables

### 2.9.1. Absorption

Absorption of a medicine is possible when it is present in solution form. Medicine absorption rates may vary widely between individuals and in the same individual at different times and in different physiological states. Drugs taken after a meal are delivered to the small intestine much more slowly than in the fasting state, leading to much lower medicine concentrations. In pregnancy gastric emptying is also delayed, while some drugs may increase or decrease gastric emptying and affect absorption of other drugs.

### 2.9.2 Distribution

Medicine distribution varies widely: fat soluble drugs are stored in adipose tissue, water soluble drugs are distributed chiefly in the extracellular space, acidic drugs bind strongly to plasma protein albumin and basic drugs to muscle cells. Hence variation in plasma albumin levels, fat content or muscle mass may all contribute to dose variation. With very highly albumin bound drugs like warfarin, a small change of albumin concentration can produce a big change in free medicine concentration and a dramatic change in therapeutic action of a medicine.

### 2.9.3. Metabolism

Medicine metabolic rates are determined both by genetic and environmental factors. Medicine acetylation shows genetic polymorphism, whereby individuals fall clearly into either fast or slow acetylator types. Medicine oxidation, however, is polygenic, and although a small proportion of the population can be classified as very slow oxidizers of some drugs, for most drugs and most subjects there is a normal distribution of medicine metabolizing capacity, and much of the variation is under environmental control. Also refer 2.10.2.

### 2.9.4. Excretion

Many drugs are eliminated by the kidneys without being metabolized. Renal disease or competitive tubular secretion of drugs can therefore slow down the excretion of certain drugs.



## 2.10. Pharmacodynamic Variables

There is significant variation in receptor response to some drugs, especially central nervous system responses, for example pain and sedation. Some of this is genetic, some due to tolerance, some due to interactions with other drugs and some due to addiction, for example, morphine and alcohol.

### 2.10.1. Disease Variables

Both liver and kidney disease can have major effects on medicine response, chiefly by the effect on metabolism and elimination respectively (increasing toxicity), but also by their effect on plasma albumin (increased free medicine also increasing toxicity). Heart failure can also affect metabolism of drugs with rapid hepatic clearance (for example lidocaine, propranolol). Respiratory disease and hypothyroidism can both impair medicine oxidation.

### 2.10.2. Environmental Factors and Genetic Factors (Pharmacogenetics)

Many drugs and environmental toxins can induce the hepatic microsomal enzyme oxidizing system (MEOS) or cytochrome P450 oxygenases, leading to more rapid metabolism and elimination and ineffective treatment. Environmental pollutants, carcinogens, tobacco smoke, alcohol, anaesthetic drugs and pesticides can also induce metabolism. Diet and nutritional status also have an impact on pharmacokinetics. For example, in infantile malnutrition and in malnourished elderly populations medicine oxidation rates are decreased, while high protein diets, charcoal cooked foods and certain other foods act as metabolizing enzyme inducers. Sedative and hypnotics induce sleep better in calm environment and when administered at night. Pharmacogenetic variation will affect the medicine response, by 4-6 fold among different individuals. All major determinants of medicine response such as transporters, metabolizing enzymes, and receptors are controlled genetically. These factors in certain cases may result in toxicity- for example toxicity caused by inhibitory effect of isoniazid on phenytoin metabolism seems to be more significant in slow acetylators of isoniazid than in those patients who metabolize the drug more rapidly. The Appendix 10 summarizes the pharmacogenetic variation, the frequency of occurrence, drugs involved and the outcome.

## 2.11. Adherence (Compliance) with Medicine Treatment

It is often assumed that once an appropriate medicine is chosen, the prescription correctly written and the medication correctly

dispensed, that it will be taken correctly then the treatment will be successful. Unfortunately this is very often not the case, and physicians overlook one of the most important reasons for treatment failure that is poor adherence (compliance) with the treatment plan. There are sometimes valid reasons for poor adherence. The medicine may be poorly tolerated, may cause obvious adverse effects or may be prescribed in a toxic dose. Failure to adhere with such a prescription has been described as 'intelligent non-compliance'. Bad prescribing or a dispensing error may also create a problem, and regarding which patients may have neither the insight nor the courage to question. Even with good prescribing, failure to adhere to treatment is common. Factors may be related to the patient, the disease, the doctor, the prescription, the pharmacist or the health system and can often be avoided. Low-cost strategies for improving adherence increase effectiveness of health interventions and reduce costs. Such strategies must be tailored to the individual patient. Health care providers should be familiar with techniques for improving adherence and they should employ systems to assess adherence and to determine what influences it.

### **2.11.1. Patient Reasons**

In general, women tend to be more adherent than men, younger patients and the very elderly are less adherent, and people living alone are less adherent than those with partners or spouses. Specific education interventions have been shown to improve adherence. Patient disadvantages such as illiteracy, poor eyesight or cultural attitudes (for example preference for traditional or alternative drugs and suspicion of modern medicine) may be very important in some individuals or societies, as may economic factors. Such disabilities or attitudes need to be discussed and taken account of.

### **2.11.2 Disease Reasons**

Conditions with a known worse prognosis (for example cancer) or painful conditions (for example rheumatoid arthritis) elicit better adherence rates than asymptomatic 'perceived as benign' conditions such as hypertension. Doctors should be aware that in most settings less than half of patients initiated on antihypertensive medicine treatment are still taking it a year later. Similarly, in epilepsy, where events may occur at long intervals, adherence is notoriously unsatisfactory.

### **2.11.3 Doctor Reasons**

Doctors may cause poor adherence in many ways-by failing to inspire confidence in the treatment offered, by giving too little or no explanation, by thoughtlessly prescribing too many

drugs, by making errors in prescribing, or by their overall attitude towards the patient.

#### **2.11.4. The Doctor-Patient Interaction**

There is considerable evidence that this is crucial to concordance. 'Satisfaction with the interview' is one of the best predictors of good adherence. Patients are often well informed and expect a greater say in their health care. If they are in doubt or dissatisfied they may turn to alternative options, including 'complementary medicine'. There is no doubt that the medicine 'doctor' has a powerful effect to encourage confidence and perhaps contribute directly to the healing process.

#### **2.11.5. Prescription Reasons**

Many aspects of the prescription may lead to non-adherence (noncompliance). It may be illegible or inaccurate; it may get lost; it may not be refilled as intended or instructed for a chronic disease. Also, the prescription may be too complex; it has been shown that the greater the number of medications the poorer the adherence, while multiple doses also decrease adherence if more than two doses per day are given. Not surprisingly adverse effects like drowsiness, impotence or nausea reduce adherence and patients may not admit to the problem.

#### **2.11.6. Pharmacist Reasons**

The pharmacist's behaviour and professionalism, like the doctor's, may have a positive impact, supporting adherence, or a negative one, raising suspicions or concerns. This has been reported in relation to generic drugs when substituted for brand-name drugs. Pharmacist information and advice can be a valuable reinforcement, as long as it agrees with the doctor's advice.

#### **2.11.7. The Healthcare System**

The healthcare system may be the biggest hindrance to adherence. Long waiting times, uncaring staff, uncomfortable environment, exhausted medicine supplies and so on, are all common problems in developing countries, and have a major impact on adherence. An important problem is the distance and accessibility of the clinic from the patient. Some studies have confirmed the obvious, that patients farthest from the clinic are least likely to adhere to treatment in the long term.

### **2.12. Adverse Effects and Interactions**

An Adverse Drug Reaction (ADR) may be defined as 'any response to a medicine which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis, or therapy'. ADRs are therefore unwanted or unintended effects

of a medicine, including idiosyncratic effects, which occur during its proper use. They differ from accidental to deliberate excessive dosage or medicine maladministration. ADRs may be directly linked to the properties of the medicine in use, the so-called 'A' type reactions. An example is hypoglycaemia induced by an antidiabetic medicine. ADRs may also be unrelated to the known pharmacology of the medicine, the 'B' type reactions including allergic effects, for example anaphylaxis with penicillins. Thalidomide marked the first recognized public health disaster related to the introduction of a new medicine. It is now recognized that clinical trials, however thorough, cannot be guaranteed to detect all adverse effects likely to be caused by a medicine and hence necessitating post-marketing surveillance. Health workers are thus encouraged to record and report to the National Pharmacovigilance Centre for any unexpected adverse effects with any medicine to achieve faster recognition of serious related problems. The National Regulatory Authority takes appropriate action on drugs showing serious ADRs.

### **2.12.1. Major Factors Predisposing to Adverse Effects**

It is well known that different patients often respond differently to a given treatment regimen. For example, in a sample of 2422 patients who had been taking combinations of drugs known to interact, only 7 (0.3%) showed any clinical evidence of interactions. Therefore, in addition to the pharmaceutical properties of the medicine, the characteristics of the patients may be responsible for causing predisposition to ADRs.

### **2.12.2. Extremes of Age**

The very old and the very young persons are more susceptible to ADRs. Drugs which commonly cause problems in the elderly include hypnotics, diuretics, non-steroidal anti-inflammatory drugs, antihypertensives, psychotropics, digoxin etc. All children, and particularly neonates, differ from adult in their response to drugs. Some drugs are likely to cause problems in neonates (for example morphine), but are generally tolerated in children. Valproic acid is associated with increased risk of ADRs in children of all ages. Other drugs associated with problems in children include chloramphenicol (grey baby syndrome), antiarrhythmics (worsening of arrhythmias), acetylsalicylic acid (Reye's syndrome etc).

### **2.12.3. Intercurrent Illness**

If besides the condition being treated the patient concomitantly suffers from another disease, such as kidney, liver or heart disease, special precautions may be necessary to prevent ADRs. Remember also that, apart from the above factors, the

genetic make-up of the individual patient may also predispose to ADRs.

#### **2.12.4. Drug Interactions**

Interactions (see Appendix 6) may occur between drugs which compete for the same receptor or act on the same physiological system. They may also occur indirectly when a medicine-induced disease or a change in fluid or electrolyte balance alters the response to another medicine. Interactions may occur when one medicine alters the absorption, distribution, metabolism or elimination of another medicine, such that the amount which reaches the site of action is increased or decreased. Medicine-medicine interactions are some of the commonest causes of adverse effects. When two drugs are administered to a patient, they may either act independent of each other, or interact with each other. Interactions may increase or decrease the effects of the drugs concerned and may cause unexpected toxicity. As newer and more potent drugs become available, the number of serious medicine interactions is likely to increase. Remember that interactions which modify the effects of a medicine may involve non-prescription drugs, non-medicinal chemical agents, and social drugs such as alcohol, marijuana, tobacco and traditional remedies, as well as certain types of food. The physiological changes in individual patients, caused by such factors as age and gender, also influence the predisposition to ADRs resulting from medicine interactions.

#### **2.12.5. Pharmaceutical Interactions**

Certain drugs, when added to intravenous fluids, may be inactivated by pH changes, by precipitation or by chemical reaction. Benzylpenicillin and ampicillin lose potency after 6-8 hours if added to dextrose solutions, due to the acidity of these solutions. Some drugs bind to plastic containers and tubing, for example diazepam and insulin. Aminoglycosides are incompatible with penicillins and heparin. Hydrocortisone is incompatible with heparin, tetracycline and chloramphenicol.

#### **2.12.6. Adverse Effects Caused by Traditional Drugs**

Patients who have been or are taking traditional herbal remedies may develop ADRs. It is not always easy to identify the responsible plant or plant constituent. For further details, refer to the Medicine and Toxicology Information Service if

available and/or to suitable literature. Appendix 6d summarises the Drug Herbal/Food Interactions.

### 2.12.7. The Effect of Food on Medicine Absorption

Food delays gastric emptying and reduces the rate of absorption of many drugs; the total amount of medicine absorbed may or may not be reduced. However, some drugs are preferably taken with food, either to increase absorption or to decrease the irritant effect on the stomach. Appendix 6d summarises the Drug Food Interactions.

#### Recommendations

- Review the prescription to make sure that it is correct.
- Spend time explaining the health problem and the reason for the medicine.
- Counselling of patients.
- Establish good rapport with the patient.
- Explore problems, for example difficulty with reading the label or getting the prescription filled.
- Encourage patients to bring their medication to the clinic, so that tablet/capsule counts etc. can be done to monitor compliance.
- Encourage patients to learn the names of their drugs, and review their regimen with them. Write notes for them.
- Keep treatment regimens simple.
- Communicate with other health care professionals, to develop a team approach and to collaborate on helping and advising the patient.
- Involve the partner or another family member in eliciting clinical history of the patient and explaining the advice.
- Listen to the patient.

Pharmacist plays an important role as a connecting link between the physician and patient.

<b>1.</b>	<b>Analgesics, Antipyretics, Non-Steroidal Anti-Inflammatory Drugs</b>	<b>3</b>
1.1	Non-Opioid, Non-Steroidal Anti-Inflammatory Drugs	4
1.2	Opioid Analgesics	10

# 1. Analgesics, Antipyretics, Non-Steroidal Anti-Inflammatory Drugs

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Analgesics are used to relieve/reduce body pain and antipyretics are used to reduce elevated body temperature. Non-opioid analgesics are particularly suitable for relieving or management of pain in musculoskeletal conditions whereas the opioid analgesics are more suitable for moderate to severe visceral pain. Those non-opioid analgesics which also have anti-inflammatory actions include salicylates and NSAIDs; they can reduce both pain and inflammation of chronic inflammatory disorders such as rheumatoid arthritis, but they do not alter or modify the disease process itself. For the management of rheumatoid arthritis, DMARDs (disease-modifying antirheumatic drugs) may favourably influence the outcome of the disease. The pain and inflammation of an acute attack of gout is treated with a NSAID or colchicine; a xanthine-oxidase inhibitor is used for long-term control of gout. Neurogenic pain generally responds poorly to conventional analgesics; treatment can be difficult and includes the use of carbamazepine for trigeminal neuralgia and amitriptyline for diabetic neuropathy and post-therapeutic neuralgia.



## 1.1 Non-Opioid, Non-Steroidal Anti-Inflammatory Drugs

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Non-opioid analgesics with anti-inflammatory activity include salicylates such as acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs such as ibuprofen. Non-opioid analgesics with little or no anti-inflammatory activity include paracetamol.

### Acetylsalicylic Acid\* (Refer Page No. 281 and 317)

#### Pregnancy Category-D

#### Indications

*Management of mild to moderate pain such as headache, acute migraine attacks, transient musculoskeletal pain, dysmenorrhoeal pain and for reducing fever; pain and inflammation of rheumatoid arthritis; antiplatelet agent for prophylaxis of myocardial infarction, stable angina pectoris; stroke prophylaxis.*

#### Availability

**TABLETS** 50, 60, 75, 80, 150, 300 and 325 mg.

#### Dose

#### Oral

**Adult-** Analgesic and antipyretic including migraine attacks: 0.3 to 0.9g, 3 to 4 times a day (max. 4g daily). Acute Rheumatic fever: 4 to 6g or 75 to 100 mg/kg daily in divided doses. Antiplatelet: 75-325 mg/day .

**Child-** Under 16 years: not recommended (can cause Reye's syndrome).

#### Contraindications

Hypersensitivity (including asthma; angioedema; urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; children and adolescents under 16 years (may cause Reye's syndrome); gastrointestinal ulceration; haemophilia and other bleeding disorders; not for treatment of gout; severe renal or hepatic impairment; lactation. It is known to cause haemolytic anaemia in people who have the genetic disease- G-6-PD-deficiency.

#### Precautions

Asthma, allergic disease; impaired renal or hepatic function (Appendices 7d and 7a); lactation (Appendix 7b); pregnancy (Appendix 7c); elderly; G-6-PD-deficiency; dehydration; interactions (Appendix 6a, 6c, 6d).

**Adverse Effects** Generally mild and infrequent for lower doses, but common with anti-inflammatory doses; gastrointestinal discomfort or nausea, ulceration with occult bleeding (occasionally major haemorrhage); also other haemorrhage (including subconjunctival); hearing disturbances such as tinnitus (rarely, deafness); vertigo; confusion; hypersensitivity reactions (angioedema; bronchospasm and rash); increased bleeding time, blood disorders (particularly thrombocytopenia); rarely, oedema; myocarditis; Reye's syndrome.

**Storage** Store protected from moisture at a temperature not exceeding 30°C.

## Diclofenac

**Pregnancy Category-B**

**Schedule H**

**Indications** *Acute musculo-skeletal pain; arthritis; gout; spondylitis; migraine; post-operative pain.*

**Availability** **TABLETS** 25 and 50 mg Plain; 75 and 100 mg SR; **CAPSULES** 100 mg, 100 mg CR; **INJECTION** 3 ml ampoule (25 mg/ml); **EYE/EAR DROPS** 0.1% w/v; **SUPPOSITORIES** 25, 50 and 100 mg; **GEL** 1%w/w.

**Dose**

### **Oral**

100 to 150 mg daily in 2 to 3 divided doses, (max 150 mg/day) maintenance by 50 to 100 mg in divided doses.

### **Intramuscular injection**

75 mg, 2 to 3 times daily.

### **Topically**

**Adult-** Apply 1% w/w gel on to affected area 3 to 4 times daily.

### **Instill to eye**

Post-operative ocular inflammation:

**Adult-** as sodium (1% w/v), 4 times daily starting 24 h after surgery for up to 28 days.

### **Rectal**

Post-operative pain.

**Adult-** 75 to 150 mg daily in divided doses (max. 150 mg/day, inclusive of diclofenac administered through other routes).

**Child-** 6 to 12 year: 1 to 2 mg/kg/day in divided doses for max. of 4 days.

**Contraindications**

Porphyria; avoid injections containing benzyl alcohol in neonates; history of gastric ulcers, bleeding or perforation.

Additional contraindications include concomitant NSAID or anticoagulant use (including low-dose heparin); history of haemorrhagic diathesis; history of confirmed or suspected cerebrovascular bleeding; operations with high risk of haemorrhage; history of asthma; moderate or severe renal impairment; hypovolaemia; dehydration.

### Precautions

NSAIDs should be used with caution in the elderly (risk of serious side-effects and fatalities); interactions (Appendix 6a, 6c, 6d); pregnancy (Appendix 7c); patients with coagulation disorders; hepatic, renal and cardiac impairment; history of gastrointestinal lesions.

### Adverse Effects

Injection site reactions; transient epigastric pain, risk of thrombotic events; toxic epidermal necrolysis; Abnormality in kidney function.

### Storage

Store protected from light.

## Ibuprofen\*

### Pregnancy Category-C

**Schedule H**

### Indications

*Pain and inflammation in rheumatic disease and other musculoskeletal disorders including juvenile arthritis; mild to moderate pain including dysmenorrhoeal pain, headache; pain in children; acute migraine attack.*

### Availability

**TABLETS** 200, 400 and 600 mg; **CAPSULES** 400 mg Plain, 300 mg SR; **SUSPENSION** 100 mg/5 ml.

### Dose

#### **Oral**

**Adult-** and Child over 12 years- initially 300 to 400 mg 3 to 4 times daily, increase if necessary (max. 2.4g daily), maintenance dose of 0.6 to 1.2g daily may be adequate.

**Infant or Child over 3 months-** 5-10 mg/kg 3 to 4 times/day, Maximum daily dose: 40 mg/kg/day.

#### **Intravenous injection and infusion**

**Neonate-** initially by intravenous injection (over at least 5 min) 25-100 µg/kg then by continuous intravenous infusion 5-40 µg/kg/h. adjusted according to response.

**Child-** 1-6 months: initially by intravenous injection (over at least 5 min) 100-200 µg/kg then by continuous infusion 10-30 µg/h. adjusted according to response.

6 months-12 years: initially by intravenous injection (over at least 5 min) 100-200 µg/kg, adjusted according to response.

Juvenile rheumatoid arthritis: 20 to 40 mg/kg/day in 3 to 4 divided doses.

**Contraindications** Hypersensitivity (including asthma; angioedema; urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; active peptic ulceration; for treatment of pre-operative pain in the setting of coronary artery bypass graft surgery; neonates with congenital heart disease.

**Precautions** Renal and hepatic impairment (Appendix 7a); preferably avoid if history of peptic ulceration; cardiac disease; elderly; pregnancy (Appendix 7c); lactation (Appendix 7b); coagulation defects; allergic disorders; interactions (Appendix 6a, 6c, 6d).

**Adverse Effects** Gastrointestinal disturbances including nausea, diarrhoea, dyspepsia, gastrointestinal haemorrhage; hypersensitivity reactions including rash, angioedema; bronchospasm; headache; dizziness; nervousness; depression; drowsiness; insomnia; vertigo; tinnitus; photosensitivity; haematuria; renal failure; fluid retention (rarely, precipitating congestive heart failure in elderly), raised blood pressure; rarely, hepatic damage; alveolitis, pulmonary eosinophilia; pancreatitis; visual disturbances; erythema multiforme (Stevens-Johnson syndrome); toxic dermal necrolysis (Lyell's syndrome); colitis; aseptic meningitis. Skin reactions like dermatitis.

**Storage** Store protected from light and moisture.

## Mefenamic Acid

### Pregnancy Category-C

**Indications** *Treatment of rheumatoid arthritis, osteoarthritis, dysmenorrhoea, mild to moderate pain, inflammation, fever dental pain.*

**Availability** **TABLETS** 100 mg, 250 mg, 500 mg. **CAPSULES** 250 mg. **SUSPENSION** 50 mg/5 ml.

**Dose** **Adult**

**Pain:** 500 mg orally, followed by 250 mg every 6 hours as needed, not to exceed 7 days.

**Dysmenorrhea:** 500 mg orally, followed by 250 mg every 6 hours starting with the onset of menses.

**Children**

**Pain:** 14 to 18 years: 500 mg orally followed by 250 mg every 6 hours as needed, not to exceed 7 days.

**Contraindications**

Known hypersensitivity to mefenamic acid; patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs; peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery, active ulceration or chronic inflammation of the gastrointestinal tract, pre-existing renal disease, pregnancy (Appendix 7c), interactions (Appendix 6c).

**Precautions**

Hepatic effects: Borderline elevations of one or more liver function tests may occur. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), the drug should be discontinued.

Anaemia: Patients on long-term treatment should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anaemia.

Asthma: Mefenamic acid should not be administered to patients with aspirin sensitive asthma and should be used with caution in patients with preexisting asthma.

**Adverse Effects**

Gastrointestinal experiences including-abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, gastrointestinal ulcers, vomiting, abnormal renal function, bronchospasm, anaemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, tinnitus.

**Storage**

Store protected from light and moisture.

**Paracetamol\***

**Pregnancy Category-B**

**Indications**

*Mild to moderate pain including dysmenorrhoeal pain, headache; pain relief in osteoarthritis and soft tissue lesions; pyrexia including post-immunisation pyrexia; acute migraine attack.*

<b>Availability</b>	<b>TABLETS</b> 500 and 650 mg Plain; 750 mg DT; <b>SYRUPS/SUSPENSION</b> 125 and 250 mg/5 ml; <b>INJECTION</b> 2 ml ampoule 125 mg/ml.; Intra- venous infusion 500 mg and 1g.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> 0.5 to 1g every 4 to 6 h (max. 4g, max 2g in alcoholics per day).  <b>Child-</b> for post-immunisation pyrexia, up to 2 months: 60 mg. 3 month to 1 year: 60 to 120 mg every 4 to 6 h. 1 to 5 years: 120 to 250 mg every 4 to 6 h. 6 to 12 years: 250 to 500 mg every 4 to 6 h.  <b>Intramuscular injection</b>  <b>Adult-</b> 250 mg every 4 to 6 h or as required.  <b>Intravenous infusion</b>  <b>Adult-</b> 1g every 6 hours, maximum daily dose 4 g.  <b>Child-</b> 15 mg/kg upto 4 times a day, maximum daily dose 60 mg/kg.
<b>Precautions</b>	Hepatic impairment (Appendix 7a); renal impairment; alcohol dependence; lactation (Appendix 7b); pregnancy (Appendix 7c); overdosage: chapter 7.2; interactions (Appendix 6a); G-6-PD deficiency.
<b>Adverse Effects</b>	Rare but rashes and blood disorders reported; <b>important:</b> liver damage (and less frequently renal damage) following overdosage; dyspepsia.
<b>Storage</b>	Store protected from light and moisture.

## 1.2 Opioid Analgesics

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Morphine is effective in relieving moderate to severe pain, particularly of visceral origin; there is a large variation in patient response. Weaker opioids such as codeine are suitable for mild to moderate pain.

**Morphine** remains the most valuable analgesic for severe pain. In addition to pain relief it confers a state of euphoria and mental detachment; repeated administration may cause dependence and tolerance, but this should not be a deterrent in the control of pain in terminal illness. Regular use may also be appropriate for certain cases of non-malignant pain, but specialist supervision is required. In normal doses common adverse effects include nausea, vomiting, constipation and drowsiness; larger doses produce respiratory depression and hypotension.

**Codeine** is an opioid analgesic much less potent than morphine and much less liable, in normal doses, to produce adverse effects including dependency. It is effective for mild to moderate pain but is too constipating for long-term use.

**Codeine\*** (Refer Page No. 72)  
(Controlled Medicine Under the Narcotic Drugs and Psychotropic Substances Act 1985)

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>Mild to moderate pain; diarrhoea; cough suppressant; irritable bowel syndrome.</i>
<b>Availability</b>	<b>TABLET</b> 10 mg; <b>SYRUP</b> 15 mg/5 ml.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> 30 to 60 mg every 4 h. (max. 240 mg/day). <b>Child-</b> 1 year to 12 year: 3 mg/kg daily in divided doses.
<b>Contraindications</b>	Respiratory depression; obstructive airways disease; acute asthma attack; where risk of paralytic ileus; hypersensitivity; head injury; increased intracranial pressure.
<b>Precautions</b>	Hepatic impairment (Appendix 7a) and renal impairment; opioids dependence; lactation; overdose: chapter 7.2; pregnancy (Appendix 7c); interactions (Appendix 6c); hypothyroidism; shock.

### Adverse Effects

Constipation particularly troublesome in long-term use, dizziness, nausea, vomiting; difficulty with micturition; ureteric or biliary spasm; dry mouth; headaches; sweating; facial flushing; in therapeutic doses, codeine is much less liable than morphine to produce tolerance, dependence, euphoria, sedation or other adverse effects; orthostatic hypotension; respiratory depression; rhabdomyolysis; convulsions (especially in children).

## Morphine\* (Refer Page No. 422)

(Controlled Medicine Under the Narcotic Drugs and Psychotropic Substances Act, 1985)

Pregnancy Category-C

Schedule H, X

### Indications

*In severe pain (acute and chronic); myocardial infarction, acute pulmonary oedema; adjunct during major surgery and postoperative analgesia; prolonged relief of severe and intractable pain.*

### Availability

**INJECTION** 10 ml ampoule (1 mg/ml, 10 mg/ml, 15 mg/ml); **TABLETS** 10, 20, 30 and 60 mg.

### Dose

#### **Subcutaneous or intramuscular injection**

**Adult-** Acute pain: 10 mg every 4 h.

**Elderly or frail-** Acute pain: 5 mg, adjust according to response (not suitable for patients having oedema).

**Child-** Acute pain: can be given to children in dose range of 0.2 to 0.8 mg/kg every 12 h. After 1 to 6 months: initially 100 to 200 µg/kg every 6 h, 2 to 12 years: initially 200 µg/kg every 4 h, 12 to 18 years: initially 2.5 to 10 mg every 4 h.

#### **Slow intravenous injection**

**Adult-** Acute pain: 2.5 mg every 4 h. Myocardial infarction: 10 mg (2 mg/min), followed by another 5 to 10 mg if necessary.

**Elderly or frail-** Acute pain: reduced dose.

**Child-** 0.1-0.15 mg/kg

#### **Subcutaneous or intramuscular injection**

Premedication: up to 10 mg, 1 to 1.5 h before operation.

#### **Oral or subcutaneous or intramuscular injection**

Chronic acute pain: 5 to 20 mg every 4 h or as per recovery (not suitable for patient having oedema).



**Contraindications** Acute respiratory depression, obstructive airway disease; acute alcoholism; where risk of paralytic ileus; raised intracranial pressure or head injury (interferes with respiration, also affects pupillary responses vital for neurological assessment); avoid injection in pheochromocytoma.

**Precautions** Renal and hepatic impairment (Appendix 7a); reduce dose or avoid in elderly and debilitated; dependence (severe withdrawal symptoms if withdrawn abruptly); hypothyroidism; convulsive disorders, seizure disorder; decreased respiratory reserve and acute asthma; hypotension; prostatic hypertrophy; pregnancy (Appendix 7c) and lactation (Appendix 7b); overdose: chapter 7.2; interactions (Appendix 6a, 6c, 6d); driving and operating machinery.

**Adverse Effects** Nausea, vomiting (particularly in initial stages) constipation, drowsiness, also dry mouth, anorexia; spasm of urinary and biliary tract; bradycardia/tachycardia; palpitations; decreased *libido*; rash, urticaria, pruritus; sweating; headache; facial flushing; vertigo; postural hypotension; hypothermia; hallucinations, euphoria, confusion, dependence; miosis; larger doses produce respiratory depression and hypotension; somnolence; sepsis, peripheral oedema.

**Storage** Store protected from light and moisture.

## Pentazocine

**Pregnancy Category-C**

**Indications** *Moderate to severe pain; pre-anaesthetic medication; colic; trauma; surgical procedures; burns.*

**Availability** **TABLETS** 25 mg Plain, Combination: Paracetamol 500 mg + Pentazocine 15 mg; **INJECTION** 1 ml ampoule (30 mg/ml).

**Dose** **Oral**

**Adult-** Pentazocine 50 mg every 3 to 4 h preferably after food (range 25 to 100 mg, max. 600 mg daily).

**Child-** 6 to 12 years: 25 mg.

**Subcutaneous, intramuscular or intravenous injection**

**Adult-** Moderate pain: 30 mg. Severe pain: 45 to 60 mg every 3 h to 4 h when necessary.

**Child** (Over 1 year)- by subcutaneous or intramuscular injection: 1 mg/kg; by intravenous injection: 500 µg/kg.

**Contraindications** Patients dependent on opioids; arterial or pulmonary hypertension; heart failure; narcotic dependence; hypersensitivity; ischaemia; myocardial infarction.

**Precautions** Avoid in porphyria; interactions (Appendix 6a); impaired respiratory function; pregnancy (Appendix 7c); renal or hepatic function; thyroid dysfunction; biliary tract impairment.

**Adverse Effects** Nausea, vomiting; euphoria, sedation, occasional hallucinations.

**Storage** Store protected from light and moisture.

## Tramadol\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *Moderate or severe pain, post operative pain, in patients contraindicated to NSAIDs.*

**Availability** **TABLETS** 50 mg and 100 mg SR; **CAPSULE** 50 and 100 mg SR; **INJECTION** 1 and 2 ml ampoule (50 mg/ml).

**Dose** **Adult-** Moderate to severe pain: 50 to 100 mg, 4 to 6 hourly (max 400 mg/day).

Post operative pain: 100 mg i.v. initially followed by 50 mg every 10 to 20 min upto max. of 250 mg in the 1<sup>st</sup> h. Maintenance dose 50 to 100 mg, 4 to 6 hourly (max 600 mg/day).

**Contraindications** Patients with suicidal tendency; raised intracranial pressure; severe renal impairment; acute alcoholism; lactation.

**Precautions** Renal or hepatic impairment; history of epilepsy; inflammatory or obstructive bowel disease; myasthenia gravis; hypothyroidism; adreno-cortical insufficiency; respiratory depression; prostatic hyperplasia; pregnancy (Appendix 7c).

**Adverse Effects** Same as other opioids, however it has less addictive potential.

## **2.     Antacids and Antiulcer Drugs           15**

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## 2. Antacids and Antiulcer Drugs

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Antacids (usually containing aluminium or magnesium compounds) can often relieve symptoms in ulcer dyspepsia and in non-erosive gastro-oesophageal reflux; they are also sometimes used in non-ulcer dyspepsia but the evidence of benefit is uncertain. Antacids are best given when symptoms occur or are expected, usually between meals and at bedtime, **Liquid preparations are more effective than solids.**

Aluminium- and magnesium-containing antacids (for example aluminium hydroxide and magnesium hydroxide), being relatively insoluble in water, are long-acting if retained in the stomach. They are suitable antacids for most purposes. **Magnesium-containing antacids have a laxative effect whereas aluminium-containing antacids may be constipating.**

H<sub>2</sub>-receptor antagonists heal gastric and duodenal ulcers by reducing the secretion of gastric acid as a result of histamine H<sub>2</sub>-receptor blockade; they can also relieve gastro-oesophageal reflux disease. High doses of H<sub>2</sub>-receptor antagonists have been used in the Zollinger-Ellison syndrome, but a proton-pump inhibitor is now preferred.

Maintenance treatment with low doses has largely been replaced in *Helicobacter pylori* positive patients by eradication regimens. Maintenance treatment may occasionally be used for those with frequent severe recurrences and for the elderly who suffer ulcer complications.

Treatment of undiagnosed dyspepsia with H<sub>2</sub>-receptor antagonists may be acceptable in younger patients but care is required in older patients because their symptoms may be caused by gastric cancer.

H<sub>2</sub>-receptor antagonist therapy can promote healing of NSAID-associated ulcers (particularly duodenal). Treatment also reduces the risk of acid aspiration in obstetric patients at delivery (Mendelson syndrome).

## Peptic Ulcer

Ulcer disease is caused by peptic ulceration that involves the stomach, duodenum and lower oesophagus. General and inexpensive measures like introducing healthy life-style, stopping smoking and taking antacids should be promoted. The possibility of malignant disease should be considered in all patients over the age of 40 years who are suspected of having an ulcer.

Gastric and duodenal ulcers are healed by 4-8 weeks treatment with H<sub>2</sub>-receptor antagonists but there is a high rate of relapse (greater than 70% over 2 years) requiring maintenance therapy. Relapses can be prevented very successfully by eradicating *Helicobacter pylori* which is causally associated with most peptic ulcers (except those related to NSAID use). Eradication of *H. pylori* reduces the relapse rate to about 4-8%. This is undoubtedly cost-effective compared to the alternatives of long-term maintenance therapy with low-dose H<sub>2</sub>-receptor antagonists or repeated treatment of recurrent ulcers. **It is recommended that the presence of *H. pylori* is confirmed before starting eradication treatment, particularly for gastric ulcers.** The urea breath test is used widely to test for *H. pylori*, but it may produce false negative results if used soon after proton-pump inhibitors or antibacterials. Eradication regimens are based on a combination of an acid-reducing ('antisecretory') drug and antibiotics.

The following model eradication regimen is suggested on the basis of its efficacy and simplicity (only doses suitable for adults are shown):

- **Omeprazole** 40 mg daily for 1 week  
plus
- **Metronidazole** 400 mg thrice daily for 1 week  
plus
- **Amoxicillin** 500 mg thrice daily for 1 week

The decision on choosing an eradication regimen should take into account local resistance to antibacterials, cost and availability of the necessary drugs.

## NSAID-Associated Ulcers

Gastrointestinal bleeding and ulceration may occur with NSAID use. To avoid this, emphasis should be on stopping NSAID use but this is not always possible. A proton-pump inhibitor may be considered for protection against NSAID-associated gastric and duodenal ulcers. An H<sub>2</sub>-receptor antagonist may be effective for protection against NSAID-associated duodenal ulcers only.

Patients who must continue NSAID therapy after ulcer

development may take high-dose H<sub>2</sub>-receptor antagonists concomitantly, but ulcers tend to heal more slowly with H<sub>2</sub>-receptor antagonists if NSAIDs are continued. A proton-pump inhibitor such as omeprazole is more effective but it is also more expensive.

In patients who can discontinue NSAID therapy after ulcer development, treatment with an H<sub>2</sub>-receptor antagonist is effective, but a treatment period of up to 8 weeks may be necessary. A proton-pump inhibitor usually produces the most rapid healing. After healing, continued prophylaxis is required.

## Dyspepsia

Dyspepsia covers pain, fullness, early satiety, bloating, or nausea. It can occur with gastric and duodenal ulceration and gastric cancer but most commonly it is of uncertain origin.

Patients with non-ulcer dyspepsia should be advised to avoid smoking, alcohol and aggravating foods and to eat small regular meals to aid digestion. Non-ulcer dyspepsia tends to be self-limiting but antacids and H<sub>2</sub>-receptor antagonists are often used to suppress gastric acid.

Effective treatment is important in the presence of severe oesophageal ulceration to prevent longer term complications such as oesophageal stricture and carcinoma.

## Gastro-Esophageal Reflux Disease (GERD)

GERD (including non-erosive gastro-esophageal reflux and erosive esophagitis) is characterized by symptoms which include heartburn, acid regurgitation and sometimes difficulty in swallowing (dysphagia); esophageal inflammation (esophagitis), ulceration and stricture formation may occur and there is an association with asthma.

The management of GERD includes drug treatment, lifestyle changes and, in some cases, surgery. Initial treatment is guided by the severity of symptoms and treatment is then adjusted according to response.

For mild symptoms of GERD, initial management may include the use of antacids. H<sub>2</sub>-receptor antagonists suppress acid secretion and they may relieve symptoms and permit reduction in antacid consumption. Severe symptoms initially require a short-course of a proton-pump inhibitor.

## Zollinger-Ellison Syndrome

Management of Zollinger-Ellison syndrome requires high dose H<sub>2</sub>-receptor antagonist treatment. The proton pump inhibitors are more effective particularly for cases resistant to other treatment but they are more expensive.

## Aluminium Hydroxide

### Pregnancy Category-C

**Indications** *Ulcer and non-ulcer dyspepsia; GERD; hyperphosphataemia.*

**Availability** **TABLETS** 300 and 840 mg; **GEL** 610 mg/10 ml;  
**In combination as Tablet/Suspension/Gel/Syrup.**

**Dose** **Oral**

**Adult-** Dyspepsia, GERD: 1 to 2 tablets chewed 4 times daily and at bedtime or 5 to 10 ml suspension 4 times daily between meals and at bedtime. Hyperphosphataemia: 2 to 10g daily in divided doses with meals.

**Child-** 6 to 12 years: 5 ml up to three times daily.

**Contraindications** Hypophosphataemia; undiagnosed gastrointestinal or rectal bleeding; appendicitis; porphyria; hypersensitivity to aluminium salts.

**Precautions** Impaired renal function and renal dialysis; hepatic impairment (Appendix 7a); constipation; dehydration; fluid restriction; gastrointestinal disorders associated with decreased bowel motility or obstruction; pregnancy (Appendix 7c); interactions (Appendix 6c); oedema, cirrhosis and low sodium diets.

**Adverse Effects** Constipation, intestinal obstruction (large doses); hypophosphataemia with increased bone resorption, hypercalciuria and risk of osteomalacia (patients on low phosphate diet or prolonged therapy); hyperalbuminaemia-resulting in osteomalacia, encephalopathy, dementia, microcytic anaemia (in chronic renal failure treated with aluminium hydroxide as phosphate-binding agent); loss of appetite.

**Storage** Store protected from moisture at a temperature not exceeding 30°C. Do not freeze Gel.

## Famotidine\*

### Pregnancy Category-B

**Schedule H**

**Indications** *Duodenal or benign gastric ulcers, GERD. Zollinger-Ellison syndrome.*

**Availability** **TABLETS** 10, 20, 40 & 100 mg; **CAPSULES** 20 & 40 mg; **INJECTION** 2 ml (10 mg/ml).

**Dose****Oral****Benign gastric and duodenal ulceration**

**Adult:** 40 mg daily at bedtime for 4-8 weeks or 20 mg twice daily. To prevent recurrence of duodenal ulceration: 20 mg at bedtime may be taken.

**Gastro-oesophageal reflux disease**

**Adult:** 20 mg twice daily for 6-12 week or up to 40 mg twice daily if there is oesophageal ulceration. Maintenance dose: 20 mg twice daily may be given to prevent recurrence.

**Child:** 1-16 yr: 1-2 mg/kg/day divided twice daily up to 40 mg twice daily.

**Zollinger-Ellison syndrome**

**Adult:** Initially, 20 mg every 6 hr, up to 640 mg daily if necessary.

**Child:** 1-16 yr: 0.5-1 mg/kg/day up to 40 mg/day, given once at bedtime or taken twice daily.

**Non-ulcer dyspepsia**

**Adult:** 10 mg twice daily.

**Heartburn**

**Adult:** 10 mg twice daily.

**Intravenous****Benign gastric and duodenal ulceration**

**Adult:** 20 mg every 12 hr, as an injection over at least 2 minutes or as an infusion over 15-30 minutes.

**Contraindications**

Hypersensitivity

**Precautions**

Possibility of gastric malignancy should be excluded, Impaired renal function, liver cirrhosis, pregnancy (Appendix 7c), lactation, children and elderly, interactions (Appendix 6c).

**Adverse Effects**

Headache, dizziness, constipation, diarrhoea, nausea, vomiting, anorexia, rash, fatigue, gynaecomastia and impotence.

**Storage**

Store protected from light, Tablets to be stored at room temperature, 15 -30°C (59-86°F). Injection to be stored between 2-8°C (36-46°F).

**Magnesium Hydroxide****Pregnancy Category-B****Indications**

*Ulcer and non-ulcer dyspepsia; GERD.*

**Availability**

**TABLET** 310 mg; **SUSPENSION** 110 ml and 340 ml (8%).

**Dose****Oral**



**Adult-** Dyspepsia, GERD: 5 to 10 ml repeated according to patient's needs.

**Contraindications** *Severe renal impairment.*

**Precautions** Renal impairment; hepatic impairment (Appendix 7a); interactions (Appendix 6c); abdominal pain.

**Adverse Effects** Diarrhoea; in renal impairment-hypermagnesaemia resulting in loss of deep tendon reflexes and respiratory depression with other symptoms including nausea, vomiting, flushing of skin, thirst, hypotension, drowsiness, confusion, muscle weakness, bradycardia, coma and cardiac arrest; allergic reaction.

**Storage** Store protected from light. Do not store Gel in refrigerator.

## Omeprazole\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *Benign gastric and duodenal ulcers; Zollinger Ellison syndrome; gastric acid reduction during gastric surgery; GERD, NSAID- induced ulcer, prophylaxis during NSAIDs treatment in patients with high risk for peptic ulceration, eradication of H.pylori, as preoperative medication, systemic mastocytosis and in patients not responsive to H<sub>2</sub> blockers.*

**Availability** **TABLETS** 20 and 40 mg; **INJECTION** 10 ml vial (40 mg/10 ml); **CAPSULES** 10, 20 and 40 mg.

**Dose** **Oral**

Benign gastric and duodenal ulcers: 20 mg once a day for 4 weeks in duodenal ulcers, for 8 weeks in gastric ulcers, Increase to 40 mg in severe case. Maintenance for recurrent duodenal ulcers: 20 mg once daily. Prevention of relapse: 10 mg daily. NSAIDs associated gastric or duodenal ulcers or gastro-duodenal erosions: 20 mg daily for 4 weeks. Prophylaxis in case of history associated with gastric/duodenal ulcers or dyspepsia: 20 mg daily. Zollinger-Ellison syndrome: 60 mg to 120 mg/day or more, into divided doses.

Gastric acid reduction during gastric surgery: 40 mg on preceding evening then 40 mg 2 to 6 h before surgery.

**Contraindications** Hypersensitivity.

**Precautions** Interactions (Appendix 6c, 6d); pregnancy (Appendix 7c); concomitant gastric malignancy.

**Adverse Effects** Nausea, abdominal pain, constipation, flatulence, diarrhoea, headache, skin rashes, subacute, myopathy, arthralgias, increased risk of hip fractures, decreased B<sub>12</sub> absorption, hypergastrinemia, respiratory and *Clostridium difficile* infections, hepatic dysfunction.

**Storage** Store protected from light and moisture at a temperature not exceeding 30°C.

## Pantoprazole\*

**Pregnancy Category-B**

**Schedule H**

**Indications** *Duodenal ulcer, gastric ulcer, GERD, erosive esophagitis.*

**Availability** **TABLETS** 20 and 40 mg, **INJECTIONS** 20 and 40 mg/vial, **CAPSULES** 20 and 40 mg.

**Dose** **Oral**

**Adult-** 40 mg once daily up to 8 weeks.

**Intravenous**

**Adult-** 40 mg twice daily.

**Contraindications** Hypersensitivity.

**Precautions** Hepatic impairment; monitor liver function; pregnancy (Appendix 7c); cyanocobalamin deficiency; tumorigenicity.

**Adverse Effects** Diarrhoea; pruritus; dizziness; pyrexia; blurred vision; vertigo.

## Ranitidine\*

**Pregnancy Category-B**

**Schedule H**

**Indications** *Benign gastric and duodenal ulceration, GERD, Zollinger-Ellison syndrome, other conditions where gastric acid reduction is beneficial. Prophylaxis during NSAIDs treatment in patients with high risk for peptic ulceration, eradication of H.pylori, as preoperative medication, systemic mastocytosis*

**Availability** **TABLETS** 150 and 300 mg. **INJECTION** 2 ml ampoule (25 mg/ml), **SYRUP** 375 mg/5 ml.

**Dose** **Oral**

**Adult-** Benign gastric and duodenal ulceration: 150 mg twice daily or 300 mg at night for 4 to 8 weeks, up to 6 weeks in chronic episodic dyspepsia and up to 8 weeks in NSAID-associated ulceration (in duodenal ulcer 300 mg can be given twice daily for 4 weeks to achieve a higher healing rate); maintenance, 150 mg at night. Prophylaxis of NSAID-induced duodenal ulcer: 150 mg twice daily. Reflux oesophagitis: 150 mg twice daily or 300 mg at night for up to 8 weeks, or if necessary 12 weeks (moderate to severe, 150 mg 4 times daily for up to 12 weeks). Long-term treatment of healed oesophagitis: 150 mg twice daily.

Zollinger- Ellison syndrome: 150 mg 3 times daily (up to 6g daily in divided doses has been used). Gastric acid reduction (prophylaxis of acid aspiration) in obstetrics: 150 mg at onset of labour, then every 6 h. Surgical procedures: 150 mg 2 h before induction of anaesthesia and also, when possible on the preceding evening.

**Child-** Peptic ulcer: 2 to 4 mg/kg twice daily (max. 300 mg daily).

#### ***Intramuscular injection***

**Adult-** Benign gastric and duodenal ulceration, reflux oesophagitis, Zollinger-Ellison syndrome: 50 mg every 6 to 8 h. Surgical procedures: 50 mg 45 to 60 min before induction of anaesthesia.

#### ***Slow intravenous injection***

Benign gastric and duodenal ulceration, reflux oesophagitis, Zollinger-Ellison syndrome: 50 mg diluted to 20 ml and given over at least 2 min, may be repeated every 6 to 8 h. Surgical procedures: 50 mg 45 to 60 min before induction of anaesthesia (intravenous injection diluted to 20 ml and given over at least 2 min).

#### ***Intravenous infusion***

Benign gastric and duodenal ulceration, reflux oesophagitis, Zollinger-Ellison syndrome: 25 mg/h for 2 h, may be repeated every 6 to 8 h.

Prophylaxis of stress ulceration: initial slow intravenous injection of 50 mg diluted to 20 ml and given over at least 2 min then by continuous intravenous infusion, 125-250 µg/kg per h (may be followed by 150 mg twice daily by mouth when oral feeding commences).

#### **Contraindications**

Porphyria.

**Precautions**

Hepatic impairment (Appendix 7a); renal impairment; lactation (Appendix 7b); middle-aged or older patients and those whose symptoms change-may mask gastric cancer; interactions (Appendix 6a); pregnancy (Appendix 7c).

**Adverse Effects**

Diarrhoea and other gastrointestinal disturbances; headache; dizziness; rash; tiredness; acute pancreatitis; bradycardia, tachycardia; AV block, confusion; depression; rarely, hallucinations (particularly in the elderly or the very ill); hypersensitivity reactions (including fever, arthralgia, myalgia, anaphylaxis); blood disorders (including agranulocytosis, leukopenia, pancytopenia, thrombocytopenia); hepatitis; agitation; visual disturbances; erythema multiforme; alopecia; gynaecomastia and impotence; malaise; somnolence.

**Storage**

Store protected from light and moisture.

<b>3. Antiallergics and Drugs used in Anaphylaxis</b>	<b>25</b>
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## 3. Antiallergics and Drugs used in Anaphylaxis

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Antihistamines are used to treat drug allergies, food allergies, insect stings and some of the symptoms of anaphylaxis and angioedema. Drug treatment and other supportive care should not be delayed in critically ill patients. Specific precipitants should be sought and if identified, further exposure avoided and desensitization considered.

Drowsiness and sedation are particular disadvantages of the older antihistamines and the patient should be warned against driving or operating machinery. Other central nervous system depressants, including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytics and neuroleptics, may enhance the sedative effects of antihistamines. Since antihistamines interfere with skin tests for allergy, they should be stopped at least one week before conducting a skin test.

**Allergic reactions of limited duration and with mild symptoms, such as urticaria or allergic rhinitis, usually require no treatment.** If on the other hand, symptoms become persistent, antihistamines constitute the mainstay of treatment. However, oral corticosteroids may be required for a few days in an acute attack of urticaria or for severe skin reactions. Oral corticosteroids are also used to relieve severe exacerbations in chronic urticaria, but long-term use should be avoided.

Corticosteroids may be used topically to reduce inflammation in allergic rhinitis but should only be used systemically for this condition when symptoms are disabling.

### Allergic Emergencies

Anaphylactic shock and conditions such as angioedema are medical emergencies that can result in cardiovascular collapse and/or death. They require prompt treatment of possible laryngeal oedema, bronchospasm or hypotension. Atopic individuals are particularly susceptible. Insect stings and certain foods including eggs, fish, cow's milk protein, peanuts and nuts are a risk for sensitized persons. Therapeutic substances particularly associated with anaphylaxis include blood products, vaccines, hyposensitizing (allergen) preparations, antibiotics (especially penicillins), iron injections, heparin and neuromuscular blocking drugs. Acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs) may cause bronchoconstriction in leukotriene-

sensitive patients. In the case of drug allergy, anaphylaxis is more likely to occur after parenteral administration. Resuscitation facilities should always be available while injecting a drug associated with risk of anaphylactic reactions.

**First-line treatment of a severe allergic reaction includes administering epinephrine, keeping the airway open (with assisted respiration if necessary) and restoring blood pressure (laying the patient flat, raising the feet).** Epinephrine should immediately be given by intramuscular injection to produce vasoconstriction and bronchodilation and injection should be repeated if necessary at 5-min intervals until blood pressure, pulse and respiratory function have stabilized. If there is cardiovascular shock with inadequate circulation, epinephrine must be given cautiously by slow intravenous injection of a *dilute solution*. Oxygen administration is also of primary importance.

An antihistamine such as chlorpheniramine is a useful adjunctive treatment given after epinephrine injection and continued for 24 to 48 h to reduce the severity and duration of symptoms and to prevent relapse. An intravenous corticosteroid such as hydrocortisone has an onset of action that is delayed by several hours but should be given to help prevent later deterioration in severely affected patients.

Further treatment of anaphylaxis may include intravenous fluids, an intravenous vasopressor such as dopamine, intravenous aminophylline or injected or nebulized bronchodilator, such as salbutamol.

## Steps in the Management of Anaphylaxis:

- 1. Sympathomimetic:** Epinephrine by intramuscular injection using epinephrine injection 1 in 1000, ADULT and ADOLESCENT, 500  $\mu\text{g}$  (0.5 ml); INFANT under 6 months 50  $\mu\text{g}$  (0.05 ml); CHILD 6 months-6 years 120  $\mu\text{g}$  (0.12 ml), 6-12 years 250  $\mu\text{g}$  (0.25 ml)

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*Note: The above doses may be repeated several times if necessary at 5-min intervals, according to blood pressure, pulse and respiratory function*

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If circulation inadequate, by slow intravenous injection using epinephrine injection 1 in 10,000 (given at a rate of 1 ml/min), ADULT 500  $\mu\text{g}$  (5 ml); CHILD 10  $\mu\text{g}/\text{kg}$  (0.1 ml/kg), given over several min.

- 2. Vital Functions:** Maintain an open airway; give oxygen by mask, restore blood pressure (lay patient flat, raise feet)
- 3. Antihistamine:** such as chlorpheniramine by intravenous injection over 1 min, ADULT 10-20 mg, repeated if required (max. total dose 40 mg in 24 h)
- 4. Corticosteroids:** such as hydrocortisone by slow intravenous injection, ADULT 100-300 mg; CHILD up to 1 year, 25 mg; 1-5 years, 50 mg; 6-12 years, 100 mg
- 5. Intravenous Fluids:** start infusion with sodium chloride (0.5-1 litre during the first h)
- 6.** If the patient has asthma-like symptoms, give salbutamol 2.5-5 mg by nebulization or aminophylline 5 mg/kg by intravenous injection over at least 20 min.



## Adrenaline (Epinephrine)\* (Refer Page No. 561)

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Severe anaphylactic reaction; severe angioedema; cardiac arrest; hemostatic agent.</i>
<b>Availability</b>	<b>INJECTION</b> 1 ml ampoule (1 mg/ml).
<b>Dose</b>	<b><i>Intramuscular injection</i></b>  Anaphylaxis: preferable site is the midpoint in anterior thigh [1:1000 solution]. This route should be used by specialists only with extreme care.  <b><i>Slow intravenous injection</i></b>  When there is doubt regarding adequacy of circulation and absorption from the intramuscular site; slow intravenous injection of 1:10000 (10 mg/ml) solution be injected in severely ill patients only.
<b>Contraindications</b>	Narrow angle glaucoma, organic brain damage, cardiac dilation, coronary insufficiency.
<b>Precautions</b>	Hyperthyroidism, hypertension, diabetes mellitus, heart disease, arrhythmias, cerebrovascular disease; second stage of labour; interactions (Appendix 6c); pregnancy (Appendix 7c); lactation (Appendix 7b).
<b>Adverse Effects</b>	“Epinephrine fastness”, tachycardia and arrhythmias, hypertension, tremor, anxiety, sweating, nausea, vomiting, weakness, hyperglycaemia, dizziness, pulmonary oedema have all been reported; headache common.
<b>Storage</b>	Store protected from light preferably in containers filled with nitrogen.

## Chlorpheniramine\*

Pregnancy Category-C

Schedule H,G

<b>Indications</b>	<i>Symptomatic relief of allergy, allergic rhinitis (hay fever); conjunctivitis; urticaria; insect stings and pruritus of allergic origin; adjunct in the emergency treatment of anaphylactic shock and severe angioedema.</i>
<b>Availability</b>	<b>TABLETS</b> 2, 4 and 6 mg; <b>INJECTIONS</b> 10 mg/10 ml, <b>CAPSULE</b> 8 mg; <b>SYRUP</b> 10 mg/50 ml, 100 mg/100 ml.
<b>Dose</b>	<b><i>Oral</i></b>  <b>Adult-</b> Allergic reactions: 4 mg every 4 to 6 h (max. 24 mg daily).

**Child-** 1 to 2 years: 1 mg twice daily. 2 to 5 years: 1 mg every 4 to 6 h (max. 12 mg daily). 6 to 12 years: 2 mg every 4 to 6 h (max. 12 mg daily)

***Intramuscular or intravenous injection***

**Adult-** Allergic reactions: 10 to 20 mg, repeated if required (max. 40 mg in 24 h).

***Subcutaneous injection***

**Child-** Allergic reactions: 87.5 µg/kg, repeated if necessary up to 4 times daily.

***Intravenous injection*** (over 1 min).

**Adult-** Anaphylaxis (adjunct): 10 to 20 mg.

**Child-** Anaphylaxis (adjunct)- under 1 year: 250 µg/kg. 1 to 5 years: 2.5 to 5 mg. 6 to 12 years: 5 to 10 mg.

**Contraindications**

Prostatic enlargement, urinary retention; ileus or pyloroduodenal obstruction; asthma; child under 1 year; hypersensitivity, narrow angle glaucoma, pregnancy (Appendix 7c), lactation (Appendix 7b).

**Precautions**

Performing works requiring utmost alertness such as vehicle driving, operating machines etc within 24 h of taking the drug should be avoided. Lactation (Appendix 7b); renal and hepatic impairment (Appendix 7a); epilepsy; interactions (Appendix 6a); atropic gastritis, elderly.

**Adverse Effects**

Drowsiness (rarely, paradoxical stimulation with high doses, or in children or elderly), hypotension, headache, palpitations, psychomotor impairment, urinary retention, dry mouth, blurred vision, gastrointestinal disturbances; liver dysfunction; blood disorders; also rash and photosensitivity reactions, hypersensitivity reactions (including bronchospasm, angioedema, anaphylaxis); sweating and tremor, injections may be irritant; flatulence, diarrhoea.

**Storage**

Store protected from light and moisture.

**Cinnarizine**

**Pregnancy Category-C**

**Schedule H**

**Indications**

*Motion sickness, nausea, vomiting, vertigo and tinnitus associated with Meniere disease and other middle ear disorders, as a nootropic drug, adjunct therapy for symptoms of peripheral arterial disease.*

<b>Availability</b>	<b>TABLETS 25 &amp; 75 mg Plain and 75 mg SR.</b>
<b>Dose</b>	<b>Oral</b> <b>Motion sickness</b> <b>Adult:</b> 30 mg 2 hr before travel and 15 mg every 8 hr during travel if needed. <b>Vertigo</b> <b>Adult:</b> 30 mg thrice daily. <b>Child:</b> 5-12 year: half of adult dose. <b>Peripheral circulatory disorders</b> <b>Adult:</b> 75 mg tablets three times daily.
<b>Contraindications</b>	Hypersensitivity, Parkinson's disease, children below 5 years.
<b>Precautions</b>	Hypotension, patients should not drive or operate machinery, pregnancy (Appendix 7c), lactation, elderly, children and neonates, interactions (Appendix 6c).
<b>Adverse Effects</b>	Drowsiness, rarely skin and hypersensitivity reactions, dry mouth, extrapyramidal symptoms sometimes associated with severe depression, muscular weakness, headache, euphoria, GI upsets, blurred vision, urinary difficulty or retention, constipation and increased gastric reflux, fatigue, hypolipidaemic effect.
<b>Storage:</b>	Store below 25°C, protected from light

## **Dexamethasone\*** (Refer Page No. 478)

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>Adjunct in the emergency treatment of anaphylaxis; short-term suppression of inflammation in allergic disorders; adrenocortical insufficiency, ocular inflammation, autoimmune disorders, rheumatic disorder, cerebral oedema, unresponsive shock, bacterial meningitis along with antibiotics.</i>
<b>Availability</b>	<b>TABLETS 0.5 mg; INJECTION 2 ml vial (4 mg/ml); CREAM 5 and 15 g (0.1% w/w).</b>
<b>Dose</b>	<b>Oral</b> <b>Adult-</b> 0.5 to 10 mg daily in divided doses, repeat if necessary. <b>Child-</b> 0.02 to 0.3 mg/kg in three or four divided doses daily.

**Intravenous injection**

4 to 10 mg every 6 h.

<b>Contraindications</b>	Untreated systemic infection (unless condition life-threatening); administration of live virus vaccines; renal failure, diabetes mellitus, psychosis, osteoporosis, pregnancy (Appendix 7c), CHF, tuberculosis, fungal infections of the eye.
<b>Precautions</b>	Increased susceptibility to and severity of infection; activation or exacerbation of tuberculosis, amoebiasis, strongyloidiasis; risk of severe chickenpox in non-immune patient (varicella-zoster immunoglobulin required if exposed to chickenpox); avoid exposure to measles (normal immunoglobulin possibly required if exposed); diabetes mellitus; peptic ulcer; hypertension; precautions relating to long-term use of corticosteroids; glaucoma, epilepsy; drug should not be abruptly withdrawn; interactions (Appendix 6c), lactation (Appendix 7b).
<b>Adverse Effects</b>	Nausea, dyspepsia, malaise, hiccups; hypersensitivity reactions including anaphylaxis; perineal irritation after intravenous administration; adverse effects associated with long-term corticosteroid treatment; hyperglycaemia, abdominal distension, angioedema, bradycardia, acne, erythema, Cushing's syndrome, oropharangeal candidiasis, hypothalamic pituitary adrenal axis suppression.
<b>Storage</b>	Store protected from light at a temperature not exceeding 30°C.

**Fexofenadine****Pregnancy Category-C****Schedule H**

<b>Indications</b>	<i>Allergic rhinitis, urticaria.</i>
<b>Availability</b>	<b>TABLETS</b> 30, 60, 120 and 180 mg; <b>SYRUP</b> 30 mg/5 ml.
<b>Dose</b>	Allergic rhinitis: <b>Adult-</b> 120 mg once daily. <b>Child (6-11year)-</b> 30 mg twice daily. Urticaria and skin allergy: <b>Adult-</b> 180 mg once daily. <b>Child-</b> (6 month to 2 years): 15 mg twice daily, more than 2 years: 30 mg twice daily.

<b>Contraindications</b>	Hypersensitivity.
<b>Precautions</b>	Bradycardia, hypokalemia, preexisting long QT interval, renal impairment, pregnancy (Appendix 7c), lactation, interactions (Appendix 6a, 6c).
<b>Adverse Effects</b>	Dizziness, stomach discomfort, pain in extremity, back pain, vomiting, diarrhoea, upper respiratory tract infection, headache, dysmenorrhoea.

## Hydrocortisone\* (Refer Page No. 355, 429 and 479)

Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Adjunct in the emergency treatment of anaphylaxis; inflammatory skin conditions; inflammatory bowel disease; adrenocortical insufficiency; As acetate: rheumatology, neurology, episcleritis, sinusitis; Addison's disease, Simmond's disease, tuberculous meningitis; perineal trauma, joint inflammation, subaortic dermatitis.</i>
<b>Availability</b>	<b>TABLETS</b> 5, 10 and 20 mg, <b>CREAM</b> 10g (1% w/w), <b>OINTMENT</b> 1%, 2.5% w/w <b>INJECTION</b> 100, 200 and 400 mg/vial, (25 mg/5 ml).
<b>Dose</b>	<b><i>Intramuscular injection or slow intravenous injection or intravenous infusion</i></b>  <b>Adult</b> -100 mg to 500 mg, 3 to 4 times in 24 h or as required.  <b><i>Slow intravenous injection</i></b>  <b>Child</b> - Up to 1year: 25 mg. 1 to 5 years: 50 mg.
<b>Contraindications</b>	Not relevant to emergency use but for contra-indications relating to long-term use; ulcers.
<b>Precautions</b>	Not relevant to emergency use but for precautions relating to long-term use, interactions (Appendix 6d), lactation (Appendix 7b), pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Adverse effects associated with long-term corticosteroid treatment; opportunistic infections.

## Levocetirizine

Pregnancy Category-B

**Schedule H**

<b>Indications</b>	<i>Allergic rhinitis, chronic urticaria.</i>
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<b>Availability</b>	<b>TABLETS</b> 5 mg; <b>SYRUP</b> 2.5 mg/5 ml.
<b>Dose</b>	<b>Oral</b>  <b>Rhinitis, chronic urticaria: Adult &amp; children (&gt;12 years)</b> - 5 mg once daily in the evening. <b>Children (6-12 yrs)</b> - 2.5 mg once daily. <b>Children (6 months - 5 yrs)</b> – 1.25 mg once daily.
<b>Contraindications</b>	Hypersensitivity, end-stage renal disease with creatinine clearance < 10 ml/min. Not recommended for lactating mothers or children below 6 months.
<b>Precautions</b>	May impair the ability to drive or operate machinery, concurrent use of alcohol or CNS depressant drugs should be avoided, pregnancy (Appendix 7c), elderly, interactions (Appendix 6c).
<b>Adverse Effects</b>	Somnolence, fatigue, dry mouth, nasopharyngitis have been reported in adults. Fever, cough, epistaxis and diarrhoea may occur in children <12 years.
<b>Storage</b>	Store protected from heat, light and moisture at a temperature not exceeding 30°C.

## Noradrenaline

### Pregnancy Category-C

<b>Indications</b>	<i>Acute hypotension, adjunct in cardiac arrest, upper gastrointestinal haemorrhage.</i>
<b>Availability</b>	<b>INJECTIONS</b> Vials (4 mg/ml, 4 mg/2 ml and 2 mg/2 ml)
<b>Dose</b>	<b>Parenteral Intravenous</b>  <b>Acute hypotension</b> <b>Adult:</b> 8-12 µg/minute, up to 8-30 µg/minute in refractory shock. Infused using a solution of 4 µg/ml in glucose 5%, or sodium chloride 0.9% and glucose 5% at a rate of 2-3 ml/minute. Adjust according to blood pressure response. Average maintenance dose: 0.5-1 ml/minute (2-4 µg/minute). Infuse via a central venous catheter or into a large vein. <b>Child:</b> Administer at a rate of 2 µg/minute. Alternatively, 2 µg/m <sup>2</sup> /minute. Adjust rate according to BP response and perfusion. <b>Elderly:</b> Initial dose should be at low end of dose range.

### Upper gastrointestinal haemorrhage

**Adult:** 8 mg in 250 ml of 0.9% sodium chloride injection via intraperitoneal route. Alternatively, instill 8 mg in 100 ml of 0.9% sodium chloride solution through a nasogastric tube every hr for 6–8 hrs, then every 2 hrs for 4–6 hrs. Withdraw drug gradually.

#### Reconstitution

Dilute with 5% glucose injection, with or without sodium chloride; dilution with sodium chloride injection alone is not recommended.

#### Contraindications

Hypertension, pregnancy (Appendix 7c), patients with peripheral or mesenteric vascular thrombosis unless necessary as a life-saving procedure.

During cyclopropane and halothane anaesthesia, noradrenaline is considered contraindicated because of the risk of producing ventricular tachycardia or fibrillation.

#### Precautions

Monitor BP frequently during infusion. Use large vein for infusion to avoid skin necrosis, interactions (Appendix 6c).

#### Adverse Effects

Elevation of blood pressure, bradycardia, peripheral ischemia, arrhythmias, anxiety, transient headache, respiratory difficulty, extravasation necrosis at injection site.

#### Storage

Store protected from light, in single dose containers.

Store at room temperature (25°C) and protect from light. Store in tight, light-resistant containers as it is readily oxidised. Do not use if discoloured (e.g. pink, dark yellow, brown) or if there is a precipitate.

## Pheniramine\*

Pregnancy Category-C

Schedule H

#### Indications

*Symptomatic relief of allergy; allergic rhinitis; urticaria.*

#### Availability

**TABLETS** 25 and 50 mg; **INJECTION** 2 ml ampoule (22.75 mg/ml); **SYRUP** 15 mg/ml.

#### Dose

##### **Oral**

**Adult-** 25 mg, 2 to 3 times a day or 50 mg twice daily.

##### **Intramuscular injection**

**Adult-** 1 to 2 ml twice a day.

**Child**- 6 months to 3 years: 0.4 to 1 ml once or twice daily. Over 4 years: 0.8 to 2 ml once or twice daily.

**Contraindications** Epilepsy; pregnancy (Appendix 7c); acute asthma; acute porphyria; symptomatic prostatic hypertrophy; neonates and premature infants.

**Precautions** Glaucoma; driving or operating machinery; asthma or severe cardiovascular disease, pregnancy (Appendix 7c), lactation.

**Adverse Effects** Drug abuse; CNS depression; dry mouth; blurred vision; dizziness; excitation in children.

**Storage** Store protected from light and moisture.

## **Prednisolone\*** (Refer Page No. 436, 481 and 557)

**Pregnancy Category-C**

**Schedule H**

**Indications** *Short-term as well as long term suppression of inflammation in allergic disorders; malignant disease; Autoimmune disease, bronchial asthma.*

**Availability** **TABLETS** 5, 10, 20, 30 and 40 mg; **SYRUP** 1 mg/ml and 3 mg/ml; **EYE DROPS** 1% w/v; **INJECTION** 2 ml vial (40 mg/ml).

**Dose** **Oral**

**Adult and Child**- Initially up to 10 to 20 mg daily in divided doses (severe diseases up to 60 mg), preferably after breakfast.

### ***Intramuscular injection***

**Adult and Child**- 25 mg to 100 mg once or twice weekly.

**Contraindications** Untreated systemic infection; administration of live virus vaccines; hypersensitivity.



### Precautions

Increased susceptibility to and severity of infection; activation or exacerbation of tuberculosis, amoebiasis, strongyloidiasis; risk of severe chickenpox in non-immune patient (varicella-zoster immunoglobulin required if exposed to chickenpox); avoid exposure to measles (normal immunoglobulin possibly required if exposed); diabetes mellitus; peptic ulcer; hypertension; further precautions relating to long-term use of corticosteroids; myasthenia gravis, congestive heart failure, renal insufficiency, pregnancy (Appendix 7c), osteoporosis, glaucoma, psychological disorders, diverticulitis, interactions (Appendix 6c, 6d), lactation (Appendix 7b), hepatic impairment (Appendix 7a).

### Adverse Effects

Nausea, dyspepsia, malaise, hiccups; hypersensitivity reactions including anaphylaxis; supraclavicular lump, fragile skin.

### Storage

Store protected from light and moisture.



<b>4.</b>	<b>Anti-Alzheimer and Anti-Parkinsonism Drugs</b>	<b>39</b>
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## 4. Anti-Alzheimer and Anti-Parkinsonism Drugs

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### 4.1 Anti-Alzheimer Drugs

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Alzheimer's disease is a slowly progressive neurodegenerative disorder characterized by loss of neurons and synapses in cerebral cortex and certain subcortical regions. The disease mainly affects the older population and is the most common cause of dementia (early stage). Advancing age is one of the predominant risk factors for Alzheimer's disease. As the disease advances behavioural changes such as confusion, irritability and aggression, mood swings, language breakdown, long term loss of memory etc. appear. The biochemical mechanisms involved in its pathogenesis are suggested to be the accumulation of abnormally folded amyloid  $\beta$  and  $\tau$  proteins in the brain, involvement of inflammatory cytokines, alteration in distribution of different neurotrophic factors and expression of their receptors etc.

Alzheimer's Association has pointed out 10 warning symptoms for this disease which are as under:

1. Memory loss
2. Difficulty performing familiar task
3. Problems with language
4. Disorientation to time and place
5. Poor or decreased judgement
6. Problems with abstract thinking
7. Misplacing things
8. Changes in mood or behaviour
9. Changes in personality
10. Loss of initiative

There is no cure for this disease, drug therapy is mainly symptomatic and palliative in nature. Following drugs are used for the treatment of Alzheimer's disease:

## Donepezil

Pregnancy Category-C

**Schedule H**

**Indications** *For the treatment of mild to moderate Alzheimer's disease.*

**Availability** **TABLETS** 5 and 10 mg Plain.

**Dose** **Oral**

**Adult-** Initially 5 mg daily in the evening. If necessary increase upto 10 mg once daily after 4-6 weeks.

**Extended release tablet-** once daily (23 mg/day).

**Maximum dose-** 10 mg daily.

**Contraindications** Hypersensitivity, severe hepatic and renal impairment, pregnancy (Appendix 7c), lactation, not recommended for children.

**Precautions** Mechanicalintestinalobstructionorperitonitis, Recent intestinal or bladder surgery, bronchial asthma or COPD, arrhythmias, bradycardia, recent MI and hypotension, vagotonia, epilepsy, hyperthyroidism, parkinsonism, moderate renal or hepatic impairment or peptic ulcer, sick sinus syndrome.

**Adverse Effects** Nausea, vomiting, diarrhoea, fatigue, insomnia, muscle cramps, bradycardia, convulsions, gastrointestinal, haemorrhage, hepatitis, urinary incontinence, influenza, pruritus, increased liver transaminases.

**Storage** Store protected from moisture, at a temperature not exceeding 25°C.

## Galantamine

Pregnancy Category-B

**Schedule H**

**Indications** *To treat the symptoms of mild to moderate Alzheimer's disease, Dementia syndrome.*

**Availability** **TABLETS** 4 mg, 8 mg and 12 mg; **CAPSULES ER** 8, 16 and 24 mg; **ORAL SOLUTION** 4 mg/ml.

**Dosage:** **Oral with meals**

For Alzheimer's disease: 4 mg twice daily.

For Dementia Syndrome: 8 to 12 mg twice daily.

Extended Release Capsule: 16 to 24 mg once daily.

Oral Solution: Initially 4 mg twice daily, Maximum 12 mg twice daily (24 mg/day) and in hepatic/renal impairment (max. dose:16 mg/day).

- Contraindications** Hypersensitivity to galantamine, severe kidney and liver problems, pregnancy (Appendix 7c), lactating mothers, children.
- Precautions** Patients with asthma or lung disease, epilepsy, stomach ulcer, take plenty of fluids during treatment.
- Adverse Effects** Diarrhoea, nausea, anorexia and weight loss, chest pain or shortness of breath.

## Memantine

### Pregnancy Category-B

- Indications** *Treatment of moderate to severe dementia of Alzheimer's disease.*
- Availability** **TABLETS** 5 and 10 mg; **CAPSULES** 10 mg; **ORAL SOLUTION** 2 mg/ml.
- Dose** 5 mg once daily; (max. dose upto 20 mg/day).
- Contraindications** Hypersensitivity to memantine.
- Precautions** Seizure, rise in urine pH results in increased plasma levels, pregnancy (Appendix 7c), lactation, children.
- Adverse Effects** Fatigue, pain, hypertension, dizziness, headache, constipation, vomiting, back pain, confusion, somnolence, hallucination, coughing, dyspnea, insomnia, urinary tract infections, anxiety, peripheral oedema, arthralgia.

## Rivastigmine

### Pregnancy Category-B

**Schedule H**

- Indications** *Moderate to severe dementia.*
- Availability** **TABLETS** 3 and 4.5 mg; **CAPSULES** 1.5, 3, 4.5 and 6.0 mg.  
**Transdermal patches** containing 9 mg in 5cm<sup>2</sup> and 18 mg in 10cm<sup>2</sup>.
- Dose** **Adult** - Initially 1.5 mg twice daily; (max. dose 6 mg twice daily).
- Contraindications** Hypersensitivity to carbamate derivatives and severe hepatic impairment, children, lactation.

**Precautions** Renal or hepatic impairment, acid peptic disease, pregnancy (Appendix 7c), asthma, sick-sinus syndrome.

**Adverse Effects** Mild peripheral cholinergic effect, nausea, vomiting, anorexia, dyspepsia, asthenia, abdominal pain, depression, gastrointestinal haemorrhage, weight loss, urinary tract infections, insomnia, hallucinations, hypertension, elevated LFTs.

Smaller patch associated with fewer adverse effects.

## Tacrine

**Pregnancy Category-C**

**Schedule H**

**Indications** *Mild to moderate Alzheimer's type dementia.*

**Availability** **CAPSULES** 10, 20, 30 and 40 mg.

**Dose** 10 mg, 4 times par day; (max. dose 40 mg 4 times par day).

**Contraindications** Hepatic impairment, hyperbilirubinaemia, bradycardia, bronchial asthma, seizures and gastro intestinal obstruction.

**Precautions** Haematological disorders, pregnancy (Appendix 7c), lactation.

**Adverse Effects** Hepatotoxicity, cholinergic side effects.

## 4.2 Anti-Parkinsonism Drugs

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The use of pharmacotherapy will depend upon the degree of incapacity of the patient and is generally not justified until symptoms compromise working ability and social relationships; although levodopa is used in the early stages in some patients. Close supervision is then needed to ensure that treatment regimens are tolerated and that appropriate changes are made to the regimen as the disease progresses.

The most effective form of therapy is a combination of **levodopa** and a peripheral dopa-decarboxylase inhibitor, such as **carbidopa**. The response to levodopa with carbidopa is a compromise between increased mobility and adverse effects. Dyskinesias may be dose limiting and increasingly frequent with increased duration of treatment. Many factors including tolerance and progression of the disease may result in complications after 2-5 years of treatment. 'End-of-dose' deterioration occurs when there is a reduced duration of benefit from a dose, resulting in disability and dystonias. The 'on-off' phenomenon is characterized by sudden swings from mobility to episodes of akinesia, tremor and rigidity lasting from a few minutes to several hours. Amelioration of these effects can sometimes be achieved by administering levodopa in a sustained-release preparation or in a greater number of fractionated doses throughout the day. Psychiatric symptoms inducing disruption of sleep, vivid dreams and hallucinations are characteristic adverse effects that may occur at any time, especially in the elderly and may require dose reduction or withdrawal of levodopa.

Treatment for idiopathic parkinsonism is often initiated with a dopamine receptor agonist such as bromocriptine. Supplementary use of amantadine, bromocriptine or the monoamine-oxidase-B inhibitor, selegiline can be of value either to enhance the effect of levodopa or to reduce 'end-of-dose' fluctuations and 'on-off' effects.

Anticholinergic (more correctly termed antimuscarinic) drugs such as **biperiden** are usually sufficient in drug-induced parkinsonism.

### Drugs Used in Essential Tremor and Related Disorders:

#### Essential Tremor:

It can be treated with  $\beta$ -blockers such as **propranolol** (120 mg daily) (chapter 13.4) which may be of value if the tremor results in physical or social disability.



## Dystonias:

If no identifiable cause is found and the patient does not go into spontaneous remission, a trial of **levodopa** should be given to determine whether the patient has dopamine-responsive dystonia. If there is no response within three months, the drug should be withdrawn and small doses of an anticholinergic drug such as biperiden should be given. The dosage may be increased gradually and up to 16 mg daily may be tolerated. In patients who fail to respond to either levodopa or an anticholinergic, other drugs including diazepam, baclofen, carbamazepine or phenothiazines may be of value. Psychological treatments have also been used successfully in the management of dyskinesias.

## Chorea:

Choreiform movements can be induced by certain drugs including levodopa, phenytoin and antipsychotic drugs. Huntington's disease is the most common of the hereditary choreas. Drug treatment is symptomatic and does not alter the progression of the disease. The aim of therapy is to reduce dopaminergic transmission which results from excessive or enhanced cholinergic activity. Antipsychotic drugs antagonize dopamine and usually lessen the chorea temporarily. Tetrabenazine, the dopamine-depleting drug, is used to control movement disorders in Huntington's chorea and related disorders.

## Tics:

Tics which resemble choreiform movements are commonly associated with anxiety. However, in the more complex multiple tic disorder, Tourette syndrome, treatment with antipsychotic drugs may be required.

## Tardive Dyskinesia:

It is associated with chronic administration of antipsychotic drugs. It is characterized by involuntary, repetitive, choreiform movement of the cheek, mouth and fingers. The first step of treatment should always be discontinuation of the antipsychotic drug or dosage reduction if the underlying psychotic disorder permits.

## Biperiden

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Medicine-induced extrapyramidal symptoms (but not tardive dyskinesias) and adjunctive treatment of parkinsonism.</i>
<b>Availability</b>	<b>TABLET</b> 2 mg; <b>INJECTION</b> 1 ml ampoule (5 mg/ml).
<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> Medicine-induced extra-pyramidal symptoms, parkinsonism: initially 1 mg twice daily, increased gradually to 2 mg thrice daily; usual maintenance dose 3 to 12 mg daily in divided doses.</p> <p><b>Intramuscular injection or Slow intravenous injection</b></p> <p><b>Adult-</b> Medicine-induced extra-pyramidal symptoms, parkinsonism: 2.5 to 5 mg repeated as necessary to max. 20 mg in 24 h.</p>
<b>Contraindications</b>	Angle-closure glaucoma; bowel obstruction; megacolon; untreated urinary retention; prostatic hypertrophy; myasthenia gravis; gastrointestinal obstruction.
<b>Precautions</b>	<p>Elderly; cardiovascular disease, hepatic or renal impairment; avoid abrupt withdrawal; paediatric use; pregnancy (Appendix 7c); lactation.</p> <p>May impair ability to perform skilled tasks, for example operating machinery, driving.</p>
<b>Adverse Effects</b>	Drowsiness, dry mouth, constipation, blurred vision; hesitancy of micturition, dizziness, tachycardia, arrhythmias; confusion, euphoria, excitement, agitation, hallucinations and psychiatric disturbances with high dosage, especially in the elderly and other susceptible patients, may require withdrawal of treatment; impaired memory, mild postural hypotension; urinary retention.
<b>Storage</b>	Store protected from light.

## Bromocriptine\*

Pregnancy Category-B

Schedule H

**Indications** *Parkinsonism.*

**Availability** TABLETS 1.25, 2.5 and 5 mg.

**Dose** *Oral*

**Adult-** First week 1 to 1.25 mg at night, second week 2 to 2.5 mg at night, third week 2.5 mg twice daily, fourth week 2.5 mg 3 times daily, then increasing by 2.5 mg every 3 to 14 days according to response to a usual range of 10 to 40 mg daily. Take with food.

**Child-** Under 15 years; not recommended.

**Contraindications** Hypersensitivity to bromocriptine or other ergot alkaloids; ischaemic heart disease; toxæmia of pregnancy and hypertension in postpartum women or in puerperium.

Should not be used postpartum or in puerperium in women with high blood pressure, coronary artery disease or symptoms (or history) of serious mental disorder; monitor blood pressure carefully (especially during first few days) in postpartum women. Very rarely, hypertension, myocardial infarction, seizures or stroke (both sometimes preceded by severe headache or visual disturbances) and mental disorders have been reported in postpartum women given bromocriptine for lactation suppression-caution with antihypertensive therapy and avoid other ergot alkaloids. Discontinue immediately if hypertension, unremitting headache or signs of CNS toxicity develop.

**Precautions** Specialist evaluation-monitor for pituitary enlargement, particularly during pregnancy, annual gynaecological assessment (post-menopausal, every 6 months), monitor for peptic ulceration in acromegalic patients; contraceptive advice if appropriate (oral contraceptives may increase prolactin concentration); avoid lactation for about 5 days if lactation prevention fails; history of serious mental disorders (especially psychotic disorders) or cardiovascular disease or Raynaud's syndrome; monitor for retroperitoneal fibrosis; porphyria; hepatic impairment; interactions (Appendix 6a, 6c, 6d).

Hypotensive reactions may be disturbing in some patients during the first few days of treatment and particular care should be exercised when driving or operating machinery; tolerance may be reduced by alcohol.

### Adverse Effects

Nausea, constipation, headache, drowsiness, nasal congestion; less commonly vomiting, postural hypotension, fatigue, dizziness, dyskinesia, dry mouth, leg cramps; also, particularly with high doses, confusion, psychomotor excitation, hallucinations; rarely, constrictive pericarditis, pericardial effusion, pleural effusion (may necessitate discontinuation), retroperitoneal fibrosis reported (monitoring required), hair loss and allergic skin reactions; very rarely, gastro-intestinal bleeding, gastric ulcer, vasospasm of fingers and toes particularly in patients with Raynaud's syndrome and effects like neuroleptic malignant syndrome on withdrawal, increased *libido* and hypersexuality also reported; conjunctival infection.

### Storage

Store protected from light.

## Levodopa + Carbidopa\*

### Pregnancy Category-C

**Schedule H**

### Indications

*All forms of parkinsonism other than medicine-induced.*

### Availability

**TABLETS** Levodopa 100 mg + Carbidopa 10 mg; Levodopa 100 mg + Carbidopa 25 mg; Levodopa 200 mg + Carbidopa 50 mg; Levodopa 250 mg + Carbidopa 25 mg.

### Dose

#### **Oral**

**Adult-** Parkinsonism: expressed in terms of levodopa, initially 100 mg (with carbidopa 10 mg) twice daily, increased by 100 mg (with carbidopa 10 mg) every few days as necessary, to a max. of 1.5g.

Optimum daily dose must be determined for each patient by careful monitoring and be taken after meals.

### Contraindications

Concurrent use of monoamine oxidase inhibitors; undiagnosed chin lesion; lactation; psychosis; decompensated endocrine; angle-closure glaucoma; confirmed or suspected malignant melanoma.

**Precautions** Pulmonary disease, peptic ulceration, cardiovascular disease (including previous myocardial infarction); diabetes mellitus, osteomalacia, open-angle glaucoma, history of melanoma (risk of activation), psychiatric illness (avoid if severe); close monitoring of hepatic, haematological, psychiatric, cardiovascular and renal function required in long-term therapy; elderly: avoid rapid dose increases; warn patients to resume normal activities gradually; avoid abrupt withdrawal; pregnancy (toxicity in animals) (Appendix 7c), lactation; interactions (Appendix 6c).

**Adverse Effects** Nausea, anorexia and vomiting, particularly at the start of treatment; postural hypotension at the start of treatment, particularly in elderly and those receiving antihypertensives; excessive drowsiness and sudden onset of sleep (warn patient of these effects); confusion, vivid dreams, dizziness, tachycardia, arrhythmias; reddish discolouration of body fluids; insomnia, headache, flushing, gastrointestinal bleeding, peripheral neuropathy; taste disturbances, pruritus, rash, liver enzyme changes; psychiatric symptoms including psychosis, depression, hallucinations, delusions and neurological disturbances including dyskinesias may be dose-limiting; painful dystonic spasms ('end-of-dose' effects) and ('on-off' effects) after prolonged treatment (see notes above); neuroleptic malignant syndrome, on sudden withdrawal; rarely, hypersensitivity, dyspnoea; upper respiratory infection.

**Storage** Store protected from light and moisture.

## Trihexyphenidyl (Benzhexol)\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *All forms of parkinsonism other than medicine-induced, control of extrapyramidal disorders caused by CNS drugs.*

**Availability** **TABLETS** 2 and 5 mg; **INJECTION** vial 2 mg/ml.

**Dose** 1 mg daily, increased gradually; usual maintenance dose 5 to 15 mg daily in 3 to 4 divided doses (max. 20 mg daily); elderly preferably lower end of range.

- Contraindications**      Avoided in gastro-intestinal obstruction and myasthenia gravis; closed angle glaucoma; chronic pulmonary disease; sick sinus syndrome; thyrotoxicosis; tachycardia.
- Precautions**              Use with caution in cardiovascular disease, hypertension, psychotic disorders, prostatic hypertrophy, pyrexia, in those susceptible to angle-closure glaucoma and in the elderly. It should not be withdrawn abruptly in patients receiving long-term treatment. Antimuscarinics are liable to abuse. Elderly males with possible prostate hypertrophy; tardive dyskinesia; neuroleptic malignant syndrome. Use with caution in renal impairment and hepatic impairment, lactation and interactions (Appendix 6a).
- Adverse Effects**          Constipation, dry mouth, nausea, vomiting, tachycardia, dizziness, confusion, euphoria, hallucinations, impaired memory, anxiety, restlessness, urinary retention, blurred vision and rash. Angle-closure glaucoma may occur very rarely, paralytic ileus; dilation of colon.

## **5. Anticonvulsants/Antiepileptics 51**

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## 5. Anticonvulsants/ Antiepileptics

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### Control of Epilepsy:

Treatment of seizures should always be started with a single antiepileptic drug (AED), and the choice of an anticonvulsant should be made on an individual basis. The drug of choice will depend on the primary diagnosis, seizure type, efficacy of the drug and the patient's tolerance of treatment. **If a drug fails to control the seizures after it has been used in full therapeutic dosage for an adequate period, or if it is not tolerated, it should be gradually substituted with another drug, with the first drug being withdrawn only when the new regimen is established. If monotherapy is ineffective, next alternative drug should be started, and try to withdraw first drug if there was no response for that drug or continue with that if there was partial response for initial drug.**

Initial dose of the drug of choice should be determined on the basis of the degree of urgency, the size and age of the patient. It should be increased gradually until an effective response is obtained. All antiepileptics commonly produce neurological adverse effects at higher dose ranges and patients should be monitored closely for adverse effects to help in accurate dose titration. Except for phenytoin, it is rarely, useful to measure plasma-drug concentrations as an aid to dose adjustment. Non-compliance, inappropriate dosing and overdosing is a major impediment to effective antiepileptic treatment. Patients should ideally remain under supervision throughout treatment period.

### Withdrawal:

**Treatment is normally continued for a minimum of two years of seizure free period.** In certain circumstances like in juvenile myoclonic epilepsy, antiepileptic drugs may need to be continued throughout life, because of the high relapse rate of seizure after AED withdrawal. Withdrawal should be extended over a period of several months because abrupt withdrawal can lead to recurrence of seizure and or/status epilepticus. A general rule for duration of tapering is how many years patient had taken that particular drug, over a period of so many months it should be tapered. In patients receiving several antiepileptic drugs, only one drug should be withdrawn at a time. Many adult patients relapse once treatment is withdrawn and it may be justified to continue



treatment indefinitely, particularly when the patient's livelihood or lifestyle can be endangered by recurrence of a seizure.

### **Pregnancy and Lactation:**

Untreated epilepsy during pregnancy may cause harm to the fetus; there is therefore no justification for abrupt withdrawal of treatment although withdrawal of therapy may be an option if the patient has been seizure-free for at least 2 years; resumption of treatment may be considered after the first trimester. If antiepileptics are continued in pregnancy, monotherapy with the lowest effective dose is preferred, with adjustment made to take account of changes in plasma levels associated with pregnancy. There is an increased risk of birth defects with the use of anticonvulsants, particularly carbamazepine, valproate and phenytoin. However, if there is good seizure control, there is probably no advantage in changing pregnant patients' antiepileptic drugs. In view of the risks of neural tube and other defects, patients who may become pregnant should be informed of the risks and referred for advice and pregnant patients should be offered counselling and antenatal screening. To counteract the risk of neural tube defects, adequate folate supplements are advised for women before and during pregnancy. In view of the risk of neonatal bleeding associated with carbamazepine, phenobarbital and phenytoin, prophylactic phytomenadione (vitamin K1 ) is recommended for the neonate and the mother before delivery. Antiepileptic drugs can be continued during lactation (see also Appendix 7b).

### **Driving:**

Regulations are in place in many countries which may, for example, restrict driving by patients with epilepsy to those whose seizures are controlled. Further, antiepileptic drugs may cause CNS depression, particularly in the early stages of treatment and patients affected by adverse effects such as drowsiness or dizziness should not operate machinery or drive.

## **Choice of Antiepileptic in Management of Convulsive Disorders**

### **Generalized Tonic-Clonic Seizures:**

Phenobarbital, phenytoin and valproate are widely used in the treatment of these conditions. However, each of these drugs is associated with dose-related and idiosyncratic adverse effects and monitoring of haematological and hepatic function is routinely not advised.

## **Simple Partial and Complex Partial Seizures:**

Carbamazepine, oxcarbamazepine, clobazam, lamotrigine and zonisamide are effective in partial epilepsy.

## **Absence Seizures:**

Both ethosuximide and valproate are recommended in the treatment of absence seizures (petit mal) and are usually well tolerated. However, ethosuximide can, rarely, cause lupus erythematosus and psychoses which call for immediate, but cautious, discontinuation. Absence seizures are commonly associated with tonic-clonic seizures and valproate is preferred since it has a broad spectrum of activity.

## **Tonic Seizures, Atonic Seizures and Atypical Absence Seizures:**

Phenobarbital or phenytoin is widely used for tonic seizures, valproate or clonazepam for atonic seizures and clonazepam for atypical absence seizures. However, tonic seizures most of the times are associated with multiple seizures types like Lennox-Gastaut syndrome (LGS), where phenytoin and phenobarbitone should be avoided as they can precipitate other type of seizures.

## **Myoclonic Seizures:**

Valproate is widely used and most effective for juvenile myoclonic seizures. As juvenile myoclonic epilepsy is associated with a high relapse rate, it is often necessary to continue therapy indefinitely. Other myoclonic seizures are often resistant to treatment and some do not have an epileptic basis. Valproate or clonazepam can be of value in this case and other antiepileptic drugs may be useful in intractable cases. Both drugs are generally well accepted, although tolerance to clonazepam has been reported.

## **Infantile Spasm (Infantile Myoclonic Epilepsy):**

Infantile spasms, which are often associated with severe brain damage, can be resistant to antiepileptic drugs. Drugs effective in this type of seizures are benzodiazepines (nitrazepam, clonazepam, clobazam), valproic acid, ACTH, vigabatrin, levetiracetam, topiramate, zonisamide, lamotrigine, and ketogenic diet.

## **Febrile Convulsions:**

Sponging with tepid water and antipyretic such as paracetamol is effective in controlling the temperature. Recurrent febrile convulsions or prolonged convulsions (those lasting >5 min) are treated with diazepam, either rectally in solution or

by intravenous injection, or intranasal or buccal midazolam, to prevent possible brain damage.

Intermittent prophylaxis, with diazepam (or clobazam) administered at the onset of fever, may prevent recurrence of febrile convulsions. Use of antiepileptics for *continuous prophylaxis* is controversial; it is probably indicated in only a small proportion of children including those who already have evident neurological abnormalities, or who have had previous prolonged or focal convulsions. Phenobarbital may be used for this purpose but careful clinical monitoring and dosage adjustment are necessary in order to minimize the risk of adverse effects. Valproate can also be used.

### Status Epilepticus:

Status epilepticus is a medical emergency which carries a high mortality rate. Initial management includes positioning the patient to avoid injury, supporting respiration including provision of oxygen, maintaining blood pressure and the correction of any hypoglycaemia; hypocalcaemia or any other electrolyte disturbance; maintenance of the airway and assisted ventilation are crucial even when the seizures are controlled, because the drugs used in its management may cause respiratory depression.

Intravenous lorazepam, midazolam are often effective in status epilepticus. Lorazepam, which acts rapidly, should be administered first and should be followed immediately by a loading dose of phenytoin which has a longer-acting effect. When cannulation is difficult or impossible, diazepam may be administered rectally as a solution (absorption from suppositories is too slow for treatment of status epilepticus). Intravenous phenobarbital is also effective but is more likely to cause respiratory depression; it is used in refractory cases but should be avoided in patients who have recently received oral phenobarbital. Rectal paraldehyde may also be used; it causes little respiratory depression and is therefore useful where facilities for resuscitation are poor.

If seizures continue despite treatment, intravenous valproate, levetiracetam, midazolam infusion, propofol infusion, barbiturate coma and general anaesthesia may be required. The underlying cause must be identified and remedied in all cases.

**Carbamazepine\*** (Refer Page No. 585)**Pregnancy Category-D****Schedule H**

**Indications** *Partial seizures with or without secondary generalisation; trigeminal neuralgia; bipolar disorder.*

**Availability** **TABLETS** 100, 200 and 400 mg Plain; 100 mg DT; 200, 300 and 400 mg CR and SR; **SYRUP** 100 ml (100 mg/5 ml).

**Dose** **Oral**

**Adult-** Initially 100 and 200 mg 1 to 2 times daily increased slowly to usual dose of 400 mg to 1.2g daily in divided doses. In some cases 1.6 to 2g may be needed. Administer lower initial dose to elderly.

**Child-** Start with 5 - 10 mg/kg/day in two to three divided doses then gradually increase at weekly intervals to a max. dose of 30-35 mg/kg/day.

**Contraindications** Atrioventricular conduction abnormalities; history of bone-marrow depression; porphyria.

**Precautions** Hepatic impairment (Appendix 7a); renal impairment; cardiac disease (see also Contraindications); skin reactions (see Adverse effects); history of blood disorders (blood counts before and during treatment); glaucoma; lactation (Appendix 7b); avoid sudden withdrawal; interactions (Appendix 6b, 6c, 6d); pregnancy (Appendix 7c).

Patients or their caretakers should be told how to recognize signs of blood, liver or skin disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising or bleeding develop. Leukopenia which is severe, progressive and associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative).

May impair ability to perform skilled tasks, for example operating machinery, driving; see also notes above.

**Adverse Effects** Dizziness, drowsiness, headache, ataxia, blurred vision, diplopia (may be associated with high plasma levels); gastrointestinal intolerance including nausea and vomiting, anorexia, abdominal pain, dry mouth, diarrhoea or constipation; commonly, mild transient generalized erythematous rash (withdraw if worsens or is accompanied by other symptoms); leukopenia and other blood disorders (including thrombocytopenia, agranulocytosis and aplastic anaemia); cholestatic jaundice, hepatitis, acute renal failure, Stevens-Johnson syndrome (erythema multiforme), toxic epidermal necrolysis, alopecia, thromboembolism, arthralgia, fever, proteinuria, lymph node enlargement, arrhythmias, heart block and heart failure, dyskinesia, paraesthesia, depression, impotence, male infertility, gynaecomastia, galactorrhoea, aggression, activation of psychosis, photosensitivity, pulmonary hypersensitivity, hyponatraemia, oedema, disturbances of bone metabolism with osteomalacia also reported; confusion and agitation in elderly.

**Storage** Store protected from light and moisture.

## Clobazam

**Pregnancy Category-D**

**Schedule H**

**Indications** *Add-on for refractory partial, complex and generalized seizures, add-on in West syndrome, LGS, myoclonic epilepsy, absence seizures, to cover short period of increased seizure susceptibility addition of new AED examinations overnight travel catamenial epilepsy, intermittent prophylaxis in febrile seizures.*

**Availability** TABLETS 5, 10 and 20 mg.

**Dose** Oral

0.3-2.9 mg/kg/day, (average 1 mg/kg/day) single at bed time or twice daily dose.

**Precautions** Pregnancy (Appendix 7c), interactions (Appendix 6c).

**Adverse Effects** Sedation, dizziness, hyperactivity, behavioural problem, irritability, drooling, weight gain, sleep disturbance, blurring, diplopia.

## Clonazepam

Pregnancy Category-D

Schedule H

**Indications** *Absence seizures, myoclonic seizures, akinetic seizures, panic disorder, subcortical myoclonus, adjuvant treatment of refractory epilepsy.*

**Availability** TABLETS 0.25, 0.5, 1 and 2 mg.

**Dose** **Adult-** 0.5 - 5 mg thrice daily, initial dose should not exceed 1.5 mg/day, slow titration is recommended Maintenance dose 4-8 mg daily, Maximum dose 20 mg daily.

**Infants and child:** Initial dose 0.01-0.03 mg/kg/day (not to exceed 0.05 mg/kg/day) given in 2-3 divided doses. Maintenance dose 0.1-0.2 mg/kg/day in 3 divided doses.

**Panic disorder: Adult-** Initial dose 0.25 mg twice daily, usual maintenance dose 1 mg/day, maximum dose 4 mg/day.

**Contraindications** Hypersensitivity to benzodiazepines, acute pulmonary insufficiency, acute narrow angle glaucoma.

**Precautions** Neonates, chronic pulmonary insufficiency, hepatic and renal dysfunction, porphyria, elderly, pregnancy (Appendix 7c), lactation (Appendix 7b), interactions (Appendix 6a, 6c); avoid sudden withdrawal.

**Adverse Effects** Sedation, dullness, CNS depression, ataxia, bronchial hypersecretion, abnormal eye movement, blood dyscrasias.

## Diazepam\* (Refer Page No. 420 and 567)

Pregnancy Category-D

Schedule H

**Indications** *Status epilepticus; emergency management of recurrent seizures; febrile convulsions; seizures associated with poisoning and medicine withdrawal; adjunct in acute alcohol withdrawal; premedication; anxiety disorders; psychosomatic behaviour disorder; spasticity.*

**Availability** TABLETS 2, 5 and 10 mg; CAPSULE 10 mg; SUSPENSION 2 mg/ml; INJECTION 2 ml ampoule (5 mg/ml).

**Dose** *Intravenous injection*

**Adult**-Treatment of status epilepticus and convulsions due to poisoning: 10 mg at the rate of 1 ml/min (5 mg) repeated if necessary after 10 min.

**Child**-Under 12 years: 300 to 400 µg/kg, repeated after 10 min if necessary.

**Contraindications** Respiratory depression; acute pulmonary insufficiency; sleep apnoea; severe hepatic impairment; myasthenia gravis; avoid injections containing benzyl alcohol in neonates, narrow angle glaucoma; hypersensitivity to benzodiazepine.

**Precautions** Respiratory disease, muscle weakness, history of alcohol or drug abuse, marked personality disorder; pregnancy (Appendix 7c); lactation (Appendix 7b); reduce dose in elderly or debilitated patients and in hepatic impairment (avoid if severe, Appendix 7a), renal impairment; avoid prolonged use and abrupt withdrawal; when given intravenously, facilities for reversing respiratory depression with mechanical ventilation must be at hand (see below); porphyria; interactions (Appendix 6a, 6c); blood count test on prolonged treatment.

Intravenous infusion of diazepam is potentially hazardous (especially if prolonged) calling for close and constant observation and best carried out in a speciality centre with intensive care facilities. Prolonged intravenous infusion may lead to accumulation and delay recovery.

May impair ability to perform skilled tasks, for example operating machinery, driving; see also notes above.

**Adverse Effects** Drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia; dependence; paradoxical increase in aggression; muscle weakness; occasionally headache, vertigo, salivation changes, gastrointestinal disturbances, skin reactions, visual disturbances, dysarthria, tremors, incontinence, urinary retention; blood disorders and jaundice; hypotension and apnoea, pain and thrombophlebitis (with injection); increased appetite; weight gain.

**Storage** Store protected from light.

## Fosphenytoin

Pregnancy Category-D

Schedule H

- Indications** *Generalized tonic-clonic status epilepticus.*
- Availability** **INJECTION** 2 ml vial (75 mg/ml).
- Dose** **Adult-** 15 mg/kg i.v. infusion at the rate of 100-150 mg/min.
- Contraindications** Porphyria.
- Precautions** Uremia, hypoalbuminemia, interactions (Appendix 6b, 6c); pregnancy (Appendix 7c).
- Adverse Effects** Cardiovascular collapse and/or central nervous system depression, nystagmus, dizziness, pruritus, paresthesia, headache, somnolence, ataxia, hypotension.

## Gabapentin

Pregnancy Category-C

Schedule H

- Indications** *Add-on drug in resistant partial seizures with or without secondary generalization, rolandic epilepsy- preferred for safety reason, first line in epilepsy patients with hepatic disease.*
- Availability** **TABLETS/CAPSULES** 100 and 300 mg.
- Dose** **Oral**  
Initially 10 mg/kg/day, increase 10 mg/kg/day to maintenance dose 30-100 mg/kg/day, in three divided doses.
- Contraindications** Pregnancy (Appendix 7c)
- Adverse Effects** Somnolence, dizziness, fatigue, nystagmus, behavioral changes (<10%)-aggression, hyperexcitability, tantrum, euphoria, weight gain.

## Lamotrigine

Pregnancy Category-C

Schedule H

- Indications** *Partial seizures and secondary generalised tonic-clonic seizures.*



**Availability** TABLETS 25, 50 and 100 mg Plain; 5, 150 and 200 mg DT.

**Dose** *Oral*

**Adult and Child over 12 years-** 25 mg once daily for 2 weeks followed by 50 mg once daily for 2 weeks, increase by 50 to 100 mg every 1 to 2 weeks to maintenance dose of 100 to 200 mg daily.

**Child-** Monotherapy- Initial dose 2 mg/kg/day for 2 weeks then 5 mg/kg/day for 2 weeks. max. dose 5 - 15 mg/kg/day once or twice daily.

With valproic acid- Initial dose - 0.5 mg/kg/day to max. dose of 1 - 5 mg/kg/day in single dose.

With enzyme inducer- 2 mg/kg/day for 2 weeks than 5 mg/kg/day for 2 weeks. Max. 5 - 15 mg/kg/day once or twice daily, when valproic acid added to already regimen with lamotrigine, reduce dose of lamotrigine by 25 - 50%.

**Contraindications** **Child** less than 12 years; hypersensitivity; severe hepatic and renal impairment.

**Precautions** Monitoring of liver and renal function; abrupt withdrawal to be avoided; pregnancy (Appendix 7c) and lactation; avoid in patients who need to undertake task requiring mental alertness; patients taking sodium valproate.

**Adverse Effects** Skin eruptions; nausea; vomiting; headache; toxic epidermal necrosis; hepatotoxicity; leucopenia; thrombocytopenia; confusion; hallucination.

## Levetiracetam

**Pregnancy Category-C**

**Schedule H**

**Indications** *Good effect difficult-to-treat idiopathic focal epilepsies of childhood, including variations such as continuous spike and wave during sleep or Landau-Kleffner syndrome (LKS), photosensitivity and myoclonus- Generalised epilepsy with photosensitivity, idiopathic epilepsy- control of GTCS and Myoclonic, treatment of postanoxic and post-encephalitic myoclonic epilepsy, epileptic encephalopathies- LGS, West Syndrome, severe myoclonic epilepsy, absence seizure, rolandic epilepsy.*

**Availability** TABLETS 250, 500 and 750 mg, SYRUP 100 mg/ml, INJECTION 5 ml ampoule (100 mg/ml).

**Dose** *Oral*

Initial dose- 10-20 mg/kg/day, increase by 10 mg/kg/day every 1-2 week upto 40-60 mg/kg/day in two divided doses.

***Intravenous injection***

20-30 mg/kg at the rate of 5 mg/kg/min.

- Contraindications** Hypersensitivity.
- Precautions** Renal disease; pregnancy (Appendix 7c).
- Adverse Effects** Most frequent somnolence, asthenia (dose dependent); headache, hair loss, vertigo, nausea, infection; behavioral changes such as hostility aggression, apathy, anxiety, depression, psychosis.

## Magnesium Sulphate

**Pregnancy Category-A**

- Indications** *Prevention of recurrent seizures in eclampsia; prevention of seizures in pre-eclampsia; acute nephritis in children.*
- Availability** **INJECTION** 500 mg/ml.
- Dose** ***Intravenous injection (concentration of magnesium sulphate should not exceed 20%)***
- Prevention of seizure occurrence in eclampsia: initially 4g over 5 to 15 min, followed by infusion 1g/hr for at least 24 h after last seizure. If seizures recur, additional dose of 2g (or 4g if body weight is over 70 kg).
- Contraindications** Not to be injected parenterally in patients with heart block or myocardial damage.
- Precautions** Hepatic impairment (Appendix 7a); pregnancy (Appendix 7c); renal impairment; in severe hypomagnesaemia administer initially via controlled infusion device (preferably syringe pump); monitor blood pressure, respiratory rate, urinary output and for signs of overdosage (loss of patellar reflexes, weakness, nausea, sensation of warmth, flushing, drowsiness, double vision and slurred speech).
- Adverse Effects** Generally associated with hypermagnesaemia, nausea, vomiting, thirst, flushing of skin, hypotension, arrhythmias, coma, respiratory depression, drowsiness and confusion, loss of tendon reflexes, muscle weakness; colic and diarrhoea following oral administration; hypothermia; stupor.

**Storage** Store protected from moisture.

## Oxcarbamazepine

**Pregnancy Category-C**

**Schedule H**

**Indications** *Monotherapy or adjunctive therapy in the treatment of partial seizures, secondary generalized seizure, substitution for carbamazepine can be made abruptly with an oxcarbamazepine-to-carbamazepine ratio of 300:200.*

**Availability** **TABLETS** 150, 300, 450, 500 and 600 mg; **SUSPENSIONS** 300 mg/5 ml.

**Dose** Initial dose: 8-10 mg/kg/day, increasing by 8-10 mg/kg/day as tolerated at 3-7 day interval. Given in two divided doses. Maximum- 30 mg/kg.

**Precautions** Pregnancy (Appendix 7c); interactions (Appendix 6c).

**Adverse Effects** Less frequently than they do with carbamazepine (2.8% vs 6.5%), hyponatremia is more common but not clinically significant, rash, weight gain, alopecia, nausea, headache, somnolence.

## Phenobarbitone\*

**Pregnancy Category-D**

**Schedule H**

**Indications** *Generalized tonic-clonic seizures; partial seizures; neonatal seizures; febrile convulsions; status epilepticus; sedative, hypnotic, pre-anaesthetic.*

**Availability** **TABLETS** 30 and 60 mg; **INJECTION** 1 ml ampoule (200 mg/ml); **SYRUP** 20 mg/ml.

**Dose** *Slow intravenous injection*

**Status epilepticus:** (dilute injection 1 in 10 with water for injections), **Adult-** 10 mg/kg at a rate of not more than 100 mg/min (up to max. total dose of 1 g); **Child-** 10-20 mg/kg at a rate of not more than 30 mg/min.

**Oral**

**Adult-** 60-180 mg daily at night.

**Child-** 1 month-12 years: 1-1.5 mg/kg twice daily, maintenance dose 2.5-4 mg/kg once/twice daily. 12-18 years: Initially 60-180 mg twice daily, maintenance dose 60-180 mg once daily.

**Contraindications** Absence seizures; latent porphyria.

**Precautions** Elderly, debilitated, children (may cause behavioural changes); impaired renal function or hepatic function (Appendix 7a), respiratory depression (avoid if severe); pregnancy (see notes above; Appendix 7c); lactation (Appendix 7b); avoid sudden withdrawal; interactions (Appendix 6a, 6b, 6c); habit forming.

**Adverse Effects** Sedation, mental depression, agitation, hallucination, syncope; ataxia, nystagmus; allergic skin reactions including rarely, exfoliative dermatitis, toxic epidermal necrolysis, Steven's-Johnson syndrome (erythema multiforme); paradoxical excitement, restlessness and confusion in the elderly; irritability and hyperactivity in children; megaloblastic anaemia (may be treated with folic acid); osteomalacia; status epilepticus (on treatment withdrawal); hypotension, bradycardia, shock; laryngospasm and apnoea (with intravenous injection); cognitive impairment; aplastic anaemia; hepatic failure; connective tissue disorder; hyperkinesias.

**Storage** Store protected from moisture.

## Phenytoin\*

**Pregnancy Category-D**

**Schedule H**

**Indications** *Generalized tonic-clonic seizures; partial seizures; status epilepticus.*

**Availability** **TABLETS** 100, 150 and 200 mg Plain; 300 mg SR; **CAPSULES** 25 mg, 100 mg; **INJECTION** 2 ml ampoule (50 mg/ml); **SUSPENSION** 25 mg/ml.

**Dose** **Oral or slow intravenous injection or infusion**

**Adult- Status epilepticus:** (with regular BP and ECG monitoring) 18 mg/kg at rate not exceeding 50 mg/min as loading dose, maintenance dose of about 100 mg should be given thereafter at an interval of 6 to 8 h (dose can be reduced according to weight).

**Child- Status epilepticus:** 20 mg/kg at a rate not exceeding 1 mg/kg/min, maintenance dose 4-7 mg/kg/day in 2 divided doses, max dose 300 mg/day.

**Contraindications** Porphyrria; avoid parenteral use in sinus bradycardia, sino-atrial block, second- and third-degree heart block, Stokes-Adams syndrome; pregnancy (Appendix 7c).

**Precautions** Hepatic impairment (reduce dose; Appendix 7a); lactation (Appendix 7b); diabetes mellitus; monitor blood counts; hypotension and heart failure (caution with parenteral use); intravenous administration-resuscitation facilities must be available; injection solution alkaline (irritant to tissues); interactions (Appendix 6a, 6b, 6c); hypersensitivity; osteomalacia, it worsens myoclonus and absence seizures.

Patients or their caretakers should be told how to recognize signs of blood or skin disorders and advised to seek immediate medical attention if symptoms such as sore throat, rash, mouth ulcers, bruising or bleeding develop. Leukopenia which is severe, progressive or associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative).

May impair ability to perform skilled tasks, for example operating machinery, driving; see notes above.

**Adverse Effects** Gastric intolerance, headache, sleeplessness, agitation (during initial phase); sedation, hallucinations, confusion; blurred vision, ataxia, nystagmus, diplopia; slurred speech, cerebellar-vestibular symptoms, behavioural disorders, hyperglycaemia (may be signs of overdosage); gingival hyperplasia, acne, coarse facies, hirsutism, fever; neurological changes (peripheral neuropathy, choreiform movements, impaired cognition, increased seizure frequency); osteomalacia, rickets (associated with reduced plasma calcium levels); lymph-node enlargement; rashes (discontinue; if mild re-introduce cautiously, but discontinue if recurrence); very rarely, Stevens-Johnson syndrome (erythema multiforme), systemic lupus erythematosus, toxic epidermal necrolysis; rarely, blood disorders including megaloblastic anaemia (may be treated with folic acid), leukopenia, thrombocytopenia, agranulocytosis with or without bone marrow depression; intravenous administration-cardiovascular and CNS depression (particularly if administered too rapidly) with arrhythmias, hypotension and cardiovascular collapse, alterations in respiratory function (including respiratory collapse); dyskinesia; hepatitis, hepatic failure.

**Storage** Store protected from moisture at temperature not exceeding 30°C.

## Sodium Valproate\*

Pregnancy Category-D

**Schedule H**

<b>Indications</b>	<i>Generalized tonic-clonic seizures; partial seizures; atonic seizures; absence seizures; myoclonic seizures; acute mania; migraine.</i>
<b>Availability</b>	<b>TABLETS</b> 125, 200, 250, 300 and 500 mg Plain; 200, 300 and 500 mg CR; <b>SYRUP</b> 200 mg/5 ml; <b>INJECTION</b> 100 mg/vial, 5 ml ampoule (100 mg/5 ml) CR.
<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> 600 mg daily in two divided doses (preferably after food) thereafter increase by 200 mg at 3 days interval clinical response till desired.</p> <p><b>Child-</b> Initial dose 20 mg/kg/day, max. dose 60 mg/kg/day.</p>
<b>Contraindications</b>	Active liver disease, family history of severe hepatic dysfunction; pancreatitis; porphyria; hypersensitivity.
<b>Precautions</b>	Monitor liver function before and during first 6 months of therapy (Appendix 7a), especially in patients at most risk (children under 3 years of age, those with metabolic disorders, degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation, or multiple antiepileptic therapy); ensure no undue potential for bleeding before starting and before major surgery or anticoagulant therapy; renal impairment; pregnancy {important see notes above, (neural tube screening)} (Appendix 7c); lactation (see notes above; Appendix 7b); systemic lupus erythematosus; false-positive urine tests for ketones; avoid sudden withdrawal; interactions (Appendix 6a, 6c, 6d); hyperammonemia.

**Adverse Effects** Gastrointestinal irritation, nausea, increased appetite and weight gain, hyperammonaemia; ataxia, tremor; transient hair loss (regrowth may be curly); oedema, thrombocytopenia, inhibition of platelet aggregation; impaired hepatic function and rarely, fatal hepatic failure (see Precautions-withdraw treatment immediately if malaise, weakness, lethargy, oedema, abdominal pain, vomiting, anorexia, jaundice, drowsiness or loss of seizure control); sedation reported and also increased alertness; behavioural disturbances; rarely, pancreatitis (measure plasma amylase if acute abdominal pain), extrapyramidal symptoms, leukopenia, pancytopenia, red cell hypoplasia, fibrinogen reduction; irregular periods, amenorrhoea, gynaecomastia, hearing loss, Fanconi syndrome, dementia, toxic epidermal necrolysis, Steven's-Johnson syndrome (erythema multiforme), vasculitis, hirsutism and acne reported; hallucinations; abnormal gut; pneumonia; headache; taste perversion; polycystic ovary.

**Storage** Store protected from light.

## Topiramate

**Pregnancy Category-C**

**Schedule H**

**Indications** *Resistant partial seizures, LGS- I.S, Generalized Tonic-Clonic Seizures (GTCS), severe myoclonic epilepsy of infancy.*

**Availability** TABLETS 25, 50, 100 and 200 mg.

**Dose** **Oral**

Initial dose: 0.5 - 1 mg/kg/day (two divided doses) increase by 0.5 - 1 mg/kg/day at 1 to 2 week intervals, maintenance dose usually 5 - 9 mg/kg/day, max.-24 mg/kg/day.

**For prophylaxis of migraine headache:** 100 mg/day.

**Precautions** Pregnancy (Appendix 7c); interactions (Appendix 6a, 6c).

**Adverse Effects** Anorexia, weight loss, cognitive slowing and behavior changes, difficulty with memory, somnolence, dizziness, ataxia, fatigue, kidney stones (1.5%) 2-4 times higher than general population, paresthesias, liver functions- in 1% transient and mild enzymes, metabolic acidosis, Ac. myopia and sec, angle glaucoma- mostly at start, oligohydrosis, hyperthermia and sec rash, hyperammonemia and encephalopathy with concomitant valproic acid use, behavioral reactions (26%), Most frequent such as aggressiveness, hyperactivity, excitement, anxiety, obsessive behaviour, cognitive delay of various degree more in children than adults because of preexisting behavioral problems in children with drug resistant epilepsy.

## Vigabatrin

**Pregnancy Category-C**

**Indications** *Infantile spasms, refractory partial seizures with or without secondary generalization.*

**Availability** **CAPSULES** 500 mg.

**Dose** **Initial dose-** 40 mg/kg/day in two divided doses, increase to 80-100 mg/kg/day.  
**In infantile spasms-** Initial dose 40-50 mg/kg/day increase by 50 mg/kg/day till spasm control or to 150-200 mg/kg/day.

**Precautions** Pregnancy (Appendix 7c).

**Adverse effects** Psychosis (5%), behavioral problems, hyperactivity (most common cause for discontinuation), confusion, fatigue, insomnia, ataxia, drowsiness, weight gain, facial oedema, GIT upset (dose related), no effect on cognition. Chronic toxicity-most serious: persistent ncentric visual field defects in 1/3<sup>rd</sup> cases (rarely, reversible with early withdrawal), many patients are asymptomatic.

## Zonisamide

**Pregnancy Category-C**

**Schedule H**

**Indications** *Add-on in partial seizures, primary generalized tonic clonic seizures, myoclonic epilepsy, absence seizures, LGS, infantile spasms.*

**Availability** **CAPSULES** 25, 50 and 100 mg; **TABLET** 100 mg.

**Dose** **Oral**



**Child-** Initial dose - 2-4 mg/kg/day divided twice daily, with increments at 2- week intervals to 6-8 mg/kg/day and a possible maximum of 12 mg/kg/day.

**Precautions**

Pregnancy (Appendix 7c).

**Adverse Effects**

Drowsiness, anorexia, ataxia, fatigue (dose related), photosensitivity; cognitive effects-reversible psychotic effects, behavioral abnormalities, abnormal thinking, irritability (Do slow titration); weight loss, renal stones (mostly small); idiosyncratic-in 1.4% skin rash (including SJS, TEN), blood dyscrasias, hepatic failure; oligohidrosis and hyperthermia (more in children).



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## 6. Antidiarrhoeals and Laxatives

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Acute diarrhoeal diseases are a leading cause of childhood morbidity and mortality; frail and elderly patients are also at risk. In adults acute diarrhoea is the most frequent health problem of travellers and is increasingly common among HIV-infected persons. Assessment and correction of dehydration and electrolyte disturbance is the priority in all cases of acute diarrhoea. Symptomatic relief in adults may be warranted in some cases but antidiarrhoeals should never be used in children since they do not reduce fluid and electrolyte loss and may cause adverse effects.

Diarrhoea persisting for longer than a month is known as chronic diarrhoea. A mild malabsorption syndrome, tropical enteropathy, is apparent in most healthy indigenous populations of tropical countries. However the majority of cases of chronic diarrhoea have non-infectious causes including gluten-sensitivity, inherited metabolic disorders or inflammatory bowel disease.

Bloody diarrhoea is usually a sign of invasive enteric infection and should be treated with an appropriate anti-infective agent.

## 6.1 Antidiarrhoeal Symptomatic Drugs in Adult

### Codeine\* (Refer Page No. 10)

Pregnancy Category-C

Schedule H

**Indications** *Short-term symptomatic relief of acute diarrhoea in adult; pain.*

**Availability** **TABLET** 30 mg.

**Dose** **Oral**

**Adult-** Symptomatic relief of acute diarrhoea: 30 mg 3 to 4 times daily.

**Child-** (1-12 years) 500 µg/kg 4-6 times daily.

**Contraindications** Conditions where inhibition of peristalsis should be avoided; abdominal distension; acute diarrhoeal conditions such as ulcerative colitis or antibiotic-associated colitis; acute respiratory depression.

**Precautions** Tolerance or dependence may occur with prolonged use; elderly and debilitated patients; hepatic impairment (Appendix 7a); renal impairment; lactation; overdose: see chapter 7.2; interactions (Appendix 6c); pregnancy (Appendix 7c).

**Adverse Effects** Nausea, vomiting, constipation, drowsiness; respiratory depression and hypotension (large doses); dependence; difficulty with micturition; ureteric or biliary spasm; dry mouth, sweating, headache, facial flushing, vertigo, bradycardia, tachycardia, palpitations, hypothermia, hallucinations, dysphoria, mood changes, miosis, decreased *libido* or potency, rash, urticaria, pruritus; convulsions (large doses).

### Furazolidone

Pregnancy Category-C

Schedule H

**Indications** *Giardiasis; cholera; gastrointestinal infections; protozoal or bacterial diarrhoea and enteritis; food poisoning.*

**Availability** **TABLETS** 100 mg; **CAPSULE** 100 mg; **SUSPENSION** 25 mg/5 ml.

**Dose** **Oral**

**Adult-** 100 mg 3 to 4 times a day.

**Child-** 5 mg/kg body weight daily in 4 divided doses.

<b>Contraindications</b>	Hypersensitivity; alcoholics; primaquine sensitivity.
<b>Precautions</b>	Urine colour changes to yellow after administration; orthostatic hypotension; hypoglycaemia; pregnancy (Appendix 7c); interactions (Appendix 6a, 6c).
<b>Adverse Effects</b>	Nausea, vomiting, headache; hypotension; urticaria; dyspnea; dizziness.
<b>Storage</b>	Store protected from light at temperature not exceeding 30°C.

## Loperamide

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>For the control and symptomatic relief of acute nonspecific diarrhoea and chronic diarrhoea associated with inflammatory bowel disease or gastroenteritis; for reducing the volume of discharge from ileostomies.</i>
<b>Availability</b>	<b>TABLET/CAPSULE</b> 2 mg; <b>LIQUID</b> 1 mg/5 ml.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> 4 mg initially thereafter 2 mg after every motion.  <b>Child-</b> 2 mg followed by 2 mg after every motion.
<b>Contraindications</b>	Conditions where inhibition of peristalsis should be avoided, where abdominal distension develops, or in conditions such as active ulcerative colitis or antibiotic-associated colitis.
<b>Precautions</b>	Liver disease; pregnancy: (Appendix 7c); interactions (Appendix 6c); glaucoma; Crohn's disease; urinary bladder obstruction.
<b>Adverse Effects</b>	Abdominal cramps, dizziness, drowsiness and skin reactions including urticaria; paralytic ileus and abdominal bloating also reported; constipation; headache; meteorism; nausea; dry mouth; urinary retention.
<b>Storage</b>	Store protected from light and moisture.

## 6.2 Laxatives

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A balanced diet, including adequate fluid intake and fibre is of value in preventing constipation.

Before prescribing laxatives, it is important to be sure that the patient is constipated and that the constipation is not secondary to an underlying undiagnosed complaint. It is also important that the patient understands that bowel habit can vary considerably in frequency without doing harm. For example, some people consider themselves constipated if they do not have a bowel movement each day. A useful definition of constipation is the passage of hard stools less frequently than the patient's own normal pattern and this should be explained to the patient since misconceptions about bowel habits have led to excessive laxative use which in turn has led to hypokalaemia and an atonic non-functioning colon.

Laxatives should generally be avoided except where straining will exacerbate a condition such as angina or increase the risk of rectal bleeding as in haemorrhoids. Laxatives are of value in drug-induced constipation, for the expulsion of parasites after anthelmintic treatment and to clear the alimentary tract before surgery and radiological procedures. Prolonged treatment of constipation is rarely, necessary except occasionally in the elderly.

There are many different laxatives. These include bulk-forming laxatives which relieve constipation by increasing faecal mass and stimulating peristalsis, stimulant laxatives which increase intestinal motility and often cause abdominal cramp, faecal softeners which lubricate and soften impacted faeces and osmotic laxatives which act by retaining fluid in the bowel by osmosis. Bowel cleansing solutions are used before colonic surgery, colonoscopy or radiological examination to ensure that the bowel is free of solid contents; they are not a treatment for constipation.

## Bisacodyl\*

### Pregnancy Category-B

<b>Indications</b>	<i>Constipation.</i>
<b>Availability</b>	<b>TABLETS</b> 5 mg; <b>SUPPOSITORIES</b> 5 and 10 mg.
<b>Dose</b>	<b>Oral/Rectal</b>  <b>Adult and child over 10 years-</b> 5 to 10 mg daily at night. Before radiological procedure and surgery: 16 to 20 mg at night before procedure.
<b>Contraindications</b>	Intestinal obstruction (causes abdominal cramps), acute surgical abdominal conditions, acute inflammatory bowel disease, severe dehydration; faecal impaction, chronic use.
<b>Precautions</b>	Excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia; however, prolonged use may be justifiable in some circumstances; don't give antacid within 1 hour, pregnancy (Appendix 7c), inflammatory bowel disease, pre-existing heart disease or bowel disease, allergies, interactions (Appendix 6d).
<b>Adverse Effects</b>	Tablets- griping; suppositories-local irritation; fainting, dizziness, soreness in anal region due to suppository leakage; abdominal discomfort, electrolyte imbalance, hypokalaemia.

## Ispaghula\*

<b>Indications</b>	<i>Constipation; irritable colon syndrome.</i>
<b>Availability</b>	<b>GRANULES</b> (flavoured and sweetened) 37.5 and 100g.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> 6 teaspoonful of water or milk at night before bed time.  <b>Child-</b> 1-3 teaspoonful in water or milk before bed time.
<b>Contraindications</b>	Intestinal obstruction; colonic atony; difficulty in swallowing.
<b>Precautions</b>	Salt restriction; interactions (Appendix 6c).



**Adverse Effects** Abdominal discomfort, flatulence, gastrointestinal obstruction.

**Storage** Store protected from light and moisture.

## Lactulose

**Indications** *Constipation, hepatic encephalopathy.*

**Availability** **SOLUTION/SYRUP** 3.35g/5 ml.

**Dose** 10 to 20g (15 to 20 ml/day, max 45 ml/day).

**Contraindications** Galactosemia, intestinal obstruction, patients on low galactose diet.

**Precautions** Lactose intolerance, diabetes mellitus.

**Adverse effects** Diarrhoea (dose related), nausea, vomiting, hypokalaemia; dehydration; hypernatremia; bloating and abdominal cramps.

## Senna

**Pregnancy Category-C**

**Indications** *Constipation.*

**Availability** **TABLETS** (containing Sennoside B-11.5 mg).

**Dose** **Oral**

**Adult-** 2 to 4 tablets, usually at night; initial dose should be low, then gradually increased.

**Child-** over 6 years, half the adult dose in the morning (on doctor's advice).

**Contraindications** Intestinal obstruction; undiagnosed abdominal symptoms.

**Precautions** Avoid prolonged use unless indicated for prevention of faecal impaction; pregnancy (Appendix 7c), lactation (Appendix 7b); hypersensitivity, undiagnosed abdominal pain, intestinal blockage.

**Adverse Effects** Abdominal discomfort; atonic non-functioning colon and hypokalaemia (with prolonged use or overdosage); red or yellow brown urine, diarrhoea, nausea, vomiting, bloating.

**Storage** Store protected from light and moisture.

## 6.3 Oral Rehydration

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Acute diarrhoea in children should always be treated with oral rehydration solution according to plan A, B or C as shown. Severely dehydrated patients must be treated initially with intravenous fluids until they are able to take fluids by mouth. For oral rehydration it is important to administer the solution in small amounts at regular intervals as indicated below.

### Treatment of Dehydration:

#### WHO Recommendations

According to the degree of dehydration, health professionals are advised to follow one of the three management plans.

**Plan A: No dehydration:** Nutritional advice and increased fluid intake are sufficient (soup, rice, water and yoghurt, or even water). For infants aged under 6 months who have not yet started taking solids, oral rehydration solution must be presented before offering milk. Mother's milk or dried milk must be given without any particular restrictions. In the case of mixed breast-milk/formula feeding, the contribution of lactation must be increased.

**Plan B: Moderate dehydration:** Whatever the child's age, a 4-h treatment plan is applied to avoid short-term problems. Feeding should not therefore be envisaged initially. It is recommended that parents are shown how to give approximately 75 ml/kg of oral rehydration solution with a spoon over a 4-h period and it is suggested that parents should be watched to see how they cope at the beginning of the treatment. A larger amount of solution can be given if the child continues to have frequent stools. In case of vomiting, rehydration must be discontinued for 10 min and then resumed at a slower rate (about one teaspoonful every 2 min). The child's status must be re-assessed after 4 h to decide on the most appropriate subsequent treatment. Oral rehydration solution should continue to be offered once dehydration has been controlled, for as long as the child continues to have diarrhoea.

**Plan C: Severe dehydration:** Hospitalization is necessary, but the most urgent priority is to start rehydration. In hospital (or elsewhere), if the child can drink, oral rehydration solution must be given pending, and even during intravenous infusion (20 ml/kg every h by mouth before infusion, then 5 ml/kg every h by mouth during intravenous rehydration). For intravenous supplementation, it is recommended that compound solution of sodium lactate (see chapter 28.2) is administered at a rate adapted to the child's age (infant under 12 months: 30 ml/kg over 1 h then 70 ml/kg over 5 h; child over 12 months:

the same amounts over 30 min and 2.5 h respectively). If the intravenous route is unavailable, a nasogastric tube is also suitable for administering oral rehydration solution, at a rate of 20 ml/kg every h. If the child vomits, the rate of administration of the oral solution should be reduced.

## Oral Rehydration Salts\*

<b>Indications</b>	<i>Dehydration from acute diarrhoea.</i>
<b>Availability</b>	<b>GLUCOSE SALT SOLUTION 5 and 37.5g.</b>
	Sodium chloride      2.6 g/litre of water
	Sodium citrate        2.9 g/litre of water
	Potassium chloride    1.5 g/litre of water
	Glucose (anhydrous) 13.5 g/litre of water
	When glucose and sodium citrate are not available, they may be replaced by
	Sucrose (common sugar) 27 g/litre of water
	Sodium bicarbonate    2.5 g/litre of water
	In cases of cholera, oral rehydration salts containing a higher concentration of sodium may be required to prevent hyponatraemia.

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*Note: The solution may be prepared either from prepackaged sugar/salt mixtures or from bulk substances and water. Solutions must be freshly prepared, preferably with recently boiled and cooled water. Accurate weighing and thorough mixing and dissolution of ingredients in the correct volume of clean water is important. Administration of more concentrated solutions can result in hypernatraemia.*

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<b>Dose</b>	<b>Oral</b>
	5g (single use): dissolve in water and drink; 37.5g: to reconstitute it with 1 litre of clean water.
	<b>Adult-</b> Fluid and electrolyte loss in acute diarrhoea; 200 to 400 ml solution after every loose motion.
<b>Precautions</b>	Renal impairment.
<b>Adverse Effects</b>	Vomiting- may indicate too rapid administration; hypernatraemia and hyperkalaemia may result from overdose in renal impairment or administration of too concentrated a solution.

### Storage

Store protected from moisture in a sachet preferably made of aluminium foil containing sufficient powder for single dose or for a day treatment or for use in hospital.

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## 7. Antidotes and Substances Used in Poisoning

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These notes are only guidelines and it is strongly recommended that poisons information centres (Appendix 5) be consulted in cases where there is doubt about the degree of risk or about appropriate management.

## 7.1 Non specific

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### General Care and Non-Specific Treatment:

All patients who show features of poisoning should generally be admitted to hospital. Patients who have taken poisons with delayed actions should also be admitted, even if they appear well; delayed-action poisons include acetylsalicylic acid, iron, lithium, paracetamol, paraquat, tricyclic antidepressants and warfarin. The effects of modified-release or prolonged-release preparations are also delayed. However, it is often impossible to establish with certainty the identity of the poison and the size of the dose but information on the type and timing of poisoning may be useful for symptomatic management. Few patients require active removal of the poison.

Most patients must be treated symptomatically and monitored. Particular care must be given to maintenance of respiration and blood pressure. Assisted ventilation may be required. Cardiac conduction defects and arrhythmias often respond to correction of underlying hypoxia, acidosis, or other biochemical abnormalities. Hypothermia which may develop in patients who have been unconscious for some hour is best treated by wrapping the patient in blankets to conserve body heat. Convulsions which are prolonged or recurrent may be controlled by intravenous diazepam. In some situations removal of the poison from the stomach by gastric lavage may be appropriate (see below). Activated charcoal can bind many poisons in the stomach and therefore prevent absorption. Active elimination techniques such as repeated administration of activated charcoal can enhance the elimination of some drugs after they have been absorbed (see below). Other techniques to enhance elimination of poisons after their absorption are only practical in hospital and are only suitable for a small number of patients and only to a limited number of poisons. Methods include haemodialysis and haemoperfusion. Alkalinization of urine can be used to increase the elimination of salicylates. Forced alkaline diuresis is no longer recommended.

### Gastric Lavage:

The dangers of attempting to empty the stomach have to be balanced against the toxicity of the ingested poison, as assessed by the quantity ingested, the inherent toxicity of the poison and the time since ingestion. Gastric emptying is clearly unnecessary if the risk of toxicity is small or if the patient presents too late. Emptying the stomach may be of value if undertaken within 1-2 h after ingestion. The main

risk is with inhalation of stomach contents and gastric lavage should not be undertaken in drowsy or comatose patients without assistance of an anaesthetist so that the airway can be protected by a cuffed endotracheal tube. Gastric lavage must not be attempted after corrosive poisoning or for hydrocarbon products which could be dangerous if aspirated.

### **Emesis:**

Induction of emesis for the treatment of poisoning is not recommended. There is no evidence that it prevents absorption of the poison and it may increase the likelihood of aspiration. Furthermore, the effects of the emetic substance may complicate diagnosis.

### **Prevention of Absorption:**

Given by mouth activated charcoal can bind many poisons in the gastrointestinal system, thereby reducing their absorption. The sooner it is given, the more effective it is, but it may be effective for up to 1 hour after ingestion of the poison. It may be effective several hours after poisoning with modified-release preparations or drugs with anticholinergic (antimuscarinic) properties. It is relatively safe and particularly useful for prevention of absorption of poisons which are toxic in small amounts, for example, antidepressants. Furthermore, repeated doses of activated charcoal enhance the faecal elimination of some drugs (that undergo enterohepatic or enteroenteric recycling) several hours after ingestion and after they have been absorbed, for example phenobarbital, theophylline.



## Activated Charcoal

<b>Indications</b>	<i>Treatment of acute poisoning.</i>
<b>Availability</b>	<b>POWDER</b> (for oral suspension), <b>TABLETS</b> 500 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult and child over 12years-</b> 50g, 0.5g/kg may be repeated every 4-6 h for upto 12-24 h.  <b>Child- Below 12years;</b> 1g/kg (max 50g). May be repeated every 4 h.
<b>Contraindications</b>	Poisoning by hydrocarbons with high potential for harm if aspirated; poisoning by corrosive substances-may prevent visualization of lesions caused by poison.
<b>Precautions</b>	Drowsy or unconscious patients-risk of aspiration (intubate before administration via nasogastric or gastric tube); not effective for poisoning with alcohols, clofenotane (dicophane, DDT), cyanides, malathion and metal salts including iron and lithium.
<b>Adverse Effects</b>	Black stools; vomiting, constipation or diarrhoea; pneumonitis-due to aspiration.
<b>Storage</b>	Store protected from moisture.

## Calcium Disodium Edetate

### Pregnancy Category-B

<b>Indications</b>	<i>Lead poisoning (acute and chronic) and lead encephalopathy.</i>
<b>Availability</b>	<b>AMPOULE</b> 5 ml (200 mg/ml).
<b>Dose</b>	<b>Intravenous injection</b>  Lead poisoning without encephalopathy: 1000 mg/m <sup>2</sup> /day as continuous infusion for 5 days. Lead encephalopathy: 1500 mg/m <sup>2</sup> /day by continuous intravenous infusion in 5% dextrose or 0.9% NaCl (Final Concentration of edetate < 500 mg/100 ml), starting 4 h after first dose of BAL and after an adequate urine flow is established. Infusion is continued for 5 days.  <b>Intramuscular injection</b> to be used if fluid overload is a concern.  1000 mg/m <sup>2</sup> /day divided into equal doses spaced 8 to 12 h apart.  Lignocaine or procaine should be added to the injection to minimize pain at the injection site.

- Contraindications** Anuria; patients with active renal disease or hepatitis; pregnancy (Appendix 7c).
- Precautions** Ensure adequate urine output, pre-existing mild renal disease; patients with lead encephalopathy and cerebral edema may experience a lethal increase in intracranial pressure following intravenous infusion, the intramuscular route is preferred for these patients.
- Adverse Effects** Renal tubular toxicity which may lead to acute renal failure, fever, chills, lacrimation, increased prothrombin time, pain at intramuscular injection site; hypotension; cardiac rhythm irregularities; thirst; headache; fatigue; malaise; urinary frequency; glycosuria; proteinuria; microscopic hematuria; histamine-like reactions.

## 7.2 Specific

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### Paracetamol Overdosage:

Paracetamol in a dose of 10-15g or 150 mg/kg of paracetamol taken within 24 h may cause severe hepatocellular necrosis and less frequently renal tubular necrosis. The only early features of poisoning, nausea and vomiting, usually settle within 24 h. Persistence beyond this time, often with the onset of right subcostal pain and tenderness, usually indicates the development of liver damage which is maximal 3-4 days after ingestion. In spite of a lack of significant early symptoms, patients who have taken an overdose of paracetamol should be transferred to hospital urgently.

Administration of activated charcoal should be considered if paracetamol in excess of 150 mg/kg or 12g, whichever is smaller, is thought to have been ingested within the previous hour.

N-Acetylcysteine or N-methionine protect the liver if given within 10-12 h of ingesting paracetamol. Acetylcysteine, given intravenously is most effective within 8 h of overdose, but is effective for up to and possibly beyond 24 h. Alternatively, methionine may be given by mouth provided the overdose was ingested within 10-12 h and the patient is not vomiting. However, acetylcysteine is the preferred treatment. Concurrent use of activated charcoal and specific oral antidotes should be avoided.

In remote areas methionine should be given, since administration of acetylcysteine outside hospital is not generally practicable. Once the patient is in hospital the need to continue antidote treatment can be assessed from plasma-paracetamol concentrations.

### Opioid Analgesic Overdosage:

Opioids cause varying degrees of coma, respiratory depression and pinpoint pupils. Naloxone is a specific antidote indicated if there is coma or bradypnoea. Naloxone has a shorter duration of action than many opioids so close monitoring and repeated injections are required depending on respiratory rate and depth of coma; naloxone may alternatively be given by intravenous infusion. The effects of some opioids such as buprenorphine are only partially reversed by naloxone.

Acute withdrawal syndromes may be precipitated by the use of naloxone in patients with a physical dependence on opioids or in overdose with large doses; a withdrawal syndrome may occur in neonates of opioid-dependent mothers.

## Organophosphate and Carbamate Poisoning:

Organophosphates are absorbed through the bronchi and intact skin as well as from the gastrointestinal tract. Initial treatment of organophosphate or carbamate poisoning includes prevention of further absorption by emptying the stomach by gastric lavage, moving patient to fresh air supply, removing contaminated clothing and washing contaminated skin. A clear airway must be maintained.

Organophosphates inhibit cholinesterases and thus prolong the effects of acetylcholine. Toxicity depends on the particular compound involved and onset after ingestion, skin exposure may be delayed. Atropine will reverse the muscarinic effects of acetylcholine and is used (in conjunction with oximes such as pralidoxime) with additional symptomatic treatment.

Additional treatment for carbamate poisoning is generally symptomatic and supportive. Atropine may be given but may not be required because of the rapidly reversible type of cholinesterase inhibition produced (oximes should not be given).

## Iron Poisoning and Iron and Aluminium Overload:

Mortality from iron poisoning is reduced by specific therapy with desferrioxamine which chelates iron. Before administration of desferrioxamine the stomach should be emptied by gastric lavage (with a wide-bore tube) within 1 h of ingesting a significant quantity of iron or if radiography reveals tablets in the stomach. Desferrioxamine is also used to diagnose and treat chronic iron overload. It is used in the diagnosis of aluminium overload and to treat aluminium overload in patients with end-stage renal failure undergoing maintenance haemodialysis.

## Heavy Metal Poisoning:

Heavy metal poisoning may be treated with a range of antidotes including dimercaprol, penicillamine, potassium ferric hexacyanoferrate and Sodium calcium edetate. Penicillamine is also used to promote excretion of copper in Wilson's disease.

## Methaemoglobinaemia:

Methylthionium chloride can lower the levels of methaemoglobin in red blood cells and is used in the treatment of methaemoglobinaemia. In large doses, it may cause methaemoglobinaemia and therefore methaemoglobin levels should be monitored during treatment.

## Cyanide Poisoning:

Cyanide poisoning may be treated with Sodium nitrite followed by Sodium thiosulphate.

## Atropine\* (Refer Page No. 419 and 560)

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Organophosphate and carbamate poisoning; premedication; antispasmodic; as mydriatic; cycloplegic refraction procedures.</i>
<b>Availability</b>	<b>INJECTION</b> 1 ml ampoules and 50 ml vial (0.6 mg/ml).
<b>Dose</b>	<b><i>Intramuscular and intravenous injection</i></b>  <b>Adult-</b> 1.8 - 3.0 mg intravenous bolus followed by doubling dose every 3 to 5 minutes depending upon response. End-point for atropinization include clear chest with no wheeze, systolic BP >80mm Hg, pulse >80 beats/min., pupils no longer pinpoint and dry axillae. Following that infusion of atropine at 10-20 % of total initial dose required/hour; may require boluses during infusion.  <b>Child-</b> 20-30 µg/kg initially with same schedule as above.
<b>Contraindications</b>	In myasthenia gravis (but may be used to decrease muscarinic side-effects of anticholinesterases), paralytic ileus, pyloric stenosis and prostatic enlargement; reflux oesophagitis; unstable cardiac rhythm.
<b>Precautions</b>	Elderly, Down syndrome; angle-closure glaucoma; myasthenia gravis; prostatic enlargement; pyrexia; lactation (Appendix 7b); interactions (Appendix 6a); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Constipation, transient bradycardia (followed by tachycardia, palpitation and arrhythmias), reduced bronchial secretions, urinary urgency and retention, dilatation of the pupils with loss of accommodation, photophobia, dry mouth, flushing and dryness of the skin. Occasionally, confusion (particularly in the elderly), nausea, vomiting and giddiness; very rarely, angle-closure glaucoma may occur.

## Desferrioxamine Mesylate\*

Pregnancy Category-C

<b>Indications</b>	<i>Acute iron poisoning; chronic iron overload; aluminium overload; primary hemochromatosis.</i>
<b>Availability</b>	<b>INJECTION</b> 5 ml and 10 ml vial (500 mg/vial).
<b>Dose</b>	<b><i>Continuous intravenous infusion</i></b>

**Adult and Child-** Begin with 5 mg/kg/h, increasing over 15 minutes if tolerated to 15 mg/kg/h, to minimize the risk of hypotension. After 1 to 2 h reduce to 3-4 mg/kg/h for the next 22-23 hrs (max dose is 100 mg/kg over 24 hrs).

Patients with cardiovascular collapse: 5 mg/kg/h (up to max. of 80 mg/kg in 24 h.)

Chronic iron overload: Intramuscular 500 to 1000 mg daily, in addition 2g by intravenous infusion with each unit of blood transfused.

**Contraindications** Severe renal disease; pregnancy (Appendix 7c).

**Precautions** Renal impairment; eye and ear examinations before and at 3-month intervals during treatment; aluminium encephalopathy (may exacerbate neurological dysfunction); children under 3 years (may retard growth); lactation; interactions (Appendix 6c).

**Adverse Effects** Anaphylaxis; flushing, urticaria, hypotension, shock (especially if given by too rapid intravenous infusion); gastrointestinal disturbances; fever, headache, arthralgia, myalgia; arrhythmias; renal impairment; blood disorders; neurological disturbances including neuropathy, paraesthesia and dizziness; convulsions; Yersinia and mucormycosis infections; visual disturbances (including lens opacity and retinopathy) and hearing loss; rash; rarely, growth retardation (in young children); rarely, acute respiratory distress syndrome; pain on intramuscular or subcutaneous injection; local irritation on prolonged subcutaneous infusion; reddish-brown discolouration of urine.

**Storage** Store protected from light in refrigerator (2-8°C). Do not freeze.

## Dimercaprol (BAL)\*

**Pregnancy Category-C**

**Indications** *Acute poisoning by antimony, arsenic, bismuth, copper gold, mercury and possibly thallium; adjunct (with sodium calcium edetate) in lead poisoning.*

**Availability** **OILY INJECTION** 2 ml ampoule (50 mg/ml).

**Dose** **Intramuscular injection**

***To be administered by deep intramuscular injection only***

Lead poisoning: Adults-4 mg/kg every 4 h for 5 days. Child- 75 mg/m<sup>2</sup> every 5 h for 5 days.  
 Arsenic poisoning: 3 mg/kg every 4 h for 48 h and then twice a day for 7-10 days.  
 Mercury poisoning: 5 mg/kg followed by 2.5 mg/kg every 12-24 h for upto 10 days

<b>Contraindications</b>	Not indicated for iron, selenium or cadmium poisoning; severe hepatic impairment (unless due to arsenic poisoning); hypertension; tellurium poisoning, peanut allergy, G-6-PD deficiency.
<b>Precautions</b>	Hypertension; renal impairment (discontinue or use with extreme caution if renal failure occurs during treatment); any abnormal reaction such as hyperpyrexia should be assessed; elderly; pregnancy (Appendix 7c); lactation, alkalinize urine to pH of 7.5-8.0 using sodium bicarbonate.
<b>Adverse Effects</b>	Hypertension, tachycardia; malaise, nausea, vomiting, abdominal pain, salivation, lacrimation, sweating, burning sensation in the mouth, throat and eyes; feeling of constriction in throat and chest; headache, muscle spasms, tingling of the extremities; fever in children; local pain and abscess at injection site, iron toxicity potentiation.
<b>Storage</b>	Store protected from light.

**D-Penicillamine\*** (Refer Page No. 385)**Pregnancy Category-D****Schedule H**

<b>Indications</b>	<i>Poisoning by heavy metals, particularly lead and copper; Wilson's disease; severe rheumatoid arthritis.</i>
<b>Availability</b>	<b>CAPSULE/TABLET 250 mg.</b>
<b>Dose</b>	<b><i>Oral (given before food)</i></b>  <b>Adult-</b> 1 to 2g daily in three divided doses starting with 250 mg OD and gradually increasing to full dose over 2-3 weeks.  <b>Child-</b> 20 mg/kg/day administered in 3-4 divided doses, initiating treatment at 25% of this dose and gradually increasing to full dose over 2-3 weeks to minimize adverse reactions. Continue till blood lead levels <45 µg/dl.

**Contraindications** Hypersensitivity; lupus erythematosus; gold or antimalarial drug; penicillamine-induced agranulocytosis; aplastic anaemia; thrombocytopenia, pregnancy, lactation (for rheumatoid arthritis).

**Precautions** Monitor throughout treatment including blood counts and urine tests; renal impairment; immunosuppressive treatment; avoid oral iron within 2 h of a dose; hepatic impairment; pregnancy (Appendix 7c).

In Wilson's disease, consider withdrawal if platelet count falls below 120 000/mm<sup>3</sup> or white blood cells below 2500/mm<sup>3</sup> or if 3 successive falls within reference range (can restart at reduced dose when counts return to reference range but permanent withdrawal necessary if neutropenia or thrombocytopenia recur).

In Wilson's disease warn patient to tell doctor immediately if sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers or rashes develop.

**Adverse Effects** Initially nausea (less of a problem if taken with food and on retiring), anorexia, fever; taste loss (mineral supplements not recommended); blood disorders including thrombocytopenia, neutropenia, agranulocytosis and aplastic anaemia; proteinuria, rarely, haematuria (withdraw immediately); haemolytic anaemia, nephrotic syndrome, lupus erythematosus-like syndrome, myasthenia gravis-like syndrome, polymyositis (rarely, with cardiac involvement), dermatomyositis, mouth ulcers, stomatitis, alopecia, bronchiolitis and pneumonitis, pemphigus, Goodpasture syndrome and Stevens-Johnson syndrome also reported; male and female breast enlargement reported; rash early in treatment (usually allergic-may need temporary withdrawal), late rashes (reduce dose or withdraw treatment).

## Flumazenil\*

**Pregnancy Category-C**

**Indications** *Antidote for benzodiazepine overdose, reversal of sedative effects produced by benzodiazepenes administered during general anaesthesia or diagnostic or therapeutic procedures.*

**Availability** **INJECTION** 0.1 mg/ml.



<b>Dose</b>	<b>Adult-</b> 0.2 mg (2 ml) administered over 30 seconds, i.v, repeat 0.3 mg and 0.5 mg at 1-2 minute intervals. Not more than 3 mg over one hour.  <b>Child-</b> 10 µg/kg, i.v, for 2 doses.
<b>Contraindications</b>	Epilepsy, neuromuscular blockade, hypersensitivity to benzodiazepines, patients of suspected tricyclic antidepressant overdose, raised intracranial pressure.
<b>Precautions</b>	History of seizures, panic attack, alcohol drug dependence, bleeding disorder, liver disease, head injury, respiratory depression, pregnancy (Appendix 7c).
<b>Adverse effects</b>	Convulsions, fatigue, injection site pains, increased sweating, facial erythema, raised intracranial pressure, agitation, dizziness, abnormal vision, may cause complete heart block, flushing, transient increase in blood pressure and heart-rate.

## Methylene Blue (Methylthionium Chloride)\*

### Pregnancy Category-C

<b>Indications</b>	<i>Acute methaemoglobinaemia.</i>
<b>Availability</b>	<b>INJECTION</b> 10 mg/ml.
<b>Dose</b>	<b><i>Intravenous injection</i></b>  Methaemoglobinaemia caused by high dosage of prilocaine infusion: 1-2 mg/kg intravenously over 5 minutes, followed immediately by a fluid flush of 15-30 ml to minimize local pain. May be repeated in 30-60 minutes. Maximum dose: 7 mg/kg.
<b>Contraindications</b>	Severe renal impairment; methaemoglobinaemia due to chlorate or induced by sodium nitrite in treatment of cyanide poisoning; affects ability to drive machinery.
<b>Precautions</b>	G-6-PD deficiency-may cause haemolytic anaemia; monitor blood methaemoglobin throughout treatment; pregnancy (Appendix 7c); lactation.
<b>Adverse Effects</b>	Nausea, vomiting, abdominal pain, chest pain, headache, dizziness, confusion, profuse sweating; hypertension or hypotension reported; haemolytic anaemia-in G-6-PD deficiency; methaemoglobinaemia-with high dosage; bluish skin discolouration; blue saliva, urine and faeces.

**Storage** Store protected from light in an airtight container.

## Naloxone\*

**Pregnancy Category-B**

**Schedule X**

**Indications** *Opioid overdose; postoperative respiratory depression.*

**Availability** **INJECTION** 0.4 mg/ml.

**Dose** ***Intravenous injection***

Subcutaneous or intramuscular route (if i.v. route is not feasible but the dose is same, can be given oral as well).

**Adult-** Opioid poisoning: Start with 0.4 to 2 mg (at all ages) as intravenous bolus, Repeat every 2 minutes if no response to a total of 10 mg. Once response occurs start infusion of naloxone at 2/3<sup>rd</sup> the total loading dose given every hour with continuous monitoring for recurrence of respiratory depression. May require additional bolus during infusion.

**Child-** Opioid poisoning: 10 µg/kg, followed by 100 µg/kg if there is no response.

**Contraindications** Hypersensitivity.

**Precautions** Physical dependence on opioids or other situations where acute withdrawal syndrome may be precipitated (see above); lactation; cardiovascular disease; pregnancy (Appendix 7c).

**Adverse Effects** Nausea, vomiting, sweating-may also be due to opioid withdrawal.

**Storage** Store protected from light in an airtight container.

## Pralidoxime (2-PAM)\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *Adjunct to atropine in the treatment of organophosphate poisoning and anticholinesterase overdose used in the treatment of myasthenia gravis (mg), respiratory depression or severe muscle weakness due to carbamate poisoning.*

**Availability** **INJECTION** i.v infusion 500 mg/20 ml, 1g/20 ml (as chloride and iodide salt).

**Dose** **For Chloride salt**, 30 mg/kg i.v. over 15-20 minutes followed by infusion at 8-10 mg/kg/h. To be continued 12-24 hours after atropine is no longer required.

**For iodide salt**, dose is about 30% higher than chloride salt.

**Child-** 25 to 50 mg/kg, diluted to 5% concentration in NS and infused over 5-30 minutes. May be repeated after one h, then every 6 to 12 h.

**Severe poisoning:**

**Adult-** 500 mg/h via continuous infusion. max.- 12g/24 h.

**Child-** 9 to 19 mg/kg/h.

**For anticholinesterase overdose in MG:**

**Adult-** 1-2g i.v. initially, then 250 mg every 5 minutes.

**Child (0-18 years)-** 15-25 mg/kg by slow i.v (up to 1 g).

Maintenance dose- (< 12 years) 15-50 mg/kg i.v every 5 minutes (up to 250 mg).

**Contraindications** Carbamate poisoning and organophosphates without anticholinesterase activity; hypersensitivity to the drug.

**Precautions** Impaired renal function; large doses can cause neuromuscular blockade, myasthenia gravis; atropinization occur faster on concurrent use with atropine; paediatrics; allergies; pregnancy (Appendix 7c).

**Adverse effects** Headache, nausea; blurred vision, drowsiness, dizziness, impaired accommodation, tachycardia, hyperventilation, muscular weakness; transient elevation in SGOT and/or SGPT levels; laryngospasm and rigidity.

**Storage** Store protected from moisture.

## Sodium Nitrite\*

**Pregnancy Category-C**

**Indications** *Cyanide poisoning (together with Sodium thiosulphate).*

<b>Availability</b>	<b>INJECTION</b> 30 mg/ml (10 ml).
<b>Dose</b>	<b><i>Intravenous injection (over 5 to 20 min)</i></b>  <b>Adult</b> -300 mg at 2.5-5.0 mg/minute.  <b>Child</b> - 4 to 10 mg/kg (max 300 mg) at 5 mg/minute.

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*Note: Prepare as 3% solution of Sodium nitrite in Water for Injections (30 mg/ml) at the time of administration.*

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<b>Contraindications</b>	Methaemoglobinaemia; hemolytic anaemia; G-6-PD deficiency.
<b>Precautions</b>	Monitor plasma methaemoglobin levels; severe cardiovascular or cerebrovascular disease; hypotension; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Nausea, vomiting and abdominal pain, vasodilatation resulting in syncope, hypotension, tachycardia, flushing, headache; methaemoglobinaemia; cyanosis, dyspnoea, tachypnoea.

## Sodium Thiosulphate\* (Refer Page No. 352)

### Pregnancy Category-C

<b>Indications</b>	<i>Prophylactically with prolonged use of nitro prusside to prevent cyanide toxicity, cyanide poisoning (together with Sodium nitrite); pityriasis versicolor; skin disease.</i>
<b>Availability</b>	<b>INJECTION</b> 250 mg/ml; 500 mg/ml (50 ml).
<b>Dose</b>	<b><i>Intravenous injection (over 10 min).</i></b>  <b>Adult</b> - 12.5g intravenously over 10-30 minutes may be repeated at half the initial dose at 1-2 hours.  <b>Child</b> - 500 mg/kg intravenously over 10-30 minutes may be repeated at half the initial dose at 1-2 hours (12.5g maximum)
<b>Contraindications</b>	Hypersensitivity; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Irritation; urticaria; hypotension; burning; stinging on application.

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*Note: Freshly prepare by dissolving Sodium thiosulphate IP in Water for Injections.*

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## **8.    Antiemetics**

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## 8. Antiemetics

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Antiemetics are drugs effective against nausea and vomiting. They are typically used to treat motion sickness and the side effects of opioid analgesics, general anaesthetics and chemotherapy induced nausea and vomiting in cancer patients either alone or in combination.

They act on the brain by preventing the stimulation of the vomiting centre (chemoreceptor trigger zone-CTZ). Some medications act on the gut by speeding up the rate at which the stomach empties and help to facilitate the quick transit of food through intestine (prokinetic action).

### Classification:

- 5-HT<sub>3</sub> receptor antagonists block serotonin receptors in the central nervous system and gastrointestinal tract: Ondansetron, Granisetron, Dolasetron etc.
- Dopamine D<sub>2</sub>-receptor antagonists act in the brain: Domperidone, Metoclopramide, Mosapride etc.
- Antihistamines or H<sub>1</sub>- histamine receptor antagonists: Diphenhydramine, Promethazine etc.
- Benzodiazepines: Midazolam, Lorazepam etc.
- Anticholinergics: Scopolamine, Hyoscine, Dicyclomine etc.
- Steroids: Dexamethasone etc.

Metoclopramide has antiemetic properties and also stimulates upper gastrointestinal motility. It is effective against nausea and vomiting associated with gastrointestinal disorders or migraine, following surgery and chemotherapy and is also effective against radiation-induced nausea and vomiting. Combining metoclopramide with corticosteroids (such as dexamethasone) can improve its antiemetic effect in chemotherapy-induced nausea and vomiting. Metoclopramide may be useful in the management of gastro-oesophageal reflux and gastroparesis, as well as preoperatively in the prevention of aspiration syndromes. It is also used to facilitate intubation of the small bowel during radiographic examinations. It is not effective in the prevention or treatment of motion sickness.

Metoclopramide may cause acute dystonic reactions with facial and skeletal muscle spasms and oculogyric crisis. These reactions are most common in the young (especially girls and young women) and the elderly; they occur shortly after the start of treatment and subside within 24 h of drug withdrawal.

Promethazine is a phenothiazine derivative. In addition to D<sub>2</sub>

dopaminergic blockade it has pronounced histamine H<sub>1</sub> and muscarinic receptor blocking properties. It is effective in the prevention and treatment of vertigo and motion sickness. Promethazine may be useful in the prevention and treatment of postoperative and drug-induced nausea and vomiting. It has limited effect on chemotherapy-induced mild to moderate emesis.

## Domperidone\*

**Schedule H**

<b>Indications</b>	<i>Nausea and vomiting from any cause in adult, epigastric senses of fullness; upper abdominal distress; non ulcer dyspepsia; migraine.</i>
<b>Availability</b>	<b>TABLETS</b> 5 and 10 mg; <b>SYRUP</b> 30 ml (1 mg/ml); <b>CAPSULE</b> 30 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult</b> - 10 to 20 mg 3 to 4 times a day <b>Child</b> - 0.3 to 0.6 mg/kg TDS.
<b>Contraindications</b>	Hypersensitivity; prolactinoma, hepatic impairment; where increased gastro-intestinal motility harmful; pregnancy; gastro intestinal haemorrhage; intestinal obstruction.
<b>Precautions</b>	Children; renal impairment, interactions (Appendix 6c); history of breast cancer; allergies; pheochromocytoma; i.v. administration can lead to hypokalaemia and cardiac arrhythmias.
<b>Adverse Effects</b>	Rarely, gastro-intestinal disturbances (including cramps) and hyperprolactinaemia; very rarely, extrapyramidal effects and rashes; headache; dizziness; dry mouth; nervousness; flushing.
<b>Storage</b>	Store protected from light and moisture.

## Metoclopramide\* (Refer Page No. 421)

**Pregnancy Category-B**

**Schedule H**

<b>Indications</b>	<i>Nausea and vomiting in gastrointestinal disorders and treatment with cytotoxics or radiotherapy; gastro-oesophageal reflux disease; gastroparesis; premedication and postoperatively; aid to gastrointestinal intubation; nausea and vomiting in migraine; diabetic gastric stasis.</i>
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<b>Availability</b>	<b>TABLETS</b> 10 and 15 mg; <b>INJECTION</b> 2 ml ampoule (5 mg/ml); <b>SYRUP</b> 30 ml (1 mg/ml).
<b>Dose</b>	<p><b>Oral or intramuscular injection or Slow intravenous injection</b></p> <p><b>Adult-</b> Nausea and vomiting, gastroesophageal reflux, gastroparesis: (over 1 to 2 min for slow intravenous injection), 10 mg 3 times daily. 15 to 19 years (under 60 kg) 5 mg 3 times daily. Aid to gastrointestinal intubation: 20 mg as a single dose 5 to 10 min before examination; Adolescent (15 to 19 years), 10 mg.</p> <p><b>Child-</b> Up to 1 year (up to 10 kg) 1 mg twice daily; 1 to 3 years (10 to 14 kg) 1 mg 2 to 3 times daily; 3 to 5 years (15 to 19 kg) 2 mg 2 to 3 times daily; 5 to 9 years (20 to 29 kg) 2.5 mg 3 times daily; 9 to 14 years (30 kg and over) 5 mg 3 times daily (usual max. 500 µg/kg daily, particularly for children and young adult).</p> <p><b>Slow intravenous injection only</b></p> <p><b>Adult-</b> Premedication: 10 mg as a single dose.</p>
<b>Contraindications</b>	Gastrointestinal obstruction, haemorrhage or perforation, 3-4 days after gastrointestinal surgery; convulsive disorders; pheochromocytoma; hypersensitivity.
<b>Precautions</b>	Elderly, children and young adults; hepatic impairment (Appendix 7a); renal impairment (Appendix 7d); pregnancy (Appendix 7c); may mask underlying disorders such as cerebral irritation; avoid for 3-4 days after gastrointestinal surgery; lactation (Appendix 7b); interactions (Appendix 6a); Parkinson's disease; epilepsy; depression; porphyria; driving or operating machines; hypertension; cirrhosis; congestive heart failure.
<b>Adverse Effects</b>	Extrapyramidal symptoms (especially in children and young adults; see notes above); tardive dyskinesias on prolonged use; hyperprolactinaemia; drowsiness, restlessness, dizziness, headache, diarrhoea, depression, hypotension and hypertension reported; rarely, neuroleptic malignant syndrome; rashes, pruritus, oedema; cardiac conduction abnormalities following intravenous administration; rarely, methaemoglobinaemia (more severe in G-6-PD deficiency); galactorrhoea; amenorrhoea; bradykinesia; gynaecomastia; insomnia.
<b>Storage</b>	Store protected from light and moisture.



## Ondansetron\*

Pregnancy Category-B

**Schedule H**

**Indications** *Postoperative nausea and vomiting, chemotherapy and/or radiotherapy induced nausea and vomiting.*

**Availability** **TABLETS** 4 and 8 mg; **INJECTION** 2 and 4 ml ampoule (2 mg/ml); **DROPS** 2 mg/5 ml; **SYRUP** 2 mg/5 ml; **SUSPENSION** 1 mg/5 ml.

**Dose** **Oral**

**Prevention of post-operative nausea and vomiting:** Adult 16 mg, 1 h before induction of anaesthesia.

**Nausea and vomiting associated with cancer chemotherapy:**

**Adult-** 24 mg as a single dose taken 30 min before start of single day chemotherapy.

**Child (4-11 yrs)-** 4 mg tablets 3 times a day; continue for 1-2 days after completion of chemotherapy.

**Parenteral**

**Post-operative nausea and vomiting:**

**Adult-** 4 mg by i.m or slow i.v as a single dose.

**Prevention of chemotherapy-induced nausea and vomiting:**

**Adult-** single 32 mg i.v dose infused over 15 min beginning 30 min before start of emetogenic chemotherapy.

**Contraindications** Hypersensitivity.

**Precautions** Moderate to severe liver impairment; pregnancy (Appendix 7c), lactation; hypersensitivity to other selective 5-HT<sub>3</sub> - receptor antagonists, subacute intestinal obstruction; cardiac disease, electrolyte abnormalities, QT interval prolongation (avoid concomitant administration of drugs that prolong QT interval), interactions (Appendix 6c).

**Adverse Effects** Headache, constipation or diarrhoea, dizziness; flushing, hypersensitivity reaction, anaphylaxis/anaphylactoid reactions, angioedema; bronchospasm, hypotension, laryngeal edema, urticaria, hiccups, oculogyric crisis.

## Prochlorperazine

Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Nausea and vomiting.</i>
<b>Availability</b>	<b>TABLETS</b> 3 and 5 mg; <b>INJECTION</b> 1 ml ampoule (2.5 mg/ml).
<b>Dose</b>	<p><b>Oral and intravenous injection</b></p> <p><b>Adult-</b> Nausea, vomiting acute attack: initially 20 mg then 20 mg every 2 h. Prevention; 5 to 10 mg 2 to 3 times daily.</p> <p><b>Child-</b> (over 10 kg only).</p> <p><b>Oral:</b> 0.4 mg/kg/day in 3-4 divided doses.</p> <p><b>Intravenous injection:</b> 0.13 mg/kg/day in 3-4 divided doses.</p> <p><b>Adult-</b> Labyrinthine disorder: 5 mg 3 times daily increased to 30 mg daily in divided doses that decrease after meal to 5 to 10 mg daily.</p> <p><b>Child-</b> Labyrinthine disorder Not recommended.</p> <p><b>Intravenous injection:</b> 0.13 mg/kg/day in 3-4 divided doses.</p>
<b>Contraindications</b>	Comatose states, CNS depression and pheochromocytoma. Most antipsychotics are best avoided during pregnancy; hypersensitivity; prolactin dependant tumors.

**Precautions**

Patients with hepatic impairment, renal impairment, cardiovascular disease, Parkinson's disease (may be exacerbated by antipsychotics), epilepsy (and conditions predisposing to epilepsy), depression, myasthenia gravis, prostatic hypertrophy, or a susceptibility to angle-closure glaucoma. Caution is also required in severe respiratory disease and in patients with a history of jaundice or who have blood dyscrasias (perform blood counts if unexplained infection or fever develops). Caution should be taken in elderly, who are particularly susceptible to postural hypotension and to hyper- or hypothermia in very hot or cold weather. Serious consideration should be given before prescribing these drugs for elderly patients. As photosensitisation may occur with higher dosages, patients should avoid direct sunlight; extrapyramidal syndrome; pregnancy (Appendix 7c); interactions (Appendix 6a).

**Adverse Effects**

Less sedating; extrapyramidal symptoms, particularly dystonias, more frequent; respiratory depression may occur in susceptible patients; amenorrhoea; blurred vision; cholestatic jaundice; neuroleptic malignant syndrome; leucopenia; agranulocytosis.

**Storage**

Store protected from light and moisture.

**Promethazine\*** (Refer Page No. 423)**Pregnancy Category-C****Schedule G****Indications**

*Nausea, vomiting, labyrinthine disorders, motion sickness; premedication; allergic rhinitis; vasomotor rhinitis.*

**Availability**

**TABLETS** 10 and 25 mg; **SYRUP** 60 ml (5 mg/5 ml); **INJECTION** 2 ml ampoule (25 mg/ml).

**Dose****Oral**

Nausea and vomiting (including postoperative): 12.5 to 25 mg, repeated at intervals of not less than 4 h (usual max., 100 mg in 24 h). Motion sickness, prevention: 20 to 25 mg at bedtime on night before travel, repeated on day of travel if necessary.

**Child-** Motion sickness, prevention; 2 to 5 years: 5 mg at night and on day of travel, if necessary. 5 to 10 years: 10 mg at night and on day of travel, if necessary.

***Intramuscular injection or Slow intravenous injection***

Nausea and vomiting (including postoperative); (diluted to 2.5 mg/ml in water for injection); 12.5 to 25 mg, repeated at intervals of not less than 4 h (usual max., 100 mg in 24 h).

**Contraindications** Porphyria; hypersensitivity; coma; hypokalaemia.

**Precautions** Prostatic hypertrophy; urinary retention; glaucoma; hepatic disease (Appendix 7a); epilepsy; elderly and children (more susceptible to adverse effects); lactation (Appendix 7b); pregnancy (Appendix 7c); interactions (Appendix 6a).

May impair ability to perform skilled tasks, for example operating machinery, driving.

**Adverse Effects** Drowsiness, dizziness, sedation (but paradoxical stimulation may occur, especially with high doses or in children and elderly); headache, psychomotor impairment; urinary retention, dry mouth, blurred vision, gastrointestinal disturbances; hypersensitivity reactions, rashes, photosensitivity reactions; jaundice; blood disorders; cardiovascular adverse effects-after injection; venous thrombosis at site of intravenous injection; pain on intramuscular injection; somnolence; torticollis; tinnitus; leucopenia; thrombocytopenia, agranulocytosis; apnoea; angioneurotic edema.

**Storage** Store protected from light and moisture.

<b>9.</b>	<b>Anti-Infectives</b>	<b>105</b>
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## 9. Anti-Infectives

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### 9.1 Antiamoebic, Antigiardiasis and Antitrichomoniasis Drugs

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#### Amoebiasis:

Amoebic dysentery is caused by *Entamoeba histolytica*. It is transmitted by the faeco-oral route and infection is usually caused by ingestion of cysts from contaminated food and drink. Asymptomatic carriers are common in endemic areas. In non-endemic areas, symptomless carriers should be treated with a luminal amoebicide which will reduce the risk of transmission and protect the patient from invasive amoebiasis. Diloxanide furoate is most widely used, but other compounds, including clefamide, etofamide and teclozan, are also effective. Treatment with diloxanide furoate is regarded as successful if stools are free of *E. histolytica* for one month. Several specimens should be examined in evaluating response to treatment.

Symptomatic (invasive) amoebiasis may be classified as intestinal or extra-intestinal. Intestinal amoebiasis is either amoebic dysentery or non-dysenteric amoebic colitis. Extra-intestinal amoebiasis most commonly involves the liver, but may involve the skin, genito-urinary tract, lung and brain. Invasive amoebiasis is more likely in malnutrition, immunosuppression and pregnancy. Amoebic dysentery may take a fulminating course in late pregnancy and the puerperium; treatment with metronidazole may be life saving. In less severe infection, metronidazole should, if possible, be avoided in the first trimester. All patients with invasive amoebiasis require treatment with a systemically active compound such as metronidazole, ornidazole and tinidazole followed by a luminal amoebicide in order to eliminate any surviving organisms in the colon. Combined preparations are useful. In severe cases of amoebic dysentery, tetracycline given in combination with a systemic amoebicide lessens the risk of superinfection, intestinal perforation and peritonitis. Hepatic abscesses should be lanced by needle aspiration.

#### Giardiasis:

Giardiasis is caused by *Giardia intestinalis* and is acquired by oral ingestion of *Giardia* cysts. Giardiasis can be treated with tinidazole in a single dose or with another 5-nitroimidazole

such as metronidazole ; both are highly effective and should be offered when practicable to all infected patients. Family and institutional contacts should also be treated. Larger epidemics are difficult to eradicate because of the high proportion of symptomless carriers and because excreted cysts can survive for long periods outside the human host.

### Trichomoniasis:

Trichomoniasis is an infection of the genito-urinary tract caused by *Trichomonas vaginalis* and transmission is usually sexual. In women it causes vaginitis although some are asymptomatic. It is usually asymptomatic in men but may cause urethritis. Patients and their sexual partners should be treated with metronidazole or other nitroimidazole.

### Diloxanide Furoate\*

**Schedule H**

<b>Indications</b>	<i>Amoebiasis (asymptomatic carriers in non-endemic areas; eradication of residual luminal amoebae after treatment of invasive disease with other drugs).</i>
<b>Availability</b>	<b>TABLET</b> 500 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> 500 mg every 8 h for 10 days.  <b>Child-</b> 20 mg/kg body weight daily in three divided doses for 10 days.
<b>Contraindications</b>	Lactation (Appendix 7b); systemic amoebiasis.
<b>Precautions</b>	Pregnancy (defer treatment until after first trimester).
<b>Adverse Effects</b>	Flatulence; occasionally vomiting, pruritus and urticaria; furred tongue.
<b>Storage</b>	Store protected from light.

### Metronidazole\* (Refer Page No. 140)

**Pregnancy Category-B**

**Schedule H**

<b>Indications</b>	<i>Invasive amoebiasis and giardiasis; trichomoniasis; tissue nematode infections; bacterial infections; Helicobacter pylori eradication; ulcerative gingivitis.</i>
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**Availability** **TABLETS** 200 and 400 mg; **SUSPENSION** 200 mg/5 ml; **INJECTION** 500 mg in 100 ml infusion.

**Dose** **Oral**

**Adult- Amoebiasis:** 400 to 800 mg three times a day for 5 to 7 days. **Giardiasis:** 200 mg three times a day for 7 to 10 days.

**Child-** 35 to 50 mg/kg body weight in amoebiasis and 10 to 15 mg/kg body weight in giardiasis.

**Intravenous injection**

**Adult-** 500 mg every eight h up to 7 days.

**Child-** (Below 12 years) 7.5 mg/kg body weight.

**Contraindications** Chronic alcohol dependence; neurological disease, blood dyscrasias, first trimester of pregnancy.

**Precautions** Disulfiram-like reaction with alcohol; hepatic impairment and hepatic encephalopathy (Appendix 7a); pregnancy (Appendix 7c); see also notes above); lactation (Appendix 7b); clinical and laboratory monitoring in courses lasting longer than 10 days; interactions (Appendix 6a, 6c, 6d); prolonged use may result in fungal or bacterial superinfection, phenobarbitones, history of seizure disorder.

**Adverse Effects** Nausea, vomiting, unpleasant metallic taste, furred tongue and gastrointestinal disturbances; rarely, headache, drowsiness, dizziness, ataxia, darkening of urine, erythema multiforme, pruritus, urticaria, angioedema and anaphylaxis; abnormal liver function tests, hepatitis, jaundice; thrombocytopenia, aplastic anaemia; myalgia, arthralgia; peripheral neuropathy, epileptiform seizures; leukopenia on prolonged or high dosage regimens; anorexia, glossitis, dryness of mouth.

**Storage** Store protected from light and moisture. Store injection in a single dose container.

## Tinidazole

**Pregnancy Category-C**

**Schedule H**

**Indications** *Amoebiasis, trichomoniasis and giardiasis, anaerobic infections, necrotising ulcerative gingivitis, bacterial vaginosis, H. pylori associated peptic ulcers, abdominal surgery prophylaxis.*



<b>Availability</b>	<b>TABLETS</b> 300 and 500 mg, 1g; <b>INJECTION</b> 400 ml infusion (2 mg/ml); <b>SUSPENSION</b> 75 mg/5 ml, 150 mg/5 ml.
<b>Dose</b>	<b>Oral</b> <b>Anaerobic infections:</b> <b>Adult-</b> 2g on first day, followed by 1g daily or 0.5g twice daily for 5-6 days. <b>Amoebiasis:</b> <b>Adult-</b> 1.5 - 2g daily as a single dose for 3 - 6 days. <b>Child-</b> 30-50 mg/kg daily as a single dose for 3 days. <b>Trichomoniasis and giardiasis:</b> <b>Adult-</b> 2g as a single dose. <b>Child-</b> 50 to 75 mg/kg as a single dose. <b>Parenteral</b> <b>Bacterial vaginosis and ulcerative gingivitis:</b> <b>Adult-</b> 2g as a single dose parenterally. <b>Anaerobic infections:</b> <b>Adult-</b> Initially 800 mg/400 ml infused i.v. at a rate of 10 ml/minute followed by 800 mg daily. <b>Abdominal surgical prophylaxis:</b> <b>Adult-</b> 2.0g as single i.v. infusion 12 h prior to surgery.
<b>Contraindications</b>	Hypersensitivity to nitroimidazole derivatives, first trimester of pregnancy (Appendix 7c), lactation, blood dyscrasias, porphyria; interactions (Appendix 6a).
<b>Precautions</b>	Seizures, peripheral neuropathy, CNS disease, disulfiram-like reaction with alcohol.
<b>Adverse effects</b>	Similar to metronidazole.
<b>Storage</b>	Store protected from light and moisture.

## 9.2 Antibacterial Drugs

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### Beta-Lactams:

Beta-lactam antibiotics including penicillins, cephalosporins and carbapenems share a common structure; they are bactericidal, their mechanism of action resulting from inhibition of peptidoglycan, a mucopeptide in bacterial cell walls. Benzylpenicillin and phenoxymethylpenicillin are active against susceptible strains of Gram-positive bacteria and Gram-negative bacteria, spirochaetes and actinomycetes, but are inactivated by penicillinase and other beta-lactamases. Benzathine benzylpenicillin and procaine benzylpenicillin are long-acting preparations which slowly release benzylpenicillin on injection. A range of penicillins with improved stability to gastric acid and penicillinases have been produced by substitution of the 6-amino position of 6-aminopenicillanic acid. Cloxacillin is an isoxazolyl penicillin which is resistant to staphylococcal penicillinase. Broad-spectrum penicillins such as ampicillin are acid-stable and active against Gram-positive and Gram-negative bacteria, but are inactivated by penicillinase. Beta-lactamase inhibitors such as clavulanic acid are often necessary to provide activity against beta-lactamases produced by a wide range of both Gram-negative and Gram-positive bacteria.

Cephalosporins are classified by generation, with the first generation agents having Gram-positive and some Gram-negative activity; the second generation drugs have improved Gram-negative activity and the third generation cephalosporin have a wider spectrum of activity, although may be less active against Gram-positive bacteria than first generation drugs, but they are active against Gram-negative Enterobacteriaceae and *Pseudomonas aeruginosa*.

Carbapenems are semisynthetic derivatives of *Streptomyces cattleya*. They have a broad spectrum of activity and are stable to most penicillinases. They should be reserved for severe infections resistant to other antibiotics.

Penicillins may cause encephalopathy due to cerebral irritation. This rare, but serious adverse effect may result from very high doses or in severe renal failure. Penicillins should not be given by intrathecal injection because they can cause encephalopathy which may be fatal.

### Hypersensitivity:

The most important adverse effect of penicillins is hypersensitivity which causes rashes and, occasionally anaphylaxis, which can be fatal. A careful history should be taken with regard to

previous allergic reactions. If rash develops, another antimicrobial should be substituted. Allergic reactions to penicillins occur in 1-10% of exposed individuals, while anaphylactic reactions occur in fewer than 0.05% of treated patients. Individuals with a history of anaphylaxis, urticaria or rash immediately after penicillin administration are at risk of immediate hypersensitivity to penicillin. These individuals should not receive penicillin, rather a cephalosporin or another beta-lactam antibiotic may be used. Patients who are allergic to one penicillin will be allergic to them all because the hypersensitivity is related to the basic penicillin structure and about 10% of penicillin-sensitive patients will be allergic to cephalosporins and other beta-lactams. Individuals with a history of a minor rash (a non-confluent rash restricted to a small area of the body) or a rash occurring more than 72 h after penicillin administration are possibly not allergic to penicillin and in these individuals a penicillin should not be withheld unnecessarily for a serious infection; however, the possibility of an allergic reaction should be borne in mind and facilities should be available for treating anaphylaxis.

### **Ampicillin, Amoxicillin, Amoxicillin with Clavulanic Acid and Cloxacillin:**

**Ampicillin** is active against certain Gram-positive and Gram-negative organisms. It is used to treat a wide range of infections including otitis media, respiratory-tract and urinary-tract infections and gonorrhoea due to susceptible bacteria. However, ampicillin is inactivated by penicillinases including those produced by *Staphylococcus aureus* and by common Gram-negative bacilli such as *Escherichia coli*; many strains of *Haemophilus influenzae*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae* and *Salmonella* and *Shigella* spp. are resistant. There are geographical variations in the incidence of resistance and an awareness of local patterns is important. In some areas, oral use should be restricted to treatment of *Shigella* infections; it is given in an oral dose of 1g every 6 h for 7-10 days.

**Amoxicillin** has a similar spectrum of activity to ampicillin, but is also inactivated by penicillinases. However, it is better absorbed after oral administration than ampicillin and higher plasma and tissue levels are achieved. Amoxicillin is preferred to ampicillin for the treatment of some infections including otitis media and respiratory-tract and urinary-tract infections.

**Clavulanic acid** is a beta-lactamase inhibitor. It has no significant antibacterial activity but in combination with Amoxicillin widens Amoxicillin's spectrum of activity and allows its use against Amoxicillin-resistant strains of bacteria. It is used in respiratory-tract, genito-urinary and abdominal infections, cellulitis, animal bites and dental infections.

**Cloxacillin** is used to treat infections due to penicillinase-producing *staphylococci* which are resistant to benzylpenicillin. It is acid-stable and may therefore be given by mouth as well as by injection.

These antibiotics may also be administered with an aminoglycoside to increase their spectrums of activity. The penicillin and aminoglycoside should not be mixed before or during administration, because loss of aminoglycoside activity can occur on mixing.

### **Benzylpenicillin and Phenoxyethylpenicillin:**

Benzylpenicillin remains an important and useful antibiotic but it is inactivated by bacterial beta-lactamases. It is effective for many streptococcal (including pneumococcal), gonococcal and meningococcal infections and also for anthrax, diphtheria, gas gangrene, leptospirosis, tetanus and treatment of Lyme disease in children. Pneumococci, meningococci and gonococci often have decreased sensitivity to penicillin and benzylpenicillin is no longer the first choice for pneumococcal meningitis. Benzylpenicillin is given by injection as it is inactivated by gastric acid and absorption from the intestinal tract is low.

Depot preparations are used when therapeutic concentrations need to be sustained for several h. Benzathine benzylpenicillin or procaine benzylpenicillin provides a tissue depot from which the drug is slowly absorbed over a period of 12 hour to several days. They are the preferred choice for the treatment of syphilis or yaws.

**Phenoxyethylpenicillin** is suitable for oral administration; it has a similar spectrum of activity but is less effective than benzylpenicillin. It should not be used for serious infections because absorption can be unpredictable and plasma concentrations variable.

### **Cephalosporins and Imipenem with Cilastatin:**

**Ceftazidime** and **ceftriaxone** are third generation cephalosporins. Ceftriaxone is used for serious infections such as septicaemia, pneumonia and meningitis; it is used as a reserve antimicrobial to treat meningitis due to *Streptococcus pneumoniae* in some areas where penicillin resistance is found. Ceftazidime is active against *Pseudomonas aeruginosa* and other Gram-negative bacteria; it is used in the treatment of pseudomonas infections and in some areas is restricted to use only where gentamicin resistance is high.

**Imipenem** is a broad-spectrum antibiotic. As it is partially

inactivated by enzymatic activity in the kidney, it is administered with **cilastatin** which inhibits the renal metabolism of imipenem. It is active against many aerobic and anaerobic Gram-positive and Gram-negative bacteria; in some areas it is reserve agent for the treatment of infections due to *Acinetobacter* spp. and *P. aeruginosa*, which are resistant to other more usual treatments.

### Quinolones:

**Ciprofloxacin** is active against both Gram-positive and Gram-negative bacteria. It is particularly active against salmonella, shigella, campylobacter, neisseria, *Bacillus anthracis* and pseudomonas. It is also active against chlamydia and some mycobacteria. Most anaerobic organisms are not susceptible. Ciprofloxacin is used with doxycycline and metronidazole to treat pelvic inflammatory disease.

**Nalidixic acid** is an older quinolone effective in uncomplicated urinary-tract infections and, in the treatment of shigella in areas where it remains susceptible.

### Tetracyclines:

**Doxycycline** is a tetracycline and is a broad-spectrum antibiotic effective for conditions caused by chlamydia, rickettsia, brucella and the spirochaete, *Borrelia burgdorferi* (Lyme disease). It is the preferred tetracycline since it has a more favourable pharmacokinetic profile than tetracycline. It is deposited in growing bone and teeth causing staining and occasionally dental hypoplasia. It should not be given to children under 8 years or pregnant women; in some countries, use in children under 12 years is contraindicated.

### Aminoglycosides:

Aminoglycosides including **gentamicin** are bactericidal and active against some Gram-positive and many Gram-negative organisms including *Pseudomonas aeruginosa*. Aminoglycosides are not absorbed from the gut and must therefore be given by injection for systemic infections. Excretion is mainly by the kidney and accumulation occurs in renal impairment.

Use of gentamicin should be restricted to trained health personnel and care must be taken to ensure correct dosage and duration of treatment are not exceeded, because most adverse effects are dose related. The most important adverse effects are ototoxicity and nephrotoxicity and they are most common in the elderly and in patients with renal impairment. These groups and, if possible, all patients should be monitored for ototoxicity by audiometry. If there is impairment of renal function the dose interval must be increased; in severe renal impairment, the dose should also be reduced. Serum concen-

tration monitoring avoids both excessive and subtherapeutic concentrations and can prevent toxicity and ensure efficacy. If possible serum concentrations should be monitored in all patients, but must be measured in infants, the elderly, in obesity, in cystic fibrosis, in high-dosage regimens, in renal impairment, or if treatment lasts for longer than 7 days.

For most infections, doses of up to 5 mg/kg daily in divided doses are used if renal function is normal; higher doses are used occasionally for serious infections. Loading and maintenance doses are based on the patient's weight and renal function (for example, using a nomogram) with adjustments based on plasma gentamicin concentration.

### Chloramphenicol:

**Chloramphenicol** is a potent broad-spectrum antibiotic. It is associated with serious haematological adverse effects and should be reserved for the treatment of severe infections, particularly those caused by *Haemophilus influenzae* and typhoid fever. The oily suspension should be reserved for use in situations of catastrophic epidemics of meningococcal meningitis occurring mainly in sub-Saharan Africa, during which the medical services are overwhelmed by the epidemic and in which the overwhelming scale of the epidemic precludes any other form of antimicrobial therapy.

### Macrolides:

**Erythromycin** is a macrolide; it has an antibacterial spectrum that is similar but not identical to penicillin and is used as an alternative in penicillin-allergic patients. It is effective in respiratory infections, whooping cough, legionnaires' disease and campylobacter enteritis.

**Azithromycin** is more active than erythromycin against some Gram-negative organisms such as *Chlamydia trachomatis*. The concentration and persistence of azithromycin is much higher in the tissue than in plasma; a single dose of azithromycin is used in the treatment of uncomplicated genital chlamydia and trachoma. Azithromycin is not recommended if there is a possibility of gonorrhoea because macrolide resistance emerges rapidly when it is used in this setting.

### Metronidazole:

**Metronidazole** has high activity against anaerobic bacteria and protozoa. Metronidazole by the rectal route is an effective alternative to the intravenous route when oral administration is not possible.

## Nitrofurantoin:

**Nitrofurantoin** is bactericidal *in vitro* to most Gram-positive and Gram-negative urinary-tract pathogens and it is used to treat acute and recurrent urinary-tract infections. It is also used prophylactically in chronic urinary-tract infections.

## Sulfonamides and Trimethoprim:

The usefulness of sulfonamides is limited by an increasing incidence of bacterial resistance. For many indications they have been replaced by antibiotics that are more active and safer. **Sulfadiazine** is used in the prevention of rheumatic fever recurrence. **Sulfamethoxazole** is used in combination with **trimethoprim** because of their synergistic activity. In some countries, indications for the use of this combination have been restricted. The treatment of *Pneumocystis carinii* infections must only be undertaken with specialist supervision where there are appropriate monitoring facilities. Trimethoprim is also used alone for respiratory-tract infections and, in particular, for urinary-tract infections.

## Vancomycin:

Vancomycin is not significantly absorbed from the gastrointestinal tract and must be given intravenously for systemic infections which cannot be treated with other effective, less toxic antimicrobials. It is used to treat serious infections due to Gram-positive cocci including methicillin-resistant staphylococcal infections, brain abscess, staphylococcal meningitis and septicaemia.

## Amoxicillin\*

Pregnancy Category-B

Schedule H

### Indications

*Urinary-tract infections, upper respiratory-tract infections, bronchitis; pneumonia; otitis media; dental abscess; osteomyelitis; Lyme disease in children; endocarditis prophylaxis; post-splenectomy prophylaxis; gynaecological infections; gonorrhoea; Helicobacter pylori eradication.*

### Availability:

**TABLETS** 250 mg, 500 mg; **KID TABLETS** 125, 250 mg; **CAPSULES** 250, 500 mg; **DRY SYRUP** 125 and 250 mg per 5 ml; **INJECTION** 1 ml ampoule (100 mg/ml), 250 mg/vial; **DROP** 10 ml (100 mg/ml).

### Dose

**Oral**

**Adult-** 250 mg every 8 h, double in severe infection.

**Otitis media:** 1g every 8 h.

**Enteric fever:** 2 to 4g daily in divided doses for 14 to 21 days.

***Intramuscular injection***

500 mg every 8 h.

***Intravenous injection or infusion***

500 mg every 8 h, increase to 1g every 6 h in case of severe infection.

**Child up to 10 years-** 125 mg every 8 h, double in severe infections.

**Otitis media:** 40 mg/kg body weight daily in three divided doses.

**Enteric fever:** 50 to 100 mg/kg body weight in three divided doses for 14 to 21 days.

***Intramuscular injection***

50 to 100 mg/kg body weight in divided doses.

***Intravenous injection or infusion***

50 to 100 mg/kg body weight in divided doses.

**Contraindications**

Hypersensitivity to penicillins (see notes above).

**Precautions**

History of allergy; renal impairment; erythematous rashes common in glandular fever, chronic lymphatic leukaemia and possibly HIV infection; lactation (Appendix 7b); interactions (Appendix 6b, 6c, 6d); possibility of super infection with mycotic pathogens, mononucleosis, hepatic impairment (Appendix 7a); pregnancy (Appendix 7c).

**Adverse Effects**

Nausea and vomiting, diarrhoea; rashes (hypersensitivity or toxic response, may be serious reaction-discontinue treatment); hypersensitivity reactions including Steven's Johnson syndrome, urticaria, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, interstitial nephritis; rarely, antibiotic-associated colitis; neutropenia, thrombocytopenia, coagulation disorders; rarely, central nervous system disorders including convulsions associated with high doses or impaired renal function; mucocutaneous candidiasis, with discolouration; agitation.



**Storage**

**Tablet, Capsule and Oral suspension:** Store protected from moisture at a temperature not exceeding 30°C. **Injection:** Store protected from moisture in a sterile, tamper evident container sealed so as to exclude micro-organisms at temperature not exceeding 30°C.

**Amoxicillin + Clavulanic acid\*****Pregnancy Category-B****Schedule H****Indications**

*Treatment of infections caused by susceptible organisms, sinusitis, otitis media, dental abscesses, severe respiratory tract infections, urinary tract infections, skin and soft tissue infections, surgical prophylaxis.*

**Availability****TABLETS**

Amoxicillin + Clavulanic acid  
 500 mg + 125 mg  
 250 mg + 125 mg  
 875 mg + 125 mg  
 200 mg + 28.5 mg (DT)

**CAPSULES**

Amoxicillin + Clavulanic acid  
 500 mg + 125 mg  
 250 mg + 125 mg

**SUSPENSION**

Amoxicillin + Clavulanic acid  
 200 mg + 28.5 mg/5 ml  
 125 mg + 31.25 mg/5 ml  
 250 mg + 62.5 mg/5 ml

**INJECTION**

Amoxicillin + Clavulanic acid  
 250 mg + 50 mg  
 1g + 200 mg  
 125 mg + 25 mg  
 500 mg + 100 mg

**Dose****Oral**

**Upper and lower respiratory tract infections, sinusitis, otitis media, skin and soft tissue infections, susceptible infections:**

**Adult-** 250-500 mg every 8 hours or 500-750 mg every 12 hours.

**Child-** 125-250 mg every 8 hours;

**Children weighing <40 kg:** 20-40 mg/kg/day in divided doses every 8 hours;

**Infants <3 months:** up to 30 mg/kg/day in divided doses every 12 hours.

**Dental abscesses:** Adult- 3 g as a single dose, followed by a second dose 8 hours later.

**Severe or recurrent respiratory tract infections: Adult**- 3 g twice daily.  
**Child (2-6 years)**- 5 ml twice daily;  
**(7-12 years)**- 10 ml twice daily before meals, upto 14 days (dose should be specified in terms of strength).

#### **Parenteral**

**Susceptible infections and surgical prophylaxis: Adult**- 500 mg every 8 hr. In severe infections, dose may be increased to 1 g every 6 hours, upto 14 days. Can be given via i.m or slow i.v over 3-4 minutes or i.v infusion over 30-60 minutes.  
**Child: <10 years:** 50-100 mg/kg/day in divided doses.

<b>Contraindications</b>	Hypersensitivity to penicillins, infectious mononucleosis, jaundice.
<b>Precautions</b>	Renal impairment, hepatic dysfunction, patients on anticoagulant therapy, pregnancy (Appendix 7c), lactation, interactions (Appendix 6c).
<b>Adverse Effects</b>	GI upset, mycosis, rash, nausea, vomiting, anaphylaxis, cholestatic jaundice, blood dyscrasias, toxic epidermal necrolysis, convulsions, exfoliative dermatitis, Stevens Johnson syndrome, angioedema, hepatitis, tooth discolouration.
<b>Storage</b>	Store protected from moisture at a temperature not exceeding 30°C.

## **Ampicillin\***

**Pregnancy Category-B**

**Schedule H**

<b>Indications</b>	<i>Mastoiditis; gynaecological infections; septicaemia; peritonitis; endocarditis; meningitis; cholecystitis; osteomyelitis; respiratory tract infection.</i>
<b>Availability</b>	<b>TABLETS</b> 125 and 250 mg; <b>CAPSULES</b> 250, 500 mg and 1g; <b>DRY SYRUP</b> 125 and 250 mg/5 ml; <b>INJECTION</b> 100, 250 and 500 mg/vial.
<b>Dose</b>	<b>Oral</b>  <b>Adult</b> - 250 mg to 1g every 6 h at least 30 min before food.  <b>Urinary tract infection Adult</b> - 500 mg every 8 h.

**Children under 10 years-** Half of adult dose.

***Intramuscular and intravenous injection or infusion***

500 mg every 4 to 6 h.

**Listeria meningitis** (in combination with antibiotics); by intravenous infusion 2g every 4h for 10 to 14 days.

**Child-** Half of the adult dose.

**Listeria meningitis** (in combination with antibiotics); infants 1 to 3 months; 50 to 100 mg/kg body weight every 6 h. 3 months to 12 years; 100 mg/kg body weight every 76 h (max 12g daily).

**Contraindications** Hypersensitivity to penicillins (see notes above).

**Precautions** History of allergy (see notes above); renal impairment (Appendix 7d); erythematous rashes common in glandular fever, acute or chronic lymphocytic leukaemia and cytomegalovirus infection; lactation (Appendix 7b); interactions (Appendix 6b, 6c, 6d); pregnancy (Appendix 7c).

**Adverse Effects** Nausea and vomiting, diarrhoea; rashes, high fever (hypersensitivity or toxic response-may be serious reaction, discontinue treatment); hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness-like reaction, haemolytic anaemia, interstitial nephritis (see also notes above); rarely, antibiotic-associated colitis; neutropenia, thrombocytopenia, coagulation disorders; sore tongue; asthma.

**Storage** **Tablets, Capsule, Oral suspension:** Store protected from moisture and light at a temperature not exceeding 30°C. **Injection:** Store protected from light in a sterile tamper evident container sealed so as to exclude micro-organisms at a temperature not exceeding 30°C.

**Azithromycin\***

**Pregnancy Category-B**

**Schedule H**

**Indications** *Uncomplicated genital chlamydial infections and trachoma.*

**Availability** **TABLETS** 100, 250 and 500 mg; **CAPSULES** 250 and 500 mg; **INJECTION** 500 mg/vial  
**DRY SYRUP** 100, 200 mg/5 ml.

**Dose** **Oral**

**Adult-** 500 mg once daily for 3 days or 500 mg on first day then 250 mg once daily for 4 days.

**Child-** over 6 months: 10 mg/kg body weight once daily for three days.

Body weight 15 to 20 kg: 200 mg once daily for 3 days; body weight 26 to 35 kg: 300 mg daily for 3 days.

Uncomplicated genital chlamydia infection and non-gonococcal infection: 500 mg once daily for 7 days.

**Contraindications** Hepatic impairment (Appendix 7a); hypersensitivity to erythromycin.

**Precautions** Pregnancy (Appendix 7c) and lactation (Appendix 7b); renal impairment, prolongation of QT interval (ventricular tachycardia reported); interactions (Appendix 6c, 6d); exacerbation of symptoms of myasthenia gravis; impaired hepatic function.

**Adverse Effects** Fewer gastrointestinal effects as compared to erythromycin, also anorexia, dyspepsia, constipation; dizziness, headache, drowsiness; photosensitivity; hepatitis, interstitial nephritis, acute renal failure, asthenia, paraesthesia, convulsions and mild neutropenia reported; rarely, tinnitus, hepatic necrosis, hepatic failure and taste disturbances; flatulence, somnolence, angioedema; eczema, pharyngitis; arthralgia, conjunctivitis.

**Storage** Store protected from moisture.

## Benzathine Benzyl Penicillin\*

**Indications** *Mild to moderate infections of upper respiratory tract due to susceptible streptococci, Syphilis, prophylaxis of rheumatic fever.*

**Availability** **INJECTABLE SUSPENSION-** 1200,000 units/2 ml.

**Dose** **Streptococcal URTI:** 1.2 million unit (>27 kg) single dose (deep IM inj) after sensitivity test (AST); 0.6 million unit (<27 kg) single dose (deep IM inj) AST.

**Secondary prophylaxis of Rheumatic fever:** 1.2 million unit (> 27 kg) single dose (deep IM inj) after sensitivity test (AST) every 21 days; 0.6 million unit (<27 kg) single dose (deep IM inj) AST every 15 days.

**Syphilis:** Primary, secondary, or early latent: Single dose of 2.4 million Unit IM; Late latent (or latent of uncertain duration), cardiovascular, or benign tertiary: 2.4 million Unit IM weekly for 3 weeks.

<b>Contraindications</b>	Hypersensitivity, neurosyphilis.
<b>Precautions</b>	Hypersensitivity to cephalosporins or/and penicillins, elderly, infants, asthma, kidney disease, lactation (Appendix 7b); interactions (Appendix 6c).
<b>Adverse effects</b>	Hypersensitivity reactions such as exfoliative dermatitis, pain at injection site, thrombophlebitis of injected vein, diarrhoea, nausea, joint pain, angioedema, serum sickness like reactions; haemolytic anaemia, interstitial nephritis.

## Benzyl Penicillin

**Pregnancy Category-B**

**Schedule H**

<b>Indications</b>	<i>Mild to moderate infections of upper respiratory tract due to susceptible streptococci, syphilis, prophylaxis of rheumatic fever.</i>
<b>Availability</b>	<b>INJECTABLE SUSPENSION-</b> 6, 12, 24 Lac units; <b>INJECTABLE SUSPENSION-</b> 1200,000 units/2 ml.
<b>Dose</b>	<p><b>Streptococcal URTI:</b> 1.2 million unit (&gt;27 kg) single dose (deep IM inj) after sensitivity test (AST); 0.6 million unit (&lt;27 kg) single dose (deep IM inj) AST.</p> <p><b>Secondary prophylaxis of Rheumatic fever:</b> 1.2 million unit (&gt;27 kg) single dose (deep IM inj) after sensitivity test (AST) every 21 days; 0.6 million unit (&lt;27 kg) single dose (deep IM inj) AST every 15 days.</p> <p><b>Syphilis:</b> Primary, secondary, or early latent: Single dose of 2.4 million Unit IM; Late latent (or latent of uncertain duration), cardiovascular, or benign tertiary: 2.4 million Unit IM weekly for 3 weeks.</p>
<b>Contraindications</b>	Hypersensitivity, neurosyphilis.

**Precautions** Hypersensitivity to cephalosporins or/and penicillins, elderly, infants, asthma, renal impairment (Appendix 7d), lactation (Appendix 7b); pregnancy (Appendix 7c).

**Adverse Effects** Hypersensitivity reactions such as exfoliative dermatitis, pain at injection site; thrombophlebitis of injected vein, diarrhoea, nausea, joint pain, angioedema, serum sickness like reactions, haemolytic anaemia, interstitial nephritis.

**Storage** Store protected from moisture at a temperature not exceeding 30°C.

## Cefazolin

**Pregnancy Category-B**

**Schedule H**

**Indications** *Respiratory tract infection; urinary tract infection; skin and soft tissue infection; biliary tract infection; bone and joint infection; endocarditis; septicaemia; preoperative prophylaxis.*

**Availability** **INJECTION** 125, 250, 500 mg and 1g/vial.

**Dose** ***Intramuscular and intravenous injection***

**Adult-** 1 to 4g daily in 2 to 3 divided doses.

**Child-** 50 to 100 mg/kg body weight every 6 h.

**Contraindications** Hypersensitivity and cephalosporin; colitis; lactation; pregnancy (Appendix 7c).

**Precautions** Renal function impairment (Appendix 7d); over growth of non-susceptible organism; interactions (Appendix 6c).

**Adverse Effects** Eosinophilia; diarrhoea; fever; convulsions; neutropenia, anaphylaxis, phlebitis, oral candidiasis, leucopenia; transient rise in SGOT and SGPT and alkaline phosphatase.

**Storage** Store protected from light and moisture at a temperature not exceeding 30°C. The constituted solution should be stored protected from light and used within 24 hours when stored at a temperature not exceeding 30°C or within 4 days when stored between 2 to 8°C.

## Cefixime\*

Pregnancy Category-B

Schedule H

<b>Indications</b>	<i>Otitis media, respiratory tract infections, uncomplicated UTIs, effective against infections caused by Enterobacteriaceae, H. influenza species.</i>
<b>Availability</b>	<b>TABLETS</b> 50, 100, 200 and 400 mg; <b>CAPSULES</b> 100 and 200 mg; <b>SYRUP/SUSPENSION</b> 50 mg/5 ml, 100 mg/5 ml.
<b>Dose</b>	<p><b>Adult-</b> 200-400 mg/day as a single dose or in two divided doses.</p> <p><b>Child-</b> (more than 6 months) 8 mg/kg/day as a single dose or two divided doses.</p> <p><b>Uncomplicated gonorrhoea: Adult-</b> 400 mg as a single dose.</p>
<b>Contraindications</b>	Hypersensitivity to cephalosporins.
<b>Precautions</b>	History of allergy to penicillins, renal failure (Appendix 7d) or patients undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD), gastrointestinal disease, pregnancy (Appendix 7c), lactation, interactions (Appendix 6c).
<b>Adverse Effects</b>	Diarrhoea, pseudomembranous colitis, loose or frequent stools, abdominal pain, nausea, dyspepsia; hypersensitivity reactions.
<b>Storage</b>	Store protected from light and moisture at a temperature not exceeding 30°C.

## Cefoperazone

Pregnancy Category-B

Schedule H

<b>Indications</b>	<i>Urinary, biliary, respiratory, skin soft tissue infections, meningitis, septicemias, Pseudomonas, Salmonella typhi, B. fragilis infections.</i>
<b>Availability</b>	<b>INJECTIONS</b> 0.25, 1.0, 2.0 g/vial.
<b>Dose</b>	25-100 mg/kg/day in 2-3 divided doses.
<b>Contraindications</b>	Hypersensitivity, interactions (Appendix 6a).

**Adverse Effects**

Anaphylaxis, fever, skin rashes; nephritis; granulocytopenia, and hemolytic anaemia, hypoprothrombinaemia and bleeding disorders.

**Cefotaxime\*****Pregnancy Category-B****Schedule H****Indications**

*Infections due to sensitive Gram positive and Gram negative bacteria such as bacteraemia, cellulites, intra-abdominal infections, gonorrhoea, bone or joint infections, skin and skin structure infections, urinary tract infections, septicaemias, surgical prophylaxis, endometritis, life threatening resistant/hospital acquired infections, infections in immuno-compromised patients, Haemophilus epiglottitis and meningitis.*

**Availability**

**INJECTION** 125, 250, 500 mg, and 1g/vial.

**Dose**

**Susceptible infections:** 1–2g by i.v or i.m injection, 8 – 12 hourly. Max.-12 g/day.

**Child-** 50-100 mg/kg/day.

**Surgical prophylaxis:** 1g by i.v or i.m injection, 30-90 minutes before procedure.

**Gonorrhoea:** 0.5–1g by i.m injection, as a single dose.

**Septicaemia, meningitis:**

**Adult-** 2g i.v, 6-8 hourly for 14-28 days.

**Neonates-** 50 mg/kg daily in 2–4 divided doses may be increased to 150–200 mg/kg daily in severe infections.

**Child-** 100–150 mg/kg daily in 2–4 divided doses increased up to 200 mg/kg daily in very severe infections.

**Contraindications**

Renal disease (Appendix 7d); hypersensitivity to cephalosporins.

**Precautions**

Impaired kidney or liver disease, colitis; history of penicillin allergy; pregnancy (Appendix 7c), lactation; diabetes.

**Adverse effects**

Local inflammation or pain at injection site; thrombocytopenia, eosinophilia, leukopenia; pseudomembranous colitis, moniliasis, diarrhoea, candidiasis, decreased urination; seizures, headache, nausea and vomiting; jaundice; Steven's Johnson syndrome.

**Storage**

Store protected from light at a temperature not exceeding 30°C.



## Ceftazidime\*

Pregnancy Category-B

Schedule H

<b>Indications</b>	<i>Infections due to sensitive bacteria, especially those due to Pseudomonas spp. and including those resistant to aminoglycosides.</i>
<b>Availability</b>	<b>INJECTION</b> 250, 500 mg, 1g and 2g vial.
<b>Dose</b>	<p><b>Deep intramuscular and intravenous injection and infusion</b></p> <p><b>Adult-</b> 1g every 8 h or 2g every 12 h.  <b>Severe infections:</b> 2g every 12 h or 3g every 12 h (1g single dose by intravenous route).  <b>Immunocompromised or meningitis patients:</b> 150 mg/kg body weight daily in 3 divided doses (max 6g daily) given by i.v. route only.</p> <p><b>Elderly-</b> Usual max dose of 3g daily.</p> <p><b>Child-</b> Up to 2 months; 25 to 60g/kg body weight in two divided doses. Over 2 months: 30 to 100 mg/kg body weight in 2 to 3 divided doses.</p>
<b>Contraindications</b>	Cephalosporin hypersensitivity; porphyria.
<b>Precautions</b>	Penicillin sensitivity; renal impairment; lactation (Appendix 7b); false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test; interactions (Appendix 6b, 6c); pregnancy (Appendix 7c); fall in prothrombin activity, colitis.
<b>Adverse Effects</b>	Diarrhoea, nausea, vomiting, abdominal discomfort, headache; rarely, antibiotic-associated colitis (particularly with higher doses); allergic reactions including rashes, pruritus, urticaria, serum sickness-like reaction, fever and arthralgia and anaphylaxis; erythema multiforme, toxic epidermal necrolysis reported; transient hepatitis, cholestatic jaundice; eosinophilia and blood disorders (including thrombocytopenia, leukopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia); reversible interstitial nephritis; nervousness, sleep disturbances, confusion, hypertonia and dizziness; phlebitis, angioedema, myoclonia, candidiasis, transient elevation of blood urea and serum creatinine.
<b>Storage</b>	Store in sterile containers sealed so as to exclude micro-organisms protected from moisture at a temperature not exceeding 30°C.

## Ceftriaxone\*

Pregnancy Category-B

Schedule H

<b>Indications</b>	<i>Serious infections due to sensitive bacteria, including septicaemia, pneumonia and meningitis; surgical prophylaxis; prophylaxis of meningococcal meningitis; gonorrhoea; bone and joint infection.</i>
<b>Availability</b>	<b>INJECTION</b> 125, 250, 500 mg, 1g and 2g vial.
<b>Dose</b>	<p><b><i>Intramuscular and intravenous injection or infusion</i></b></p> <p><b>Adult-</b> Urinary tract infection, pneumonia, pelvic inflammatory disease, prophylaxis of surgical infections and meningitis: 4g initially once daily for 10 days or up to 72 h after fever disappears.</p> <p><b>Typhoid:</b> 4g daily for two days followed by 2g daily for next two days. 1 to 2g daily is used for any other type of condition.</p> <p><b>Child- Meningitis:</b> 75 to 100 mg/kg body weight for 7 to 9 days.</p> <p><b>Typhoid:</b> 5 mg/kg body weight for 7 days. 50 to 75 mg/kg body weight is used in case of any other condition (max 2g/day).</p>
<b>Contraindications</b>	Cephalosporin hypersensitivity; porphyria; neonates with jaundice, hypoalbuminaemia, acidosis or impaired bilirubin binding.
<b>Precautions</b>	Penicillin sensitivity; severe renal impairment; hepatic impairment if accompanied by renal impairment (Appendix 7a); premature neonates; may displace bilirubin from serum albumin; treatment longer than 14 days, renal failure, dehydration or concomitant total parenteral nutrition-risk of ceftriaxone precipitation in gallbladder; lactation (but appropriate to use, see Appendix 7b); pregnancy (Appendix 7c); false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test; interactions (Appendix 6b, 6c); prophylactic indication, patients with impaired vit K synthesis, monitoring of prothrombin time is recommended.

**Adverse Effects**

Diarrhoea, nausea and vomiting, abdominal discomfort, headache; antibiotic-associated colitis (particularly with higher doses); allergic reactions including rashes, pruritus, urticaria, serum sickness-like reactions, fever and arthralgia and anaphylaxis; erythema multiforme, toxic epidermal necrolysis reported; transient hepatitis and cholestatic jaundice; elevation of SGOT and SGPT; eosinophilia and blood disorders (including thrombocytopenia, leukopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia); reversible interstitial nephritis, hyperactivity, nervousness, sleep disturbances, confusion, hypertonia and dizziness; calcium ceftriaxone precipitates in urine (particularly in very young, dehydrated, or those who are immobilized) or in gall bladder-consider discontinuation if symptomatic; rarely, prolongation of prothrombin time, pancreatitis; local reaction, hypersensitivity.

**Storage**

Store protected from light at a temperature not exceeding 30°C.

**Cephalexin\*****Pregnancy Category-B****Schedule H****Indications**

*Respiratory tract infections; otitis media; skin and skin structure infections; genitourinary tract infection; bone infection.*

**Availability**

**CAPSULES/TABLETS** 125, 250 and 500 mg; 125 mg Kid tablets; 250 mg **DT**; **DRY SYRUP** 125 and 250 mg/5 ml.

**Dose**

**To be given preferably on empty stomach.**

**Adult-** 250 mg every 6 h or 500 mg every 8 to 12 h, increased to 1 to 1.5g every 6 to 8 h for severe infections.

**Prophylaxis of severe urinary tract infection:** 125 mg at night.

**Child-** 25 mg/kg body weight daily in divided doses doubled for severe infections (max. 100 mg/kg body weight daily); Under 1 year: 125 mg every 12 h; 1 to 5 years: 125 mg every 8 h; 5 to 12 years: 250 mg every 8 h.

**Contraindications**

Cephalosporin hypersensitivity.

**Precautions** Sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, renal impairment; lactation; false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test; poor nutritional state; pregnancy (Appendix 7c).

**Adverse Effects** Diarrhoea and rarely, antibiotic-associated colitis (more likely with higher doses), nausea and vomiting, abdominal discomfort, headache; allergic reactions including rashes, pruritus, urticaria, serum sickness-like reactions with rashes, fever and arthralgia and anaphylaxis; Stevens-Johnson syndrome, toxic epidermal necrolysis reported; disturbances in liver enzymes, transient hepatitis and cholestatic jaundice; other side-effects reported include eosinophilia and blood disorders (including thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia); reversible interstitial nephritis, hyperactivity, nervousness, sleep disturbances, hallucinations, confusion, hypertonia and dizziness; dyspnoea, colitis, increased blood urea, creatinine, alkaline phosphatase, bilirubin, LDH.

**Storage** Store protected from light and moisture at a temperature not exceeding 30°C.

## Chloramphenicol\* (Refer Page No. 551)

**Pregnancy Category-C**

**Schedule H**

**Indications** *Severe life-threatening infections, particularly those caused by Haemophilus influenzae and typhoid fever; cerebral abscess; mastoiditis; relapsing fever; gangrene; granuloma inguinale; listeriosis; severe melioidosis; plague; psittacosis; tularaemia; Whipple's disease; septicæmia; empirical treatment of meningitis; ocular infection.*

**Availability** **CAPSULES** 250 and 500 mg; **SYRUP** 125 mg/5 ml; **INJECTION** 250 and 500 mg/vial.

**Dose** **Oral, intramuscular or intravenous injection or infusion**

**Adult-** 50 mg/kg body weight in four divided doses (can be doubled in very severe infections, septicæmia, meningitis, reduce as soon as clinically indicated).

**Child-** Haemophilus epiglottitis and pyrogenic meningitis: 50 to 100 mg/kg body weight daily in divided doses (can be doubled in severe infections, reduce as soon as clinically indicated).

**Contraindications** Pregnancy (Appendix 7c); porphyria; blood dyscrasias, preexisting bone marrow depression; hypersensitivity; patients receiving radiation therapy.

**Precautions** Avoid repeated courses and prolonged use; reduce dose in hepatic impairment (Appendix 7a) and severe renal impairment; blood counts required before and during treatment; monitor plasma concentrations in neonates (see below); lactation (Appendix 7b); interactions (Appendix 6c); regular blood count; over growth of non-susceptible organism may occur; seizure disorders.

**Adverse Effects** Bone marrow depression-reversible and irreversible aplastic anaemia (with reports of leukaemia), anaemia, leukopenia and thrombocytopenia; nocturnal haemoglobinuria; peripheral neuritis and optic neuritis; nausea, vomiting, diarrhoea, dry mouth, stomatitis, glossitis; headache, depression; hypersensitivity reactions including, rashes, fever, angioedema and rarely, anaphylaxis; grey baby syndrome (vomiting, greenish diarrhoea, abdominal distension, hypothermia, pallid cyanosis, irregular respiration, circulatory collapse) may follow excessive doses in neonates with immature hepatic metabolism; also reported in infants born to mothers treated in late pregnancy; ocular irritation, angioneurotic edema.

**Storage** **Capsule:** Store protected from moisture. **Syrup and Injection:** Store protected from light and moisture.

## Ciprofloxacin\* (Refer Page No. 552)

**Pregnancy Category-C**

**Schedule H**

**Indications** *Gastroenteritis-including cholera, shigellosis, travellers' diarrhoea, campylobacter and salmonella enteritis; typhoid; gonorrhoea; chancroid; legionnaires' disease; meningitis (including meningococcal meningitis prophylaxis); respiratory-tract infections-including pseudomonal infections in cystic fibrosis, but not pneumococcal pneumonia; urinary-tract infections; bone and joint infections; septicaemia; anthrax; skin infections; prophylaxis in surgery.*

**Availability** **TABLETS** 100, 250, 500 and 750 mg; **INFUSION** 50, 100 and 200 ml (2 mg/ml).

**Dose** **Oral**

**Adult-** Urinary tract infection, respiratory tract infection: 250 to 500 mg, twice daily. Severe respiratory tract infections: up to 750 mg twice daily (however in acute uncomplicated cystitis in women 100 mg twice daily for three days).

**Chronic prostatitis:** 500 mg twice daily for 28 days.

**Gonorrhoea:** 500 mg as a single dose.

**Child-** Not recommended.

***Intravenous infusion (30 to 60 min)***

**Adult-** Urinary tract infection, ENT infection, skin, soft tissue and bone infection, joint infection, gastrointestinal tract infection, severe systemic infection, gonorrhoea, surgical prophylaxis and septicaemia; 100 to 200 mg twice daily by slow intravenous injection or infusion.

**Contraindications**

History of tendon disorders related to quinolone use; exposure to strong sunlight, hypersensitivity to quinolones derivatives; tizanidine therapy.

**Precautions**

History of epilepsy or conditions that predispose to seizures, G-6-PD deficiency, myasthenia gravis (risk of exacerbation), pregnancy (Appendix 7c), lactation (Appendix 7b), children or adolescents (see below); avoid exposure to excessive sunlight (discontinue if photosensitivity occurs); rarely, tendon damage-discontinue at first sign of pain or inflammation and rest affected limb; hepatic impairment; renal failure (Appendix 7d); avoid excessive alkalinity of urine and ensure adequate fluid intake as there is risk of crystalluria; interactions (Appendix 6c); cerebral arteriosclerosis, anxiety, paranoia, erythema, blistering.

**Use In Children.** Ciprofloxacin causes arthropathy in the weight-bearing joints of immature animals and is therefore generally not recommended in children and growing adolescents. However, the significance of this effect in humans is uncertain and in some specific circumstances short-term use of ciprofloxacin in children may be justified. Ciprofloxacin is used for pseudomonal infections in cystic fibrosis (for children over 5 years) and for treatment and prophylaxis of anthrax.

May impair ability to perform skilled tasks, for example operating machinery, driving.

**Adverse Effects**

Nausea, vomiting, dyspepsia, abdominal pain, flatulence, diarrhoea (rarely, antibiotic-associated colitis), dysphagia, tremor, hyperglycaemia, headache, dizziness, sleep disorders, rash (rarely, erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis) and pruritus; vasculitis, erythema nodosum, petechiae, haemorrhagic bullae; less frequently anorexia, increase in blood urea and creatinine; drowsiness, restlessness, asthenia, depression, confusion, hallucinations, convulsions, paraesthesia; photosensitivity, hypersensitivity reactions including fever, urticaria, angioedema, arthralgia, myalgia and anaphylaxis; blood disorders (including eosinophilia, leukopenia, thrombocytopenia), altered prothrombin time; disturbances in vision, taste, hearing and smell, tinnitus; tenosynovitis; tachycardia, oedema, syncope, hot flushes and sweating; if psychiatric, neurological or hypersensitivity reactions (including severe rash) occur discontinue; arthralgia.

**Storage**

**Eye drops and Tablet:** Store protected from light. **Injection:** Store protected from light at a temperature not exceeding 30°C. The container should not be allowed to freeze.

**Clarithromycin****Pregnancy Category-C****Schedule H****Indications**

*For the treatment of bacterial infections (pharyngitis/tonsillitis, sinusitis, bronchitis, pneumonia, uncomplicated skin and skin structure infections) caused by H. influenzae, M. catarrhalis, M. pneumoniae, S. pneumoniae, C. pneumoniae, S. aureus, S. pyogenes, Mycobacterium avium and Mycobacterium intracellulare.*

**Availability**

**TABLETS** 250 and 500 mg ; 125 mg DT.

**SUSPENSION** 125 mg/5 ml

**Dose****Oral**

**Adult-** 250 mg to 500 mg twice a day for 7 to 14 days increase in severe infections to 500 mg every 12 h up to 14 days.

**Child-** Body weight under 8 kg: 7.5 mg/kg body weight twice daily; 8 to 11 kg: 62.5 mg twice daily; 30 to 40 kg: 250 mg twice daily.

**Contraindications**

Hypersensitivity to clarithromycin; cephalosporin.

**Precautions**

Neonate under 2 weeks (risk of hypertrophic pyloric stenosis); predisposition to QT interval prolongation (including electrolyte disturbances, concomitant use of drugs that prolong QT interval); avoid in porphyria; hepatic impairment; renal impairment; pregnancy (not known to be harmful) (Appendix 7c); lactation (only small amounts in milk); interactions (Appendix 6c); myasthenia gravis.

**Adverse Effects**

Nausea, vomiting, abdominal discomfort, diarrhoea (antibiotic-associated colitis reported); less frequently urticaria, rashes and other allergic reactions; reversible hearing loss reported after large doses; cholestatic jaundice, pancreatitis, cardiac effects (including chest pain and arrhythmias), myasthenia-like syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis also reported, dyspepsia, tooth and tongue discolouration, smell and taste disturbances, stomatitis, glossitis and headache; less commonly hepatitis, arthralgia and myalgia; rarely, tinnitus; very rarely, pancreatitis, dizziness, insomnia, nightmares, anxiety, confusion, psychosis, paraesthesia, convulsions, hypoglycaemia, renal failure, leucopenia and thrombocytopenia; on intravenous infusion, local tenderness, phlebitis.

**Storage**

Store protected from moisture.

**Clindamycin\*****Pregnancy Category-B****Schedule H****Indications**

*Respiratory tract infections, penicillin resistant staphylococcal infections and many anaerobes such as bacteroides, skin, soft tissue and dental infections.*

**Availability**

**TABLETS/CAPSULES** 150 & 300 mg; **SYRUP** 4 ml (150 mg/ml); **INJECTION** 2 ml (150 mg/ml); **CREAM/GEL/OINTMENT** 10g (1%w/w); **LOTION** 25 ml (1%w/v).

**Dose****Oral****Serious anaerobic infections**

**Adult:** 150-300 mg 6 every hr; for more severe infection: 300 to 450 mg every 6 hr. **Child:** 2-4 mg/kg every 6 hr; for more severe infection: 3-6 mg/kg every 6 hr; 10 kg: 37.5 mg every 8hr.

**Prophylaxis of endocarditis** 600 mg 1 hr before dental procedure.



**Intravenous/Intramuscular****Serious anaerobic infections**

**Adult:** 0.6-2.7 g/day in 3-4 divided doses, up to 4.8 g/day for severe infections.

**Child:** 20-40 mg/kg daily in 3-4 divided dose.

**Neonate:** 15-20 mg/kg daily in 3-4 divided dose

**Toxic shock syndrome**

**Adult:** 900 mg every 8 hr along with penicillin G or ceftriaxone.

**Pelvic inflammatory disease**

**Adult:** 900 mg every 8 hr along with gentamicin.

**Vaginal****Bacterial vaginosis**

As pessary or 2% cream: 100 mg once nightly for 3-7 days.

**Topical****Acne**

As 1% preparation: Apply twice daily.

**Contraindications**

Hypersensitivity, meningitis as it has less penetration into CNS, pseudomembranous colitis.

**Precautions**

Hepatic and renal impairment, pregnancy and lactation, GI disease, elderly, atopic patients, regular monitoring of blood counts, in conjunction with antibiotic therapy, pregnancy (Appendix 7c), interactions (Appendix 6c).

**Adverse Effects**

Urticaria, rashes, contact dermatitis, exfoliative and vesiculous dermatitis, local irritation abdominal pain, oesophagitis, nausea, vomiting, diarrhoea, jaundice and liver abnormalities, eosinophilia, erythema multiforme, thrombophlebitis, gasping syndrome (premature infants and neonates) due to preservative benzoyl alcohol in parenteral formulation, pseudomembranous colitis, azotemia, oliguria, proteinuria.

**Storage**

Store protected from moisture

**Cloxacillin****Pregnancy Category-B****Schedule H****Indications**

*Multibacillary (MB) leprosy; type 2 lepra reactions; gram positive infection including resistant staphylococci.*

**Availability**

**CAPSULES** 250 and 500 mg; **INJECTION** 250 and 500 mg/vial; **DRY SYRUP** 125 mg/5 ml.

**Dose**

**Oral**

**Adult-** 250-500 mg every 6 h at least 30 min. before food. Osteomyelitis; upto 8g daily in 2 to 3 divided doses. Surgical prophylaxis; 1 to 2g at induction thereafter up to 4 further doses each of 500 mg may be given every 6 h.

***Slow intravenous injection or infusion***

**Adult-** Surgical prophylaxis; 1 to 2g at induction thereafter up to 4 further doses each of 500 mg may be given every 6 h.

**Child-** High risk procedures; Under 2 years; quarter adult dose. 2 to 10 years; half adult dose.

**Contraindications** Hypersensitivity to penicillins (see notes above).

**Precautions** History of allergy (see notes above); renal and hepatic impairment (Appendix 7a); heart failure; lactation (Appendix 7b); pregnancy (Appendix 7c).

**Adverse Effects** Nausea and vomiting, diarrhoea; hypersensitivity reactions including urticaria, fever, joint pain, rashes, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, interstitial nephritis (see also notes above); neutropenia, thrombocytopenia, coagulation disorders; antibiotic-associated colitis; hepatitis and cholestatic jaundice-may be delayed in onset; electrolyte disturbances; pain, inflammation, phlebitis or thrombophlebitis at injection sites.

**Storage** Store protected from moisture at a temperature not exceeding 30°C.

**Cotrimoxazole\***  
(Trimethoprim + Sulphamethoxazole)

**Pregnancy Category-C**

**Schedule H**

**Indications** *Urinary-tract infections; respiratory-tract infections including bronchitis, pneumonia, infections in cystic fibrosis; melioidosis; listeriosis; brucellosis; granuloma inguinale; otitis media; skin infections; Pneumocystis carinii pneumonia.*

**Availability** **TABLETS** (TMP + SMZ) 80 mg + 400 mg and 160 mg + 800 mg; **SUSPENSION** 40 mg TMP + 200 mg SMZ/5 ml.

**Dose** **Adult-** 1 to 2 tablets twice daily for 7-14 days (160 + 800 mg).

**Child-** Suspension 5 ml twice daily (40 + 200 mg). infant 2.5 ml.

**Contraindications** Hypersensitivity to sulfonamides or trimethoprim; porphyria; marked liver parenchymal damage, blood dyscrasias, severe renal insufficiency.

**Precautions** Renal impairment; hepatic impairment (avoid if severe; Appendix 7a); maintain adequate fluid intake (to avoid crystalluria); avoid in blood disorders (unless under specialist supervision); monitor blood counts and discontinue immediately if blood disorder develops; rash-discontinue immediately; predisposition to folate deficiency, elderly; asthma; G-6-PD deficiency; lactation (Appendix 7b); avoid in infants under 6 weeks; elderly.; pregnancy (Appendix 7c); interactions (Appendix 6c).

**Adverse Effects** Nausea, vomiting, diarrhoea, headache; hypersensitivity reactions including rashes, pruritus, photosensitivity reactions, exfoliative dermatitis and erythema nodosum; rarely, erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis; systemic lupus erythematosus, myocarditis, serum sickness; crystalluria—resulting in haematuria, oliguria, anuria; blood disorders including granulocytopenia, agranulocytosis, aplastic anaemia, purpura—discontinue immediately; also reported, liver damage, pancreatitis, antibiotic-associated colitis, eosinophilia, cough and shortness of breath, pulmonary infiltrates, aseptic meningitis, depression, convulsions, ataxia, tinnitus, vertigo, dizziness, hallucinations and electrolyte disturbances; megaloblastic anaemia due to trimethoprim; elevation of transaminase and bilirubin; skin rashes.

**Storage** Store protected from light and moisture. Suspension should not be allowed to freeze.

## Doxycycline\* (Refer Page No. 178)

**Pregnancy Category-D**

**Schedule H**

**Indications** *Respiratory-tract infections, including pneumonia and chronic bronchitis; urinary-tract infections; syphilis; chlamydia, mycoplasma and rickettsia; prostatitis; lymphogranuloma venereum; pelvic inflammatory disease (with metronidazole); Lyme disease; brucellosis (with rifampicin); leptospirosis, scrub typhus and travellers' diarrhoea; psittacosis; cholera; melioidosis; plague; anthrax; Q fever; Treatment of acute malaria caused by P. malariae and susceptible P. falciparum; P. vivax and P. ovale (followed by primaquine to eliminate intrahepatic forms); prophylaxis of malaria for pregnant women and non-immune individuals at risk.*

**Availability** **TABLETS/CAPSULES** 100 and 200 mg;  
**SYRUP** 25 mg/5 ml.

**Dose** **Oral**

Severe infections including refractory urinary tract infection: 200 mg daily.

Early syphilis: 100 mg twice daily for 14 days. Latent syphilis: 200 mg twice daily for 28 days.

Uncomplicated genital Chlamydia, non-gonococcal urethritis: 100 mg twice daily for 7 days.

**Child-** Only if alternate antibacterial cannot be given 5 mg/kg body weight in two divided doses.

**Contraindications** Pregnancy (Appendix 7c); children (see notes above); porphyria; systemic lupus erythematosus; hypersensitivity to tetracycline.

**Precautions** Avoid exposure to sunlight or sunlamps-photosensitivity reported; renal impairment; hepatic impairment (Appendix 7a); lactation (Appendix 7b); interactions (Appendix 6a, 6b, 6c 6d); predisposition to candidiasis.

**Adverse Effects** Gastrointestinal disturbances; anorexia, erythema (discontinue treatment); photosensitivity; hypersensitivity reactions; headache and visual disturbances; hepatotoxicity, blood disorders, pancreatitis and antibiotic-associated colitis reported; staining of growing teeth and occasional dental hypoplasia; erythematous rashes, nasopharyngitis, sinusitis, increased blood glucose levels, haemolytic anaemia, neutropenia.

**Storage** Store protected from light and moisture at a temperature not exceeding 30°C.

## Erythromycin\*

**Pregnancy Category-B**

**Schedule H**

**Indications** *Alternative to penicillin in hypersensitive patients; pneumonia; legionnaires' disease; syphilis; chancroid; chlamydia; non-gonococcal urethritis; prostatitis; lymphogranuloma venereum; campylobacter enteritis; relapsing fever; diphtheria and whooping cough prophylaxis upper respiratory tract infection, acne vulgaris, sycosis, vulgaris.*

<b>Availability</b>	<b>TABLETS</b> 125, 250 and 500 mg plain; 125 DT; <b>SYRUP</b> 125 mg/5 ml; <b>OINTMENT</b> 2 and 3% w/w; <b>CREAM</b> 3% w/w.
<b>Dose</b>	<b>Oral</b>  <b>Adult and child over 8 years-</b> 250 to 500 mg every 6 h or 0.5 to 1g every 12 h upto 4g daily in severe infections.  <b>Child-</b> 1 month to 2 years; 12.5 mg/kg body weight every 6 h; 2 to 8 years 250 mg every 6 h (doses doubled for severe infections).  <b>Early syphilis:</b> 500 mg three times daily for 14 days.
<b>Contraindications</b>	Hypersensitivity to erythromycin or other macrolides; porphyria; myasthenia gravis.
<b>Precautions</b>	Hepatic impairment (Appendix 7a) and renal impairment (Appendix 7d); prolongation of the QT interval (ventricular tachycardia reported); pregnancy (Appendix 7c); (not known to be harmful); lactation (Appendix 7b); interactions (Appendix 6c).
<b>Adverse Effects</b>	Nausea, vomiting, abdominal discomfort, diarrhoea and (antibiotic-associated colitis); urticaria, rashes and other allergic reactions (rarely, anaphylaxis); reversible hearing loss after large doses; cholestatic jaundice, cardiac effects (including chest pain and arrhythmias), myasthenia-like syndrome, erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis; burning sensation, itching, anorexia.
<b>Storage</b>	Store protected from light at a temperature not exceeding 30°C.

## Framycetin\*

**Schedule H**

<b>Indications</b>	<i>Bacterial skin infections, burns, ENT infections, surgical infections, traumatic injury, conjunctivitis, blepharitis.</i>
<b>Availability</b>	<b>CREAM</b> 1% - 5, 15 and 40g; <b>DROPS</b> 5 ml (0.5%); <b>DRESSING</b> 1%; <b>POWDER</b> 15g.
<b>Dose</b>	<b>Topical</b>  <b>Skin infections: Adult-</b> as 1% dressing.

**Ophthalmic****Blepharitis along with conjunctivitis:**

**Adult-** as 0.5 % ointment, apply 2-3 times daily.

**Otitis externa**

**Adult-** 0.5% drops.

<b>Contraindications</b>	Tuberculosis, glaucoma, perforated tympanic membrane, fungal, viral or resistant bacterial infections of eye, hypersensitivity.
<b>Precautions</b>	Pregnancy, ototoxicity due to systemic absorption may occur if applied on large areas in children, elderly and patients with renal failure, avoid prolonged use, interactions (Appendix 6c).
<b>Adverse effects</b>	Ototoxicity, gastrointestinal symptoms, inflammation, transient irritation, contact dermatitis, burning sensation, pruritus.
<b>Storage</b>	Store protected from light and moisture at a temperature not exceeding 30°C. If the material is sterile, the container should be tamper-evident and sealed so as to exclude micro-organisms.

**Gentamicin\*** (Refer Page No. 553)**Pregnancy Category-C****Schedule H**

<b>Indications</b>	<i>Pneumonia; cholecystitis; peritonitis; septicaemia; acute pyelonephritis; prostatitis; skin infections; pelvic inflammatory disease; endocarditis; meningitis; listeriosis; tularaemia; brucellosis; plague; surgical prophylaxis; ocular bacterial infection.</i>
<b>Availability</b>	<b>EYE DROPS</b> 0.3% w/v, <b>CREAM</b> 15g (0.1% w/w); <b>INJECTION</b> 2 ml ampoule (40 mg/ml), 2 and 10 ml vials (40 mg/ml).
<b>Dose</b>	<b>Intravenous infusion</b>  Once daily dose regime; 5 to 7 mg/kg body weight, then adjust as per serum gentamicin concentration.  <b>Intramuscular or slow intravenous injection</b> over at least 3 min.  Multiple daily dose regimen: 3 mg/kg body weight divided into 8 hly doses.

**Child-** 2 weeks to 12 years; 2 mg/kg body weight 8 hly.

**Contraindications** Myasthenia gravis.

**Precautions** Renal impairment (Appendix 7d), infants and elderly (dosage adjustment and monitor renal, auditory and vestibular function and serum-gentamicin concentrations); avoid prolonged use; conditions characterized by muscular weakness; significant obesity (monitor serum-gentamicin concentration closely and possibly reduce dose); see notes above; interactions (Appendix 6c); purulent discharge, discontinue if pain/inflammation becomes aggravated; pregnancy (Appendix 7c).

**Adverse Effects** Vestibular and auditory damage, nephrotoxicity; rarely, hypomagnesaemia on prolonged therapy; antibiotic-associated colitis, also nausea, vomiting, rash; bacterial/fungal corneal ulcers, ocular burning or irritation, thrombocytopenia, joint pain.

**Storage** Store protected from moisture if it is intended for use in the manufacture of parenteral preparations.

## Imipenem + Cilastatin

**Pregnancy Category-C**

**Schedule H**

**Indications** *Severe aerobic and anaerobic Gram-positive and Gram-negative infections in hospital-acquired infections (not indicated for CNS infections), including infections caused by resistant Pseudomonas and Acinetobacter species.*

**Availability**

<b>INJECTION</b>	Imipenem	+	Cilastatin
	125 mg	+	125 mg vial
	250 mg	+	250 mg vial
	500 mg	+	500 mg vial
	1g	+	1g vial
	2g	+	2g vial

**Dose** *Intravenous infusion in terms of imipenem*

**Adult-** 2g daily in 2 to 3 divided doses. Less susceptible organism may be given up to 3 to 4 divided doses (max 4g daily).

Surgical prophylaxis: 1g for induction, repeated every three h, supplemented in high risk surgery by doses of 500 mg for 8 to 16 h.

**Child-** 3 months and older: 60 mg/kg body weight in four divided doses. Over 40 kg: adult dose.

<b>Contraindications</b>	Hypersensitivity to beta-lactam antibiotics; local anaesthetics of the amide type and in patients with severe shock or heart block.
<b>Precautions</b>	Renal impairment; CNS disorders, such as epilepsy; lactation (Appendix 7b); interactions (Appendix 6c); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Nausea, vomiting, diarrhoea; antibiotic-associated colitis; taste disturbances; tooth or tongue discolouration, hearing loss; blood disorders, (decreased haematocrit, increased prothrombin time) positive Coombs' test; allergic reactions including rash, pruritus, urticaria, erythema multiforme (Steven's-Johnson syndrome), fever, anaphylactic reactions, rarely, toxic epidermal necrolysis, exfoliative dermatitis; myoclonic activity, convulsions, confusion and mental disturbances; slight increase in liver enzymes and bilirubin, rarely, hepatitis; increase in serum creatinine and blood urea; red coloration of urine in children; erythema, pain and induration and thrombophlebitis at injection sites; bone marrow depression.
<b>Storage</b>	Store protected from moisture in a single dose or multi dose container.

## Meropenem

**Pregnancy Category-B**

**Schedule H**

<b>Indications</b>	<i>Nosocomial infection like septicemia, febrile neutropenia, intraabdominal and pelvic infection etc caused by cephalosporins resistant bacteria, meningitis, cystic fibrosis.</i>
<b>Availability</b>	<b>INJECTIONS</b> 0.125, 0.250, 0.5, 1 g/vial.
<b>Dose</b>	<p><b>Adult-</b> 0.5-2 g or 10-40 mg/kg by slow i.v injection 8 hourly.</p> <p><b>Neonate</b> (less than 7 days)- 20 mg/kg 12 hourly.</p> <p>7-28 days- 20 mg/kg 8 hourly.</p> <p>1-3 months- 10 mg/kg 8 hourly.</p> <p>&gt; 3 months- 10- 20 mg/kg 8 hourly.</p> <p><b>Meningitis: Adult-</b> 2g 8 hourly.</p> <p><b>Child-</b> (&gt; 3 months)- 40 mg/kg 8 hourly.</p>
<b>Contraindications</b>	Hypersensitivity.



**Precautions** Renal insufficiency, neurological disorders, prolonged use of meropenem may result in overgrowth of nonsusceptible organisms, pregnancy (Appendix 7c), lactation, history of hypersensitivity to other  $\beta$ -lactam antibiotics; interactions (Appendix 6c).

**Adverse Effects** Inflammation at the injection site; nausea, vomiting, headache, rash; diarrhoea, thrombophlebitis, anaphylaxis, pseudomembranous colitis, disturbances in LFTs.

## Metronidazole\* (Refer Page No. 106)

**Pregnancy Category-B**

**Schedule H**

**Indications** *Anaerobic bacterial infections including gingivitis, pelvic inflammatory disease, tetanus, peritonitis, brain abscess, necrotizing pneumonia, antibiotic-associated colitis, leg ulcers and pressure sores and surgical prophylaxis; bacterial vaginosis; tissue nematode infections; trichomonal vaginitis, amoebiasis and giardiasis; Helicobacter pylori eradication.*

**Availability** **TABLETS** 200 and 400 mg; **SUSPENSION** 200 mg/5 ml; **INJECTION** 100 ml infusion (5 mg/ml).

**Dose** **Oral**

**Adult- Amoebiasis:** 400 to 800 mg every 8 h for 5 to 7 days. **Giardiasis:** 200 mg three times a day for 7 to 10 days or **intravenous injection** 500 mg 8 hly for 7 days.

**Child- Amoebiasis:** Below 12 years; 7.5 mg/kg body weight. 12 years and above; 35 to 50 mg/kg body weight daily in three divided doses.

**Contraindications** Chronic alcohol dependence; first trimester of pregnancy.

**Precautions** Disulfiram-like reaction with alcohol; hepatic impairment and hepatic encephalopathy (Appendix 7a); lactation (Appendix 7b); clinical and laboratory monitoring in courses lasting longer than 10 days; interactions (Appendix 6a, 6c, 6d); pregnancy (Appendix 7c); phenobarbitone, history of blood dyscrasias.

**Adverse Effects**

Nausea, vomiting, unpleasant metallic taste, furred tongue and gastrointestinal disturbances; rarely, headache, drowsiness, dizziness; ataxia; darkening of urine, erythema multiforme; pruritus, urticaria, angioedema and anaphylaxis; abnormal liver function tests, hepatitis, jaundice; thrombocytopenia, aplastic anaemia, myalgia, arthralgia; peripheral neuropathy, epileptiform seizures, leukopenia on prolonged or high dosage regimens; paresthesia.

**Storage**

Store protected from light and moisture. Store injection in a single dose container.

**Nalidixic Acid****Pregnancy Category-C****Schedule H****Indications**

*Urinary-tract infections; shigellosis.*

**Availability**

**TABLETS** 250, 500 mg and 1g; **SUSPENSION** 300 mg/5 ml.

**Dose****Oral**

**Adult-** 1g every 6 h for 7 days. Reduced in chronic infection to 600 mg every 6 h.

**Child- Over 3 months:** max 50 mg/kg body weight in divided doses, in prolonged therapy, reduced to 30 mg/kg body weight daily.

**Contraindications**

Hypersensitivity; children <3 years age, porphyria; convulsive disorder.

**Precautions**

History of epilepsy or conditions that predispose to seizures; G-6-PD deficiency; myasthenia gravis (risk of exacerbation); pregnancy (Appendix 7c); lactation (Appendix 7b); avoid exposure to excessive sunlight (discontinue if photosensitivity occurs); rarely, tendon damage-discontinue at first sign of pain or inflammation and rest affected limb; porphyria; hepatic impairment; renal impairment; false positive urinary glucose (if tested for reducing substances); monitor blood counts, renal and liver function if treatment exceeds 2 weeks; interactions (Appendix 6c); cerebro-arterial sclerosis.

**Adverse Effects**

Nausea, vomiting, dyspepsia, abdominal pain, diarrhoea (rarely, antibiotic-associated colitis), headache, dizziness, weakness, sleep disorders; rash (rarely, erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis) and pruritus; less frequently anorexia, increase in blood urea and creatinine; metabolic acidosis; drowsiness, restlessness, asthenia, depression, confusion, hallucinations, convulsions, paraesthesia, raised intracranial pressure, cranial nerve palsy; photosensitivity, hypersensitivity reactions including fever, urticaria, angioedema, arthralgia, myalgia and anaphylaxis; blood disorders (including eosinophilia, leukopenia, thrombocytopenia); disturbances in vision, taste, hearing and smell; also isolated reports of tendon inflammation and damage (especially in the elderly and in those taking corticosteroids); haemolytic anaemia, renal failure, interstitial nephritis and hepatic dysfunction (including hepatitis and cholestatic jaundice); if psychiatric, neurological or hypersensitivity reactions (including severe rash) occur, discontinue.

**Storage**

Store protected from light and moisture.

**Nitrofurantoin\*****Pregnancy Category-B****Schedule H****Indications**

*Urinary-tract infections; cystitis.*

**Availability**

**TABLETS** 50, 100 and 200 mg.

**Dose**

**Adult-** 50 mg every 6 h with food for 3-7 days.

**Child- Over 3 months:** 3 mg/kg body weight daily in four divided doses. Severe chronic recurrent infections: 100 mg every 6 h with food for 7 days, discontinue or reduce dosage in case of nausea.

**Contraindications**

Impaired renal function; infants less than 3 months; G-6-PD-deficiency including lactation of affected infants (Appendix 7b); pregnancy, at term (Appendix 7c); porphyria; anuria, oliguria, labour and delivery, neonates; interactions (Appendix 6a, 6d).

**Precautions** Pulmonary disorders or hepatic impairment (Appendix 7a); monitor lung and liver function on long-term therapy (discontinue if lung function deteriorates); neurological or allergic disorders; anaemia; diabetes mellitus; elderly and debilitated; vitamin B and folate deficiency; false positive urinary glucose (if testing for reducing substances); urine may be coloured yellow or brown.

**Adverse Effects** Dose-related gastrointestinal disorders, nausea; hypersensitivity reactions including urticaria, rash, sialadenitis, pruritus, angioedema; anaphylaxis reported; rarely, cholestatic jaundice, hepatitis, exfoliative dermatitis; erythema multiforme, pancreatitis, arthralgia; blood disorders; pulmonary reactions (pulmonary fibrosis; possible association with lupus erythematosus-like syndrome); peripheral neuropathy; benign intracranial hypertension; transient alopecia; dyspepsia, dizziness, nystagmus.

**Storage** Store protected from light and moisture.

## Norfloxacin

**Pregnancy Category-C**

**Schedule H**

**Indications** *Uncomplicated gonorrhoea; chronic bacterial prostatitis; complicated UTI; gastroenteritis; conjunctivitis.*

**Availability** **TABLETS** 200, 400, 800 mg; 100 mg DT; **SUSPENSION** 100 mg/5 ml.

**Dose** **Oral**

Urinary tract infection and upper respiratory tract infections: 200 to 400 mg daily preferably in the morning. Increase if necessary in upper urinary tract infection to 400 mg twice daily. Uncomplicated gonorrhoea: 400 mg as a single dose.

Uncomplicated genital chlamydia infections, non-gonococcal urethritis: 400 mg daily in single dose for 7 days or divided doses for 7 days.

**Contraindications** History of hypersensitivity, tendinitis.

**Precautions**

Should be used with caution in patients with a history of epilepsy or conditions that predispose to seizures, in G-6-PD deficiency, myasthenia gravis (risk of exacerbation), in renal impairment; during lactation. Exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs). Quinolones may induce convulsions in patients with or without a history of convulsions; taking NSAIDs at the same time, organ system assessment, haemolytic reaction, pregnancy (Appendix 7c).

**Adverse Effects**

Nausea, vomiting, dyspepsia, abdominal pain, diarrhoea (rarely, antibiotic-associated colitis), headache, dizziness, sleep disorders; rash (rarely, Stevens-Johnson syndrome and toxic epidermal necrolysis) and pruritus. Less frequent side-effects include anorexia, increase in blood urea and creatinine; drowsiness, restlessness, asthenia, depression, confusion, hallucinations, convulsions, tremor, paraesthesia, hypoaesthesia; photosensitivity, hypersensitivity reactions including fever, urticaria, angioedema, arthralgia, myalgia and anaphylaxis; blood disorders (including eosinophilia, leucopenia, thrombocytopenia); disturbances in vision, taste, hearing and smell. The drug should be discontinued if psychiatric, neurological or hypersensitivity reactions (including severe rash) occur; rash, heart burn, abdominal cramps, irritability.

**Storage**

Store protected from light and moisture.

**Ofloxacin\*****Pregnancy Category-C****Schedule H****Indications**

*Acute uncomplicated cystitis, community acquired pneumonia, acute exacerbation of chronic bronchitis.*

**Availability**

**TABLETS** 100, 200 and 400 mg; **SYRUP** 30 ml (50 mg/5 ml, 100 mg/5 ml); **INJECTION** 100 ml (2 mg/ml); **EYE DROPS** 0.3% w/v.

**Dose****Oral****Community acquired pneumonia:**

**Adult-** 400 mg twice daily for 10 days.

**Pelvic inflammatory disease:**

**Adult-** 400 mg twice daily for 14 days.

**Complicated UTI:**

**Adult-** 200 mg twice daily for 10 days.

**Parenteral****Complicated UTI:**

**Adult-** 200 mg daily by i.v infusion over at least 30 minutes, max. 400 mg twice infused over at least 1 h.

**Septicaemia, lower respiratory tract infection:**

**Adult-** 200 mg twice daily by i.v infusion over at least 30 minutes, max. 400 mg twice daily infused over at least 1 h.

**Bacterial corneal ulcer:**

**Adult-** 0.3%, 1-2 drops every 30 minutes.

**Ophthalmic****Bacterial conjunctivitis:**

**Adult-** 0.3%, 1-2 drops every 2-4 h.

**Child-** >1year, 1-2drops every 2-4 h.

<b>Contraindications</b>	Hypersensitivity.
<b>Precautions</b>	Patients with epilepsy, kidney disease, tendon problem, nervous system problem, liver disease (Appendix 7a), limit alcohol intake, pregnancy (Appendix 7c); lactation (Appendix 7b).
<b>Adverse effects</b>	Sinus tachycardia, hallucination, Steven's Johnson syndrome, seizure; dizziness, headache, nausea, vomiting, diarrhoea; insomnia, pruritus, photosensitivity.
<b>Storage</b>	<b>Tablets:</b> Store protected from light and moisture. <b>Eye Drops:</b> Store protected from light.

**Phenoxymethyl Penicillin (Penicillin V)**

**Pregnancy Category-B**

**Schedule H**

<b>Indications</b>	<i>Streptococcal pharyngitis; otitis media; erysipelas; mouth infections; secondary prophylaxis of rheumatic fever; post-splenectomy prophylaxis.</i>
<b>Availability</b>	<b>TABLETS</b> 125 and 250 mg.
<b>Dose</b>	<b>Adult-</b> 500 mg every 6 hour increased to 750 mg every 6 h in severe cases. <b>Child-</b> up to 1 year: 62.5 mg every 6 h. 1 to 5 years: 125 mg every 6 h. 6 to 12 years: 250 mg every 6 h.
<b>Contraindications</b>	Hypersensitivity to penicillins (see notes above); serious infections (see notes above).

**Precautions** History of allergy (see notes above); lactation (Appendix 7b); pregnancy (Appendix 7c); interactions (Appendix 6c); cross sensitivity with cephalosporins may occur.

**Adverse Effects** Hypersensitivity reactions including urticaria, serum sickness reaction; joint pain, rash, angioedema, anaphylaxis (see notes above); nausea and diarrhoea; epigastric distress, skin eruptions; haemolytic anaemia.

**Storage** Store protected from moisture.

## Piperacillin + Tazobactam

**Pregnancy Category-B**

**Schedule H**

**Indications** *Nosocomial pneumonia, infections following burns, urinary tract infections.*

**Availability** **INJECTIONS** Piperacillin 4g + Tazobactam 0.5g Piperacillin 2g + Tazobactam 0.25g, Piperacillin 1g + Tazobactam 0.0125g.

**Dose** 4.5g (Piperacillin 4g + Tazobactam 0.5g) every 6 h for 7-14 days.

**Contraindications** Hypersensitivity to penicillins.

**Precautions** Pregnancy (Appendix 7c), lactation; prolonged treatment may increase super infections, interactions (Appendix 6c).

**Adverse Effects** Hypersensitivity reactions like rash, fever, bronchospasm, vasculitis, serum sickness, exfoliative dermatitis, Steven's-Johnson syndrome, and anaphylaxis.

**Storage** Store below 25°C.

## Procaine Benzyl Penicillin (Procaine Penicillin G)

**Pregnancy Category-B**

**Schedule H**

**Indications** *Syphilis; anthrax; childhood pneumonia; diphtheria carrier state; cellulitis; mouth infections; bites.*

**Availability** **VIALS** 5 and 10 lac units.

**Dose** ***Intramuscular and intravenous injection or infusion***

**Adult-** Streptococcal infection and pyoderma: single dose 12 lac units. Syphilis: 24 lac units every week for three weeks. Rheumatic fever: 12 lac units every 3 to 4 weeks.

<b>Contraindications</b>	Hypersensitivity to penicillins (see notes above); intravascular injection.
<b>Precautions</b>	History of allergy (see notes above); renal failure; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Hypersensitivity reactions including urticaria, fever, joint pains, rashes, angioedema, anaphylaxis, serum sickness-like reaction, haemolytic anaemia, interstitial nephritis (see also notes above); neutropenia, thrombocytopenia, coagulation disorders and central nervous system toxicity (associated with high doses and severe renal failure); Jarisch-Herxheimer reaction (during treatment for syphilis and other spirochaete infections, probably due to release of endotoxins); rarely, non-allergic (embolictoxic) reactions; pain and inflammation at injection site.
<b>Storage</b>	The constituted solution should be used immediately after preparation but in any case within the period recommended by the manufacturer.

## Roxithromycin

**Pregnancy Category-B**

**Schedule H**

<b>Indications</b>	<i>Susceptible infections; pneumonia, acute bronchitis, sinusitis, pharyngitis, tonsillitis, genital infection.</i>
<b>Availability</b>	<b>TABLETS</b> 150 and 300 mg; <b>SUSPENSION</b> 50 mg/ml; <b>DROPS</b> 10 ml (25 mg/ml).
<b>Dose</b>	<b>Adult-</b> 150 mg twice a day at least 15 min before meals. <b>Child-</b> 5 to 8 mg/kg body weight in two divided doses for not more than 10 days.
<b>Contraindications</b>	Concomitant use with ergot alkaloid type compounds.
<b>Precautions</b>	Hepatic dysfunction; paediatrics (reduce dose); interactions (Appendix 6d); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Diarrhoea; vomiting; nausea; transient rise in liver transaminase; skin rash; gastralgia.
<b>Storage</b>	Store protected from light and moisture.



## Sulphadiazine\*

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Prevention of recurrences of rheumatic fever; toxoplasmosis; prophylaxis of meningococcal infections.</i>
<b>Availability</b>	<b>TABLET</b> 500 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> 500 mg twice a day.  <b>Child-</b> Up to 8 years: 125 mg twice daily. 8 to 12 years: 250 mg twice daily.
<b>Contraindications</b>	Hypersensitivity to sulfonamides; porphyria; severe renal hepatic impairment, blood dyscrasias, elderly.
<b>Precautions</b>	Hepatic impairment (avoid if severe; Appendix 7a); renal impairment; maintain adequate fluid intake (to avoid crystalluria); avoid in blood disorders (unless under specialist supervision); monitor blood counts and discontinue immediately if blood disorder develops; rashes-discontinue immediately; predisposition to folate deficiency; elderly; asthma; G-6-PD deficiency; lactation (Appendix 7b); avoid in infants under 6 weeks; interactions (Appendix 6d); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Nausea, vomiting, diarrhoea, headache; hypersensitivity reactions including rashes, pruritus, photosensitivity reactions, exfoliative dermatitis and erythema nodosum; rarely, erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis; systemic lupus erythematosus, myocarditis, serum sickness; crystalluria-resulting in haematuria, oliguria/anuria; blood disorders including granulocytopenia, agranulocytosis, aplastic anaemia, purpura-discontinue immediately; also reported, liver damage, pancreatitis, antibiotic-associated colitis, eosinophilia, cough and shortness of breath, pulmonary infiltrates; aseptic meningitis, depression, ataxia, tinnitus, vertigo, dizziness, hallucinations, and electrolyte disturbances; convulsions, hypoprothrombinemia, methaemoglobinemia, anorexia, pancreatitis.
<b>Storage</b>	Store protected from light and moisture.

## Tetracycline (Refer Page No. 555)

Pregnancy Category-D

Schedule H

### Indications

*Rocky Mountain spotted fever; typhus; Q fever; rickettsial pox; tick fever caused by Rickettsiae; respiratory tract infections caused by Mycoplasma pneumoniae; chlamydia infection; nongonococcal urethritis; chancroid; plague; tularemia; cholera; brucellosis; bartonellosis; granuloma inguinale; haemophilus and klebsella infections; psittacosis.*

### Availability

**CAPSULES/TABLETS** 250 and 500 mg.

### Dose

**Adult-** 250 mg every 6 h, increase to 500 mg every 6 to 8 h in severe infections.

Non-gonococcal urethritis: 500 mg every 6 h for 7 to 14 days (21 days if failure or relapse after course is seen).

To be taken with plenty of fluid while sitting or standing.

**Child-** 25 to 50 mg/kg body weight, daily in three divided doses. Avoid in children below 8 years.

### Contraindications

Deposition of tetracyclines in growing bone and teeth (by binding to calcium) causes staining and occasionally dental hypoplasia and they should not be given to children under 12 years, or to pregnant (Appendix 7c) or lactating women (Appendix 7b). However, doxycycline may be used in children for treatment and post-exposure prophylaxis of anthrax when an alternative antibacterial cannot be given (unlicensed indication). With the exception of doxycycline and minocycline, the tetracyclines may exacerbate renal failure and should not be given to patients with kidney disease; hypersensitivity; interactions (Appendix 6c, 6d)

### Precautions

Used with caution in patients with hepatic impairment or those receiving potentially hepatotoxic drugs. Tetracyclines may increase muscle weakness in patients with myasthenia gravis and exacerbate systemic lupus erythematosus; antacids and aluminium, calcium, iron, magnesium and zinc salts decrease the absorption of tetracyclines; milk also reduces the absorption of tetracyclines, demeclocyclines and oxytetracycline; cerebrovascular sensitisation, maculopapular rashes, increased blood urea nitrogen, anaemia.

**Adverse Effects**

Nausea, vomiting, diarrhoea (antibiotic-associated colitis reported occasionally), dysphagia and oesophageal irritation. Other rare side-effects include hepatotoxicity, pancreatitis, blood disorders, photosensitivity (particularly with demeclocycline) and hypersensitivity reactions (including rash, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria, angioedema, anaphylaxis, pericarditis). Headache and visual disturbances may indicate benign intracranial hypertension (discontinue treatment); bulging fontanelles have been reported in infants; anaemia.

**Storage**

Store protected from light and moisture.

**Trimethoprim****Pregnancy Category-C****Schedule H****Indications**

*Urinary-tract infections; bronchitis.*

**Availability**

Refer cotrimoxazole above.

**Dose****Oral**

**Adult-** 200 mg every 12 h.

**Child-** 1 month to 12 years: 4 mg/kg body weight (max. 200 mg) every 12 h. 6 weeks to 6 months: 25 mg every 12 h.

**Contraindications**

Blood disorders; porphyria; hypersensitivity.

**Precautions**

Renal impairment; lactation (Appendix 7b); predisposition to folate deficiency; elderly; blood counts on long-term therapy (but practical value not proven); neonates (specialist supervision required); pregnancy (Appendix 7c).

**Adverse Effects**

Rashes, pruritus; depression of haematopoiesis; gastrointestinal disturbances including nausea and vomiting; rarely, exfoliative dermatitis and toxic epidermal necrolysis, photosensitivity and other allergic reactions including angioedema and anaphylaxis; aseptic meningitis; erythema, multiforme, elevation of transaminase and bilirubin.

**Storage**

Store protected from light and moisture.

## Vancomycin\*

**Pregnancy Category Oral Capsules- B**  
**Parenteral Formulation- C**

**Schedule H**

<b>Indications</b>	<i>Methicillin-resistant staphylococcal pneumonia; staphylococcal meningitis; endocarditis prophylaxis (with gentamicin).</i>
<b>Availability</b>	<b>TABLETS</b> 500 mg; <b>INJECTION</b> 250 mg, 500 mg and 1g/vial; <b>CAPSULE</b> 125 and 250 mg.
<b>Dose</b>	<b>Adult-</b> 1 to 1.5g every 12 h. <b>Elderly</b> over 65 years; 500 mg every 12 h or 1g once daily. <b>Child-</b> Over 1 month; 15 mg/kg body weight every 8 h (max. 2g daily).

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*Note: Oral for antibiotic associated colitis, 125 mg every 6 h for 7 to 10 days. Not very common therapy.*

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<b>Contraindications</b>	Allergy to corn/corn products, hypersensitivity.
<b>Precautions</b>	Avoid rapid infusion (risk of anaphylactoid reactions, see Adverse effects); rotate infusion sites; renal impairment (Appendix 7d); elderly; history of deafness-avoid; plasma-vancomycin concentration measured after 3 or 4 doses (earlier if renal impairment), blood counts, urinalysis and renal function tests-use only in hospital setting; monitor auditory function and plasma-vancomycin concentrations in elderly or in renal impairment; lactation (Appendix 7b); pregnancy (Appendix 7c); interactions (Appendix 6c); Pseudomembranous colitis.
<b>Adverse Effects</b>	Nephrotoxicity including renal failure and interstitial nephritis; ototoxicity (discontinue if tinnitus occurs); blood disorders; nausea, chills, fever, eosinophilia, anaphylaxis, rashes, including exfoliative dermatitis, erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis and vasculitis; phlebitis; on rapid infusion, severe hypotension (with shock, cardiac arrest), wheezing, dyspnoea, urticaria, pruritus, flushing of the upper body ('red man' syndrome), pain and muscle spasm of back and chest; hypotension, pruritus, haematopoietic flebitis.
<b>Storage</b>	Store in an air tight container protected from light.

## 9.3 Antifilarial Drugs

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### Loiasis:

Loiasis is an infection with the filarial nematode *Loa loa* and is transmitted by the biting of tabanid fly *Chrysops*. Diethylcarbamazine is effective against both adult worms and larvae; a single weekly dose is normally effective as prophylaxis. During individual treatment, particularly of persons with heavy microfilaraemia (>50 000 microfilariae/ml blood), a condition simulating meningoencephalitis occasionally occurs. This probably results from sludging of moribund microfilariae within cerebral capillaries. The frequency of meningoencephalitis associated with diethylcarbamazine therapy of loiasis is reported as 1.25%, with a mortality rate of about 50% in affected patients; treatment with diethylcarbamazine should be stopped at the first sign of cerebral involvement (and specialist advice sought). Permanent cerebral damage is common among patients who survive and this possibility should be considered when deciding on treatment. Treatment of heavily infected patients should thus begin at low dosage and corticosteroid and antihistamine cover should be provided for the first 2 to 3 days.

### Lymphatic Filariasis:

Lymphatic filariasis is caused by infection with *Wuchereria bancrofti* (bancroftian filariasis), *Brugia malayi* or *B. timori* (brugian filariasis). Occult filariasis (tropical pulmonary eosinophilia) is a clinical variant of *W. bancrofti* infection. Individual treatment with diethylcarbamazine which has both microfilaricidal and macrofilaricidal activity is effective. Total cumulative dosages of 72 mg/kg are generally recommended for *Wuchereria bancrofti* infections with half this dose used for *Brugia malayi* and *B. timori* infections. In all cases treatment is best initiated with smaller doses for 2-3 days to avoid the danger of immunological reactions. Rigorous hygiene to the affected limbs with adjunctive measures to minimize infection and promote lymph flow is important for reducing acute episodes of inflammation.

In communities where filariasis is endemic, annual administration of single doses of albendazole 400 mg with either diethylcarbamazine (6 mg/kg) or ivermectin (200 µg/kg) is effective for interrupting transmission; this treatment is continued for at least 5 years. Trials in India and China have shown that the consistent use for 6-12 months of table salt containing diethylcarbamazine 0.1% can eliminate *W. bancrofti*; a concentration of 0.3% for 3-4 months may be required where *B. malayi* is endemic.

## Diethylcarbamazine\*

**Indications** *Treatment of loiasis; prophylaxis of loiasis in temporary residents in endemic areas; tissue nematode infections; lymphatic filariasis; toxocariasis.*

**Availability** **TABLETS** 50 and 100 mg; **SYRUP** 5 mg/ml and 120 mg/5 ml.

**Dose** **Oral**

**Adult and child-** 11 mg/kg body weight daily in three divided doses on the first day. Thereafter increase gradually to 6 mg/kg body weight given after food daily for two to three days. Hookworm infection: treat for 21 days. Filariasis: 2 mg/kg body weight is given three times a day for 3 to 4 weeks. 1 mg/kg body weight for an adult of 50 kg. Treatment may be repeated once after 6 months.

**Contraindications** Pregnancy (delay treatment until after delivery); infants, elderly, debilitated (usually excluded from mass treatment programmes; see also Precautions); cardiac disease, hypersensitivity, impaired renal function.

**Precautions** Renal impairment; cardiac disorders; other severe acute diseases-delay diethylcarbamazine treatment until after recovery; risk of meningoencephalitis in severe infection (see notes above).

**Adverse Effects** Headache, dizziness, drowsiness, nausea and vomiting; immunological reactions, within a few hour of the first dose, subsiding by fifth day of treatment and including fever, headache, joint pain, dizziness, anorexia, malaise, nausea and vomiting, urticaria and asthma in asthmatics (similar to Mazzotti reaction), induced by disintegrating microfilariae; microencephalitis (with heavy microfilaraemia, see notes above); reversible proteinuria; enlargement of lymph nodes.

**Storage** Store protected from moisture.

## Ivermectin

**Pregnancy Category-C**

**Indications** *Nematodal infections such as ascariasis, trichuriasis, strongyloidiasis, enterbiasis, lymphatic filariasis, scabies and pediculosis.*

**Availability** **TABLETS** 3, 6, 9 and 12 mg; **INJECTION** 10 ml (0.1% w/v).

**Dose**

**Oral**

**Strongyloidiasis:** 200 µg/kg of body weight once daily for 1-2 days.

**Lymphatic filariasis:** 400 µg/kg of body weight simple annual dose for 4-6 years.

**Scabies and pediculosis:** 150-200 µg/kg of body weight single oral dose highly effective. Second dose may be required 7-10 days later.

**Contraindications**

Hypersensitivity, CNS disorders, pregnancy, meningitis, trypanosomiasis, seizures, contraindicated to children below the age of < 5 years old or under 15 kg body weight.

**Precautions**

Concurrent Loa Loa infection, impaired blood-brain barrier function, pregnancy (Appendix 7c), lactation, hepatic, cardiovascular, renal or pulmonary disease, anaemia, coagulation disorder, severe asthma, interactions (Appendix 6c).

**Adverse Effects**

Nausea, vomiting, constipation, abdominal pain and fatigue, rash, arthralgia, fever, myalgia, asthenia, hypotension, tachycardia, edema, lymphadenopathy, sore throat, cough, headache, somnolence, transient eosinophilia, dizziness, diarrhoea, pruritus, orthostatic hypotension, lymph-node tenderness, rare but serious adverse effects such as marked disability and encephalopathies in patients coinfecting with heavy burdens of Loa microfilaria.

## 9.4 Antifungal Drugs

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Fungal infections can be superficial or systemic. Superficial infections affect only the skin, hair, nails or mucous membranes whereas systemic fungal infections affect the body as a whole.

Systemic fungal infections are sometimes caused by inhalation, ingestion or inoculation of primary pathogens and sometimes by opportunistic invasion of commensals in patients with lowered host resistance. They are increasing in prevalence not only because of the pandemic of HIV infection, but also because of the rise in illicit intravenous drug use in many countries and greater use of broad spectrum antibiotics and invasive medical procedures. In immunodeficient patients systemic fungal infections are often disseminated.

**Amphotericin B** is a lipophilic polyene antibiotic; it is fungistatic against a broad spectrum of pathogenic fungi, including *Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, *Mucor*, *Absidia* and *Phicopes* spp.; it is active against algal *Prototheca* spp. and against the *Leishmania* protozoa. It is used for the empirical treatment of serious fungal infections and is used in conjunction with flucytosine to treat cryptococcal meningitis and systemic candidosis.

Amphotericin B has to be administered parenterally as there is little or no absorption from the gastrointestinal tract; amphotericin B is liable to cause nephrotoxicity. Duration of therapy varies with the initial severity of the infection and the clinical response of the patient. In some infections a satisfactory response is only obtained after several months of continuous treatment. Intrathecal infusion has been used successfully in patients with meningeal coccidioidomycosis.

**Fluconazole** an orally active synthetic imidazole derivative, possesses fungistatic activity against dermatophytes, yeasts and other pathogenic fungi. It is widely used in the treatment of serious gastrointestinal and systemic mycoses as well as in the management of superficial infections. Fluconazole is also used to prevent fungal infections in immunocompromised patients.

**Flucytosine**, is a synthetic fluorinated pyrimidine with a narrow spectrum of antifungal activity, particularly against *Cryptococcus* and *Candida* spp. In susceptible fungi, it is converted to 5-fluorouracil by cytosine deaminase. Flucytosine is myelosuppressive and plasma concentrations above 75 µg/ml are associated with myelotoxicity.



**Griseofulvin** is a fungistatic antibiotic derived from *Penicillium griseofulvum* with selective activity against the dermatophytes causing ringworm, *Microsporum canis*, *Trichophyton rubrum* and *T. verrucosum*. It has no activity against pityriasis versicolor or candida infections. Griseofulvin is deposited selectively in keratin precursor cells of skin, hair and nails where it disrupts the mitotic apparatus of fungal cells thus preventing fungal invasion of newly-formed cells. It is unsuitable for prophylactic use. Close attention should be given to hygiene and to possible reservoirs of reinfection in clothing, footwear and bedding.

**Nystatin**, a polyene antifungal antibiotic derived from *Streptomyces noursei*, is effective against infections caused by a wide range of yeasts and yeast-like fungi. It is poorly absorbed from the gastrointestinal tract and it is not absorbed from the skin or mucous membranes when applied topically. It is used for the prophylaxis and treatment of candidosis.

**Potassium iodide** aqueous oral solution is a clear liquid with a characteristic, strong salty taste. It is effective against sporotrichosis and subcutaneous phycomycosis, which are fungal infections caused by *Sporothrix schenckii* and *Basidiobolus haptosporus* respectively. In subcutaneous sporotrichosis, amphotericin B is often effective in patients unable to tolerate iodides. Itraconazole, by mouth has been tried as an alternative to potassium iodide in both cutaneous and extracutaneous sporotrichosis. In phycomycosis, fluconazole may be effective.

## Amphotericin B\*

Pregnancy Category-B

Schedule H

### Indications

*Life-threatening fungal infections including histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis, aspergillosis, cryptococcosis, mucormycosis, sporotrichosis and candidiasis; visceral and mucocutaneous leishmaniasis unresponsive to pentavalent antimony compounds; severe meningitis, perioral candidiasis.*

### Availability

**VIALS** 10, 25, 50 and 100 mg plain, 50 mg/ vial (liposomal).

### Dose

**Intravenous infusion (plain)**

**Adult-** Systemic fungal infection: 250 µg/kg body weight daily, increase gradually 1 mg/kg body weight if tolerated (max 1.5 mg/kg body weight daily) or alternate days.

**Child-** Same as for Adult based on body weight.

### ***Intravenous (liposomal)***

For fever in neutropenic patients: 3 mg/kg/day, max. dose 5 mg/kg/day i.v.

For cryptococcal meningitis: 3-4 mg/kg, max. 6 mg/kg, i.v. once daily.

Visceral leishmaniasis:

Immunocompetent patients: 3 mg/kg.

Immunocompromized patients: 4 mg/kg.

### **Contraindications**

Toxic effects must be weighed against benefits. Regular kidney, liver function tests and blood counts must be conducted; lactation; antineoplastic therapy.

### **Precautions**

Close medical supervision throughout treatment and initial test dose required (see note, below); renal impairment (Appendix 7d); pregnancy (Appendix 7c); hepatic and renal function tests; blood counts and plasma electrolyte monitoring; corticosteroids (avoid, except to control reactions); lactation; avoid rapid infusion (risk of arrhythmias); interactions (Appendix 6c); geriatric use.

Anaphylaxis occurs rarely, with intravenous amphotericin B and a test dose is advisable before the first infusion. The patient should be observed for about 30 min after the test dose.

### **Adverse Effects**

Fever, headache, anorexia, weight loss, nausea and vomiting, malaise, diarrhoea, muscle and joint pain, dyspepsia and epigastric pain; renal function disturbances including hypokalaemia, hypomagnesaemia and renal toxicity; blood disorders; cardiovascular toxicity (including arrhythmias); neurological disorders (including peripheral neuropathy); abnormal liver function (discontinue treatment); rash; anaphylactoid reactions (see above); pain and thrombophlebitis at injection site; respiratory failure.

### **Storage**

Store in a tightly closed container between 2 to 8°C, protected from light.

## Clotrimazole\*

Pregnancy Category-B

Schedule H

<b>Indications</b>	<i>Vulvo-vaginal candidiasis, trichomoniasis, vaginitis, non-specific vaginitis, mixed vaginal infection, Gram-positive and Gram-negative bacterial infection, infective leucorrhoeas; prevention of athletes foot and ringworm disease of skin folds.</i>
<b>Availability</b>	<b>PESSARIES/VAGINAL TABLETS</b> 100 and 200 mg; <b>CREAM</b> 1% w/w; <b>POWDER</b> 75g; <b>LOTION</b> 50 ml.
<b>Dose</b>	<b>Adult-</b> Pessaries/vaginal tablets: 100 mg pessary/vaginal tablet to be inserted into vagina at night before going to bed as deep as possible for consecutive 6 to 7 days or 200 mg for 3 consecutive night before going to bed or 500 mg single dose.  <b>Child-</b> Pessaries/vaginal tablets: not recommended. Cream: Rub on affected area 2 to 3 times by applying in thin layer and rubbing, continue for 14 days after healing.
<b>Contraindications</b>	Ophthalmic use; hypersensitivity.
<b>Precautions</b>	Avoid contact with eyes, pregnancy (Appendix 7c) and lactation.
<b>Adverse Effects</b>	Local irritation, burning sensation and itching, abnormal liver function, unpleasant mouth sensation.
<b>Storage</b>	Store protected from light and moisture. Do not crush pessaries.

## Fluconazole\*

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Systemic mycosis including histoplasmosis, non-meningeal coccidioidomycosis, paracoccidioidomycosis and blastomycosis treatment and, in AIDS and other immunosuppressed patients, prophylaxis of cryptococcal meningitis; oesophageal and oropharyngeal candidiasis, vaginal candidiasis and systemic candidiasis.</i>
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**Availability** **TABLETS/CAPSULES** 50, 100, 150 and 200 mg; **EYE DROPS** 5 ml (0.3% w/v).

**Dose** **Adult-** Mucosal: 50 to 100 mg daily for 14 to 30 days. Vaginal: 150 mg as a single dose. Oral: systemic loading dose of 400 mg on first day and thereafter 200 to 400 mg once daily for at least 28 days.

Prophylaxis of fungal infection: 50 to 100 mg once daily.

**Contraindications** Sensitivity to primaquine; infants below 1 year of age; alcohol; coadministration of cisapride, terfenadine.

**Precautions** Renal impairment (Appendix 7d); lactation (Appendix 7b); monitor liver function-discontinue if signs or symptoms of hepatic disease (risk of hepatic necrosis; Appendix 7a); interactions: (Appendix 6b, 6c); pregnancy (Appendix 7c); immunocompromised patients.

**Adverse Effects** Nausea, vomiting, abdominal pain; flatulence, diarrhoea; headache, taste disturbance, hepatic disorders, dizziness, seizures, alopecia, pruritus; rash (withdraw treatment); angioedema, anaphylaxis, bullous lesions, toxic epidermal necrolysis and erythema multiforme (Stevens-Johnson syndrome) reported (skin reactions more common in AIDS); hyperlipidaemia, leukopenia, thrombocytopenia, hypokalaemia.

**Storage** Stor in an airtight container.

## Flucytosine

**Pregnancy Category-C**

**Schedule H**

**Indications** *Adjunct to amphotericin B (or fluconazole) in cryptococcal meningitis; adjunct to amphotericin B in systemic candidiasis; septicemia, pulmonary infection.*

**Availability** **CAPSULE** 250 mg; **INFUSION** 2.5g in 250 ml.

**Dose** **Oral**

**Adult-** 250 mg four times a day for not more than 7 days.

**Intravenous infusion-** over 20 to 40 min;

**Adult and Child-** 200 mg/kg body weight daily in four divided doses.

**Contraindications** Renal impairment; elderly; blood disorders, pregnancy (Appendix 7c); hypersensitivity.

**Precautions** Elderly; renal impairment; also the use with amphotericin B (both nephrotoxic); liver- and kidney function tests and blood counts required (weekly in renal impairment or in blood disorders); lactation (Appendix 7b); interactions (Appendix 6c); pregnancy (Appendix 7c).

**Adverse Effects** Rash, nausea, vomiting and diarrhoea; alterations in liver function tests; less frequently, confusion, hallucinations, convulsions, headache, sedation, vertigo; blood disorders including leukopenia, potentially fatal thrombocytopenia and aplastic anaemia; cardiac arrest, myocardial toxicity, dyspnoea, azotemia, ataxia, hypoglycemia.

**Storage** Store protected from light.

## Griseofulvin\*

**Pregnancy Category-C**

**Indications** *Fungal infections of the skin, scalp, hair and nails where topical treatment has failed or is inappropriate; athlete's foot.*

**Availability** **TABLETS** 125, 250, 375 and 500 mg; **CAPSULES** 125 mg.

**Dose** **Oral**

**Adult-** 500 mg once a day or in divided doses, in severe infections dose may be doubled. Reduce when response occurs. Administer with meals.

**Child-** Under 50 kg: 10 mg/kg body weight once daily or divided doses with meals.

**Contraindications** Severe liver disease (Appendix 7a); pregnancy (Appendix 7c) (avoid pregnancy during and for 1 month after treatment; men should not father children within 6 months of treatment; porphyria; systemic lupus erythematosus and related disorders.

**Precautions** Pre-existing hepatic insufficiency (closely monitor hepatic function throughout treatment); blood disorders (monitor blood count weekly during first month of treatment); lactation; interactions (Appendix 6a, 6b, 6c, 6d); avoid exposure to sunlight/artificial light.

May impair ability to perform skilled tasks, for example operating machinery, driving.

**Adverse Effects** Headache, nausea, vomiting, diarrhoea, rashes, dizziness, fatigue reported; dry mouth and angular stomatitis; leukopenia, agranulocytosis; proteinuria reported; photosensitivity; lupus erythematosus, toxic epidermal necrolysis, erythema multiforme; serum sickness, angioedema; peripheral neuropathy; confusion and impaired coordination.

**Storage** Store in a well closed container.

## Ketoconazole

**Pregnancy Category-C**

**Schedule H**

**Indications** *Malassezia fulliculitis dermatophytosis and chronic conditions which cannot be treated topically; infections resistant to fluconazole; blastomycosis, candidiasis, chromomycosis.*

**Availability** **TABLETS** 200 mg; **CREAM** 2% and 5% w/w; **SOLUTION** 2%w/v; **LOTION** 2%w/v.

**Dose** **Adult-** 200 to 400 mg daily once preferably after food.

**Child-** (Over 2 years) 3.3 to 6.6 mg/kg body weight once daily after food.

Local application- 3 to 4 times daily, apply thoroughly.

**Contraindications** Hepatic impairment; lactation; concomitant use with cisapride.

**Precautions** Predisposition to adrenocortical insufficiency; avoid in porphyria; pregnancy (Appendix 7c); interactions (Appendix 6a, 6c), hepatotoxicity

Potentially life-threatening hepatotoxicity reported very rarely,; risk of hepatotoxicity greater if given for longer than 14 days. Monitor liver function before treatment, then on weeks 2 and 4 of treatment, then every month. Avoid or use with caution if abnormal liver function tests (avoid in active liver disease) or if history of hepatotoxicity with other drugs.

#### Adverse Effects

Nausea, vomiting, abdominal pain; pruritus; less commonly diarrhoea, headache, dizziness, drowsiness and rash; very rarely, fatal liver damage (see Hepatotoxicity above), dyspepsia, raised intracranial pressure, adrenocortical insufficiency, erectile dysfunction, menstrual disorders, azoospermia (with high doses), gynaecomastia, thrombocytopenia, photophobia and alopecia.

## Nystatin\*

### Pregnancy Category-C

**Schedule H**

#### Indications

*Oral, oesophageal, intestinal, vaginal and cutaneous candidiasis.*

#### Availability

**TABLETS** 5,00,000 units; **OINTMENT** 3g (100000 IU).

#### Dose

##### **Oral**

**Adult-** Intestinal candidiasis: 5,00,000 units every six h, doubled in severe infections.

**Child-** 1 month to 12 years: 1,00,000 units 4 times daily, immunocompromised children may require higher doses up to 5,00,000 units.

##### **Topical application**

Dissolve one tablet in glycerine and apply locally 3 to 4 times.

##### **Intravaginal**

Insert one tablet deep into vagina before bed time once at night.

#### Contraindications

Hypersensitivity.

**Precautions** Lactation; discontinue if sensitivity develops, teratogenic effect, should not be used for the treatment of systemic, oral, intravaginal or ophthalmic infections; pregnancy (Appendix 7c).

**Adverse Effects** Nausea, vomiting, diarrhoea at high doses; oral irritation and sensitization; rash and rarely, erythema multiforme (Steven's-Johnson syndrome); eczema, burning.

**Storage** Store protected from light and moisture.

## Tolnaftate

### Pregnancy Category-C

**Indications** *Ringworm infections, athlete's foot.*

**Availability** **CREAM** 10% w/w.; **OINTMENT-** 10 % w/w.  
**SOLUTION-** 10% w/v.

**Dose** Rub sufficient quantity gently into affected area 2-3 times daily.

**Contraindications** Hypersensitivity, deep infections.

**Precautions** Avoid contact with eyes and mucous membranes; mixed infections. Discontinue if irritation occurs on application, pregnancy (Appendix 7c).

**Adverse Effects** Stinging, irritation, sensitization.



## 9.5 Anthelmintics

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### Cestode Infections:

Cestode infections (tapeworms) include intestinal taeniasis and cysticercosis, hymenolepiasis (dwarf tapeworm), diphyllbothriasis and echinococcosis (hydatid disease). Cysticercosis is a systemic infection caused by the larval form (cysticercus) of *Taenia solium*.

Neurocysticercosis occurs when the infection involves the brain. In man, echinococcosis is due to the larval stage of *Echinococcus granulosus* or *E. multilocularis*. The larvae (oncospheres) develop by expansion (cystic echinococcosis) or tumour-like infiltration (alveolar echinococcosis), respectively, in the liver, lungs, or other organs.

#### 1. Diphyllbothriasis:

In diphyllbothriasis, niclosamide or praziquantel in a single dose is highly effective. Hydroxocobalamin and folic acid supplements may also be required.

#### 2. Echinococcosis:

In echinococcosis, surgery (or, if this is not possible, a technique such as 'puncture-aspiration-injection-reaspiration') is the treatment of choice for operable cystic disease due to *Echinococcus granulosus* but chemotherapy with benzimidazoles, such as mebendazole and albendazole, may be of value as adjunctive therapy. Alveolar echinococcosis due to *E. multilocularis* requires both surgery and long-term treatment with either mebendazole or albendazole to inhibit spread of the infection.

In animal studies, albendazole and mebendazole have been found to be teratogenic. They are contraindicated for the treatment of cestode infections in pregnancy; pregnancy should be excluded before treatment with albendazole (non-hormonal contraception during and for 1 month after treatment). For single-dose or short-term use in pregnancy.

#### 3. Hymenolepiasis:

In hymenolepiasis, praziquantel is more effective than niclosamide, although resistance to praziquantel has been reported. Repeated treatment may be necessary to cure intense infections or to eliminate the parasite within a family group or institution.

#### 4. Taeniasis:

In taeniasis, praziquantel is well tolerated and extensively absorbed and kills adult intestinal taenia worms in a single

dose. Praziquantel also kills *T. solium* cysticerci when taken for 14 days in high doses. It thus offers the prospect of a cure for neurocysticercosis, which has been treatable only by surgery, anti-inflammatory corticosteroids and anticonvulsants. However, because dying and disintegrating cysts may induce localized cerebral oedema, treatment with praziquantel must always be undertaken in a hospital setting. In addition, a corticosteroid is usually given to reduce the inflammatory response. Albendazole also kills neurocysticerci when given daily for one month; a corticosteroid or an antihistamine is also given to reduce any inflammatory reaction. The longer-established niclosamide acts only against the adult intestinal worms. Cestode infections due to *T. solium*, occurring during pregnancy should always be treated immediately (with praziquantel or niclosamide, but not with albendazole) because of the risk of cysticercosis.

## Intestinal Nematode Infections:

Intestinal nematode infections include ascariasis, capillariasis, enterobiasis, hookworm infection, strongyloidiasis, trichostongyliasis and trichuriasis.

### 1. Ascariasis:

Ascariasis is an infection, usually of the small intestine, caused by *Ascaris lumbricoides* (roundworm). Single doses of levamisole or pyrantel are effective; the broad-spectrum anthelmintics, albendazole or mebendazole are also effective.

### 2. Capillariasis:

Capillariasis is caused by infection of the intestine with *Capillaria philippinensis*. Prolonged treatment with mebendazole or albendazole offers the only prospect of cure.

### 3. Enterobiasis:

Enterobiasis is an infection of the large intestine caused by *Enterobius vermicularis* (pinworm, threadworm). All household members should be treated concurrently with a single dose of mebendazole, albendazole or pyrantel. Since reinfection readily occurs, at least one further dose should be given 2-4 weeks later. Piperazine is also effective but must be taken regularly for at least 7 consecutive days.

### 4. Hookworm Infections:

Hookworm infections are caused by *Ancylostoma duodenale* (ancylostomiasis) and *Necator americanus* (necatoriasis); they are a major cause of iron-deficiency anaemia in the tropics and sub-tropics. Ideally all cases of hookworm infection should be treated. However, when this is impracticable, priority should be given to women in second- and third-trimester of

pregnancy, children and debilitated patients. In hookworm, broad-spectrum anthelmintics are preferred wherever other nematode infections are endemic. Both mebendazole and albendazole are effective.

In animal studies, albendazole and mebendazole have been found to be teratogenic. There is some evidence to suggest that the use of mebendazole in pregnancy is not associated with an increased incidence of adverse effects on the fetus. However, neither mebendazole nor albendazole should be used during the first trimester of pregnancy to treat nematode infections. Both drugs are contraindicated for the treatment of cestode infections in pregnancy.

Levamisole is effective in the treatment of mixed *Ascaris* and hookworm infections and pyrantel has been highly effective in some community-based control programmes, although several doses are often needed to eliminate *Necator americanus* infection. Patients with iron-deficiency anaemia caused by hookworm infection require supplementary iron salts and should receive ferrous sulphate (200 mg daily for adults) for at least 3 months after the haemoglobin concentration of 12g/100 ml is obtained.

### 5. Strongyloidiasis:

Strongyloidiasis is an infection of the small intestine caused by *Strongyloides stercoralis*. All infected patients should be treated. Ivermectin in a single dose of 200 µg/kg or 200 µg/kg/day on two consecutive days is the treatment of choice for chronic strongyloidiasis but it may not be available in all countries. Albendazole 400 mg once or twice daily for 3 days is well tolerated by both adults and children aged over 2 years and it may eradicate up to 80% of infections. Mebendazole has also been used but, to be effective, it must be administered for longer periods as it has a limited effect on larvae and hence the prevention of autoinfection.

### 6. Trichostrongyliasis:

Trichostrongyliasis is an infection of the small intestine caused by *Trichostrongylus* spp. In symptomatic trichostrongyliasis, a single dose of pyrantel (10 mg/kg) or albendazole (400 mg) is effective.

### 7. Trichuriasis:

Trichuriasis is an infection of the large intestine caused by *Trichuris trichiura* (whipworm). Chemotherapy is required whenever symptoms develop or when faecal samples are found to be heavily contaminated (up to 10,000 eggs per gram). A single dose of albendazole (400 mg) or mebendazole (500 mg) can be effective in mild to moderate infections; severe infec-

tions require a 3-day course.

## Tissue Nematode Infections:

Tissue nematode infections include angiostrongyliasis, anisakiasis, cutaneous larva migrans, dracunculiasis, trichinellosis and visceral larva migrans.

### 1. Angiostrongyliasis:

Angiostrongyliasis is caused by infection with the larvae of the rat lungworm, *Parastrongylus cantonensis* (*Angiostrongylus cantonensis*). Symptomatic treatment pending spontaneous recovery is often all that is required.

### 2. Anisakiasis:

Anisakiasis is caused by infection with seafood containing larvae of *Anisakis*, *Contracaecum* or *Pseudoterranova* spp. In anisakiasis, anthelmintic treatment is rarely necessary. Prevention is dependent upon informing communities of the hazards of eating raw or inadequately prepared salt-water fish; and early evisceration of fish after capture and freezing of seafood at -20°C for at least 60 h before sale.

### 3. Cutaneous Larva Migrans:

Cutaneous larva migrans (creeping eruption) is caused by infection with larvae of animal hookworms, usually *Ancylostoma braziliense* and *A. caninum* which infect cats and dogs. Albendazole in a single dose of 400 mg is effective.

### 4. Dracunculiasis:

Dracunculiasis (dracontiasis, guinea-worm infection) is caused by infection with *Dracunculus medinensis*, acquired through drinking water containing larvae that develop in small fresh-water crustaceans. Metronidazole (25 mg/kg daily for 10 days, with a daily max. of 750 mg for children) provides rapid symptomatic relief. It also weakens the anchorage of the worms in the subcutaneous tissues and they can then be removed by traction. However, since it has no effect on the larvae of pre-emergent worms, it does not immediately prevent transmission.

### 5. Trichinellosis:

Trichinellosis (trichinosis) is caused by infection with the larvae of *Trichinella spiralis*. Each case of confirmed or even suspected trichinellosis infection should be treated in order to prevent the continued production of larvae. In both adults and children, mebendazole (200 mg daily for 5 days), albendazole (400 mg daily for 3 days) and pyrantel (10 mg/kg daily for 5 days) are all effective. Prednisolone (40-60 mg daily) may be needed to alleviate the allergic and inflammatory symptoms.

## 6. Visceral Larva Migrans:

Visceral larva migrans (toxocariasis) is caused by infection with the larval forms of *Toxocara canis* and less commonly, *T. cati* (which infect dogs and cats). Treatment should be reserved for symptomatic infections. A 3 week oral course of diethyl-carbamazine kills the larvae and arrests the disease, but established lesions are irreversible. To reduce the intensity of allergic reactions induced by dying larvae, dosage is commonly commenced at 1 mg/kg twice daily and raised progressively to 3 mg/kg twice daily (adults and children).

Ocular larva migrans occurs when larvae invade the eye, causing a granuloma which may result in blindness. In order to suppress allergic inflammatory responses in patients with ophthalmic lesions, prednisolone should be administered concurrently, either topically or systemically.

### Albendazole\*

Pregnancy Category-C

Schedule H

#### Indications

*Echinococcus multilocularis* and *E. granulosus* infections prior to or not amenable to surgery; neurocysticercosis; nematode infections; filariasis; ascariasis, hookworm infections, strongyloidiasis, enterobiasis, trichuriasis, trichostrongyliasis and capillariasis; cestode infections; tissue nematode infections.

#### Availability

**CHEWABLE/PLAIN TABLET** 150, 200, 400 mg & 1.5g; **CAPSULE** 400 mg; **ORAL SUSPENSION** 200 mg/5 ml; **SYRUP** 200 mg/5 ml; **DROPS** 10 ml (200 mg/ml)

#### Dose

**Oral**

**Adult and child above 2 years-** 400 mg daily as a single dose.

Strongyloidiasis, taeniasis and *H. nana* infection: 400 mg once daily is given for 3 consecutive days. Hydatid disease: 400 mg twice daily with meals for 28 days (therapy may be repeated after 14 days in three cycles).

**Child-** 1 to 2 years: 200 mg as a single dose.

#### Contraindications

Pregnancy, adequate measures must be taken for non-hormonal contraceptive during and one month after therapy; hypersensitivity.

#### Precautions

Pregnancy (see notes above and Appendix 7c); liver impairment, increased intracranial pressure; seizures; monitor blood count and liver function.

**Adverse Effects** Gastrointestinal discomfort; headache; adverse effects associated with use in cestode infections; reversible alopecia; leucopenia, neurocystercosis; Steven's Johnson syndrome.

**Storage** Store protected from light.

## Mebendazole

**Pregnancy Category-C**

**Schedule H**

**Indications** *Echinococcus granulosus* and *E. multilocularis* infections before surgery or not amenable to surgery; nematode infections.

**Availability** **TABLET** 100 mg; **ORAL SUSPENSION** 100 mg/5 ml.

**Dose** **Oral**

**Adult and child over 2 years-** Threadworm infection: 100 mg single dose. If re-infection occurs second dose may be needed after 2 weeks. Whip worm, roundworm and hookworm infection: 100 mg twice daily for 3 days.

**Contraindications** Pregnancy; lactation; hypersensitivity; patients with CNS disorders.

**Precautions** Pregnancy (Appendix 7c; see also notes above); lactation; interactions (Appendix 6c, 6d); expulsion of ascaris from mouth or nose; monitor blood count or hepatic function.

**Adverse Effects** Gastrointestinal disturbances; headache and dizziness; adverse effects associated with use in cestode infections; abdominal pain, diarrhoea; rashes, urticaria, angioedema.

**Storage** Store protected from light and moisture.

## Niclosamide

**Pregnancy Category-B**

**Schedule H**

**Indications** *Taenia saginata*, *T. solium*, *Hymenolepis nana* and *Diphyllobothrium latum* infections.

**Availability** **TABLETS** 500 mg and 1g.

**Dose** **Oral**

**Adult-** 1g (2 tablets) chewed and swallowed with water on empty stomach. Followed by another dose of 1g one h later. Brisk purgative after 2 h of last dose is recommended.

*H. nana* infection: 2g daily after food on first day thereafter 1g for next 6 days.

<b>Contraindications</b>	Hypersensitivity; purgative must be given after two h to clear bowel since ova in dead segments are not cleared without purgative. Infection may recur if purgative is not given.
<b>Precautions</b>	Chronic constipation (restore regular bowel movement before treatment); give antiemetic before treatment; not effective against larval worms; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Nausea; retching; abdominal pain; lightheadedness; pruritus; anorexia, emesis, perianal itching.
<b>Storage</b>	Store protected from light and moisture.

## Pyrantel Pamoate

Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Ascariasis; hookworm infections; enterobiasis; trichostrongyliasis; tissue nematode infection.</i>
<b>Availability</b>	<b>TABLET</b> 250 mg; <b>ORAL SUSPENSION</b> 250 mg/ml.
<b>Dose</b>	<b>Oral</b>  11 mg/kg (max 1g) in a single dose (given for 2 consecutive days in case of heavy hookworm infestation).
<b>Contraindications</b>	Hepatic diseases.
<b>Precautions</b>	Pregnancy (Appendix 7c; lactation; liver disease (reduce dose); severe malnutrition, anaemia, concurrent administration with piperazine.
<b>Adverse Effects</b>	Mild gastrointestinal disturbances; headache; dizziness; drowsiness; insomnia; rash and elevated liver enzymes.
<b>Storage</b>	Store protected from light at temperature not exceeding 30°C.

## 9.6 Anti-Leishmaniasis Drugs

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Leishmaniasis is caused by the parasitic protozoa *Leishmania*. It can be categorized as visceral, cutaneous or mucocutaneous. It may be a self-limiting localized skin lesion but may range from this to disseminated progressive disease. In endemic areas there is usually a reservoir of disease in a mammalian host and the usual vectors are sandflies.

### Visceral Leishmaniasis:

Visceral leishmaniasis (kala-azar) is caused by *Leishmania donovani* and *L. infantum* (Old World) and by *L. chagasi* (New World) and it is usually responsive initially to the pentavalent antimony compounds, meglumine antimoniate or Sodium stibogluconate. Both dosage and duration of treatment need to be adjusted according to the clinical response. Patients are considered to be clinically cured when no parasites are detected in splenic or bone marrow aspirates. However, biopsies should be repeated after 3 and 12 months since relapse is frequent. Antimonials combined with allopurinol, pentamidine isothionate and amphotericin B have been used with success in patients in relapse who have become unresponsive to antimonials alone.

### Cutaneous Leishmaniasis:

Cutaneous leishmaniasis comprises two conditions. The Old World variety is caused by *L. tropica*, *L. major*, *L. infantum* and *L. aethiopica*. The New World variety is caused by *L. amazonensis*, *L. mexicana*, *L. peruviana*, *L. guyanensis*, *L. panamensis* and *L. braziliensis*. These conditions are characterized by a cell-mediated reaction of varying intensity at the site of inoculation. The New World variety tends to be more severe and slower to heal. Infections caused by *L. major*, *L. mexicana*, *L. tropica* and *L. peruviana*, are responsive to intral-lesional injections of antimonial compounds. Mild lesions can often be left to heal spontaneously. However, it is preferable to treat *L. tropica* infections with a view to reducing transmission since humans seem to be the only host. When the lesion is inflamed or ulcerated or when obstruction of lymphatic drainage or destruction of cartilage creates a risk of serious disfigurement or disability, antimonials should be administered systemically as well as locally. Infections due to *L. braziliensis* and the less common *L. panamensis* should be treated with antimonials because of the risk of mucosal involvement. *L. aethiopica* is less responsive at conventional doses and the sores should be left to heal spontaneously if there is no evidence of diffuse cutaneous involvement. *L.*



*guyanensis* infections should be treated with pentamidine

### Mucocutaneous Leishmaniasis:

Mucocutaneous leishmaniasis is caused by *L. braziliensis* and *L. panamensis*. In this form of the disease the primary lesions do not heal and spread to the mucosa may occur. It usually responds to antimonials and, when relapses occur, more extended courses of treatment are often successful. Patients who still fail to respond should receive amphotericin B or pentamidine isothionate, although neither treatment is highly satisfactory. Because of resistance to antimonials, *L. aethiopica* infections should be treated with pentamidine from the outset until complete healing occurs.

Emergency use of corticosteroids may be needed to control pharyngeal or tracheal oedema produced by severe inflammation resulting from antigens liberated from dead parasites during the early phase of treatment.

Antibiotics may also be needed to treat secondary infections and plastic surgery offers the only means of ameliorating disfiguring scars.

### Diffuse Cutaneous Leishmaniasis:

Diffuse cutaneous leishmaniasis usually occurs following infection with *L. amazonensis*, *L. aethiopica* or *L. mexicana* and is usually treated with antimonial compounds, but relapses must be expected and repeated courses of pentamidine isothionate may be needed until clinical immunity is established.

## Miltefosine

Pregnancy Category-X

Schedule H

<b>Indications</b>	<i>As directly observed therapy (DOT) of visceral Leishmaniasis caused by Leishmania donovani.</i>
<b>Availability</b>	<b>CAPSULES</b> 10 mg, 50 mg
<b>Dose</b>	<b>Oral</b>  <b>Adult- (&gt;12 years): Weighing &gt;25 kg:</b> 100 mg/day, twice a day, after meals for 28 days. <b>&lt;25 kg:</b> 50 mg/day, after meals for 28 days <b>Child (2-11 years):</b> 2.5 mg/kg daily after meals for 28 days, i.e., 50 mg once daily.
<b>Contraindications</b>	Children below 2 years, patients with HIV, newborns, pregnancy (Appendix 7C) and lactation.

<b>Precautions</b>	Avoid contact with eyes, kidney or liver impairment, may impair ability to drive or operate machinery.
<b>Adverse Effects</b>	Nausea and vomiting, GI irritation, diarrhoea, constipation, ocular, hepatic, renal toxicity, skin rash, leukocytosis, thrombocytosis
<b>Storage</b>	Store in a cool place, protected from light and moisture.

## Pentamidine\*

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>Leishmaniasis; African trypanosomiasis; Pneumocystis carinii pneumonia.</i>
<b>Availability</b>	<b>INJECTION</b> 200 and 300 mg Vials.
<b>Dose</b>	<b>Deep intramuscular injection.</b>  3 to 4 mg/kg body weight on alternate days to a max. of 10 injection. Course may be repeated if necessary.
<b>Contraindications</b>	Severe renal impairment.
<b>Precautions</b>	Risk of severe hypotension following administration (establish baseline blood pressure and administer with patient lying down); monitor blood pressure during administration and treatment period; hypertension; hypoglycaemia or hyperglycaemia; hepatic impairment; leukopenia, thrombocytopenia, anaemia; immunodeficiency-if acute deterioration in bone marrow, renal or pancreatic function, interrupt or discontinue treatment; renal impairment; pregnancy-in potentially fatal visceral leishmaniasis, pregnancy (Appendix 7c); lactation (Appendix 7b); history of asthma.
<b>Adverse Effects</b>	Nephrotoxicity; acute hypotension-with dizziness, headache, breathlessness; tachycardia and syncope following rapid intravenous injection; hypoglycaemia-may be followed by hyperglycaemia and type I diabetes mellitus; pancreatitis; also hypocalcaemia, gastrointestinal disturbances; confusion, hallucinations; arrhythmias; thrombocytopenia, leukopenia, abnormal liver function tests; hyperkalaemia; rash, Stevens-Johnson syndrome, reported; pain, local induration, sterile abscess and muscle necrosis at injection site; night sweat, diarrhoea, nausea, anaemia, wheezing, bad taste, anxiety, insomnia, miscarriage, erythema.
<b>Storage</b>	Store protected from moisture in a single dose container.

## Sodium Stibogluconate\*

<b>Indications</b>	<i>Leishmaniasis/Kala-azar.</i>
<b>Availability</b>	<b>INJECTION</b> vial 30 ml (0.33g equivalent to total antimony 100 mg/ml).
<b>Dose</b>	4 to 6g for full course. <b><i>Slow intravenous infusion</i></b> 20 mg/kg/day.
<b>Contraindications</b>	Severe kidney disorders; lactation.
<b>Precautions</b>	Provide protein-rich diet throughout treatment and, if possible, correct iron and other nutritional deficiencies; renal and hepatic impairment; monitor cardiac, renal and hepatic function—reduce dose or withdraw treatment if abnormalities occur; pregnancy—in potentially fatal visceral leishmaniasis, treat without delay; intravenous injections must be given slowly over 5 min (to reduce risk of local thrombosis) and stopped if coughing or substernal pain; mucocutaneous disease (see below); treat intercurrent infection (for example pneumonia); lactation; ECG monitoring.  Successful treatment of mucocutaneous leishmaniasis may induce severe inflammation around lesions (may be life-threatening if pharyngeal or tracheal involvement)—may require corticosteroids.
<b>Adverse Effects</b>	Anorexia, nausea, vomiting, abdominal pain, ECG changes (possibly requiring dose reduction or withdrawal), headache, lethargy, myalgia; raised liver enzymes; renal function impairment; coughing and substernal pain (see Precautions); rarely, anaphylaxis, fever, sweating, flushing, vertigo, bleeding from nose or gum, jaundice, rash; pain and thrombosis on intravenous administration; pain on intramuscular injection; phlebotoxicity, metallic taste in mouth, dizziness.
<b>Storage</b>	Store protected from moisture.

## 9.7 Antimalarial Drugs

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Human malaria, which is transmitted by female anopheline mosquitoes (and rarely, by congenital transmission, transfusion of infected blood or use of contaminated syringes among drug addicts), is caused by four species of plasmodial parasites. *Plasmodium vivax* is the most extensively distributed and causes much debilitating disease. *P. falciparum* is also widespread and causes the most severe infections which are responsible for nearly all malaria-related deaths. *P. ovale* is mainly confined to Africa and is less prevalent, while *P. malariae*, which causes the least severe but most persistent infections, also occurs widely.

Certain tissue forms of *P. vivax* and *P. ovale* which persist in the liver for many months and even years are responsible for the relapses characteristic of malaria. Such latent forms are not generated by *P. falciparum* or *P. malariae*. Recrudescence of these infections results from persistent blood forms in inadequately treated or untreated patients.

### Treatment of Malaria:

Blood schizonticides, which suppress malaria by destroying the asexual blood forms of the parasites, are the mainstay of the treatment of acute malaria and some are used for prophylaxis. They include the 4-aminoquinolines (example amodiaquine and chloroquine), the related arylaminoalcohols (example mefloquine and quinine) and artemisinin and its derivatives (example artemether and artesunate). Blood schizonticides are not active against intrahepatic forms and therefore they do not eliminate infections by *P. vivax* and *P. ovale*.

Some antimetabolites act synergistically when given in combination. For example, pyrimethamine in combination with a sulfonamide (sulfadoxine) or sulfone and some antibiotics (for example doxycycline) are blood schizonticides. Because they act more slowly, these substances are of little value when used alone. The tetracyclines are used primarily as adjuncts to quinine where multiple-drug-resistant *P. falciparum* is prevalent.

Chloroquine, a rapidly acting schizonticide, is well tolerated, safe and inexpensive. It should be used to treat malaria whenever the parasites remain susceptible. *P. malariae* and *P. ovale* remain fully sensitive to chloroquine.

A 3-day course of chloroquine by mouth is sufficient to eliminate susceptible *P. falciparum* infections because effective plasma-chloroquine concentration is sustained for several weeks.

If subsequent relapse occurs in *P. ovale* and *P. vivax* infections primaquine should be administered, after a second course of chloroquine, to eliminate the intrahepatic infection.

Amodiaquine is an alternative to chloroquine for the treatment of uncomplicated *P. falciparum* infection; but cross-resistance with chloroquine exists in some areas. It should preferably be used as part of combination therapy with other antimalarials, for example artesunate. Hepatitis and blood disorders were reported when amodiaquine was used for prophylaxis of malaria; patients should be told how to recognise the symptoms of these conditions and advised to seek medical help if they occur.

The combination of sulfadoxine with pyrimethamine is recommended for the treatment of malaria only in areas of high chloroquine resistance. A single dose of sulfadoxine with pyrimethamine is usually sufficient to eliminate infection; quinine should also be given for 3 days in patients in whom quinine may accelerate reduction of parasitaemia and in those at risk of fulminating disease. Because sulfonamides are associated with a risk of haemolysis and methaemoglobinaemia in the newborn, quinine is preferred to treat chloroquine-resistant malaria during pregnancy.

Mefloquine is generally well tolerated, although, some adverse effects have been reported (see notes). However, because of the danger of the emergence of mefloquine-resistant strains of *P. falciparum* and because of its potential toxicity, it should be used only following either microscopic or careful clinical diagnosis of *P. falciparum* infections that are known or strongly suspected to be resistant to chloroquine or sulfadoxine with pyrimethamine.

Quinine, given orally, should be reserved for *P. falciparum* infections likely to be unresponsive to other drugs. Doxycycline, which is an effective oral schizonticide, should be given in combination with quinine except in pregnant women and children under 8 years.

In multi-drug resistant malaria, preparations of artemisinin or its derivatives (artemether or artesunate) offer the only prospect of cure. They should not be used in the first trimester of pregnancy. For the treatment of multi-drug resistant falciparum malaria oral artesunate may be an effective antimalarial. It should always be given in combination with mefloquine. Parenteral artemether or artesunate, whose use is restricted, are effective alternatives to quinine for the treatment of severe falciparum malaria and are preferred in areas where decreased efficacy of quinine has been documented. To ensure radical cure following parenteral treatment with artemether or oral treatment with artesunate, a full therapeutic dose of mefloquine should be given. A fixed-dose oral formulation of artemether with lumefantrine has recently become available and is recommended for the treatment of uncomplicated falciparum malaria in areas with significant resistance. The combination is not for use in pregnancy or lactation.

## Prophylaxis Against Malaria:

No drug regimen gives assured protection to everybody and indiscriminate use of antimalarials can increase the risk of inducing resistance.

Chloroquine, which is usually well tolerated at the required dosage, is preferred where *P. falciparum* remains fully sensitive. The combination of proguanil with chloroquine may overcome mild chloroquine resistance. Chloroquine must be started 1 week before exposure and be continued in pregnant women until after delivery and for at least 4 weeks after the last risk of exposure in the case of non-immune individuals. This is sufficient to ensure elimination of *P. falciparum* and *P. malariae*, but not of *P. vivax* and *P. ovale*, whose residual hepatic forms survive.

Mefloquine may be used for prophylaxis in areas of high risk or where multiple-drug resistance has been reported. Where possible prophylaxis should be started 2-3 weeks before travel to enable any adverse reactions to be identified before exposure (over three-quarters of adverse reactions occur by the third dose) and should be continued for 4 weeks after last exposure. Mefloquine may be used for prophylaxis during the second and third trimesters. It should be used in early pregnancy only if alternative drugs are either not available or unlikely to be effective and when it is impracticable for the woman to leave the endemic area.

Proguanil, a predominantly tissue schizonticide with little blood schizonticidal activity, is a causal prophylactic agent since it is active against pre-erythrocytic intrahepatic forms, particularly of *P. falciparum*. The latent persistent liver forms of *P. ovale* and *P. vivax* are unresponsive. However, there is evidence that it may be effective against *P. vivax* only immediately after the initial infection. *P. falciparum* resistance to proguanil or related compounds may occur in malaria endemic areas and particularly where it has been employed in mass prophylaxis. Proguanil is used for prophylaxis with chloroquine in areas where there is resistance to chloroquine but a low risk of infection as it may give some protection against and may alleviate symptoms if an attack occurs. Proguanil and chloroquine may also be used prophylactically in areas of high risk or multi-drug resistance as a second choice where mefloquine is not appropriate.

There is no evidence that proguanil is harmful in prophylactic doses during pregnancy. Because of the vulnerability of pregnant women to falciparum malaria, it should be used at full prophylactic dosage wherever the disease is prevalent and likely to be responsive to proguanil, if chloroquine is not available or with chloroquine, if the latter alone is unlikely to be effective.

## 9.7.1 Drugs for Prophylaxis

### Chloroquine\* (Refer Page No. 383)

#### Pregnancy Category-D

<b>Indications</b>	<i>Treatment of acute malaria caused by P. malariae and susceptible P. falciparum; P. vivax and P. ovale (followed by primaquine to eliminate intrahepatic forms); prophylaxis of malaria for pregnant women and non-immune individuals at risk; rheumatic disorders.</i>
<b>Availability</b>	<b>TABLETS</b> 250 and 500 mg; <b>INJECTION</b> 10 and 30 ml (40 mg/ml); <b>SUSPENSION</b> 50 mg/ml.
<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> Immediately 600 mg, after 6 h 300 mg followed by 300 mg daily for 2 days.</p> <p><b>Child-</b> 10 mg/kg body weight followed by 5 mg/kg body weight after 6 h, thereafter once a day for 2 days.</p> <p><b>Intramuscular injection</b></p> <p><b>Adult-</b> 10 ml followed by 5 ml after 6 h. Thereafter 5 ml daily for two days.</p> <p><b>Child-</b> 5 mg/kg body weight administered every 12 h followed by oral therapy.</p>
<b>Contraindications</b>	Severe haematologic distress or gastrointestinal distress; eye dysfunction; liver disease.
<b>Precautions</b>	If patient continues to deteriorate after chloroquine-suspect resistance and administer quinine intravenously as emergency measure; hepatic impairment; renal impairment (Appendix 7d); pregnancy (but in malaria, benefit considered to outweigh risk; Appendix 7c); lactation (Appendix 7b); may exacerbate psoriasis; neurological disorders (avoid for prophylaxis if history of epilepsy); may aggravate myasthenia gravis; severe gastrointestinal disorders; G-6-PD deficiency; avoid concurrent therapy with hepatotoxic drugs; interactions (Appendix 6c, 6d).

**Adverse Effects**

Headache, gastrointestinal disturbances; also convulsions; visual disturbances (retinopathy associated with long-term, high dose therapy or inappropriate self-medication); depigmentation or loss of hair; rashes; pruritus-may become intolerable; bone-marrow suppression; hypersensitivity reactions such as urticaria and angioedema; atrioventricular block (may be result of inappropriate self-medication); porphyria and psoriasis in susceptible individuals.

**Storage**

Store protected from light.

**Doxycycline\*** (Refer Page No. 134)**Pregnancy Category-D****Schedule H****Indications**

*Supplement to quinine in treatment of multiple-medicine resistant P. falciparum malaria (where quinine resistance, in cases of hypersensitivity to sulfonamides); short-term prophylaxis of multiple-medicine resistant P. falciparum malaria; bacterial infections.*

**Availability**

**CAPSULES/TABLETS** 50, 100, 150 and 200 mg; **SYRUP** 25 mg/5 ml.

**Dose****Oral**

**Adult-** 200 mg on the first day then 100 mg daily.

Severe infections including refractory urinary tract infection: 200 mg daily can be used.

Early syphilis: 100 mg twice daily for 14 days and for latent syphilis 200 mg twice daily for 28 days is used.

Uncomplicated genital Chlamydia, non-gonococcal urethritis: 100 mg twice daily for 7 days.

**Child-** Only if alternate antibacterial cannot be given 5 mg/kg body weight in two divided doses.

**Contraindications**

Pregnancy (Appendix 7c); children under 8 years; porphyria; systemic lupus erythematosus; prolonged exposure to sunlight, severe hepatic dysfunction.

**Precautions**

Avoid exposure to sunlight or sunlamps-photosensitivity reported; renal impairment; hepatic impairment (Appendix 7a); lactation (Appendix 7b); interactions (Appendix 6c).



**Adverse Effects** Gastrointestinal disturbances; anorexia; erythema (discontinue treatment); photosensitivity; hypersensitivity reactions; headache and visual disturbances; hepatotoxicity, blood disorders, pancreatitis and antibiotic-associated colitis reported; staining of growing teeth and occasional dental hypoplasia; nasopharyngitis, reduced tibular growth rate, diarrhoea, sinusitis.

**Storage** Store protected from light and moisture at a temperature not exceeding 30°C.

## Primaquine\*

**Indications** *Radical cure of P. vivax and P. ovale malaria (after chloroquine therapy to eradicate erythrocytic forms), elimination of gametocytes of P. falciparum, malaria prophylaxis.*

**Availability** TABLETS 2.5, 7.5 and 15 mg.

**Dose** **Radical treatment**

**Adult-** 15 mg daily for 14 days, may be increased to higher dose.

**Child-** 250 µg/kg daily for 14 days.

### **Malaria prophylaxis**

**Adult-** 30 mg once daily; **Child-** 0.5 mg/kg once daily (to be started 1-2 days before travel and continue for 7 days after departure from malaria endemic area).

**Gametocidal treatment of P. falciparum malaria** (after standard blood schizonticide therapy).

**Adult and Child-** 500–50 µg/kg as a single dose.

**Contraindications** Hypersensitivity, granulocytopenia, pregnancy, lactation, children below 1 year.

**Precautions** Patients with history of granulocytosis/methaemoglobinaemia, G-6-PD deficiency, monitor Hb levels, blood counts routinely and withdraw if signs of haemolysis or methaemoglobinaemia occur; lactation (Appendix 7b).

**Adverse effects** Nausea, vomiting, abdominal cramps, haemolytic anaemia in G-6-PD deficient patients; rarely, leukopenia, agranulocytosis, leukocytosis, methaemoglobinaemia and cardiac arrhythmias.

**Storage** Store protected from moisture.

## Proguanil

**Pregnancy Category-B**

**Schedule H**

**Indications** *With chloroquine, prophylaxis of malaria in areas of low resistance.*

**Availability** **TABLET** 100 mg.

**Dose** **Oral**

### **Prophylaxis**

**Adult-** Preferably 200 mg once daily, start 1 to 2 days before entering endemic area and continue for 4 weeks after leaving.

**Child-** (11-20 kg) - 25 mg once daily;  
(21-30 kg)- 50 mg once daily;  
(31-40 kg)- 75 mg once daily;  
more than 40 kg- 100 mg once daily.

### **Treatment**

**Adult and child-** over 40 kg; 100 mg once daily.

**Child-** Up to 1 year: 25 mg; 1 to 4 years; 50 mg; 5 to 8 years: 100 mg; 9 to 14 years: 150 mg; above 14 years: 200 mg.

**Contraindications** Use in areas of known resistance to either proguanil or pyrimethamine.

**Precautions** Renal impairment; pregnancy (folate supplements required, Appendix 7c); lactation.

**Adverse Effects** Mild gastric intolerance, diarrhoea; occasional mouth ulcers and stomatitis; skin reactions and hair loss reported; rarely, hypersensitivity reactions such as urticaria and angioedema.

**Storage** Store protected from light and moisture.

## 9.7.2 Drugs for Curative Treatment

### Amodiaquine

**Schedule H**

**Indications** *Treatment of uncomplicated malaria caused by P. falciparum.*

**Availability** **TABLET** 200 mg; **SUSPENSION** 50 mg/5 ml.

**Dose** **Oral**

**Adult-** Prophylaxis: 300 mg once weekly, start one week before entering endemic area and continue for 4 weeks after leaving.

**Infant-** up to 12 weeks, body weight under 6 kg: 37.5 mg once weekly,  
1 year body weight 6 to 10 kg: 75 mg once weekly.

**Child-** 1 to 4 years, body weight 10 to 16 kg: 11 to 12.5 mg once weekly.  
4 to 8 years: body weight 16 to 25 kg: 150 mg once a week.  
8 to 13 years, body weight over 45 kg: adult dose is used.

**Contraindications** Hepatic impairment (Appendix 7a); blood disorders, retinopathy.

**Precautions** Pregnancy and lactation; G-6-PD deficiency; avoid concurrent therapy with hepatotoxic drugs.

Patients and their caretakers should be told how to recognize the signs of blood disorders and advised to seek medical attention as soon as possible if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop. They should also be told how to recognize signs of hepatitis and advised to seek medical attention if symptoms such as anorexia, abnormal weight loss, asthenia, abdominal pains, fever, nausea or vomiting develop.

**Adverse Effects** Blood disorders including leukopenia and agranulocytosis; hepatitis; gastrointestinal disturbances, visual disturbances (retinopathy associated with long-term, high-dose therapy); rarely, rash, pruritus, skin pigmentation, neuromyopathy.

### Arteether

**Pregnancy Category-C**

**Schedule H**

**Indications** *Complicated falciparum malaria; chloroquine resistant malaria; cerebral malaria.*

**Availability** **INJECTION** 2 ml ampoule (150 mg/2 ml).

(Arteether is an ethyl derivative of dihydro-artemisinin. It is a mixture of  $\alpha$  and  $\beta$  arteether in a 30:70 ratio)

<b>Dose</b>	<b>Adult-</b> 150 mg daily i.m. injection, once daily for 3 consecutive days.
<b>Contraindications</b>	Hypersensitivity to artemisinin derivatives; preganacy (Appendix 7c).
<b>Adverse reactions</b>	It is clinically very well tolerated without any significant side effects; neurological or biochemical.
<b>Storage</b>	Store protected from light in tamper evident container so as to avoid contamination by micro-organisms.

## Artemether

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>Treatment of severe P. falciparum malaria in areas where evidence is there that quinine is ineffective; multi drug resistant malaria.</i>
<b>Availability</b>	<b>CAPSULE</b> 40 mg; <b>INJECTION</b> 1 ml ampoule (80 mg/ml, 160 mg/2 ml).
<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> 160 mg in two divided doses on first day followed by 80 mg once a day for next four days.</p> <p><b>Intramuscular injection</b></p> <p><b>Adult-</b> 80 mg twice a day for 3 days.</p> <p><b>Child-</b> 1.6 mg/kg body weight twice a day followed by 1.6 mg/kg body weight once a day for 4 days, alternatively 1.6 mg/kg body weight twice a day for 3 days.</p>
<b>Contraindications</b>	First trimester of pregnancy (Appendix 7c); hypersensitivity.
<b>Precautions</b>	<p>Electrolyte disturbances, concomitant use with other drugs known to cause QT-interval prolongation; hepatic impairment; renal impairment; monitor patients unable to take food (greater risk of recrudescence); interactions (Appendix 6c); lactation (Appendix 7b).</p> <p>Dizziness may impair ability to perform skilled tasks, for example operating machinery, driving.</p>

**Adverse Effects** Headache, nausea, vomiting, abdominal pain, diarrhoea; dizziness, tinnitus, neutropenia, elevated liver enzyme values; cardiotoxicity (after high doses); neurotoxicity-in animal studies; decrease in reticulocyte count.

**Storage** Store protected from light and moisture.

## Artesunate\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *Treatment of uncomplicated P. falciparum malaria in areas of multiple drug resistance.*

**Availability** **TABLET** 25, 50 & 60 mg; **INJECTION** 50, 60, 1000 & 2000 mg/vial.

**Dose** **Oral**

**Adult-** total oral dose 600 mg can be divided into two 50 mg tablets twice a day on first day thereafter 50 mg twice a day for next 4 days.

**Child-** half adult dose.

### ***Intramuscular injection***

60 mg twice daily.

**Contraindications** First trimester of pregnancy (Appendix 7c); hypersensitivity.

**Precautions** Risk of recurrence if used alone in non-immune patients; hepatic/renal insufficiency, pregnancy (Appendix 7c), lactation, paediatrics.

Dizziness may impair ability to perform skilled tasks, for example operating machinery, driving.

**Adverse Effects** Headache, nausea, vomiting, abdominal pain, diarrhoea, dizziness, tinnitus, neutropenia, elevated liver enzyme values; ECG abnormalities, including prolongation of QT interval; temporary suppression of reticulocyte response and induction of blackwater fever reported; neurotoxicity-in animal studies.

**Storage** Store protected from light and moisture.

**Chloroquine\*** (Refer Page No. 178 and 383)

**Doxycycline\*** (Refer Page No. 134 and 179)

## Quinine\*

### Pregnancy Category-X

**Indications** Multiple drug resistant *P. falciparum* malaria.

**Availability** **TABLETS** 100, 150, 300 and 600 mg; **SUSPENSION** 150 mg/5 ml; **INJECTION** 1 and 2 ml ampoule (300 mg/ml).

**Dose** **Oral**

**Adult-** 300 to 600 mg every 8 h in divided doses for 5 to 7 days.

**Child-** 25 mg/kg body weight every 8 h in divided doses for 5 to 7 days.

**Intravenous infusion for patients unable to swallow tablets**

Loading dose 900 mg to 1.4g infused over 4 h, then 300 to 600 mg every 8 h infused over 4 h.

**Contraindications** Haemoglobinuria; optic neuritis; tinnitus; quinine resistant falciparum, pregnancy (Appendix 7c), lactation, prolonged QT interval.

**Precautions** Atrial fibrillation, conduction defects, heart block; monitor for signs of cardiac toxicity and blood glucose levels (with intravenous use); renal impairment (Appendix 7d); G-6-PD deficiency; may aggravate myasthenia gravis; interactions (Appendix 6d).

**Adverse Effects** Cinchonism (tinnitus, headache, blurred vision, temporary blindness, altered auditory acuity, nausea, diarrhoea, hot and flushed skin, rashes, confusion); hypersensitivity reactions including angioedema; rarely, haemorrhage and asthma; hypoglycaemia (especially after parenteral administration); renal damage (culminating in acute renal failure and anuria); blood disorders; cardiovascular, gastrointestinal and CNS effects; very toxic in overdose-immediate medical attention required; acute haemolytic anaemia.

**Storage** Store protected from light.

## Sulfadoxine + Pyrimethamine\*

### Pregnancy Category-C

**Schedule H**

**Indications** Treatment of malaria due to susceptible *P. falciparum* in areas of high chloroquine resistance and in patients who have not responded to chloroquine; additionally quinine may be given for 3 days.

<b>Availability</b>	<b>TABLETS</b> Sulfadoxine 500mg+Pyrimethamine 25 mg; <b>SUSPENSION</b> 5 ml (500 mg sulfadoxine+25 mg pyrimethamine).
<b>Dose</b>	<b>Oral</b> <b>Adult-</b> Prophylaxis: one tablet once a week. Treatment: 2 tablets in single dose. <b>Child-</b> Under 4 years: half a tablet. 4 to 8 years: one tablet. 9 to 14 years: two tablets single dose.  Prophylaxis: Under 4 years 1/4th tablet. 4 to 8 years: half tablet. 9 to 14 years: 3/4th tablet once a week.
<b>Contraindications</b>	Hypersensitivity to sulfonamides or pyrimethamine; severe hepatic or renal impairment (except where no alternative treatment available); blood dyscrasias, neonates, megaloblastic anaemia and folate deficiency.
<b>Precautions</b>	Avoid in blood disorders-unless specialist supervision; discontinue immediately if blood disorder occurs; rash, sore throat, mouth ulcers, or shortness of breath-withdraw treatment; G-6-PD deficiency; predisposition to folate deficiency; hepatic impairment (Appendix 7a); pregnancy (Appendix 7c); lactation (Appendix 7b); interactions (Appendix 6c).
<b>Adverse Effects</b>	Rashes, pruritus, slight hair loss; rarely, erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis; gastrointestinal disturbances including nausea, vomiting, stomatitis; rarely, hepatitis, leukopenia, thrombocytopenia, megaloblastic anaemia and purpura-withdraw treatment; fatigue, headache, fever, polyneuritis, also reported; pulmonary infiltrates such as eosinophilic or allergic alveolitis-if symptoms of cough or shortness of breath-withdraw treatment.
<b>Storage</b>	Store protected from light and moisture.

## 9.8 Antimycobacterial Drugs

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### 9.8.1 Antileprosy Drugs

Leprosy is a chronic mycobacterial infection due to *Mycobacterium leprae*, which is a slow-growing intracellular bacillus that infiltrates the skin, peripheral nerves, the nasal and other mucosa and the eyes; it affects people of all ages and both sexes. The incubation period between infection and appearance of leprosy is normally between 2 to 10 years, but may be up to 20 years. It is transmitted from person-to-person when bacilli are shed from the nose; most individuals have natural immunity and symptoms are suppressed. For treatment purposes patients may be classified as having paucibacillary (PB) or multibacillary (MB) leprosy. The 2 forms may be distinguished by skin smears, but facilities are not always available to process them and their reliability is often doubtful. In practice, most leprosy programmes classify and choose a regimen based on number of skin lesions; these are PB leprosy (1-5 skin lesions) and MB leprosy (more than 5 skin lesions).

Drugs used in the treatment of leprosy should always be used in combination; this is essential to prevent the emergence of resistance. Rifampicin is now combined with dapsones to treat PB leprosy and rifampicin and clofazimine are now combined with dapsones to treat MB leprosy. The WHO Programme for the Elimination of Leprosy currently provides, free of charge, oral multidrug therapy in colour-coded blister packs (MDT blister packs) to improve patients' adherence to treatment. Any patient with a positive skin smear should be treated with the MDT regimen for MB leprosy. The regimen for PB leprosy should never be given to a patient with MB leprosy. If diagnosis classification in a particular patient is not possible the MDT regimen for MB leprosy must be used.

Lepra reactions are episodes of sudden increase in the activity of leprosy and are often accompanied by neuritis; reactions must always be treated promptly to prevent permanent nerve damage and disability. Leprosy multidrug therapy should continue during a lepra reaction without interruption. This reduces the frequency and severity of lepra reactions.

Type 1 lepra reactions, or reversal reactions, are delayed hypersensitivity reactions and may occur in either PB or MB leprosy. If there is no nerve damage, type 1 reactions may be treated with analgesics such as acetylsalicylic acid or paracetamol. If there is nerve involvement corticosteroids, such as oral prednisolone should be used in addition to analgesics.

The type 2 lepra reaction, also known as erythema nodosum



leprosum (ENL), is an antibody response to dead leprosy bacteria and occurs only in MB leprosy. Therapy for type 2 reactions may include analgesics, such as acetylsalicylic acid or paracetamol and a corticosteroid, such as oral prednisolone. In patients not responding to a corticosteroid, clofazimine may be used. Severe type 2 lepra reactions should be treated under medical supervision in hospital.

If a patient does not respond to lepra reaction treatment within 6 weeks or seems to become worse, the patient must be sent immediately to the nearest specialist centre. Neuritis may occur during or independently of lepra reactions. It can be successfully treated with a 12-week course of oral prednisolone; if patients do not respond, specialist centre treatment is required.

### Treatment Regimens:

The recommended regimen for paucibacillary leprosy in adults (50-70 kg) is rifampicin 600 mg once monthly and dapsone 100 mg daily. Children aged 10-14 years may be given rifampicin 450 mg once monthly and dapsone 50 mg daily. Appropriate dose adjustments are required for younger children. For example, dapsone 25 mg daily and rifampicin 300 mg once a month. Treatment is continued for 6 months for PB leprosy.

The recommended regimen for MB leprosy in adults (50-70 kg) is rifampicin 600 mg and clofazimine 300 mg, both given once a month together with clofazimine 50 mg and dapsone 100 mg, both daily. Children aged 10-14 years may be given rifampicin 450 mg and clofazimine 150 mg, both once a month together with clofazimine 50 mg every other day and dapsone 50 mg daily. Appropriate dosage adjustments are required for younger children. For example, dapsone 25 mg daily, clofazimine 50 mg twice a week and clofazimine 100 mg and rifampicin 300 mg once a month. Treatment is continued for 12 months for MB leprosy.

For patients who cannot take rifampicin because of allergy, other diseases, or rifampicin-resistant leprosy and for patients who refuse to take clofazimine, there are alternative regimens which incorporate ofloxacin and minocycline

## Clofazimine\*

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>MB leprosy; type 2 lepra reactions.</i>
<b>Availability</b>	<b>TABLETS</b> 25, 50, 100 mg; <b>CAPSULES</b> 50 and 100 mg.
<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> 300 mg spread over a week. Sulfone resistant cases: 600 mg weekly preferably after meal.</p> <p>Lepra reaction: 200 mg daily for 3 weeks or as required.</p> <p><b>Child-</b> 1 to 2 mg/kg body weight daily or 4 to 6 mg/kg body weight once a month.</p>
<b>Contraindications</b>	Pregnancy (Appendix 7c), lactation, renal and hepatic impairment.
<b>Precautions</b>	Pre-existing gastrointestinal symptoms (reduce dose, increase dose interval or discontinue if symptoms develop during treatment); liver and renal impairment; may discolour soft contact lenses; paediatrics, elderly, interactions (Appendix 6d).
<b>Adverse Effects</b>	Reversible discolouration of skin, hair, cornea, conjunctiva, tears, sweat, sputum, faeces and urine; dose-related gastrointestinal symptoms including pain, nausea, vomiting and diarrhoea; severe mucosal and submucosal oedema, with prolonged treatment with high doses-may be severe enough to cause subacute small-bowel obstruction (see also Precautions); pruritus, ichthyosis, elevated blood sugar, diminished vision, dizziness, eosinophilic enteropathy.
<b>Storage</b>	Store protected from moisture.

## Dapsone\*

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>PB and MB leprosy; acne vulgaris, dermatitis, pneumocystic pneumonia.</i>
<b>Availability</b>	<b>TABLETS</b> 25, 50 and 100 mg; <b>GEL</b> 5% w/w.
<b>Dose</b>	<b>Oral</b>

**Adult-** Leprosy: 50 to 100 mg daily depending upon body weight. Dermatitis herpetiformis: start with 50 mg daily and increase up to 400 mg till full response is obtained; dose reduced to minimum maintenance level as soon as possible.

**Child-** 1 to 2 mg/kg body weight as minimum dose to start with, increased weekly so that at the end of 7th week patient is receiving max. dose.

**Contraindications** Hypersensitivity to sulfones; severe anaemia; porphyria.

**Precautions** Anaemia (treat severe anaemia before therapy and monitor blood counts during treatment); susceptibility to haemolysis including G-6-PD deficiency (including lactation affected infants); lactation (Appendix 7b); porphyria; interactions (Appendix 6c); hyperbilirubinemia, methaemoglobinemia; renal impairment (Appendix 7d); pregnancy (Appendix 7c).

On long-term treatment patients and their caretakers should be told how to recognize blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop.

**Adverse Effects** Haemolysis and methaemoglobinaemia; allergic dermatitis (rarely, including toxic epidermal necrolysis and the Stevens-Johnson syndrome); rarely, hepatitis and agranulocytosis; 'dapsons syndrome' resembling mononucleosis-rare hypersensitivity reaction with symptoms including rash, fever, jaundice and eosinophilia; gastrointestinal irritation; tachycardia, headache, nervousness, insomnia, blurred vision, paraesthesia, reversible peripheral neuropathy and psychoses reported; increase in reticulocytes, vertigo; pancreatitis; renal papillary necrosis; anorexia.

**Storage** Store protected from light.

## Rifampicin\* (Refer Page No. 200)

**Pregnancy Category-C**

**Schedule H**

**Indications** *PB leprosy; MB leprosy; tuberculosis.*

**Availability** **CAPSULES** 150, 300, 450 and 600 mg; **TABLETS** 150, 300, 350, 450, 500, 600 and 750 mg; **SYRUP** 100 mg/5 ml.

<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> 450 to 600 mg single dose before breakfast.</p> <p><b>Child-</b> 10 to 20 mg/kg body weight daily.</p>
<b>Contraindications</b>	Hypersensitivity; jaundice; patients with earlier drug induced liver disease.
<b>Precautions</b>	Reduce dose in hepatic impairment (Appendix 7a); liver function tests and blood counts required in liver disorders, alcohol dependency, elderly and on prolonged therapy; renal impairment (if dose above 600 mg daily); lactation; porphyria; discolours soft contact lenses; advise patients on oral contraceptives to use additional means; interactions (Appendix 6b, 6c, 6d); pregnancy (Appendix 7c).
<hr/> <p><i>Note: Resumption of rifampicin treatment after a long interval may cause serious immunological reactions, resulting in renal impairment, haemolysis, or thrombocytopenia-discontinue permanently if serious adverse effects occur</i></p> <hr/>	
	<p>Patients or their caretakers should be told how to recognize signs of liver disorders and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.</p>
<b>Adverse Effects</b>	Severe gastrointestinal disturbances including anorexia, nausea, vomiting and diarrhoea (antibiotic-associated colitis reported); headache, drowsiness; rashes, fever, influenza-like syndrome and respiratory symptoms, collapse, shock, haemolytic anaemia, acute renal failure and thrombocytopenic purpura-m ore frequent with intermittent therapy; alterations of liver function-jaundice and potentially fatal hepatitis (dose-related, do not exceed max. daily dose of 600 mg); oedema, muscular weakness and myopathy, exfoliative dermatitis, toxic epidermal necrolysis, pemphigoid reactions, leukopenia, eosinophilia and menstrual disturbances; urine, tears, saliva and sputum coloured orange-red; cerebral haemorrhage, visual disturbances.
<b>Storage</b>	Store protected from light and moisture.

## 9.8.2 Antituberculosis Drugs

Tuberculosis is a chronic infectious disease caused primarily by *Mycobacterium tuberculosis* or sometimes by *M. bovis*. Infection is usually due to inhalation of infected droplet nuclei with the lung generally being the first organ affected, but the primary infection is usually asymptomatic. Infection and inflammatory responses resolve with the development of acquired immunity. Surviving bacteria may become dormant or in susceptible patients, progress to active primary disease; dormant organisms may produce disease and this often occurs if immune status is altered.

Tuberculosis is the most prevalent infectious disease of adults and causes 26% of avoidable adult deaths in the developing world. More than 80% of tuberculosis cases are pulmonary (PTB). At least 30% of patients who are infected with HIV will also develop active tuberculosis. The increase in resistant strains and poor compliance of dosage regimen which may contribute to resistance and treatment failure has led to the development of regimens with directly supervised treatment. Directly observed treatment short-course (DOTS) therapy which lasts for 6 or 8 months, given under direct observation is one of the most important components of the WHO strategy against tuberculosis. Simplified drug regimens and intermittent therapy have been introduced to improve compliance. WHO does not generally recommend twice weekly regimens. If a patient receiving a twice weekly regimen misses a dose of tablets, the missed dose represents a bigger fraction of the total number of treatment doses than if the patient was receiving a three times weekly or daily dose regimen. Therefore, there is a greater risk of treatment failure with twice weekly regimens. Fixed-dose combination tablets incorporating 2 or more drugs are also used to improve compliance and decrease medication errors; they should be used unless one of the components cannot be given because of resistance or intolerance.

Modern short-course therapy is usually in 2 phases. The initial phase (2 months) involves the concurrent use of at least 3 drugs to reduce the bacterial population rapidly and prevent drug-resistant bacteria emerging. The second continuation phase (4-6 months) involves fewer drugs and is used to eliminate any remaining bacteria and prevent recurrence. Direct observation of therapy is considered essential to ensure compliance in the initial phase and also useful in the continuation phase if patients are receiving rifampicin. Five antituberculosis drugs, isoniazid, rifampicin, pyrazinamide, streptomycin (which are bactericidal) and ethambutol

(which is bacteriostatic) are used in various combinations as part of WHO-recommended treatment regimens; thiacetazone is used only if ethambutol cannot be used. In supervised regimens change of drug regimen should be considered only if the patient fails to respond after 5 months of DOTS.

Isoniazid, rifampicin and pyrazinamide are components of all antituberculosis drug regimens currently recommended by WHO. Unsupervised and alternative regimens as set out in the following tables may be administered as specified.

Additional reserve antituberculosis drugs (amikacin, p-aminosalicylic acid, capreomycin, ciprofloxacin, cycloserine, ethionamide, kanamycin, levofloxacin and ofloxacin ) for the treatment of multidrug-resistant tuberculosis should be used in specialized centres adhering to WHO standards for TB control.

Worldwide, an important predisposing cause of immunosuppression leading to tuberculosis is human immunodeficiency virus (HIV) infection; it increases susceptibility to primary infection and increases the reactivation rate of tuberculosis. Preventative antituberculosis therapy of such persons is recommended.

Chemoprophylaxis with isoniazid can prevent the development of clinically apparent disease in persons in close contact with infectious patients and also prevent the reactivation of previously dormant disease in other persons at high risk particularly those who are immunodeficient.

Where the disease remains highly prevalent routine immunization of infants within the first year of age with BCG vaccine is cost-effective. However, there is no evidence that BCG will protect children older than 15 years of age. Infants born to HIV-positive mothers should be vaccinated during the first year of life, provided they have no clinical signs suggestive of HIV.

The tuberculin test has limited diagnostic value. A positive tuberculin test indicates previous exposure to mycobacterial antigens through infection with one of the tubercle bacilli, or BCG vaccination. The tuberculin test does not distinguish between tuberculosis and other mycobacterial infection, between active and quiescent disease, or between acquired infection and seroconversion induced by BCG vaccination.

## Recommended 6-Month Treatment Regimens for Tuberculosis<sup>1</sup>

Drug	Initial phase (2 months)	Continuation phase (4 months)
Isoniazid	5 mg/kg daily	5 mg/kg daily
Rifampicin	10 mg/kg daily	10 mg/kg daily
Pyrazinamide	25 mg/kg daily	
<b>together with</b>		
Streptomycin <sup>3</sup>	15 mg/kg daily	
<b>or</b>		
Ethambutol <sup>2</sup>	15 mg/kg daily	
Isoniazid	10 mg/kg 3 times weekly	10 mg/kg 3 times weekly
Rifampicin	10 mg/kg 3 times weekly	10 mg/kg 3 times weekly
Pyrazinamide	35 mg/kg 3 times weekly	
<b>together with</b>		
Streptomycin <sup>3</sup>	15 mg/kg 3 times weekly	
<b>or</b>		
Ethambutol	30 mg/kg 3 times weekly	

<sup>1</sup>Unless otherwise indicated, doses are suitable for both adults and children

<sup>2</sup>Not suitable for children

## Recommended 8-month treatment regimen for tuberculosis<sup>1</sup>

Drug	Initial phase (2 months)	Continuation phase (6 months)
Isoniazid	5 mg/kg daily	5 mg/kg daily
Rifampicin	10 mg/kg daily	
Pyrazinamide	25 mg/kg daily	
<b>together with</b>		
Ethambutol <sup>3</sup>	15 mg/kg daily	15 mg/kg daily <sup>4</sup>
<b>or</b>		
Streptomycin <sup>2</sup>	15 mg/kg daily	

<sup>1</sup>Unless otherwise indicated, doses are suitable for both adults and children

<sup>2</sup>Streptomycin always replaces ethambutol in meningeal TB

<sup>3</sup>Not suitable for children under 5 years

<sup>4</sup>Thiacetazone (2.5 mg/kg daily) may be used (only if ethambutol cannot be given) in combination with isoniazid in the continuation phase; risk of severe toxicity, particularly in HIV-infected individuals

**Category I:** New pulmonary disease (smear-positive or smear-negative with extensive involvement of parenchyma), concomitant severe HIV disease and new severe extra-pulmonary disease

*Initial phase*<sup>1</sup> (antibacterials administered daily or 3 times weekly): isoniazid + rifampicin + pyrazinamide + ethambutol (or streptomycin) for 2 months *Continuation phase*<sup>1</sup> (antibacterials administered daily or 3 times weekly): isoniazid + rifampicin for 4 months (or isoniazid + ethambutol for 6 months but less effective than isoniazid + rifampicin)

**Category II:** Previously treated smear-positive pulmonary disease which has relapsed, or failed to respond, or if treatment was interrupted

*Initial phase*<sup>1</sup> (antibacterials administered daily or 3 times weekly): isoniazid + rifampicin + pyrazinamide + ethambutol + streptomycin for 2 months

*then:*

isoniazid + rifampicin + pyrazinamide + ethambutol for 1 month *Continuation phase*<sup>1</sup> (antibacterials administered daily or 3 times weekly): isoniazid + rifampicin + ethambutol for 5 months

**Category III:** New smear-negative pulmonary disease (other than in Category I) and less severe extra-pulmonary disease

*Initial phase*<sup>1</sup> (antibacterials administered daily or 3 times weekly): isoniazid + rifampicin + pyrazinamide + ethambutol<sup>3</sup> for 2 months

*Continuation phase*<sup>1</sup> (antibacterials administered daily or 3 times weekly): isoniazid + rifampicin for 4 months (or isoniazid + ethambutol for 6 months but less effective than isoniazid + rifampicin)

**Category IV:** Chronic and multi-drug-resistant tuberculosis (MDR-TB) (smear-positive despite supervised re-treatment)<sup>4</sup>

specially designed standardized or individualized regimens recommended

Treatment regimens by category of tuberculosis diagnosis

<sup>1</sup>Drug intake should be directly observed in patients who are smear positive during the initial phase and always when rifampicin is given

<sup>2</sup>Drug sensitivity testing recommended before prescribing Category II treatment in failure cases; patients with MDR-TB should be prescribed Category IV regimen

<sup>3</sup>Omit ethambutol in initial phase if disease is not complicated by cavitary disease or concomitant HIV disease and in patients infected with fully susceptible bacilli or young children with primary tuberculosis

<sup>4</sup>Early culture and sensitivity testing recommended for contacts of patients with MDR-TB



## Amikacin\*

Pregnancy Category-D

Schedule H

<b>Indications</b>	<i>Short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria, including Pseudomonas species, Escherichia coli, species of indole-positive and indole-negative Proteus, Providencia species, Klebsiella, Enterobacter, Serratia species and Acinetobacter (Mima-Herellea) species.</i>
<b>Availability</b>	<b>INJECTION</b> 10 ml vial (100 mg/2 ml), 2 ml vial (250 mg/2 ml), (500 mg/2 ml).
<b>Dose</b>	<p><b>Intramuscular or intravenous injection or infusion</b></p> <p><b>Adult-</b> 15 mg/kg body weight daily in two divided doses, increased to 22.5 mg/kg body weight daily in three divided doses in severe infections. (max 1.5g daily for 10 days, max. cumulative dose is 15g).</p> <p><b>Child-</b> 15 mg/kg body weight daily in two divided doses.</p> <p><b>Neonates-</b> loading dose is 10 mg/kg body weight followed by 15 mg/kg body weight in two divided doses.</p>
<b>Contraindications</b>	Myasthenia gravis; hypersensitivity.
<b>Precautions</b>	Pregnancy (Appendix 7c), renal impairment (Appendix 7d); neonates, infants and elderly; cross allergenicity.
<b>Adverse Effects</b>	Vestibular and auditory damage, nephrotoxicity; rarely, hypomagnesaemia on prolonged therapy, antibiotic-associated colitis, stomatitis; also reported, nausea, vomiting, rash, blood disorders; acute muscular paralysis; albuminuria; azotemia.

## Capreomycin

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Tuberculosis, in combination with other first line drugs for tuberculosis.</i>
<b>Availability</b>	<b>INJECTION</b> 0.5, 0.75 and 1g/vial.
<b>Dose</b>	<p><b>Deep intramuscular injection</b></p> <p><b>Adult-</b> 1g daily for 2 to 4 months (not more than 20 mg/kg body weight). Then 1 to 2g 2 to 3 times each week, in case of renal impairment reduce the dose in accordance with creatinine clearance.</p>

<b>Contraindications</b>	Not for paediatric use; hypersensitivity to capreomycin.
<b>Precautions</b>	Renal impairment; hepatic impairment; auditory impairment; monitor renal, hepatic, auditory and vestibular function and electrolytes; pregnancy (teratogenic in animals; Appendix 7c) and lactation; interactions (Appendix 6c).
<b>Adverse Effects</b>	Hypersensitivity reactions including urticaria and rashes; eosinophilia; leucocytosis or leucopenia, rarely, thrombocytopenia; changes in liver function tests; nephrotoxicity, electrolyte disturbances; hearing loss with tinnitus and vertigo; neuromuscular block after large doses, pain and induration at injection site.
<b>Storage</b>	Store protected from moisture at a temperature not exceeding 25°C.

## Cycloserine

### Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Tuberculosis resistant to first-line drugs.</i>
<b>Availability</b>	<b>CAPSULE/TABLET</b> 250 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> Initially 250 mg every 12 h for 2 weeks, increase according to blood concentration and response to 500 mg every 2 h.  <b>Child-</b> Initially 10 mg/kg body weight daily adjusted to blood concentration and response.
<b>Contraindications</b>	Severe renal impairment; epilepsy; depression, severe anxiety, psychotic states, alcohol dependence; porphyria; hypersensitivity.
<b>Precautions</b>	Reduce dose in renal impairment (avoid if severe); monitor haematological, renal and hepatic function; lactation; discontinue or reduce dose if allergic skin reactions or CNS toxicity occur, pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Mainly neurological, including headache, dizziness, vertigo, drowsiness, tremor, convulsions, confusion, psychosis, depression (discontinue or reduce dose if symptoms of CNS toxicity); rashes, allergic dermatitis (discontinue or reduce dose); megaloblastic anaemia; changes in liver function tests; heart failure at high doses reported.
<b>Storage</b>	Store at a temperature not exceeding 30°C (tablets). Store protected from moisture (capsules).

**Ethambutol \*****Pregnancy Category-C****Schedule H****Indications** *Tuberculosis, in combination with other drugs.***Availability** **TABLETS** 200, 400, 600, 800 mg and 1g.**Dose** **Oral****Adult-** 15 mg/kg body weight as a single dose, retreatment with 25 mg/kg body weight as a single dose for two months, thereafter reduce to 15 mg/kg body weight. Given as combination therapy with other anti-tubercular drugs.**Child-** Same as for Adult. Do not use under 3 years.**Contraindications** Optic neuritis; children under 5 years-unable to report symptomatic visual disturbances; severe renal impairment; hypersensitivity.**Precautions** Visual disturbances-ocular examination recommended before and during treatment (see note below); reduce dose in renal impairment (Appendix 7d) and monitor plasma concentration; elderly; pregnancy (Appendix 7c) (not known to be harmful); lactation.

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*Note: Patients should report visual disturbances immediately and discontinue treatment; children who are incapable of reporting symptomatic visual changes accurately should be given alternative therapy, as should, if possible, any patient who cannot understand warnings about visual adverse effects*

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**Adverse Effects** Optic neuritis-reduced visual acuity and red/green colour blindness (early changes usually reversible, prompt withdrawal may prevent blindness); peripheral neuritis-especially in legs; gout; rarely, rash, pruritus, urticaria, thrombocytopenia; pulmonary infiltrates gastrointestinal upset.**Storage** Store protected from moisture.**Isoniazid\*****Pregnancy Category-C****Schedule H****Indications** *Tuberculosis, in combination with other drugs; tuberculosis prophylaxis also.***Availability** **TABLETS** 100 and 300 mg.**Dose** **Oral**

**Adult-** 3 to 5 mg/kg body weight up to 300 mg as single dose daily.

**Child-** 10 to 15 mg/kg body weight as a single dose, not to exceed 300 mg/day.

### Contraindications

Drug-induced Hepatic Disease.

### Precautions

Hepatic impairment (monitor hepatic function; Appendix 7a); malnutrition, chronic alcohol dependence, chronic renal failure (Appendix 7d); diabetes mellitus and HIV infection-prophylactic pyridoxine 10 mg daily required because risk of peripheral neuritis; epilepsy; slow acetylator status (increased risk of adverse effects); history of psychosis; pregnancy (Appendix 7c) (not known to be harmful); lactation (Appendix 7b); porphyria; interactions (Appendix 6a, 6c, 6d).

Patients or their caretakers should be told how to recognize signs of liver disorder and advised to discontinue treatment and seek immediate medical attention if symptoms such as nausea, vomiting, malaise or jaundice develop.

### Adverse Effects

Gastrointestinal disorders including nausea and vomiting, diarrhoea and pain, also constipation, dry mouth; hypersensitivity reactions including fever, rashes, joint pain, erythema multiforme, purpura usually during first weeks of treatment; peripheral neuropathy; blood disorders including agranulocytosis, haemolytic anaemia, aplastic anaemia; optic neuritis, toxic psychoses and convulsions; hepatitis (especially over age of 35 years and regular users of alcohol)-withdraw treatment; also reported systemic lupus erythematosus-like syndrome, pellagra, hyperreflexia, difficulty with micturition, hyperglycaemia and gynaecomastia; memory impairment, elevated serum transaminase, rheumatic syndrome, pyridoxine syndrome.

### Storage

Store protected from light.

## Kanamycin

### Pregnancy Category-D

**Schedule H**

### Indications

*Tuberculosis; hepatic coma; penicillin resistant gonorrhoea, chronic bacterial infections.*

### Availability

**INJECTION Vial** 500, 750 mg and 1g.

### Dose

***Intramuscular and intravenous injection***

**Adult-** 1g daily as a single dose.

**Child-** 6 to 15 mg/kg body weight daily in divided doses, 8 to 12 h (slow injection), usual duration of therapy 7 to 10 days.

**Contraindications** Lactation; pregnancy (Appendix 7c); hypersensitivity; renal impairment.

**Precautions** Myasthenia gravis; renal impairment; elderly patients with neuromuscular disorder.

**Adverse Effects** Nephrotoxicity; ototoxicity; skin rash; urticaria; neuromuscular blockade; malabsorption syndrome.

**Storage** Store protected from light and moisture.

## Pyrazinamide\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *Tuberculosis, in combination with other drugs.*

**Availability** **TABLETS** 300, 500 and 750 mg; 1 and 1.5g; **SUSPENSION** 100 ml (5%).

**Dose** **Oral**

**Adult and Child-** 20 to 35 mg/kg body weight as a single dose (max. 3g daily).

**Contraindications** Severe hepatic impairment; porphyria.

**Precautions** Hepatic impairment (monitor hepatic function; (Appendix 7a); renal impairment (Appendix 7d); diabetes mellitus (monitor blood glucose-may change suddenly); gout; pregnancy (Appendix 7c) and lactation; hypouricemia.

Patients or their caretakers should be told how to recognize signs of liver disorder and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

**Adverse Effects** Hepatotoxicity including fever, anorexia, hepatomegaly, splenomegaly, jaundice, liver failure; nausea, vomiting; arthralgia; gout; sideroblastic anaemia; rash, photosensitivity; porphyria, dysuria, thrombocytopenia, hyperplasia, myalgia.

**Storage** Store in single dose containers protected from light and moisture.

## Rifampicin\* (Refer Page No. 190)

**Pregnancy Category-C**

**Schedule H**

**Indications** *Tuberculosis, in combination with other drugs.*

<b>Availability</b>	<b>CAPSULE</b> 150, 300, 350, 450, 500, 600 and 750 mg; <b>SUSPENSION</b> 100 mg/5 ml.
<b>Dose</b>	<b>Oral</b> <b>Adult-</b> 450 to 600 mg as a single dose before breakfast. <b>Child-</b> 10 to 20 mg/kg body weight daily, same dose for meningococcal carriers but for 4 days.
<b>Contraindications</b>	Hypersensitivity; jaundice.
<b>Precautions</b>	Reduce dose in hepatic impairment (Appendix 7a); liver function tests and blood counts required in liver disorders, alcohol dependency, elderly and on prolonged therapy; renal impairment (if dose above 600 mg daily); lactation; porphyria; discolours soft contact lenses; advise patients on oral contraceptives to use additional means; interactions (Appendix 6b, 6c, 6d); pregnancy (Appendix 7c); cerebral haemorrhage, visual disturbances.

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*Note: Resumption of rifampicin treatment after a long interval may cause serious immunological reactions, resulting in renal impairment, haemolysis, or thrombocytopenia-discontinue permanently if serious adverse effects occur*

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Patients or their caretakers should be told how to recognize signs of liver disorders and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

<b>Adverse Effects</b>	Severe gastrointestinal disturbances including anorexia, nausea, vomiting and diarrhoea (antibiotic-associated colitis reported); headache, drowsiness; rashes, fever, influenza-like syndrome and respiratory symptoms, collapse, shock, haemolytic anaemia, acute renal failure and thrombocytopenic purpura-more frequent with intermittent therapy; alterations of liver function-jaundice and potentially fatal hepatitis (dose related; do not exceed max. dose of 600 mg daily); oedema, muscular weakness and myopathy, exfoliative dermatitis, toxic epidermal necrolysis, pemphigoid reactions, leukopenia, eosinophilia and menstrual disturbances reported; urine, tears, saliva and sputum coloured orange-red.
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<b>Storage</b>	Store protected from light and moisture.
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## Rifampicin + Isoniazid

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>Tuberculosis.</i>
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**Availability****TABLETS/CAPSULES**

Rifampicin	+	Isoniazid
60 mg	+	30 mg
100 mg	+	100 mg
100 mg	+	300 mg
100 mg	+	50 mg
150 mg	+	100 mg
150 mg	+	75 mg
300 mg	+	150 mg
450 mg	+	300 mg
600 mg	+	300 mg

**Dose****Adult-** One tablet daily before breakfast.**Precautions**

Combined preparation usually not suitable for use in children; see under Rifampicin and Isoniazid; pregnancy (Appendix 7c).

**Storage**

Store protected from moisture.

**Rifampicin + Isoniazid + Ethambutol****Pregnancy Category-C****Schedule H****Indications***Tuberculosis.***Availability****TABLETS**

Rifampicin	+	Isoniazid	+	Ethambutol
150 mg	+	275 mg	+	275 mg
150 mg	+	75 mg	+	275 mg
450 mg	+	300 mg	+	800 mg
450 mg	+	225 mg	+	825 mg
100 mg	+	50 mg	+	800 mg
300 mg	+	150 mg	+	550 mg

**CAPSULES**

Rifampicin	+	Isoniazid	+	Ethambutol
225 mg	+	150 mg	+	400 mg

**Dose**

One tablet daily before breakfast in accordance with dose of individual drugs.

**Precautions**

Pregnancy (Appendix 7c).

**Storage**

Store protected from moisture.

**Rifampicin + Isoniazid + Pyrazinamide****Pregnancy Category-C****Schedule H****Indications***Tuberculosis, in combination with other drugs.*

**Availability****TABLETS/CAPSULES**

Rifampicin	+	Isoniazid	+	Pyrazinamide
60 mg	+	30 mg	+	150 mg
100 mg	+	50 mg	+	300 mg
150 mg	+	100 mg	+	500 mg
450 mg	+	300 mg	+	1000 mg
120 mg	+	80 mg	+	250 mg
225 mg	+	150 mg	+	750 mg
150 mg	+	100 mg	+	375 mg
450 mg	+	300 mg	+	1500 mg

**Dose****Oral**

**Adult-** One tablet daily before breakfast.

**Contraindications**

Combined preparation not suitable for use in children; see Rifampicin, Isoniazid and Pyrazinamide; pregnancy (Appendix 7c).

**Storage**

Store protected from moisture.

## Rifampicin + Isoniazid + Pyrazinamide + Ethambutol

**Pregnancy Category-C****Schedule H****Indications**

*Tuberculosis.*

**Availability****TABLETS**

Rifampicin+Isoniazid+Pyrazinamide+ Ethambutol				
150 mg	+	100 mg	+	500 mg + 800 mg
225 mg	+	150 mg	+	750 mg + 400 mg
150 mg	+	75 mg	+	400 mg + 275 mg
150 mg	+	100 mg	+	500 mg + 267 mg
450 mg	+	300 mg	+	1500 mg + 800 mg
600 mg	+	300 mg	+	800 mg + 1100 mg
1450 mg	+	225 mg	+	1200 mg + 825 mg

**Dose****Oral**

**Adult-** One tablet daily before breakfast.

**Precautions**

Pregnancy (Appendix 7c).

**Storage**

Store protected from moisture.

## Streptomycin\*

**Pregnancy Category-D****Schedule H****Indications**

*Tuberculosis, in combination with other drugs.*

**Availability**

**INJECTION vial** 750 mg and 1g.

**Dose**

Deep intramuscular injection.

**Adult-** 0.75g to 1g daily.



**Elderly-** 0.5g daily.

**Child-** 20 to 40 mg/kg body weight daily.

**Contraindications** Hearing disorders; myasthenia gravis; pregnancy (Appendix 7c).

**Precautions** **Children-** painful injection, avoid use if possible; renal impairment (Appendix 7d), infants and elderly (dosage adjustment and monitor renal, auditory and vestibular function and plasma streptomycin concentrations); interactions (Appendix 6c).

**Adverse Effects** Vestibular and auditory damage, nephrotoxicity; hypersensitivity reactions-withdraw treatment; paraesthesia of mouth; rarely, hypomagnesaemia on prolonged therapy; antibiotic-associated colitis; also, nausea, vomiting, rash; rarely, haemolytic anaemia, aplastic anaemia, agranulocytosis, thrombocytopenia; pain and abscess at injection site.

**Storage** Store protected from moisture.

## Thiacetazone + Isoniazid

**Pregnancy Category-C**

**Schedule H**

**Indications** *Tuberculosis, in combination with other drugs.*

**Availability** **TABLETS**  
Thiacetazone + Isoniazid  
150 mg + 300 mg  
37.5 mg + 750 mg

**Dose** **Oral**

**Adult-** One tablet daily before breakfast.

**Contraindications** See Isoniazid; hepatic impairment; renal impairment; HIV infection-thioacetazone associated with high incidence of serious, sometimes fatal cutaneous hypersensitivity reactions, including exfoliative dermatitis.

**Precautions** See Isoniazid; determine efficacy and toxicity of thiacetazone-geographical differences; hypersensitivity reactions-withdraw treatment; pregnancy (Appendix 7c).

**Adverse Effects** See Isoniazid; thiacetazone causes the following- nausea, vomiting, diarrhoea; hypersensitivity reactions including conjunctivitis, vertigo, rashes; fatal exfoliative dermatitis, acute hepatic failure reported; also, agranulocytosis, thrombocytopenia and aplastic anaemia.

**Storage** Store protected from light and moisture.

## **DOTS (Directly Observed Treatment, Short Course)**

The WHO-recommended Directly Observed Treatment, Short Course (DOTS) strategy was launched formally as Revised National TB Control Programme in India in 1997 after pilot testing from 1993-1996. Since then DOTS has been widely advocated and successfully applied. (Revised National TB Control Policy)

DOTS is the most effective strategy available for controlling TB.

The five key components of DOTS are

- a) Political commitment to control TB;
- b) Case detection by sputum smear microscopy examination among symptomatic patients;
- c) Patients are given anti- TB drugs under the direct observation of the health care provider/community DOT provider;
- d) Regular, uninterrupted supply of anti-TB drugs; and
- e) Systematic recording and reporting system that allows assessment of treatment results of each and every patient and of whole TB control programme.

Responsibility of ensuring regular and complete treatment of the patient lies with the health system.

In 2006, the new stop TB strategy was recommended internationally by WHO. The components of the new stop TB strategy are the following:

1. Pursue high quality DOTS expansion and enhancement
2. Address TB/HIV, MDR-TB and other challenges
3. Contribute to health system strengthening
4. Engage all health care providers
5. Empower people with TB and communities
6. Enable and promote research

DOTS involves treatment with combination of drugs -Rifampicin 300 mg + Isoniazid 150 mg + Pyrazinamide 800 mg + Ethambutol 550 mg, given thrice weekly. Twice weekly therapy can also be given but it is not recommended since it does not have margin for error and missing even one dose makes the therapy ineffective.

## 9.9 Antipneumocystosis and Antitoxoplasmosis Drugs

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### Pneumocystosis:

*Pneumocystis carinii* is classified as a protozoan although there is evidence to suggest that it is probably a fungus. *Pneumocystis carinii* pneumonia is probably acquired by the airborne route. In otherwise healthy persons it rarely, produces signs of infection. However, it is a frequent cause of opportunistic infection in immunosuppressed, debilitated or malnourished patients; it is the commonest cause of pneumonia in AIDS and the most frequent immediate cause of death in these patients.

Sulfamethoxazole with trimethoprim is the treatment of choice for *Pneumocystis carinii* pneumonia and is also used for prophylaxis in high-risk patients; pentamidine isothionate is used in patients unresponsive to or intolerant of sulfamethoxazole with trimethoprim.

The treatment of *Pneumocystis carinii* infections must only be undertaken with specialist supervision where there are appropriate monitoring facilities.

### Toxoplasmosis:

Toxoplasmosis is caused by infection with the protozoan parasite *Toxoplasma gondii*. Most infections are self-limiting and do not require treatment. However, in immunodeficiency, primary infection may result in encephalitis, myocarditis or pneumonitis; impairment of immunity (such as in AIDS) in a previously infected person, may result in encephalitis or meningoencephalitis. Congenital transmission may occur if there is a primary infection in early pregnancy or if the mother is immunodeficient. Such cases often result in spontaneous abortion, fetal death or severe congenital disease. Ocular toxoplasmosis causes chorioretinitis and is often the result of a childhood infection that becomes apparent in adulthood.

The treatment of choice for toxoplasmosis is pyrimethamine with sulfadiazine; a folate supplement is also given to counteract the megaloblastic anaemia associated with these drugs.

**Pentamidine\*** (Refer Page No 175)

## 9.10 Antiretrovirals

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Antiretroviral drugs do not cure HIV (human immunodeficiency virus) infection; they only temporarily suppress viral replication and improve symptoms. Patients receiving these drugs require careful monitoring by appropriately trained health professionals in an adequately resourced setting. Rigorous promotion of measures to prevent new infections remains essential and its need is not diminished by the availability of antiretroviral drugs. Effective therapy requires the simultaneous use of 3 or 4 drugs; alternative regimens are necessary to meet specific requirements at start-up, to substitute for first-line regimens in cases of intolerance, or to replace failing regimens. The use of a 3- or 4-drug combination as specified in the WHO treatment guidelines is recommended. The use of fixed-dose preparations for these combinations is also recommended if the pharmaceutical quality is assured and interchangeability with the single products is demonstrated as specified by the relevant drug regulatory authority.

Selection of 2 or 3 protease inhibitors from the Model List will need to be determined by each country after consideration of local treatment guidelines and experience, as well as comparative costs of available products. Low-dose ritonavir is used in combination with indinavir, lopinavir or saquinavir as a 'booster'; ritonavir is not recommended as a drug in its own right.

### Principles of Treatment:

Treatment is aimed at reducing the plasma viral load as much as possible and for as long as possible; it should be started before the immune system is irreversibly damaged. The need for early drug treatment should, however, be balanced against the development of toxicity. Commitment to treatment and strict adherence over many years are required; the regimen chosen should take into account convenience and the patient's tolerance of it. The development of resistance is reduced by using a combination of 3 or 4 drugs; such combinations should have additive or synergistic activity while ensuring that their toxicity is not additive. Testing for resistance to antiviral drugs, particularly in therapeutic failure, should be considered.

Women of childbearing age receiving antiretroviral therapy must have available effective contraceptive methods to prevent unintended pregnancy. Women who are taking non nucleoside reverse transcriptase inhibitors or protease inhibitors which can lower blood concentration of hormonal oral contraceptives, should be advised to use additional or alternative contraceptives.

## Drugs used to treat HIV Infection:

Zidovudine, a nucleoside reverse transcriptase inhibitor (or 'nucleoside analogue'), was the first anti-HIV drug introduced. Other nucleoside reverse transcriptase inhibitors include abacavir, didanosine, lamivudine, stavudine and zalcitabine.

The protease inhibitors include amprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir. Ritonavir in low doses is used in combination with indinavir, lopinavir or saquinavir as a booster. The small amount of ritonavir in such combinations has no intrinsic antiviral activity but it increases the antiviral activity of the other protease inhibitors by reducing their metabolism. Indinavir, nelfinavir, ritonavir and possibly saquinavir inhibit the cytochrome P450 enzyme system and therefore have a potential for significant drug interactions. Protease inhibitors are associated with lipodystrophy and metabolic effects (see below).

The non-nucleoside reverse transcriptase inhibitors include efavirenz and nevirapine. They interact with a number of drugs metabolized in the liver; the doses of protease inhibitors may need to be increased when they are given with efavirenz or nevirapine. 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. Efavirenz treatment has also been associated with an increased plasma cholesterol concentration.

## Initiation of Treatment

The time for initiating antiviral treatment is determined by the clinical stage of the HIV infection as indicated by symptoms and where available, by the CD4-cell count or total lymphocyte count; the plasma viral load, if available, is also a valuable guide for staging the disease (see Monitoring, below).

Recommended initial treatment with a combination of drugs ('highly active antiretroviral therapy', HAART) includes:

2 nucleoside reverse transcriptase inhibitors

*plus*

a non-nucleoside reverse transcriptase inhibitor

*or* a third nucleoside reverse transcriptase inhibitor

*or* a protease inhibitor which may be combined with ritonavir as booster.

## Monitoring:

In resource-limited settings the basic clinical assessment before initiating antiretroviral therapy includes documentation of past medical history, identification of current and past

HIV-related illnesses, identification of co-existing medical conditions that may influence the choice of therapy (for example, pregnancy or tuberculosis) as well as current symptoms and physical signs.

The absolute minimum laboratory tests before initiating antiretroviral therapy are an HIV antibody test (in patients over 18 months of age) and a haemoglobin or haematocrit measurement.

Additional basic testing should include:

- white blood cell count;
- differential cell count (to identify a decline in neutrophils and the possibility of neutropenia);
- total lymphocyte count;
- serum alanine or aspartate aminotransferase concentration to assess the possibility of hepatitis co-infection and to monitor for hepatotoxicity;
- serum creatinine and/or blood urea nitrogen to assess baseline renal function;
- serum glucose;
- pregnancy tests for women.

Desirable supplemental tests include measurement of bilirubin, amylase and serum lipids. CD4-cell determinations are, of course, very desirable and efforts should be made to make these widely available. Viral load testing is currently considered optional because of constraints on resources.

### Changing Therapy:

Deterioration of the condition (including clinical and virological changes) usually calls for replacement of the failing drugs. Intolerance to adverse effects and drug-induced organ dysfunction usually require change in therapy.

The choice of an alternative regimen depends on factors such as the response to previous treatment, tolerance and the possibility of cross-resistance. If treatment fails, a new second-line regimen will be needed. If toxicity occurs, either a new second-line regimen is indicated or, if the toxicity is related to an identifiable drug in the regimen, the offending drug can be replaced with another drug that does not have the same adverse effects.

### Pregnancy:

Treatment of HIV infection in pregnancy aims to:

- minimize the viral load and disease progression in the mother;

- reduce the risk of toxicity to the fetus (although the teratogenic potential of most antiretroviral drugs is unknown);
- prevent transmission of infection to the neonate.

In pregnant women, it may be desirable to initiate antiretroviral therapy after the first trimester, although for pregnant women who are severely ill, the benefit of early therapy outweighs the potential risk to the fetus. All treatment options require careful assessment by a specialist.

The use of zidovudine, lamivudine, nevirapine, nelfinavir and saquinavir are recommended for women of child-bearing potential or who are pregnant. Efavirenz should be avoided because of its potential teratogenic effect on the fetus in the first trimester. First-line treatment in pregnant women should when possible include zidovudine and lamivudine. Monotherapy with either zidovudine or with nevirapine reduces transmission of infection to the neonate (see also below), but combination antiretroviral therapy maximizes the chance of preventing transmission and represents optimal therapy for the mother. Low-dose ritonavir is required if either indinavir or saquinavir is used in pregnancy because adequate drug concentration is achieved only with ritonavir boosting. Information is lacking on the use of lopinavir with ritonavir in pregnancy.

Lactic acidosis and hepatic steatosis associated with nucleoside reverse transcriptase inhibitors may be more frequent in pregnant women and therefore the combination of stavudine and didanosine should be used in pregnancy only when no alternatives are available. Protease inhibitors have been associated with glucose intolerance and pregnant women should be instructed to recognize symptoms of hyperglycaemia and to seek health care advice if they occur.

Various regimens have been used to specifically prevent the transmission of HIV from mother to the neonate at term. More information is available in *New Data on the Prevention of Mother-to-Child Transmission of HIV and their Policy Implications: Conclusions and Recommendations* (WHO/RHR/01.28), which reflects an inter-agency consultation, held on 11-13 October 2000.

### **Lactation:**

Antiretroviral drugs may be present in breastmilk and may reduce viral load in breastmilk and reduce the risk of transmission through lactation. However, the concentration of antiretroviral drugs in breastmilk may not be adequate to

prevent viral replication and there is therefore the possibility of promoting the development of drug-resistant virus which could be transmitted to the infant.

Women with HIV infection should be counselled about the risks of lactation and, where possible, they should limit or avoid lactation; in particular, lactation should be avoided where replacement feeding is acceptable, affordable, sustainable and safe. HIV-infected women should be counselled on infant feeding options and they should be supported in their choice.

### Post-Exposure Prophylaxis:

Treatment with antiretroviral drugs may be appropriate following occupational exposure to HIV-contaminated material. Immediate expert advice should be sought in such cases; national guidelines on post-exposure prophylaxis for health-care workers have been developed and local ones may also be available.

### Lipodystrophy and Metabolic Effects:

Combination antiretroviral therapy, including regimens containing a protease inhibitor, is associated with redistribution of body fat in some patients (for example, decreased fat under the skin, increased abdominal fat, 'buffalo humps' and breast enlargement). Protease inhibitors are also associated with metabolic abnormalities such as hyperlipidaemia, insulin resistance and hyperglycaemia. Clinical examination should include an evaluation of fat distribution; measurement of serum lipids and blood glucose should be considered.

## 9.10.1 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

In some settings it may not be possible to carry out full monitoring described under each drug entry; in such cases the level of monitoring should be determined by local guidelines (see also notes above).

### Abacavir

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>HIV infection in combination with at least two other antiretroviral drugs.</i>
<b>Availability</b>	<b>TABLET</b> 300 mg.
<b>Dose</b>	<b>Oral</b>
	<b>Adult-</b> 300 mg twice daily or 600 mg once daily.



**Child-** 3 months to 12 years: 8 mg/kg body weight every 12 h (max. 600 mg daily).

**Contraindications** Pregnancy (Appendix 7c); lactation (Appendix 7b); hepatic dysfunction (Appendix 7a); renal disease.

**Precautions** Hepatic impairment (see below and Appendix 7a); renal impairment; pregnancy (see notes above and Appendix 7c); lactation (Appendix 7b) (see notes above); hypersensitivity reaction; interactions (Appendix 6a).

**Adverse Effects** Life-threatening hypersensitivity reactions reported-characterized by fever or rash and possibly nausea, vomiting, diarrhoea, abdominal pain, lethargy, malaise, headache, myalgia and renal failure; less frequently mouth ulceration, oedema, hypotension, dyspnoea, sore throat, cough, paraesthesia, arthralgia, conjunctivitis, lymphadenopathy, lymphocytopenia and anaphylaxis (hypersensitivity reactions presenting as sore throat, influenza-like illness, cough and breathlessness identified); rarely, myolysis; laboratory abnormalities may include raised liver enzymes and creatine kinase; symptoms usually appear in the first 6 weeks, but may occur at any time; monitor for symptoms every 2 weeks for 2 months; discontinue immediately if any symptom of hypersensitivity develops and do not rechallenge (risk of more severe hypersensitivity reaction); discontinue if hypersensitivity cannot be ruled out, even when other diagnosis possible-if rechallenge necessary it must be carried out in hospital setting; if abacavir is stopped for any reason other than hypersensitivity, exclude hypersensitivity reaction as the cause and rechallenge only if medical assistance is readily available; care needed with concomitant use of drugs which cause skin toxicity.

Patients should be told the importance of regular dosing (intermittent therapy may increase sensitization), how to recognize signs of hypersensitivity and advised to seek immediate medical attention if symptoms develop or before re-starting treatment.

Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported-caution in liver disease, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.

**Storage** Store at a temperature not exceeding 30°C.

## Didanosine\*

### Pregnancy Category-B

**Schedule H**

<b>Indications</b>	<i>HIV infection in combination with at least two other antiretroviral drugs.</i>
<b>Availability</b>	<b>TABLETS</b> 100, 250 mg and 400 mg; <b>CAPSULES</b> 250 and 400 mg.
<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> Under 60 kg: 250 mg daily in 1 to 2 divided doses. 60 kg and over: 400 mg daily in 1 to 2 divided doses, 30 min before meals or 2 h after meals.</p> <p><b>Child-</b> 2week - 8 months: 100 mg/m<sup>2</sup> twice daily. &gt;8 months: 120 mg/m<sup>2</sup> twice daily.</p>
<b>Contraindications</b>	Hypersensitivity; pancreatitis; co-administration of allopurinol and ribavirin.
<b>Precautions</b>	<p>History of pancreatitis (preferably avoid, otherwise extreme caution, see also below); peripheral neuropathy or hyperuricaemia (see under Adverse effects); history of liver disease (see below); renal and hepatic impairment (see Appendices 7d and 7a); pregnancy (Appendix 7c) and lactation (Appendix 7b) (see notes above); dilated retinal examinations recommended (especially in children) every 6 months, or if visual changes occur; interactions (Appendix 6c, 6d); immune reconstitution syndrome, fat redistribution, retinal changes and optic neuritis.</p> <p>If symptoms of pancreatitis develop or if serum amylase or lipase is raised (even if asymptomatic) suspend treatment until diagnosis of pancreatitis excluded; on return to normal values re-initiate treatment only if essential (using low dose increased gradually if appropriate). Whenever possible avoid concomitant treatment with other drugs known to cause pancreatic toxicity (for example intravenous pentamidine isothionate); monitor closely if concomitant therapy unavoidable. Since significant elevations of triglycerides cause pancreatitis monitor closely if elevated.</p> <p>Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution in liver disease, excessive alcohol intake, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis</p>

**Adverse Effects** Pancreatitis (see also under Precautions); peripheral neuropathy especially in advanced HIV infection-suspend (reduced dose may be tolerated when symptoms resolve); hyperuricaemia (suspend treatment if significant elevation); diarrhoea (occasionally serious); also reported, nausea, vomiting, dry mouth, asthenia, headache, hypersensitivity reactions; retinal and optic nerve changes (especially in children); diabetes mellitus, raised liver enzymes (see also under Precautions); liver failure.

**Storage** Store protected from light.

## Emtricitabine

**Pregnancy Category-B**

**Schedule H**

**Indications** *HIV infection.*

**Availability** **CAPSULE** 200 mg.

**Dose** **Oral**

**Adult and child over 33 kg-** 200 mg once a day.

**Child-** Under 33 kg: 6 mg/kg body weight once a day.

**Contraindications** Lactation; hypersensitivity.

**Precautions** Monitor patients with hepatitis B (risk of exacerbation of hepatitis); obesity, lactic acidosis, severe hepatomegaly, co-infection with hepatitis B virus; pregnancy (Appendix 7c).

**Adverse Effects** Gastro-intestinal disturbances (such as nausea, vomiting, abdominal pain, flatulence and diarrhoea); anorexia; pancreatitis; liver damage (see also Lactic Acidosis, above); dyspnoea; cough, headache; insomnia; dizziness; fatigue; blood disorders (including anaemia, neutropenia and thrombocytopenia); myalgia, arthralgia, rash, urticaria and fever. Lipodystrophy, abnormal dreams, pruritus and hyperpigmentation.

**Storage** Store protected from moisture.

## Lamivudine\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *HIV infection in combination with at least two other antiretroviral drugs.*

**Availability** **TABLETS** 100, 150 and 300 mg; **ORAL SOLUTION** 50 mg/ml.

<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> 150 mg twice daily administered with zidovudine.</p> <p><b>Child-</b> 3 months to 12 years: 4 mg/kg body weight twice a day (max. 150 mg twice daily).</p>
<b>Contraindications</b>	Pregnancy (Appendix 7c); lactation (Appendix 7b); hepatic dysfunction (Appendix 7a); renal disease (Appendix 7d).
<b>Precautions</b>	Renal impairment (Appendix 7d); hepatic disease (see below); pregnancy (Appendix 7c) and lactation (Appendix 7b) (see notes above); interactions (Appendix 6c).
	Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution (particularly in obese women) in liver disease, liver enzyme abnormalities, or risk factors for liver disease; suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis. Recurrent hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine.
<b>Adverse Effects</b>	Nausea, vomiting, diarrhoea, abdominal pain; cough; headache, fatigue, insomnia; malaise, fever, rash, alopecia, muscle disorders; nasal symptoms; peripheral neuropathy reported; rarely, pancreatitis (discontinue); neutropenia, anaemia, thrombocytopenia and red-cell aplasia; lactic acidosis; raised liver enzymes and serum amylase.
<b>Storage</b>	Store protected from moisture.

## Stavudine\*

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>HIV infection in combination with at least two other antiretroviral drugs.</i>
<b>Availability</b>	<b>TABLETS/CAPSULES</b> 30 and 40 mg.
<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> Under 60 kg: 30 mg every 12 h preferably at least 1 h before food. 60 kg and over: 40 mg every 12 h.</p> <p><b>Neonate under 2 weeks-</b> 500 µg/kg body weight.</p>

**Child-** over 2 weeks and body weight under 30 kg: 1 mg/kg body weight every 12 h.  
30 kg and over: 30 mg every 12 h.

### Contraindications

Hypersensitivity.

### Precautions

History of peripheral neuropathy (see below); history of pancreatitis or concomitant use with other drugs associated with pancreatitis; hepatic disease (see below); renal impairment; pregnancy (Appendix 7c) and lactation (Appendix 7b) (see notes above); fat redistribution, immune reconstitution syndrome.

Suspend if peripheral neuropathy develops—characterized by persistent numbness, tingling or pain in feet or hands; if symptoms resolve satisfactorily on withdrawal and if stavudine needs to be continued, resume treatment at half previous dose.

Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution in liver disease, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.

### Adverse Effects

Peripheral neuropathy (dose-related, see above); pancreatitis; nausea, vomiting, diarrhoea, constipation, anorexia, abdominal discomfort; chest pain; dyspnoea; headache, dizziness, insomnia, mood changes; asthenia, musculoskeletal pain; influenza-like symptoms, rash and other allergic reactions; lymphadenopathy; neoplasms; elevated liver enzymes (see hepatic disease, above) and serum amylase; neutropenia, thrombocytopenia.

### Storage

Store protected from moisture at a temperature not exceeding 30°C.

## Tenofovir

**Pregnancy Category-B**

**Schedule H**

### Indications

*HIV infection.*

### Availability

**TABLET** 300 mg.

### Dose

**Oral**

**Adult-** 300 mg once daily.

<b>Contraindications</b>	Lactation; hypersensitivity.
<b>Precautions</b>	Should be used with caution in patients with chronic hepatitis B or C (greater risk of hepatic side-effects), in hepatic impairment, in renal impairment and in pregnancy (Appendix 7c). Test renal function and serum phosphate before treatment, then every 4 weeks (more frequently if at increased risk of renal impairment) for 1 year and then every 3 months, interrupt treatment if renal function deteriorates or serum phosphate decreases; concomitant or recent use of nephrotoxic drugs; on discontinuation, monitor patients with hepatitis B (risk of exacerbation of hepatitis).
<b>Adverse Effects</b>	Gastro-intestinal disturbances (such as nausea, vomiting, abdominal pain, flatulence and diarrhoea); anorexia; pancreatitis; liver damage; dyspnoea; cough; headache, insomnia, dizziness, fatigue; blood disorders (including anaemia, neutropenia and thrombocytopenia); myalgia, arthralgia, rash, urticaria and fever. See notes above for metabolic effects and lipodystrophy; hypophosphataemia; reduced bone density; nephrogenic diabetes insipidus and renal failure; lactic acidosis, decrease in bone mineral density, acute exacerbation of hepatitis.
<b>Storage</b>	Store protected from moisture at a temperature not exceeding 30°C.

## Zidovudine (AZT)\*

Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>HIV infection in combination with at least two other antiretroviral drugs; monotherapy for prevention of maternal-fetal HIV transmission.</i>
<b>Availability</b>	<b>TABLETS</b> 30, 40, 100 and 300 mg; <b>CAPSULES</b> 100 and 300 mg; <b>SYRUP</b> 50 mg/5 ml.
<b>Dose</b>	<b>Oral</b> <b>HIV infection</b> <b>Adult-</b> 600 mg daily in divided doses in combination with other antiretroviral drugs. <b>Child- 6 weeks to 12 years:</b> 160 mg/m <sup>2</sup> every 8 hour, max. dose 200 mg every 8 hour. <b>Prevention of maternal-foetal HIV transmission.</b>

**Adult-** 100 mg five times daily or 200 mg thrice daily or 300 mg twice daily, start treatment after 14<sup>th</sup> week of gestation until the start of labour.

**Prevention of HIV transmission in neonates.**

**Child- neonates-** 2 mg/kg every 6 hour for first 6 weeks of life, starting with 12 hour after birth.

**Contraindications**

Abnormally low neutrophil counts or haemoglobin; neonates either with hyperbilirubinaemia requiring treatment other than phototherapy or with raised transaminase; life threatening allergic reactions.

**Precautions**

Haematological toxicity; vitamin B<sub>12</sub> deficiency (increased risk of neutropenia); reduce dose or interrupt treatment if anaemia or myelosuppression; renal impairment (Appendix 7d); hepatic impairment (Appendix 7a); risk of lactic acidosis; elderly; lactation (Appendix 7b); interactions (Appendix 6c, 6d); pregnancy (Appendix 7c); myopathy, use with interferon and ribavirin based regimens in HIV/HCV coinfecting patients, immune reconstitution syndrome.

**Adverse Effects**

Anaemia (may require transfusion), neutropenia and leukopenia (all more frequent with high dose and advanced disease); also nausea and vomiting, abdominal pain, dyspepsia, diarrhoea, flatulence, taste disturbance, pancreatitis, liver disorders including fatty change and raised bilirubin and liver enzymes (see hepatic disease, above); chest pain, dyspnoea, cough; influenza-like symptoms; headache; fever; paraesthesia, neuropathy; convulsions; dizziness; somnolence, insomnia; anxiety; depression; malaise; anorexia; asthenia; myopathy; myalgia; pancytopenia, thrombocytopenia; gynaecomastia; urinary frequency; rash, pruritus, pigmentation of nail, skin and oral mucosa.

**Storage**

Store protected from light and moisture.

## 9.10.2 Non-Nucleoside Transcriptase Inhibitor

In some settings it may not be possible to carry out full monitoring described under each drug entry; in such cases the level of monitoring should be determined by local guidelines (see also notes above).

### Efavirenz\*

Pregnancy Category-D

Schedule H

<b>Indications</b>	<i>HIV infection in combination with at least two other antiretroviral drugs.</i>
<b>Availability</b>	<b>TABLETS/CAPSULES</b> 200, 400 and 600 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> 600 mg once a day.  <b>Child-</b> Over 3 years 13 to 14 kg body weight: 200 mg once a day; 15 to 19 kg body weight: 250 mg once a day; 25 to 32.5 kg body weight: 400 mg once a day; over 40 kg body weight: adult dose.
<b>Contraindications</b>	Pregnancy (see notes above and (Appendix 7c); substitute nevirapine for efavirenz in pregnant women or women for whom effective contraception cannot be assured); hypersensitivity.
<b>Precautions</b>	Hepatic impairment (avoid if severe; Appendix 7a); severe renal impairment; lactation (Appendix 7b) (see notes above); elderly; history of mental illness or substance abuse; interactions (Appendix 6b, 6c); psychiatric symptoms.  Rash, usually in the first 2 weeks, is the most common adverse effect; discontinue if severe rash with blistering, desquamation, mucosal involvement or fever; if rash mild or moderate, may continue without interruption-rash usually resolves within 1 month.
<b>Adverse Effects</b>	Rash including Stevens-Johnson syndrome (see also above); dizziness, headache, insomnia, somnolence, abnormal dreams, fatigue, impaired concentration (administration at bedtime especially in the first 2-4 weeks reduces CNS effects); nausea; less frequently vomiting, diarrhoea, hepatitis, depression, anxiety, psychosis, amnesia, ataxia, stupor, vertigo; also reported raised serum cholesterol, elevated liver enzymes (especially if seropositive for hepatitis B or C), pancreatitis.
<b>Storage</b>	Store protected from light.

## **Nevirapine\***

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>HIV infection, in combination with at least two other antiretroviral drugs; prevention of mother-to-child transmission in HIV-infected patients.</i>
<b>Availability</b>	<b>TABLET/CAPSULE</b> 200 mg; <b>ORAL SUSPENSION</b> 100 mg/5 ml.
<b>Dose</b>	<b>Oral</b>



**Adult-** 200 mg once a day for 14 days, if tolerated and no rash is observed then increase to 200 mg two times a day.

**Child-** 2 months to 8 years: 4 mg/kg body weight once a day for 14 days, if tolerated and no rash is observed increase to 4 mg/kg body weight two times a day.

### Contraindications

Acute porphyria; severe hepatic impairment; post-exposure prophylaxis; breast feeding.

### Precautions

Hepatic impairment (see below and Appendix 7a); history of chronic hepatitis (greater risk of hepatic adverse effects), pregnancy (Appendix 7c) and lactation (Appendix 7b); interactions (Appendix 6b, 6c).

Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported usually occurring in first 8 weeks; monitor liver function before long-term treatment then every 2 weeks for 2 months then after 1 month and then every 3-6 months; discontinue permanently if abnormalities in liver function tests accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, granulocytopenia); suspend if severe abnormalities in liver function tests but no hypersensitivity reaction-discontinue permanently if significant liver function abnormalities recur; monitor patient closely if mild to moderate abnormalities in liver function tests with no hypersensitivity reaction.

Rash, usually in first 8 weeks, is most common adverse effect; incidence reduced if introduced at low dose and dose increased gradually; discontinue permanently if severe rash or if rash accompanied by blistering, oral lesions, conjunctivitis, swelling, general malaise or hypersensitivity reactions; if rash mild or moderate may continue without interruption but dose should not be increased until rash resolves.

Patients should be told how to recognize hypersensitivity reactions and advised to seek immediate medical attention if symptoms develop.

### Adverse Effects

Rash including Stevens-Johnson syndrome and rarely, toxic epidermal necrolysis (see also Precautions above); hepatitis or jaundice reported (see also Precautions above); nausea, vomiting, abdominal pain, diarrhoea, headache, drowsiness, fatigue, fever; hypersensitivity reactions (may involve hepatic reactions and rash, see Precautions above); anaphylaxis, angioedema, urticaria also reported; granulocytopenia.

### Storage

Store protected from light and moisture at a temperature not exceeding 30°C.

### 9.10.3 Combinations

#### Lamivudine + Nevirapine + Stavudine\*

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>HIV infection.</i>
<b>Availability</b>	<b>TABLETS</b> Lamivudine + Nevirapine + Stavudine 40 mg + 10 mg + 70 mg 150 mg + 40 mg + 200 mg 150 mg + 30 mg + 200 mg 100 mg + 30 mg + 200 mg
<b>Dose</b>	<b>Adult-</b> One tablet twice daily. Patients with body weight less than 50 kg, 2 mg/kg body weight two times a day.  <b>Child-</b> 3 months to 12 years; half adult dose is given two times a day.
<b>Precautions</b>	Pregnancy (Appendix 7c).
<b>Storage</b>	Store protected from moisture at a temperature not exceeding 25°C for DT.

#### Lamivudine + Zidovudine\*

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>HIV infection.</i>
<b>Availability</b>	<b>TABLET</b> lamivudine + zidovudine 150 mg + 300 mg.
<b>Dose</b>	<b>Adult-</b> 2 tablets three times a day or as prescribed.  <b>Child-</b> Half the adult dose.
<b>Precautions</b>	Pregnancy (Appendix 7c).
<b>Storage</b>	Store protected from moisture.

#### Zidovudine + Lamivudine + Nevirapine\*

Schedule H

<b>Indications</b>	<i>HIV infection.</i>
<b>Availability:</b>	<b>TABLETS</b> Zidovudine 300 mg + Lamivudine 150 mg + Nevirapine 200 mg.
<b>Dose</b>	<b>Adult-</b> 2 tablets three times a day.  <b>Child-</b> Half adult dose.

### 9.10.4 Protease Inhibitors

In some settings it may not be possible to carry out full monitoring described under each drug entry; in such cases the level of monitoring should be determined by local guidelines (see also notes above).

#### Indinavir\*

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>HIV infection in combination with two nucleoside reverse transcriptase inhibitors and usually with low-dose ritonavir booster.</i>
<b>Availability</b>	<b>TABLET/CAPSULE</b> 400 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> 800 mg every 8 h with water, 1 h before or 2 h after meals.  <b>Child-</b> 4 to 17 years: 500 mg every 8 h. Safety and efficacy is not established in patients less than 4 years.
<b>Contraindications</b>	Pregnancy; concurrent use of cisapride; alprazolam; midazolam.
<b>Precautions</b>	Hepatic impairment (Appendix 7a); ensure adequate hydration to reduce risk of nephrolithiasis; diabetes mellitus; haemophilia; pregnancy (see notes above and Appendix 7c); lactation (Appendix 7b) (see notes above); metabolism of many drugs inhibited if administered concomitantly; interactions (Appendix 6c, 6d); hyperbilirubinemia, tubulo-interstitial nephritis.
<b>Adverse Effects</b>	Nausea, vomiting, diarrhoea, abdominal discomfort, dyspepsia, flatulence, pancreatitis, dry mouth, taste disturbances; headache, dizziness, insomnia; myalgia, myositis, rhabdomyolysis, asthenia, hypoaesthesia, paraesthesia; hyperglycaemia; anaphylactoid reactions, rash (including Stevens-Johnson syndrome), pruritus, dry skin, hyperpigmentation, alopecia, paronychia; interstitial nephritis, nephrolithiasis (may require interruption or discontinuation; more frequent in children), dysuria, haematuria, crystalluria, proteinuria, pyuria (in children); hepatitis, transient hyperbilirubinaemia; blood disorders including neutropenia, haemolytic anaemia; lipodystrophy and metabolic effects, see notes above; hydronephrosis.
<b>Storage</b>	Store protected from light and moisture at a temperature not exceeding 30°C.

## Lopinavir + Ritonavir

Pregnancy Category-C

**Schedule H**

**Indications** *HIV infection in combination with two other antiretroviral drugs.*

**Availability** **CAPSULE/TABLET** Lopinavir + Ritonavir  
200 mg + 50 mg.

**Dose** **Adult and child with body surface area 1.4 m<sup>2</sup>, body weight 40 kg and over-** 2 tablets twice daily.

**Child over 2 years with body weight 40 kg and body surface area 0.5 to 0.9 m<sup>2</sup>** - 2 tablets (Lopinavir 100 mg + Ritonavir 25 mg), twice daily. Body surface area 0.9 to 1.4 m<sup>2</sup> - 3 tablets twice daily.

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*Note: Ritonavir increases effect of lopinavir; low dose in combination does not have intrinsic antiviral activity.*

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**Contraindications** Hypersensitivity; avoid concomitant use with ergot derivatives.

**Precautions** Hepatic impairment-avoid if severe; renal impairment; haemophilia; pregnancy (see notes above and (Appendix 7c); lactation (see notes above and Appendix 7b); diabetes mellitus.

Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated-discontinue if pancreatitis diagnosed.

**Adverse Effects** Diarrhoea, nausea, vomiting, colitis, abdominal discomfort, asthenia, headache, insomnia; rash; less frequently, dry mouth, hepatic dysfunction, pancreatitis (see also Precautions), dyspepsia, dysphagia, oesophagitis, influenza-like syndrome, appetite changes; hypertension, palpitations, thrombophlebitis, vasculitis, chest pain, dyspnoea, agitation, anxiety, ataxia, hypertonia, confusion, depression, dizziness, dyskinesia, paraesthesia, peripheral neuritis, somnolence; Cushing syndrome, hypothyroidism, sexual dysfunction, anaemia, leukopenia, dehydration, oedema, lactic acidosis; arthralgia, myalgia, abnormal vision, otitis media, taste disturbances, tinnitus; acne, alopecia, dry skin, pruritus, skin discolouration, nail disorders, sweating; lipodystrophy and metabolic effects (see notes above); raised bilirubin and lowered sodium, low platelet and low neutrophil counts also reported in children; myocardial infarction, loss of taste.

**Storage** Store protected from moisture at a temperature not exceeding 30°C for tablets and store protected from moisture in refrigerator (2 to 8°C) for capsules.

## Nelfinavir\*

**Pregnancy Category-B**

**Schedule H**

**Indications** *HIV infection in combination with two other antiretroviral drugs.*

**Availability** **TABLET** 250 mg.

**Dose** **Adult-** 750 mg thrice daily.

**Child-** 3 to 13 years: initially 25 to 30 mg/kg body weight three times a day (max. 1.25 g) or 50 to 55 mg/kg body weight twice daily. Not recommended under 3 years.

**Contraindications** Moderate to severe liver disease; concurrent use of alprazolam; midazolam; lactation; hypersensitivity.

**Precautions** Hepatic and renal impairment; diabetes mellitus; haemophilia; pregnancy (Appendix 7c) and lactation (Appendix 7b) (see notes above); interactions (Appendix 6b, 6c, 6d); HIV cross resistance, immune reconstitution syndrome.

**Adverse Effects** Diarrhoea, nausea, vomiting, flatulence, abdominal pain; rash; reports of elevated creatine kinase; hepatitis; pancreatitis; neutropenia; hypersensitivity reactions including bronchospasm, fever, pruritus and facial oedema, lipodystrophy and metabolic effects, see notes above; backpain, myopathy, anxiety, sleep disorder, kidney calculus, QT prolongation.

**Storage** Store protected from light.

## Oseltamivir

**Pregnancy Category-C**

**Schedule X**

**Indications** *Influenza A, B and its subtypes like swine flu.*

**Availability** **CAPSULES** 30, 45 and 75 mg.

**Dose** **Oral**

**Adult and adolescent-** Prevention of influenza, over 13 years: 75 mg once daily for 10 days for post exposure prophylaxis, for up to 6 weeks in epidemics. Treatment of influenza, over 13 years: 75 mg every 12 h for 5 days.

**Child-** Prevention of influenza: body weight under 15 kg: 30 mg once daily; 15 to 23 kg: 45 mg once daily; 23 to 40 kg: 60 mg once daily; above 40 kg: adult dose.

Treatment of influenza: body weight under 15 kg: 39 mg every 12 h for 5 days; 15 to 23 kg: 45 mg every 12 h for 5 days; 23 to 40 kg: 60 mg every 12 h for 5 days; above 40 kg: adult dose.

<b>Contraindications</b>	Hypersensitivity.
<b>Precautions</b>	Hepatic impairment; pregnancy (Appendix 7c); lactation; renal impairment.
<b>Adverse Effects</b>	Nausea, vomiting, abdominal pain, dyspepsia, diarrhoea; headache, fatigue, insomnia, dizziness; conjunctivitis, epistaxis; rash; very rarely, hepatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis; neuropsychiatric disorders also reported (in children); cough, bronchitis, eczema, seizures, aggravation of diabetes.
<b>Storage</b>	Store protected from moisture and light at a temperature not exceeding 30°C.

## Ritonavir\*

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>HIV infection, as a booster to increase effect of indinavir, lopinavir or saquinavir and in combination with two other antiretroviral drugs.</i>
<b>Availability</b>	<b>TABLET</b> 100 and 250 mg; <b>CAPSULE</b> 100 mg; <b>SYRUP</b> 400 mg/5 ml.
<b>Dose</b>	<p><b>Adult-</b> Initially 300 mg every 12 h for three days increased in steps of 100 mg every 12 h over not longer than 14 days to 600 mg every 12 h.</p> <p><b>Child-</b> Over 2 years: initially 250 mg/m<sup>2</sup> of body surface area every 12 h, increase by 50 mg/m<sup>2</sup> at intervals of 2 to 3 days to 350 mg/m<sup>2</sup> body surface area every 12 h (max. 600 mg/12 h).</p>
<b>Contraindications</b>	Severe hepatic impairment.
<b>Precautions</b>	<p>Hepatic impairment, diabetes mellitus; haemophilia; pregnancy (Appendix 7c) and lactation (Appendix 7b) (see notes above); interactions (Appendix 6b, 6c, 6d); PR interval prolongation, lipid disorder.</p> <p>Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated-discontinue if pancreatitis diagnosed.</p>

**Adverse Effects** Nausea, vomiting, diarrhoea (may impair absorption-close monitoring required), abdominal pain, taste disturbances, dyspepsia, anorexia, throat irritation; vasodilatation; headache, circumoral and peripheral paraesthesia, hyperaesthesia, dizziness, sleep disturbances, asthenia, rash, hypersensitivity reactions, leukopenia; raised liver enzymes, bilirubin and uric acid; occasionally flatulence, eructation, dry mouth and ulceration, cough, anxiety, fever, pain, myalgia, weight loss, decreased thyroxine, sweating, pruritus, electrolyte disturbances, anaemia, neutropenia, increased prothrombin time; pancreatitis (see also Pancreatitis, above); lipodystrophy and metabolic effects, see notes above; postural hypotension, abnormal stool, albuminuria.

**Storage** Store protected from light at temperature (2 to 8°C) for capsules.

## Saquinavir\*

**Pregnancy Category-B**

**Schedule H**

**Indications** *HIV infection in combination with two other antiretroviral drugs and usually with low-dose ritonavir booster.*

**Availability** **TABLETS** 500 mg; **CAPSULES** 200 mg.

**Dose** **Adult and adolescent over 16 years** with low dose ritonavir, 1g saquinavir every 12 h.

**Contraindications** Hypersensitivity.

**Precautions** Hepatic impairment (Appendix 7a); renal impairment; diabetes mellitus; haemophilia; pregnancy (Appendix 7c) and lactation (Appendix 7b) (see notes above); interactions (Appendix 6d); hyperlipidemia, lactose intolerance, fat redistribution, immune reconstitution syndrome.

**Adverse Effects** Diarrhoea, buccal and mucosal ulceration, abdominal discomfort, nausea, vomiting; headache, peripheral neuropathy, paraesthesia, dizziness, insomnia, mood changes, ataxia, musculoskeletal pain, asthenia; fever, pruritus, rash and other skin eruptions, rarely, Stevens-Johnson syndrome; other rare adverse effects include thrombocytopenia and other blood disorders; liver damage; pancreatitis and nephrolithiasis; reports of elevated creatine kinase, raised liver enzymes and neutropenia when used in combination therapy; lipodystrophy and metabolic effects (see notes above); cyanosis, heart murmur; decrease appetite; amnesia.

**Storage** Store protected from moisture.

## Zanamivir

**Pregnancy Category-B**

**Schedule X**

**Indications** *Most effective for the treatment of influenza if started within a few hour of the onset of symptoms; they are to be used within 48 h (36 h for children) of the first symptoms.*

**Availability** **CAPSULE** 5 mg, powder for inhalation.

**Dose** **Oral-** powder for inhalation.  
**Adult-** minimum 10 mg (2 inhalations) inhaled; orally twice a day for 5 days. Max. 20 mg.

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*Note: The formulation is not designed or intended to be administered by nebulization. To be used with a diskhaler device only.*

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**Precautions** Anaphylaxis; encephalitis; pediatric, geriatric, lactation, pregnancy (Appendix 7c).

**Adverse Effects** Nausea, vomiting, abdominal pain, dyspepsia, diarrhoea; headache, fatigue, insomnia, dizziness; conjunctivitis, epistaxis; rash; very rarely, hepatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis.



## 9.11 Antischistosomal and Antitrematode Drugs

### Schistosomiasis:

Schistosomiasis, a waterborne parasitic infection, is caused by several species of trematode worms (blood flukes). Its socio-economic impact as a parasitic disease is outstripped only by that of malaria. Intestinal schistosomiasis is caused principally by *Schistosoma mansoni* as well as *S. japonicum*, *S. mekongi* and *S. intercalatum*. Urinary schistosomiasis is caused by *S. haematobium*. The latter is an important predisposing cause of squamous cell cancer of the bladder.

Praziquantel has transformed the treatment of schistosomiasis and is often effective in a single dose, against all species of the parasite. It can be of particular value in patients with mixed infections and those who do not respond adequately to other drugs. It is also extremely well tolerated and well suited for mass treatment control programmes. Extensive use over several years has provided no evidence of serious adverse effects or long-term toxicity, nor has mutagenic or carcinogenic activity been shown in experimental animals.

Drugs still widely used in the treatment of schistosomiasis include oxamniquine, which is effective against *S. mansoni*. It is preferable to delay treatment with oxamniquine in pregnant women until after delivery unless immediate intervention is essential. Due to lack of information on whether oxamniquine is excreted in breast milk, it is preferable not to administer it to nursing mothers.

### Praziquantel\*

Pregnancy Category-B

Schedule H

#### Indications

*Taenia saginata*, *T. solium*, *Hymenolepis nana* and *Diphyllobothrium latum* infections; trematode infections, schistosomiasis.

#### Availability

TABLETS 600 mg.

#### Dose

**Schistosomiasis:** 40 mg/kg body weight is given in two divided doses 4 to 6 h apart in one day. ***S. japonicum* infection:** 60 mg/kg body weight in three divided doses in one day.

#### Contraindications

Ocular cysticercosis; hypersensitivity.

**Precautions**

Pregnancy (Appendix 7c); lactation (Appendix 7b); areas endemic for cysticercosis-possible oedematous reaction; impaired renal function, cardiac irregularities.

May impair ability to perform skilled tasks, for example operating machinery, driving.

**Adverse Effects**

Abdominal discomfort, anorexia, nausea, vomiting, malaise, headache, dizziness, drowsiness, rectal bleeding; rarely, hypersensitivity reactions, including fever, pruritus, eosinophilia (may be due to dead and dying parasites); ectopic rhythms, urticaria, erythema, convulsions.

**Storage**

Store protected from light.

## 9.12 Antiviral Drugs

### Herpes and Cytomegalovirus Infections:

#### Herpes Simplex Virus (HSV):

Acyclovir is active against herpes viruses but does not eradicate them. It is only effective if started at onset of infection; it is also used for prevention of recurrence in the immunocompromised patients. Genital lesions, oesophagitis and proctitis may be treated with oral Acyclovir. HSV encephalitis or pneumonitis should be treated with intravenous Acyclovir.

Valacyclovir, a prodrug of Acyclovir, can be given by mouth as an alternative treatment for herpes simplex infections of the skin and mucous membranes (including initial and recurrent genital herpes).

#### Herpes Zoster Virus:

While most HIV positive patients with zoster experience only one self-limiting course, some will experience repeated episodes. Treatment should be reserved for debilitating disease and when there is high risk of serious complications, such as in advanced HIV disease. Acyclovir is the treatment of choice and it can be administered in high oral dose or in the case of lack of response to oral therapy or CNS involvement, it should be given intravenously.

#### Cytomegalovirus (CMV):

Parenteral antiviral ganciclovir arrests retinochoroiditis and enteritis caused by CMV in HIV infected patients. Maintenance therapy with oral ganciclovir should be given to prevent relapse of retinitis. Alternative therapy with intravenous foscarnet can be used if necessary.

### Acyclovir\* (Refer Page No. 550)

Pregnancy Category-B

Schedule H

<b>Indications</b>	<i>Treatment of primary genital herpes; disseminated Varicella-zoster in immunocompromised patients; Herpes simplex encephalitis; chicken pox.</i>
<b>Availability</b>	<b>TABLETS Plain/DT</b> 200, 400 and 800 mg; <b>SUSPENSION</b> 400 mg/5 ml; <b>INFUSION</b> 100 ml (after reconstitution) (250 mg); <b>OINTMENT</b> 5g (3%w/w); <b>DROPS</b> 5 ml (3% w/w); <b>CREAM</b> 5g (5% w/w).
<b>Dose</b>	<b>Oral</b>

**Adult- Non-genital herpes simplex treatment**, 200 mg five times daily usually for 5 days, longer if new lesions appear during treatment or if healing is incomplete. 400 mg for immunocompromised patients or if absorption is impaired.

**Genital herpes simplex treatment**; 200 mg 5 times daily for 5 days or 400 mg three times daily for three days. Longer if new lesions appear or healing is incomplete.

**Immunocompromised or HIV positive patients**; 400 mg is given five times daily for 7 to 10 days during first episode or 400 mg three times a day for 5 to 10 days during recurrent infection.

**Herpes simplex prevention of recurrence**; 200 mg 4 times daily or 400 mg twice daily reduced to 200 mg two or three times daily interrupted every 6 to 12 months.

**Varicella and herpes zoster**; 800 mg five times daily for 7 days.

**Chicken pox**; 800 mg five times daily for 7 to 10 days.

#### ***Intravenous infusion***

**Severe initial genital herpes, Varicella zoster, Herpes simplex infection**; 5 mg/kg body weight every 8 h for five days.

**Child-** Under 2 years; half dose. Above 2 years; adult dose.

**Varicella and herpes zoster**; 20 mg/kg body weight (max. 800 mg) four times daily for 5 days, under 2 years 200 mg four times daily, for 2 to 5 years; 400 mg four times daily. Over 6 years; 800 mg four times daily.

**Chicken pox**; 20 mg/kg body weight (max 800 mg) four times daily for 5 days.

#### **Contraindications**

Hypersensitivity; glaucoma; psychiatric disease; depression.

#### **Precautions**

Maintain adequate hydration; renal impairment (Appendix 7d); lactation (Appendix 7b); pregnancy (Appendix 7c); paediatrics.

### Adverse Effects

Nausea, vomiting, abdominal pain, diarrhoea, headache, fatigue, rash, urticaria, pruritus, photosensitivity; rarely, hepatitis, jaundice, dyspnoea, angioedema, anaphylaxis; neurological reactions (including dizziness, confusion, hallucinations, drowsiness), acute renal failure; decrease in haematological indices; on intravenous infusion, severe local inflammation (sometimes resulting in ulceration), fever, agitation, tremor, psychosis and convulsions somnolence, visual abnormalities.

### Storage

Store tablets protected from light. For infusion: Store protected from moisture in a sterile tamper evident container sealed so as to exclude micro-organisms at a temperature not exceeding 30°C.



<b>10.</b>	<b>Antimigraine Drugs</b>	<b>235</b>
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## 10. Antimigraine Drugs

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Chronic recurrent headache is associated with many disorders, both somatic and psychogenic. An accurate diagnosis must consequently be made before appropriate treatment can be initiated for migraine. Untreated migraine attacks last for several hours and sometimes for as long as 3 days.

Migraine headache is frequently accompanied by episodes of gastrointestinal disturbance including nausea and vomiting. The headache may be preceded or accompanied by aura (classical migraine) which is characterised by visual disturbances such as flickering lines and fragmented vision or sensory disturbances such as tingling or numbness; rarely, hemiparesis or impaired consciousness may occur. Migraine without aura (common migraine) is the more common form occurring in about 75% of patients who experience migraine.

Emotional or physical stress, lack of or excess sleep, missed meals, menstruation, alcohol and specific foods including cheese and chocolate are often identified as precipitating factors; oral contraceptives may increase the frequency of attacks. Avoidance of such precipitating factors can be of great benefit in preventing or reducing the frequency of attacks and should be addressed in detail. Women taking combined oral contraceptives who experience an onset or increase in frequency of headaches should be advised of other contraceptive measures.

The two principal strategies of migraine management are treatment of acute attacks and prophylactic treatment.



## 10.1 For Prophylaxis

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Prophylactic treatment should be considered for patients in whom treatment of acute migraine attacks with analgesics or ergotamine is ineffective, or in whom attacks occur more than once a month, or for those with less frequent but severe or prolonged attacks. Prophylaxis can reduce the severity and frequency of attacks but does not eliminate them completely; additional symptomatic treatment is still needed. However, long-term prophylaxis is undesirable and treatment should be reviewed at 6-monthly intervals. Of the many drugs that have been advocated beta-adrenoceptor antagonists (beta-blockers) are most frequently used. **Propranolol**, a non-selective beta-blocker and other related compounds with similar profile such as **atenolol** are generally preferred. The potential for beta-blockers to interact with ergotamine should be borne in mind. Tricyclic antidepressants, such as **amitriptyline** or calcium-channel blocking drugs such as **flunarizine** or **verapamil** may be of value.

### Flunarizine

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Prophylaxis of migraine.</i>
<b>Availability</b>	<b>TABLETS/CAPSULES</b> 5 and 10 mg.
<b>Dose</b>	<b>Oral</b> <b>Adults-</b> 10 mg at night. <b>Child &lt; 40 kg-</b> 5 mg at night.
<b>Contraindications</b>	Pregnancy (Appendix 7c); lactation.
<b>Precautions</b>	Patient may have drowsiness, should not operate hazardous machines.
<b>Adverse Effects</b>	Drowsiness; weight gain; depression; gastric pain, dry mouth; insomnia; extrapyramidal side effects.

### Propranolol\* (Refer Page No. 287)

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Prophylaxis of migraine.</i>
<b>Dose</b>	<b>Oral</b> Initially 40 mg 2 to 3 times a day. Maintenance dose 80 to 160 mg daily.

**Child-** 2-4 mg/kg/day

**Contraindications** Asthma or history of obstructive airway disease; uncontrolled heart failure; Prinzmetal angina, marked bradycardia, hypotension; sick sinus syndrome, second- or third-degree atrioventricular block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease; pheochromocytoma.

**Precautions** First-degree atrioventricular block; renal impairment; liver disease; pregnancy (Appendix 7c); lactation (Appendix 7b); portal hypertension; diabetes mellitus; myasthenia gravis; history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine (adrenaline); interactions (Appendix 6a, 6b, 6d).

**Adverse Effects** Bradycardia, heart failure, hypotension, conduction disorders, bronchospasm, peripheral vasoconstriction, exacerbation of intermittent claudication and Raynaud phenomenon; gastrointestinal disturbances, fatigue, sleep disturbances including nightmares; rarely; rash, dry eyes (reversible); exacerbation of psoriasis.

**Storage** Store protected from light and moisture.

## 10.2 For Treatment of Acute Attack

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Treatment of acute attacks may be non-specific using simple analgesics, or specific using an ergot alkaloid such as ergotamine. If nausea and vomiting are features of the attack, an antiemetic drug may be given. Treatment is generally by mouth; some drugs are available as suppositories which may be administered if the oral route is not effective (poor oral bioavailability, or absorption from the gut impaired by vomiting) or not practicable (patient unable to take drugs orally).

Simple analgesics including NSAIDs (nonsteroidal anti-inflammatory drugs) can be effective in mild to moderate forms of migraine if taken early in the attack; most migraine headaches respond to **paracetamol**, **acetylsalicylic acid** or NSAID such as ibuprofen or naproxen sodium. Peristalsis is often reduced during migraine attacks and, if available, a dispersible or effervescent preparation of the drug is preferred because of enhanced absorption compared with a conventional tablet. The risk of Reye syndrome due to acetylsalicylic acid in children can be avoided by giving paracetamol instead. Frequent and prolonged use of analgesics by migraine sufferers may lead to analgesic-induced headache.

**Ergotamine** should be considered only when attacks are unresponsive to non-opioid analgesics. It is poorly absorbed when taken orally or sublingually. Rectal suppositories may offer an advantage when other routes of administration are unsatisfactory. To be fully effective ergotamine must be taken in adequate amounts as early as possible during each attack. Adverse effects limit how much ergotamine can be used in a single attack and consequently the recommended dosage should never be exceeded and at least four days should elapse between successive treatments. Even normal dosage can lead to dependence, tolerance to adverse effects and to a withdrawal syndrome on discontinuing the drug. To avoid dependence the frequency of administration should be limited to no more than twice a month. Adverse effects include nausea, vomiting, diarrhoea and vertigo; chronic ergotism is characterized by severe peripheral vasoconstriction which can lead to gangrene in the extremities. The severity of adverse effects prevents the use of ergotamine for migraine prophylaxis.

An antiemetic such as **metoclopramide**, given as a single dose orally or by intramuscular injection at the onset of a

migraine attack, preferably 10-15 min before the analgesic or ergotamine, is useful not only in relieving nausea but also in restoring gastric motility, thus improving absorption of the antimigraine drug.

Products which contain barbiturates or codeine are undesirable, particularly in combination with ergotamine, since they may cause physical dependence and withdrawal headaches.

## Acetylsalicylic Acid\* (Refer Page No. 4, 281 and 317)

## Dihydroergotamine\*

Pregnancy Category-X

Schedule H

**Indications** *Acute treatment of migraine headaches with or without aura and acute treatment of cluster headache episodes.*

**Availability** **TABLET** 1 mg; **INJECTION** 1 ml Ampoule (1 mg/ml).

**Dose** Usually in combination with other analgesics e.g. caffeine.

**Adult and child over 12 years-** 1 to 2 tablets at onset (max. 4 tablets in 24 h), not to be repeated at intervals of less than 4 days.

### *Intravenous infusion*

Termination of an acute attack of cluster headache, migraine:

**Adult-** 0.5 to 1 mg, 1 dose (Max: 3 mg/day or 6 mg/week).

**Contraindications** Peripheral vascular disease, coronary heart disease, obliterative vascular disease and Raynaud's syndrome, temporal arteritis; hepatic impairment, renal impairment, sepsis; severe or inadequately controlled hypertension, hyperthyroidism, pregnancy (Appendix 7c); lactation; porphyria, ischaemic heart disease; angina pectoris.

**Precautions** Risk of peripheral vasospasm; elderly; it should not be used for migraine prophylaxis; interactions (Appendix 6c). Warn patient to stop treatment immediately if numbness or tingling of extremities develops and to contact doctor, compromised circulation; hypertension.

**Adverse Effects** Nausea, vomiting, vertigo, abdominal pain, diarrhoea, muscle cramps and occasionally headache provoked (usually because of prolonged excessive dosage or abrupt withdrawal); precordial pain, myocardial and intestinal ischaemia, rarely, myocardial infarction; repeated high dosage may cause ergotism with gangrene and confusion; pleural, peritoneal and heart-valve fibrosis may occur with excessive use; coronary artery vasospasm; ventricular tachycardia; altered sense of taste; rhinitis.

**Storage** Store protected from light.

**Paracetamol\*** (Refer Page No. 8)

## Sumatriptan

**Pregnancy Category-C**

**Schedule H**

**Indications** *Acute treatment of migraine.*

**Availability** **TABLET** 25, 50 and 100 mg; **INJECTION** 0.5 ml ampoule (6 mg/ml).

**Dose** **Oral**

The recommended oral dose is 25-100 mg, repeatable after 2 hours upto a total dose of 200 mg over a 24 hour period.

### **Parenteral**

6 mg at onset subcutaneously, may be repeated once after 1 h for maximum of 2 doses in 24 hours.

**Contraindications** Ischaemic heart disease, hypertension; pregnancy (Appendix 7c); renal impairment.

**Precautions** Ischaemic heart disease; hepatic impairment.

**Adverse Effects** Tightness in head and chest, paraesthesia in limbs, dizziness; rise in BP, bradycardia, sudden death, seizures.



## **11. Antineoplastics and Immunosuppressives 243**

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# 11. Antineoplastics and Immunosuppressives

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## 11.1 Antineoplastics

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*Note: WHO advises that adequate resources and specialist supervision are a prerequisite for the introduction of this class of drugs. Specific expertise, diagnostic precision, individualization of dosage or special equipment are required for their proper use*

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The treatment of cancer with drugs, radiotherapy and surgery is complex and should only be undertaken by an oncologist. For this reason, the following information is provided merely as a guide. Chemotherapy may be curative or used to alleviate symptoms or to prolong life. Where the condition can no longer be managed with cytotoxic therapy, alternative palliative treatment should be considered.

For some tumours, single-drug chemotherapy may be adequate, but for many malignancies a combination of drugs provides the best response. Examples of combination therapy include:

- 'CHOP' (cyclophosphamide, doxorubicin, vincristine, prednisolone) for non-Hodgkin's disease;
- 'ABVD' (doxorubicin, bleomycin, vinblastine, dacarbazine) for Hodgkin's disease;
- 'MOPP' (chlormethine, vincristine, procarbazine, prednisolone) for Hodgkin's disease.

Cytotoxic drugs are often combined with other classes of drugs in the treatment of malignant conditions. Such drugs include hormone agonists and antagonists, corticosteroids and immunostimulant drugs. Combinations are, however, more toxic than single drugs.

### Precautions and Contraindications

Treatment with cytotoxic drugs should be initiated only after baseline tests of liver and kidney function have been performed and baseline blood counts established. It may be necessary to modify or delay treatment in certain circumstances. The patient should also be monitored regularly during chemotherapy and cytotoxic drugs withheld if there is significant deterioration in bone-marrow, liver or kidney function.

Many cytotoxic drugs are teratogenic and should not be



administered during pregnancy especially in the first trimester. Contraceptive measures are required during therapy and possibly for a period after therapy has ended. Cytotoxic drugs are also contraindicated during lactation.

Cytotoxic drugs should be administered with care to avoid undue toxicity to the patient or exposure during handling by the health care provider. All waste, including patient's body fluids and excreta (and any material contaminated by them) should be treated as hazardous.

Extravasation of intravenously administered cytotoxic drugs can result in severe pain and necrosis of surrounding tissue. If extravasation occurs, aspiration of the drug should first be attempted, then the affected limb is elevated and warm compresses applied to speed and dilute the infusion or it is localized by applying cold compresses until the inflammation subsides; in severe cases, hydrocortisone cream may be applied topically to the site of inflammation. The manufacturer's literature should also be consulted for more specific information.

## Adverse Effects

Cytotoxic drugs have a considerable potential to damage normal tissue. Specific adverse effects apply, but a number of effects are common to all cytotoxics such as bone-marrow and immunological suppression. Furthermore, the concomitant use of immunosuppressive drugs will enhance susceptibility to infections. Fever associated with neutropenia or immunosuppression requires immediate treatment with antibiotics.

**Nausea and vomiting:** Nausea and vomiting following administration of cytotoxic drugs and abdominal radiotherapy are often distressing and may compromise further treatment. Symptoms may be acute (occurring within 24 h of treatment), delayed (first occurring more than 24 h after treatment), or anticipatory (occurring before subsequent doses). Delayed and anticipatory symptoms are more difficult to control than acute symptoms and require different management.

Cytotoxic drugs associated with a low risk of emesis include etoposide, 5-fluorouracil, low-dose methotrexate and the vinca alkaloids; those with an intermediate risk include low-dose cyclophosphamide, doxorubicin and high-dose methotrexate; and the highest risk is with cisplatin, high-dose cyclophosphamide and dacarbazine.

For patients at a low risk of emesis, pretreatment with an oral phenothiazine (for example chlorpromazine), continued for up to 24 h after chemotherapy, is often helpful. For patients at a higher risk dexamethasone 6-10 mg by mouth may be added

before chemotherapy. For patients at a high risk of emesis or when other therapies are ineffective, high doses of intravenous metoclopramide may be used.

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*Note: High doses of metoclopramide are preferably given by continuous intravenous infusion: an initial dose of 2-4 mg/kg is given over 15 to 20 min, followed by a maintenance dose of 3-5 mg/kg over 8 to 12 h; the total dose should not exceed 10 mg/kg in 24 h.*

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Dexamethasone is the drug of choice for the prevention of delayed symptoms; it is used alone or with metoclopramide.

Good symptom control is the best way to prevent anticipatory symptoms and the addition of diazepam to antiemetic therapy is helpful because of its sedative, anxiolytic and amnesic effects.

**Hyperuricaemia:** Hyperuricaemia may complicate treatment of conditions such as non-Hodgkin's lymphomas and leukaemia. Renal damage may result from the formation of uric acid crystals. Patients should be adequately hydrated and hyperuricaemia may be managed with allopurinol initiated 24 h before cytotoxic treatment and continued for 7 to 10 days afterwards.

**Alopecia:** Alopecia is common during treatment with cytotoxic drugs. There is no drug treatment, but the condition often reverses spontaneously once treatment has stopped.

### Alkylating Drugs:

Alkylating drugs are among the most widely used drugs in cancer chemotherapy. They act by damaging DNA and therefore interfering with cell replication. However, there are two complications. Firstly, they affect gametogenesis and may cause permanent male sterility; in women, the reproductive span may be shortened by the onset of a premature menopause. Secondly, they are associated with a marked increase in the incidence of acute non-lymphocytic leukaemia, in particular when combined with extensive radiation therapy.

**Cyclophosphamide** requires hepatic activation; it can therefore be given orally and is not vesicant when given intravenously. Like all alkylating drugs its major toxic effects are myelosuppression, alopecia, nausea and vomiting. It can also cause haemorrhagic cystitis; an increased fluid intake for 24 to 48 h will help to avoid this complication. Cyclophosphamide is used either as part of treatment or as an adjuvant in Non-Hodgkin's lymphomas, breast cancer, childhood leukaemia and ovarian cancer. It is also used in several palliative regimens.

**Chlorambucil** is used to treat chronic lymphocytic leukaemia, Non-Hodgkin's lymphomas, Hodgkin's disease, ovarian cancer and Waldenstrom (primary) macroglobulinaemia. Adverse effects, apart from bone marrow suppression, are uncommon. However, severe widespread rash can develop and may progress to Stevens-Johnson syndrome or toxic epidermal necrolysis. If a rash occurs, further treatment with chlorambucil is contraindicated.

**Chlormethine** (mustine) forms part of the regimen for treatment of advanced Hodgkin's disease and malignant lymphomas. Its toxicity includes myelosuppression, severe nausea and vomiting, alopecia and thrombophlebitis due to vesicant effect.

### Cytotoxic Antibiotics:

**Bleomycin** is used in regimens for the treatment of Hodgkin's disease and testicular cancer. It has several antineoplastic drug toxicities; it is known to cause dose-related pneumonitis and fibrosis which can be fatal and is associated with rare acute hypersensitivity reactions. Cutaneous toxicity has also been reported.

**Doxorubicin** is the most widely used anthracycline antibiotic. It is used for acute leukaemias although other anthracyclines are more commonly used in these circumstances. Doxorubicin also plays a palliative role in the treatment of other malignancies. The primary toxic effects are myelosuppression, alopecia, nausea, vomiting and dose-related cardiomyopathy. It is also vesicant and can cause severe skin ulceration on extravasation.

**Dactinomycin** is used to treat paediatric cancers. Its toxicity is similar to that of doxorubicin, but it is not cardiotoxic.

**Daunorubicin** is used in acute leukaemias. Its toxicity is similar to that of doxorubicin.

### Antimetabolites and Related Therapy:

**Cytarabine** is used in the treatment of acute leukaemia; children may tolerate high doses better than adults. Its effects are highly dependent upon the schedule of administration. It causes myelosuppression, mucositis and in high doses, central neurotoxicity.

**5-Fluorouracil** is primarily used in the adjuvant treatment of colorectal and breast cancer. It is also employed in the palliative treatment of other malignancies. It causes myelosuppression and the palmar-plantar syndrome (erythema and painful desquamation of the hands and feet). When its action is modified by other drugs (such as calcium folinate), its toxicity

profile can change; mucositis and diarrhoea may be significant problems. Central neurotoxicity can also occur.

**6-Mercaptopurine** is frequently used in the therapy of childhood leukaemia. It can be administered orally and myelosuppression and nausea are the only important toxic effects.

**Methotrexate** is used to treat a variety of malignancies and it plays a major role as an adjuvant for the treatment of breast cancer. Like 5-fluorouracil, methotrexate is myelotoxic, but nausea and vomiting are minimal. It also causes mucositis. Renal impairment reduces methotrexate excretion and can exacerbate toxicity.

**Calcium folinate** is used to counteract the folate-antagonist action of methotrexate and thus speeds recovery from methotrexate-induced mucositis or myelosuppression. Calcium folinate also enhances the effects of 5-fluorouracil when the two are used together for metastatic colorectal cancer.

### Vinca Alkaloids and Etoposide:

The vinca alkaloids, **vinblastine** and **vincristine**, are primarily used in the treatment of acute leukaemias. Vinblastine is also used for Hodgkin's disease and some solid tumours. Vincristine is also used in the management of Non-Hodgkin's lymphomas. Both can cause neurotoxicity, but this is more of a problem with vincristine. Myelosuppression is more common with vinblastine.

**Etoposide** is an important component of the treatment of testicular carcinoma and is also used in several regimens for lung cancers and lymphomas. It causes myelosuppression and alopecia and it can cause hypotension during infusion. It does not produce significant nausea and vomiting.

### Other Antineoplastic Drugs:

The enzyme **asparaginase** is an important component in the management of childhood leukaemia, but is not used in any other malignancy. Its toxicity profile is broad and the drug must be carefully administered because of the risk of anaphylaxis.

**Cisplatin** is a platinum compound used in the treatment of ovarian and testicular malignancies. It is also a component of regimens used in non-small cell and small cell lung cancer and plays a palliative role in other malignancies. Cisplatin is myelosuppressive and also produces slight alopecia. However, it causes severe dose-related nausea and vomiting. It is also nephrotoxic and neurotoxic. Nephrotoxicity can be reduced by maintaining high urine output during cisplatin administration and immediately afterwards, but neurotoxicity is often dose-limiting.

**Dacarbazine**, thought to act as an alkylating drug, is a component of a regimen for Hodgkin's disease. It is also used in the palliative therapy of metastatic malignant melanoma. Its major toxic effects are myelosuppression and intense nausea and vomiting.

**Levamisole** is an anthelmintic with immunostimulating properties; it is used in combination with 5-fluorouracil as adjuvant therapy for colorectal cancer following resection of the tumour. Its major toxic effects are a variety of CNS symptoms, nausea, dermatitis and hypersensitivity reactions.

**Procarbazine** is used in the treatment of advanced Hodgkin's disease. Toxic effects include myelosuppression, nausea, vomiting, CNS symptoms and depression. Procarbazine possesses a weak monoamine oxidase inhibitory effect but dietary restriction is not necessary.

## Actinomycin D\*

Pregnancy Category-C

Schedule H

**Indications** *Trophoblastic tumours, Wilm's tumour, Ewing's sarcoma, rhabdomyosarcoma.*

**Availability** **INJECTION** Vial 500 mg.

**Dose** **Intravenous injection**

**Adult and child above 6 months-** 15 µg/kg/day.

Principally used to treat paediatric cancers.

**Contraindications** See notes above and consult literature; hypersensitivity; lactation; infection with children; herpes zoster; pregnancy (Appendix 7c) and lactation.

**Precautions** See notes above and consult literature.

**Adverse Effects** See notes above and consult literature. Hair loss; nausea; vomiting; mouth sores; diarrhoea.

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*Note: Irritant to tissues*

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## Alpha Interferon\*

Pregnancy Category-C

Schedule H

**Indications** *Hairy cell leukaemia, AIDS related Kaposi's sarcoma in patients above 18 years. Malignant melanoma.*

**Availability** **VIALS** 3, 5 & 6 million IU; 44 µg (Interferon B).

<b>Dose</b>	<b>Adult-</b> Hairy cell leukaemia induction: 3 million IU daily for 16 to 24 weeks. Maintenance 3 million IU three times a week. Treatment for 6 months approx. Kaposi's Sarcoma: 36 million IU for 10 to 12 weeks, maintenance 36 million IU three times a week.  <b>Child-</b> Not recommended for children.
<b>Contraindications</b>	Consult product literature; avoid injections containing benzyl alcohol in neonates; pregnancy (Appendix 7c); lactation.
<b>Precautions</b>	Consult product literature; hairy cell leukaemia; renal impairment.
<b>Adverse Effects</b>	Anorexia, nausea, influenza-like symptoms and lethargy. Ocular side-effects and depression (including suicidal behaviour) have also been reported. Myelosuppression may occur, particularly affecting granulocyte counts. Cardiovascular problems (hypotension, hypertension and arrhythmias), nephrotoxicity and hepatotoxicity have been reported. Hypertriglyceridaemia, monitoring of lipid concentration is recommended. Hypersensitivity reactions, thyroid abnormalities, hyperglycaemia, alopecia, psoriasiform rash, confusion, coma and seizures (usually with high doses in the elderly), leucopenia; thrombocytopenia; mucosities; pancreatitis.
<b>Storage</b>	Store protected from light at or below -20°C.

## Bleomycin\*

**Pregnancy Category-D**

**Schedule H, G**

<b>Indications</b>	<i>Adjunct to surgery and radiotherapy in palliative treatment of Hodgkin's and non-Hodgkin's lymphomas; reticulum cell sarcoma and lymphoma; carcinomas of the head, neck, larynx, cervix, penis, skin, vulva, testicles including embryonal cell carcinoma, choriocarcinoma and teratoma; malignant effusions.</i>
<b>Availability</b>	<b>INJECTION</b> 15 and 30 mg/vial.
<b>Dose</b>	<b><i>Intramuscular and subcutaneous injection</i></b> 30 mg twice a week, dose can also vary from 15 mg daily to 15 mg weekly; total 300 to 400 mg. Small cell cancer; 0.25 to 0.5 mg/kg body weight once or twice a week.
<b>Contraindications</b>	See notes above and literature; preexisting lung disease; pregnancy (Appendix 7c) and lactation (Appendix 7b).
<b>Precautions</b>	See notes above and consult literature; renal impairment; interactions (Appendix 6c).

<b>Adverse Effects</b>	See notes above and consult literature. Dermatitis; nephrotoxicity; hepatotoxicity.
<b>Storage</b>	Store protected from light in a sealed container.

*Note: Irritant to tissues*

## Busulphan\*

**Pregnancy Category-D**

**Schedule G**

<b>Indications</b>	<i>Chronic granulocytic leukaemia, chronic myelogenous leukaemia, polycythaemia vera, myelofibrosis, thrombocythaemia.</i>
<b>Availability</b>	<b>TABLET</b> 2 mg.
<b>Dose</b>	<b>Oral</b>  Chronic myeloid leukaemia, induction of remission: 60 µg/kg body weight daily (max 4 mg) maintenance dose 0.5 to 2 mg daily.
<b>Contraindications</b>	Pregnancy (Appendix 7c); bone marrow suppression; chronic lymphocytic leukaemia; lactation.
<b>Precautions</b>	Monitor cardiac function; pregnancy; lactation previous radiation therapy; avoid in porphyria, hepatic impairment; interactions (Appendix 6c).
<b>Adverse Effects</b>	Hepatotoxicity (including hepatic veno-occlusive disease, hyperbilirubinaemia, jaundice and fibrosis); cardiac tamponade at high doses in thalassaemic patients; pneumonia; skin hyperpigmentation; hyperuraecemia; pulmonary fibrosis.
<b>Storage</b>	Store protected from light.

## Chlorambucil\*

**Pregnancy Category-D**

**Schedule G**

<b>Indications</b>	<i>Chronic lymphocytic leukaemia; some non-Hodgkin's lymphomas; Hodgkin's disease, ovarian cancer and Waldenstrom (primary) macroglobulinaemia.</i>
<b>Availability:</b>	<b>TABLETS</b> 2 and 5 mg.
<b>Dose</b>	<b>Oral</b>

**Adult- Chronic lymphocytic leukaemia:** initially 150 µg/kg body weight daily until leucocyte count sufficiently reduced. Maintenance (started 4 weeks after first course) 100 µg/kg body weight.

**Waldarstrom's macroglobulinaemia:** 6 to 12 mg daily until leucopenia occurs, then reduce to 2 to 8 mg daily.

**Child-** Not recommended.

<b>Contraindications</b>	See notes above and consult literature; hypersensitivity; porphyria; pregnancy (Appendix 7c) and lactation (Appendix 7b).
<b>Precautions</b>	See notes above and consult literature; renal impairment; hepatic impairment (Appendix 7a).
<b>Adverse Effects</b>	See notes above and consult literature. Hepatotoxicity; peripheral neuropathy; cystitis; seizures; pulmonary fibrosis.
<b>Storage</b>	Store protected from light.

## Cisplatin\*

**Pregnancy Category-D**

**Schedule H**

<b>Indications</b>	<i>Metastatic testicular tumours, metastatic ovarian tumours, advanced bladder carcinoma and other solid tumours.</i>
<b>Availability</b>	<b>INJECTION</b> 10 ml (10 mg) and 50 ml (50 mg) vials.
<b>Dose</b>	<b><i>Intravenous injection (use syringes devoid of aluminium component)</i></b>  Ovarian tumor: 50 mg/m <sup>2</sup> of body surface area once every three weeks. Bladder cancer: 50 to 70 mg/m <sup>2</sup> once every 3 to 4 weeks. Testicular tumor: 20 mg/m <sup>2</sup> for 5 days every 3 weeks for 3 courses.
<b>Contraindications</b>	See notes above and consult literature; hypersensitivity; renal impairment (Appendix 7d); pregnancy (Appendix 7c) and lactation (Appendix 7b).
<b>Precautions</b>	See notes above and consult literature; hyperuraemia; hypomagnesaemia; hypocalcaemia; interactions (Appendix 6c).
<b>Adverse Effects</b>	See notes above and consult literature. Tinnitus; neuropathy.



**Storage** Store protected from light.

## Cyclophosphamide\*

**Pregnancy Category-D**

**Schedule G**

**Indications** *Malignant lymphomas including Non-Hodgkin's lymphomas, lymphocytic lymphoma, Burkitt's lymphoma; multiple myeloma; leukaemias, mycosis fungoides; neuroblastoma; adenocarcinoma of the ovary; retinoblastoma; breast cancer.*

**Availability** **TABLET** 50 mg; **INJECTION** 15 ml (200 mg), 30 ml (500 mg) and 50 ml (1g) vials; dry powder to be reconstituted before administration.

**Dose** **Intravenous injection**

Malignancy: 40 to 50 mg/kg body weight in divided doses over 2 to 5 days. Alternatively 10 to 15 mg/kg body weight every 7 to 10 days or 3 to 5 mg/kg body weight twice a week.

### **Oral**

1 to 5 mg/kg body weight. Minimal change nephrotic syndrome: 2.5 to 3 mg/kg body weight.

**Contraindications** See notes above and consult literature; bladder haemorrhage; thrombocytopenia; severe bone marrow depression; pregnancy (Appendix 7c) and lactation (Appendix 7b).

**Precautions** See notes above and consult literature; renal impairment (Appendix 7d) and hepatic impairment (Appendix 7a); interactions (Appendix 6c).

**Adverse Effects** See notes above and consult literature. Haemorrhagic cystitis; colitis; cardiac toxicity; anorexia; thrombocytopenia; dermatitis.

**Storage** Injection: Store in refrigerator (2 to 8°C). Avoid long exposure to temperature above 30°C. The solution should be used immediately after preparation as it deteriorates on storage. Tablet: Store at a temperature not exceeding 30°C.

## Cytosine Arabinoside (Cytarabine)\*

**Pregnancy Category-D**

**Schedule H**

**Indications** *Acute lymphoblastic leukaemia; chronic myeloid leukaemia; meningeal leukaemia; erythroleukaemia; Non-Hodgkin's lymphomas; lymphosarcoma.*

<b>Availability</b>	<b>INJECTION</b> vials 1 ml (100 mg), 5 ml (500 mg) and 10 ml (1g).
<b>Dose</b>	<b>Intravenous injection</b>  <b>Adult-</b> 100 mg/m <sup>2</sup> body surface area every 12 h for seven days.  <b>Child-</b> 100 mg/m <sup>2</sup> body surface area twice daily by rapid injection or 100 mg/m <sup>2</sup> body surface area daily by continuous infusion given by 5 to 10 days.
<b>Contraindications</b>	See notes above and consult literature; hypersensitivity; pregnancy (Appendix 7c) and lactation (Appendix 7b).
<b>Precautions</b>	See notes above and consult literature; uric acid level monitoring recommended; hepatic impairment (Appendix 7a).
<b>Adverse Effects</b>	See notes above and consult literature; g.i.t. disturbances.
<b>Storage</b>	Store protected from light.

## Doxorubicin\*

Pregnancy Category-D

Schedule H, G

<b>Indications</b>	<i>Soft tissue and bone sarcomas, acute leukemia, malignant lymphoma, Hodgkin's disease, non-Hodgkin's disease, breast carcinoma, small-cell carcinoma of lungs, AIDS-related Kaposi's sarcoma, multiple myeloma, gastro-intestinal tract carcinoma, bladder cancer, ovarian carcinoma, acute myeloblastic leukemia, thyroid carcinoma, neuroblastoma.</i>
<b>Availability</b>	<b>INJECTION</b> 10 & 50 mg lyophilized powder/vial, 2 mg/ml solution <b>LIPOSOMAL</b> injection 10 ml vial (2 mg/ml).
<b>Dose</b>	<b>Intravenous</b> 50-75 mg/m <sup>2</sup> body surface area by slow i.v injection every 3 weeks.  <b>AIDS-related Kaposi's sarcoma:</b> <b>Adult:</b> As pegylated liposome: 20 mg/m <sup>2</sup> body surface area infused over 1 hr once every 3 weeks. <b>Ovarian carcinoma:</b> <b>Adult:</b> As pegylated liposome: 50 mg/m <sup>2</sup> BSA infused over 1 hr once every 4 weeks.
<b>Contraindications</b>	Known hypersensitivity, cardiac disease, pregnancy (Appendix 7c), lactation, neonates.

<b>Precautions</b>	Avoid extravasation, monitor ECG changes, arrhythmias, blood counts, hypotension or congestive heart failure, hepatic impairment, interactions (Appendix 6c). <b>Liposomal and non-liposomal preparations are not interchangeable.</b>
<b>Adverse Effects</b>	Infusion reactions, cardiotoxicity, bone marrow suppression, liver impairment, nausea and vomiting, reversible alopecia, stomatitis, conjunctivitis, keratitis, mucositis, discolouration of body fluids, local skin reactions and tissue damage, secondary leukemias.
<b>Storage</b>	Store protected from light, in well closed containers at temperature between (15-30°C); Store intact vials of solution under refrigeration at 2-8°C. Use the solution prepared using the liquid stated on the label immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the instructions of the manufacturer. Liposomal formulations: Refrigerate at 2-8°C. Do not freeze.

## Etoposide\*

**Pregnancy Category-D**

**Schedule H**

<b>Indications</b>	<i>Refractory testicular tumours; acute leukaemia; malignant lymphoma; lung cancer.</i>
<b>Availability</b>	<b>CAPSULES</b> 25, 50 and 100 mg; <b>INJECTION</b> vial 100 mg/5 ml.
<b>Dose</b>	<b><i>Intramuscular injection</i></b>  <b>Adult-</b> Initially 50 to 100 mg/m <sup>2</sup> body surface area daily by infusing over 30 to 60 min. Thereafter, no injection for 3 to 4 weeks is given. Small cell lung cancer: 350 mg/m <sup>2</sup> daily.  <b><i>Oral</i></b>  <b>Adult-</b> 100 to 200 mg/m <sup>2</sup> body surface area from day 1 to 5 taken on empty stomach, thereafter no treatment for 3 to 4 weeks.
<b>Contraindications</b>	See notes above and consult literature; hypersensitivity; severe liver dysfunction; pregnancy (Appendix 7c) and lactation (Appendix 7b).
<b>Precautions</b>	See notes above and consult literature; hepatic impairment (Appendix 7a); interactions (Appendix 6c); renal impairment (Appendix 7d).

<b>Adverse Effects</b>	See notes above and consult literature. Alopecia; gastrointestinal disturbances; thrombophlebitis; neuritis.
<b>Storage</b>	Store protected from moisture at a temperature not exceeding 30°C. Capsules should not be stored in refrigerator.

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*Note: Irritant to tissues*

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## 5-Fluorouracil\* (Refer Page No. 361)

**Pregnancy Category-D**

**Schedule H**

<b>Indications</b>	<i>Carcinomas of the colorectum, breast, stomach, pancreas, cervix, prostate, ovary and endometrium; liver tumours; head and neck tumours; actinic keratosis.</i>
<b>Availability</b>	<b>INJECTION</b> 5 and 10 ml ampoule (50 mg/ml). <b>TABLETS</b> 50 mg.
<b>Dose</b>	<b>Intravenous injection</b>  Initially 12 mg/kg body weight once a day for 4 days, max. daily dose 800 mg. If tolerated well without toxicity 6 mg/kg body weight can be given on 6 <sup>th</sup> , 8 <sup>th</sup> , 10 <sup>th</sup> and 12 <sup>th</sup> day. Discontinue on 12 <sup>th</sup> day.  Maintenance dose 10 to 15 mg/kg body weight every week (max dose 1g/week).
<b>Contraindications</b>	See notes above and consult literature; bone marrow depression; pregnancy (Appendix 7c) and lactation (Appendix 7b).
<b>Precautions</b>	See notes above and consult literature; lactation; pelvic irradiation; renal impairment; hepatic impairment (Appendix 7a); interactions (Appendix 6c).
<b>Adverse Effects</b>	See notes above and consult literature. Cardiac toxicity; tachycardia; dermatitis; diarrhoea.
<b>Storage</b>	Store protected from light in single dose container at a temperature not exceeding 30°C. The injection should not be allowed to freeze.

## Folinic Acid\*

**Pregnancy Category-A**

<b>Indications</b>	<i>High-dose methotrexate therapy ('folate rescue'); inadvertent overdose of methotrexate; with 5-fluorouracil in the palliative treatment of advanced colorectal cancer.</i>
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<b>Availability</b>	<b>INJECTION</b> 3 mg/ml.
<b>Dose</b>	Prevention of methotrexate induced adverse reactions; started 24 h after treatment with methotrexate by intravenous infusion or by intravenous injection. 15 mg repeat every 6 h for 48 to 72 h.
<b>Contraindications</b>	Intrathecal injection.
<b>Precautions</b>	Avoid simultaneous administration of methotrexate; not indicated for pernicious anaemia or other megaloblastic anaemias due to vitamin B <sub>12</sub> deficiency; pregnancy (Appendix 7c) and lactation; interactions (Appendix 6c).
<b>Adverse Effects</b>	Hypersensitivity reactions; rarely, pyrexia after parenteral use; wheezing; swelling of facial features.

## Gemcitabine\*

**Pregnancy Category-D**

**Schedule H**

<b>Indications</b>	<i>Adenocarcinoma of pancreas.</i>
<b>Availability</b>	<b>INJECTION</b> Vial 200 mg and 1g (dry powder to be reconstituted before administration).
<b>Dose</b>	1g/m <sup>2</sup> body surface area for over 30 min once a week for up to 7 weeks, if not tolerated reduce or withhold. After one week rest administer by infusion once weekly for three weeks, withhold for 4th week before repeating.
<b>Contraindications</b>	Pregnancy (Appendix 7c); concurrent radial radiotherapy; hypersensitivity; lactation.
<b>Precautions</b>	Gemcitabine is not recommended for patients who can have potentially curative surgery. There is insufficient evidence about its use for second-line treatment of pancreatic adenocarcinoma, hepatic impairment; renal impairment, interactions (Appendix 6c).
<b>Adverse Effects</b>	Nausea, vomiting, oral mucositis, hyperuricaemia, bone marrow suppression, alopecia, thromboembolism, flu like syndrome; edema; thrombocytopenia; somnolence; hematuria; dyspnoea; loss of appetite.
<b>Storage</b>	Store in a sterile, airtight, tamperproof container.

## Imatinib\*

### Pregnancy Category-D

<b>Indications</b>	<i>Chronic myeloid leukaemia, Philadelphia chromosome positive acute lymphoblastic leukaemia, Gastrointestinal stromal tumor.</i>
<b>Availability</b>	<b>CAPSULES</b> 100 and 400 mg.
<b>Dose</b>	400-600 mg/day.
<b>Contraindications</b>	Hypersensitivity.
<b>Precautions</b>	Interactions (Appendix 6c); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Acute-nausea and vomiting; chronic fluid retention with ankle and periorbital edema, diarrhoea, myalgias, congestive heart failure.

## L- Asparaginase\*

### Pregnancy Category-C

**Schedule G**

<b>Indications</b>	<i>Acute lymphoblastic leukaemia.</i>
<b>Availability</b>	<b>INJECTION</b> 5,000, 6,000 and 10,000 IU (for reconstitution before administration).
<b>Dose</b>	<b><i>Intramuscular, intravenous or subcutaneous injection</i></b>  Exclusively in acute lymphoblastic leukaemia. Careful monitoring is required. Urine is tested for glucose because of risk of hyperglycaemia.
<b>Contraindications</b>	See notes above and consult literature; pregnancy (Appendix 7c) and lactation (Appendix 7b).
<b>Precautions</b>	See notes above and consult literature.
<b>Adverse Effects</b>	See notes above and consult literature.

## Melphalan\*

### Pregnancy Category-D

**Schedule H**

<b>Indications</b>	<i>Breast carcinoma, multiple myeloma, advanced ovarian carcinoma, malignant melanoma, polycythaemia vera.</i>
<b>Availability</b>	<b>TABLETS</b> 2 and 5 mg; <b>INJECTION</b> 50 mg/vial.
<b>Dose</b>	<b>Oral</b>

**Adult-** Multiple myeloma: usual dose 6 mg/day. Maintenance dose 2 mg/day.

Alternatively 10 mg daily for 7 days (total dose 70 mg), repeat if required after blood counts particularly neutrophils and platelets.

Ovarian carcinoma: 0.2 mg/kg body weight daily for 5 days, repeat after 4 to 5 weeks.

Child- 0.15 mg/kg body weight daily for 7 days. Maintenance dose is 0.05 mg/kg body weight daily when platelet count is rising.

#### ***Intravenous injection***

For Injection: 16 mg/m<sup>2</sup>.

<b>Contraindications</b>	Pregnancy (Appendix 7c); hypersensitivity; myelosuppression; lactation.
<b>Precautions</b>	Hepatic impairment; renal impairment; interactions (Appendix 6d).
<b>Adverse Effects</b>	Nausea, vomiting, oral mucositis, hyperuricaemia, bone marrow suppression, alopecia, thromboembolism, leucopenia; menstrual irregularities; haemolytic anaemia.
<b>Storage</b>	Store protected from light and moisture at a cool place.

## **6-Mercaptopurine\***

**Pregnancy Category-D**

**Schedule G**

<b>Indications</b>	<i>Acute leukaemias; Chronic granulocytic leukaemia; choreocarcinoma.</i>
<b>Availability</b>	<b>INJECTION</b> 2 ml ampoule (200 mg/2 ml) <b>TABLET</b> 50 mg.
<b>Dose</b>	<b>Oral</b>  Leukaemia in children (maintenance): 2.5 mg/kg body weight in continuation with other drugs daily.
<b>Contraindications</b>	See notes above and consult literature; hypersensitivity; pregnancy (Appendix 7c) and lactation (Appendix 7b).
<b>Precautions</b>	See notes above and consult literature; monitor blood count; uric acid levels; renal impairment and hepatic impairment (Appendix 7a); interactions (Appendix 6c).
<b>Adverse Effects</b>	See notes above and consult literature. Hepatotoxicity; anorexia; nausea; hyperuricaemia; ulcers.

**Storage** Store protected from light and moisture.

## Methotrexate\* (Refer Page No. 385)

**Pregnancy Category-X**

**Schedule H**

**Indications** *Carcinoma of the breast, head and neck and lung; trophoblastic tumours; acute lymphoblastic leukaemia, meningeal leukaemia; non-Hodgkin's lymphomas; advanced cases of mycosis fungoides; non-metastatic osteosarcoma; severe rheumatoid arthritis.*

**Availability** **TABLETS** 2.5, 5, 7.5, 10 and 15 mg; **INJECTION** 2, 5, 15 and 50 ml/vial; ampoule (5 mg/ml and 25 mg/ml); **VIALS** 5, 25, 100 mg/ml; **GEL** 1% w/w.

**Dose** **Oral**

Choriocarcinoma: 15 to 30 mg daily for 5 days repeat 3 to 5 full courses after 1 week.

### **Intramuscular route**

15 to 30 mg daily for 5 days, repeat 3 to 5 courses after 1 week.

Leukaemia, maintenance after remission: 30 mg/m<sup>2</sup> body surface area (max upto 15 mg twice a week).

**Contraindications** See notes above and consult literature; severe renal and hepatic impairment; alcohol liver disease; severe leucopenia; thrombocytopenia; pregnancy (Appendix 7c) and lactation (Appendix 7b).

**Precautions** See notes above and consult literature; bone marrow depression; renal and hepatic impairment (Appendix 7a); interactions (Appendix 6a, 6c, 6d).

**Adverse Effects** See notes above and consult literature. CNS toxicity; stomatitis; hepatobiliary disorder; fatigue.

**Storage** Store protected from light and moisture.

## Mitomycin\*

**Pregnancy Category-D**

**Indications** *Adrenocarcinoma, lymphosarcoma and seminoma, superficial bladder cancer (adjuvant therapy).*



<b>Availability</b>	<b>INJECTIONS</b> vial 2 and 10 mg (dry powder to be reconstituted before administration).
<b>Dose</b>	<b>Intravenous injection</b>  <b>Adult-</b> 6 to 10 mg twice a week, alternatively 0.5 mg/kg body weight daily for 5 days, repeat after 2 weeks.
<b>Contraindications</b>	Pregnancy (Appendix 7c); bone marrow depression; severe anaemia; thrombocytopenia; lactation.
<b>Precautions</b>	It causes delayed bone-marrow toxicity and therefore it is usually administered at 6-weekly intervals. Caution in handling because it is irritant to tissues, thrombocytopenia; necrosis; leucopenia.
<b>Adverse Effects</b>	Prolonged use may result in permanent bone-marrow damage. It may also cause lung fibrosis and renal damage; dyspnea.
<b>Storage</b>	Store protected from light.

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*Note: Irritant to tissues*

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## Paclitaxel\*

**Pregnancy Category-D**

**Schedule H**

<b>Indications</b>	<i>Metastatic ovarian and breast cancer.</i>
<b>Availability</b>	<b>INJECTION</b> vial 30, 100, 200, 260 and 300 mg (dry powder to be reconstituted before administration).
<b>Dose</b>	<b>Intravenous infusion</b>  <b>Adult-</b> 175 mg/m <sup>2</sup> body surface area over 3 h, repeat every 3 weeks.  Antihistamines, corticosteroids or H <sup>2</sup> antagonist may be required during treatment.  <b>Child-</b> Not recommended.
<b>Contraindications</b>	Hypersensitivity; severe hepatic impairment; lactation; pregnancy (Appendix 7c).

**Adverse Effects** Myelosuppression, peripheral neuropathy and cardiac conduction defects with arrhythmias (which are nearly always asymptomatic); alopecia, muscle pain; nausea and vomiting is mild to moderate, hypersensitivity reactions; myalgia; arthralgia.

**Storage** Store protected from light at a temperature not exceeding 25°C.

## Procarbazine\*

**Pregnancy Category-D**

**Schedule H**

**Indications** *Part of MOPP regimen in Hodgkin's and Non-Hodgkin's lymphomas.*

**Availability** **TABLETS** 50 mg.

**Dose** **Oral**

50 mg daily to start with initially, increased to 250 to 300 mg individual doses.

Maintenance (on remission): 50 to 100 mg daily to cumulative total of at least 6g.

**Contraindications** See notes above and consult literature; hypersensitivity; pregnancy (Appendix 7c) and lactation (Appendix 7b).

**Precautions** See notes above and consult literature; ulceration; haemorrhage; leucopenia: renal and hepatic impairment (Appendix 7a); interactions (Appendix 6a).

**Adverse Effects** See notes above and consult literature; leucopenia; anaemia; thrombocytopenia; hypotension; retinal haemorrhage.

## Tamoxifen\* (Refer Page No. 472)

## Thalidomide

**Pregnancy Category-X**

**Schedule H**

**Indications** *Multiple myeloma, erythema nodosum leprosum*

**Availability** **CAPSULES** 50 and 100 mg.

**Dose****Oral****Multiple myeloma**

**Adult:** The dose is 200 mg administered orally once daily with water, preferably at bedtime and at least 1-hour after the evening meal. Thalidomide is administered in combination with dexamethasone in 28-day treatment cycles.

Dexamethasone is 40 mg daily administered orally on days 1-4, 9-12, and 17-20 every 28 days.

**Erythema nodosum leprosum (ENL)**

**Adult:** For cutaneous ENL, thalidomide dosing should be initiated at 100 to 300 mg/day, administered once daily with water, preferably at bedtime and at least 1 hour after the evening meal. Not for monotherapy if moderate or severe neuritis present. Max: 400 mg/day.

**Patients < 50 kg:** Initially, 100 mg daily.

Dosing with thalidomide should continue until signs and symptoms of active reaction have subsided, usually a period of at least 2 weeks. Patients may then be tapered off medication in 50 mg decrements every 2 to 4 weeks.

Patients who have a history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who flare during tapering, should be maintained on the minimum dose necessary to control the reaction. Tapering off medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks.

**Contraindications**

Hypersensitivity, pregnancy (Appendix 7C) and lactation, interactions (Appendix 6c).

<b>Precautions</b>	During the period of treatment both males and females should take adequate means of contraception before, during and after (atleast 4 weeks) the therapy, therapy to be stopped immediately if pregnancy occurs, no blood or sperm donation during therapy, signs and symptoms of hypersensitivity include the occurrence of erythematous macular rash, possibly associated with fever, tachycardia, and hypotension, and if severe, may necessitate interruption of therapy, Serious dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, seizures, impairment of mental and/or physical abilities required for the performance of hazardous tasks such as driving a car or operating complex machinery, potentiation of somnolence caused by alcohol, peripheral neuropathy, thromboembolism reported.
<b>Adverse Effects</b>	Teratogenicity, Drowsiness/somnolence, peripheral neuropathy, constipation, dizziness, bradycardia, orthostatic hypotension, hypersensitivity, and neutropenia.
<b>Storage</b>	Store protected from moisture, at a temperature not exceeding 30°C.

## Vinblastine\*

**Pregnancy Category-D**

**Schedule H**

<b>Indications</b>	<i>Disseminated Hodgkin's and Non-Hodgkin's lymphomas; advanced testicular carcinoma, breast carcinoma; palliative treatment of Kaposi's sarcoma; trophoblastic tumours; Letterer-Siwe disease; Histolytic lymphoma.</i>
<b>Availability</b>	<b>VIAL</b> 10 ml (1 mg/ml).
<b>Dose</b>	<b><i>Intravenous injection only</i></b>  3.7 mg/m <sup>2</sup> body surface surface area in single dose. Increase on weekly intervals depending on WBC count (max 18.5 mg/m <sup>2</sup> body area).
<b>Contraindications</b>	See notes above and consult literature; hypersensitivity; severe granulocytopenia; lactation (Appendix 7b).

Intrathecal injection is contraindicated.

<b>Precautions</b>	See notes above and consult literature; neurotoxicity; ischaemic heart disease; hepatic impairment (Appendix 7a); interactions (Appendix 6c); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	See notes above and consult literature. Stomatitis; leucopenia; constipation; bone pain.
<b>Storage</b>	Store in sealed container in a deep freezer (below -18°C).

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*Note: Irritant to tissues*

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## Vincristine\*

**Pregnancy Category-D**

**Schedule H**

<b>Indications</b>	<i>Acute lymphoblastic leukaemia; neuroblastoma, Wilm's tumour, Hodgkin's and Non-Hodgkin's lymphomas; rhabdomyosarcoma, Ewing's sarcoma; mycosis fungoides.</i>
<b>Availability</b>	<b>INJECTION</b> 1 mg/ml.
<b>Dose</b>	<b><i>Intravenous route</i></b>  <b>Adult-</b> 1.4 mg/m <sup>2</sup> body surface area per week.
<b>Contraindications</b>	See notes above and consult literature; lactation (Appendix 7b).  Intrathecal injection is contraindicated.
<b>Precautions</b>	See notes above and consult literature; uric acid neuropathy; bronchospasm; hepatic impairment (Appendix 7a); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	See notes above and consult literature.
<b>Storage</b>	Store in sealed container in a deep freezer (below -18°C).

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*Note: Irritant to tissues*

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## 11.2 Immunosuppressives

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*Note: WHO advises that this class of drugs is for use only when adequate resources and specialist care are available. Specific expertise, diagnostic precision, individualization of dosage or special equipment are required for their proper use*

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Immunosuppressive drugs are used in organ transplant recipients to suppress rejection; they are also used as second-line drugs in chronic inflammatory conditions. Treatment should only be initiated by a specialist. Careful monitoring of blood counts is required in patients receiving immunosuppressive drugs and the dose should be adjusted to prevent bone-marrow toxicity. Immunosuppressed patients are particularly prone to atypical infections.

**Azathioprine** is the most widely used drug in transplant recipients. It is useful when corticosteroid therapy alone has proven inadequate or for other conditions when a reduction in the dose of concurrently administered corticosteroids is required. It is metabolized to 6-mercaptopurine and, as with mercaptopurine, doses need to be reduced when given with allopurinol. The predominant toxic effect is myelosuppression, although hepatic toxicity also occurs.

**Cyclosporine** is a potent immunosuppressant which is virtually free of myelotoxic effects, but is markedly nephrotoxic. It is particularly useful for the prevention of graft rejection and for the prophylaxis of graft-versus-host disease. The dose is adjusted according to plasma-cyclosporine concentrations and renal function. Dose-related increases in serum creatinine and blood urea nitrogen (BUN) during the first few weeks may necessitate dose reduction.

Corticosteroids such as **prednisolone** have significant immunosuppressant activity and can also be used to prevent rejection of organ transplants.

**Azathioprine\*** (Refer Page No. 382 and 434)**Pregnancy Category-D****Schedule H**

<b>Indications</b>	<i>To prevent rejection in transplant recipients; rheumatoid arthritis; inflammatory bowel disease; Multiple sclerosis; autoimmune hepatitis; atopic dermatitis (AD).</i>
<b>Availability</b>	<b>TABLETS</b> 25 and 50 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult and child over 3 months</b> -Renal transplantation: initially 5 mg/kg body weight daily. Maintenance 2 to 2.5 mg/kg daily. Atopic dermatitis (AD): 1 to 3 mg/kg/day once daily.
<b>Contraindications</b>	Hypersensitivity to azathioprine and mercaptopurine; lactation (Appendix 7b).
<b>Precautions</b>	Monitor for toxicity throughout treatment; full blood counts necessary every week (or more frequently with higher doses and in renal or hepatic impairment) for first 4 weeks of treatment and at least every 3 months thereafter; reduce dose in elderly; renal impairment; liver disease (Appendix 7a); interactions (Appendix 6c, 6d); lactation (Appendix 7b); pregnancy (Appendix 7c).  Patients should be warned to report immediately any signs or symptoms of bone marrow suppression, for example unexplained bruising or bleeding, infection.
<b>Adverse Effects</b>	Hypersensitivity reactions including malaise, dizziness, vomiting, fever, muscular pains, arthralgia; rash; hypotension or interstitial nephritis call for immediate withdrawal; haematological toxicity includes leukopenia and thrombocytopenia (reversible upon withdrawal); liver impairment, cholestatic jaundice; hair loss; increased susceptibility to infections and colitis in patients also receiving corticosteroids; nausea; rarely, pancreatitis, pneumonitis, hepatic veno-occlusive disease; microcytosis.

**Storage** Store protected from light.

## Cyclosporine\* (Refer Page No. 434)

**Pregnancy Category-C**

**Schedule H**

**Indications** *Rejection in kidney, liver, heart or bone-marrow transplantation; graft-versus-host disease; in severe recalcitrant atopic dermatitis.*

**Availability** **CAPSULES** 10, 25, 50 and 100 mg; **INFUSION** 50 and 100 ml (100 mg/ml); **INJECTION** 1 and 5 ml ampoule (250 mg/ml).

**Dose** ***Oral and intravenous infusion***

**Adult and child over 3 months-** Initially 5 mg/kg b.i.d. for 2 weeks; can be reduced to 1.5 to 3 mg/kg/day according to patients response. If no response after 2 weeks, increase dose 7 mg/kg/day.

Organ transplant: 10 to 15 mg/kg body weight 2 to 4 h before transplantation, followed by 10 to 15 mg/kg body weight for 1 to 2 weeks post operatively. Decrease thereafter gradually to 2 to 6 mg/kg body weight for maintenance (adjust according to blood cyclosporine concentration and renal function), if required 1/3rd corresponding oral dose can be administered by intravenous infusion over 2 to 6 h.

### ***Intravenous infusion***

Bone marrow transplantation; 3 to 5 mg/kg body weight by intravenous infusion over 2 to 4 h from day before transplantation.

**Contraindications** Patients affected by psoriasis.



**Precautions**

Monitor kidney function (dose dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction, exclude rejection if kidney transplant), monitor liver function (adjust dosage according to bilirubin and liver enzymes, also refer Appendix 7a); monitor blood pressure (discontinue if hypertension cannot be controlled by antihypertensives); monitor serum potassium, particularly if marked renal impairment (risk of hyperkalaemia); monitor serum magnesium; hyperuricaemia; measure blood lipids before and during treatment; avoid in porphyria; vaccination ineffective; monitor serum creatinine levels; patients affected with psoriasis; lactation (Appendix 7b); interactions (Appendix 6b, 6c); pregnancy (Appendix 7c).

**Adverse Effects**

Dose-related and reversible increases in serum creatinine and urea unrelated to tissue rejection; burning sensation in hands and feet during initial therapy; electrolyte disturbances including hyperkalaemia, hypomagnesaemia; hepatic dysfunction; hyperuricaemia; hypercholesterolaemia; hyperglycaemia, hypertension (especially in heart transplant patients); increased incidence of malignancies and lymphoproliferative disorders; increased susceptibility to infections due to immunosuppression; gastrointestinal disturbances; gingival hyperplasia; hirsutism; fatigue; allergic reactions; thrombocytopenia (sometimes with haemolytic uraemic syndrome), also mild anaemia; tremors; convulsions, neuropathy; dysmenorrhoea or amenorrhoea; pancreatitis, myopathy or muscle weakness; cramps, gout, oedema; headache; gingival hypertrophy; renal dysfunction; hypertrichosis; paresthesia; renal toxicity; gastrointestinal symptoms.

**Storage**

Store in a well closed container below 25°C.

**Tacrolimus****Pregnancy Category-C****Indications**

*Prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants. Tacrolimus ointment is indicated for atopic dermatitis and psoriasis.*

<b>Availability</b>	<b>TABLETS</b> 0.5, 1, 2 and 5 mg <b>CAPSULES</b> 0.5, 1, 2 and 5 mg <b>OINTMENTS</b> 0.03%, 0.1 %, 0.3% w/w <b>INJECTIONS</b> 5 mg/ml.
<b>Dose</b>	Starting dose for injection- 0.03 to 0.05 mg/kg/day as a continuous infusion.  <b>Oral</b>  <b>Adult-</b> Initial-0.15 to 0.2 mg/kg/day for kidney transplants, 0.1 to 0.15 mg/kg/day for liver transplants. <b>Child-</b> 0.15 to 0.2 mg/kg/day for liver transplant patients in two divided doses 12 hours apart.
<b>Contraindications</b>	Hypersensitivity to tacrolimus.
<b>Precautions</b>	Monitoring of blood trough serum concentrations for prevention of organ rejection and to reduce drug related toxicity, pregnancy (Appendix 7c); interactions (Appendix 6c, 6d).
<b>Adverse Effects</b>	Nephrotoxicity; neurotoxicity; hyperglycemia, hypertension, hyperkalemia, and gastrointestinal disturbances.
<b>Storage</b>	Store protected from light.

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## 12. Antiseptics and Disinfectants

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### 12.1 Antiseptics

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An antiseptic destroys or inhibits growth of micro-organisms on living tissues without causing injurious effects when applied to surfaces of the body or to exposed tissues. Some antiseptics are applied to the unbroken skin or mucous membranes, to burns and to open wounds to prevent sepsis by removing or excluding microbes from these areas. Iodine has been modified for use as an antiseptic. The iodophore, povidone-iodine, is effective against bacteria, fungi, viruses, protozoa, cysts and spores and significantly reduces surgical wound infections. The solution of povidone iodine releases iodine on contact with the skin. Chlorhexidine has a wide spectrum of bactericidal and bacteriostatic activity and is effective against both Gram-positive and Gram-negative bacteria although it is less effective against some species of *Pseudomonas* and *Proteus* and relatively inactive against mycobacteria. It is not active against bacterial spores. Chlorhexidine is incompatible with soaps and other anionic materials, such as bicarbonates, chlorides, and phosphates, forming salts of low solubility which may precipitate out of solution. Ethanol has bactericidal activity and is used to disinfect skin prior to injection, venepuncture or surgical procedures.

## Cetrimide\*

<b>Indications</b>	<i>Antiseptic; disinfectant for surgical instruments.</i>
<b>Availability</b>	<b>SOLUTION</b> 100 ml and 1 litre pack (2%w/v); <b>CREAM</b> 1g (0.5% w/w).
<b>Dose</b>	To be applied to the affected area.
<b>Contraindications</b>	Hypersensitivity.
<b>Precautions</b>	Avoid contact with eyes; avoid use in body cavities; meninges and middle ear.
<b>Adverse Effects</b>	Skin irritation and occasionally sensitisation; rarely, burns.

## Chlorhexidine\*

### Pregnancy Category-B

<b>Indications</b>	<i>Antiseptic; disinfection of clean instruments; gingivitis.</i>
<b>Availability</b>	<b>SOLUTION</b> 100 ml (2% and 4% w/v); <b>MOUTH WASH</b> 100 ml (0.2%, w/v).
<b>Dose</b>	Antiseptic (pre-operative skin disinfection and hand washing): use solution in alcohol (70%). Antiseptic (wounds, burns and other skin damage): apply 0.05% aqueous solution.  Disinfection of clean instruments: immerse for at least 30 min in 0.05% solution containing Sodium nitrite 0.1% (to inhibit metal corrosion). Emergency disinfection of clean instruments: immerse for 2 min in 0.5% solution in alcohol (70%).
<b>Contraindications</b>	Meningitis; middle ear surgery; sensitive tissues.

**Precautions** Aqueous solutions-susceptible to microbial contamination-use sterilized preparation or freshly prepared solution and avoid contamination during storage or dilution; instruments with cemented glass components (avoid preparations containing surface active agents); irritant-avoid contact with middle ear; eyes; brain and meninges; not for use in body cavities; alcoholic solutions not suitable before diathermy; syringes and needles treated with chlorhexidine (rinse thoroughly with sterile water or saline before use); inactivated by cork (use glass; plastic or rubber closures); alcohol based solutions are flammable; pregnancy (Appendix 7c).

**Adverse Effects** Occasional skin sensitivity and irritation; Upper respiratory tract infection.

**Storage** Store protected from light.

## Ethyl Alcohol\*

**Indications** *Disinfection of skin prior to injection, venepuncture or surgical procedures.*

**Availability** Regulated by state excise, license is required.

**Dose** Apply undiluted solution.

**Precautions** Flammable; avoid broken skin; patients have suffered severe burns when diathermy has been preceded by application of alcoholic skin disinfectants; lactation (Appendix 7b).

**Adverse Effects** Skin dryness and irritation with frequent application.

**Storage** Store in a tightly closed container at a temperature not exceeding 30°C, away from fire and protected from moisture.

## Gentian Violet\* (Refer Page No. 348)

## Povidone Iodine\*

### Pregnancy Category-D

**Indications** *Antiseptic; skin disinfection; Mouth wash.*

**Availability** **SOLUTIONS** 100 and 500 ml (5% w/v), 500 ml (7.5% w/v and 10% w/v); **OINTMENT** 15g (5% w/w).

<b>Dose</b>	<b>Adult and Child-</b> Pre- and post-operative skin disinfection: apply undiluted. Antiseptic (minor wounds and burns): apply twice daily.
<b>Contraindications</b>	Avoid regular or prolonged use in patients with thyroid disorders or those taking lithium; avoid regular use in neonates; avoid in very low birthweight infants; burn covering large surface area; hypersensitivity to iodine.
<b>Precautions</b>	Pregnancy (Appendix 7c); lactation (Appendix 7b); broken skin (see below); renal impairment; avoid contact with eyes; neonates.  The application of povidone iodine to large wounds or severe burns may produce systemic adverse effects such as metabolic acidosis; hypernatraemia; and impairment of renal function.
<b>Adverse Effects</b>	Irritation of skin and mucous membranes; may interfere with thyroid function tests; systemic effects (see under Precautions).
<b>Storage</b>	Store protected from light.

## 12.2 Disinfectants

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A disinfectant is a chemical agent, which destroys or inhibits growth of pathogenic micro-organisms in the non-spore or vegetative state. Disinfectants do not necessarily kill all organisms but reduce them to a level, which does not harm health or the quality of perishable goods. Disinfectants are applied to inanimate objects and materials such as instruments and surfaces to control and prevent infection. They may also be used to disinfect skin and other tissues prior to surgery (see also Antiseptics, above).

Disinfection of water can be either physical or chemical. Physical methods include boiling, filtration and ultraviolet irradiation. Chemical methods include the addition of chlorine releasing compounds, such as Sodium hypochlorite solution, chloramine T powder, or Sodium dichloroisocyanurate (NaDCC) powder or tablets. Where water is not disinfected at source it may be disinfected by boiling or by chemical means for drinking, cleaning teeth and food preparation.

Chlorine is a hazardous substance. It is highly corrosive in concentrated solution and splashes can cause burns and damage the eyes. Appropriate precautions must be taken when concentrated chlorine solutions or powders are handled.

The chlorinated phenolic compound, chloroxylenol, is effective against a wide range of Gram-positive bacteria. It is less effective against staphylococci and Gram-negative bacteria; it is often ineffective against *Pseudomonas* spp. and inactive against spores.

The aldehyde bactericidal disinfectant, glutaraldehyde, is strongly active against both Gram-positive and Gram-negative bacteria. It is active against the tuberculosis bacillus, fungi such as *Candida albicans*, and viruses such as HIV and hepatitis B. A 2% w/v aqueous alkaline (buffered to pH 8) glutaral solution can be used to sterilize heat-sensitive pre-cleansed instruments and other equipments.



## Bleaching Powder\*

<b>Indications</b>	<i>Disinfection of surfaces, equipments, water.</i>
<b>Availability</b>	<b>POWDER FOR SOLUTION</b> 1g chlorine/litre (1000 parts per million; 0.1%).
<b>Dose</b>	Surface disinfection (minor contamination): apply solutions containing 1000 parts per million.  Instrument disinfection: soak in solution containing 1000 parts per million for a minimum of 15 min; to avoid corrosion do not soak for more than 30 min; rinse with sterile water.
<b>Storage</b>	Store protected from moisture in a tightly closed container.

## Chloroxylenol

### Pregnancy Category-C

<b>Indications</b>	<i>Antiseptic; disinfection of instruments and surfaces.</i>
<b>Availability</b>	<b>SOLUTIONS</b> 50, 100, 200, 500 ml, 1 and 5 litres.
<b>Dose</b>	<b>Antiseptic</b> (wounds and other skin damage): apply a 1 in 20 dilution of 5% concentrate in water. <b>Disinfection of instruments:</b> use a 1 in 20 dilution of 5% concentrate in alcohol (70%).
<b>Contraindications</b>	Meningitis; ear infection.
<b>Precautions</b>	Aqueous solutions should be freshly prepared; appropriate measures required to prevent contamination during storage or dilution; pregnancy (Appendix 7c); lactation.
<b>Adverse Effects</b>	Skin sensitivity, reported dryness.

## Formaldehyde

<b>Indications</b>	<i>Warts particularly planter warts.</i>
<b>Availability</b>	Prepared as 0.75% v/v water miscible gel.
<b>Dose</b>	0.75% gel; apply twice a day.
<b>Contraindications</b>	Hepatic dysfunction; pregnancy.
<b>Precautions</b>	Significant peripheral neuropathy; patients with diabetes at risk of neuropathic ulcers; protect surrounding skin and avoid broken skin; not suitable for application to face; anogenital region; or large areas; increased levels of serum aminotransferase.

**Adverse Effects** Skin irritation; angioedema, myopathy; anaphylaxis, blurred vision; headache.

**Storage** Store protected from light at a temperature of 15 to 25°C.

## Glutaraldehyde\*

**Indications** *Disinfection and sterilization of instruments and surfaces; conditions like warts and hyperhidrosis of palms and soles.*

**Availability** **SOLUTIONS** 1, 2 and 5 Litre. (2% aqueous alkaline (pH 8) solution).

**Dose** **Disinfection of clean instruments** - immerse in undiluted solution for 10 to 20 min; up to 2 h may be required for certain instruments (for example bronchoscopes with possible mycobacterial contamination); rinse with sterile water or alcohol after disinfection.

**Sterilization of clean instruments** - Immerse in undiluted solution for up to 10 h; rinse with sterile water or alcohol after disinfection.

**Contraindications** Damaged skin.

**Precautions** Minimize occupational exposure by adequate skin protection and measures to avoid inhalation of vapour; lung damage; oral and nasal lesions, if swallowed do not induce vomiting.

**Adverse Effects** Nausea (occupational exposure); headache; airway obstruction; asthma; rhinitis; eye irritation and dermatitis and skin discolouration.

**Storage** Store at a temperature not exceeding 15°C.

## Potassium Permanganate\* (Refer Page No. 348)

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# 13. Cardiovascular Drugs

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## 13.1 Antianginal Drugs

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The three main types of angina are:

- *Stable angina* (angina of effort), where atherosclerosis restricts blood flow in the coronary vessels; attacks are usually caused by exertion and relieved by rest
- *Unstable angina* (acute coronary insufficiency), which is considered to be an intermediate stage between stable angina and myocardial infarction
- *Prinzmetal angina* (variant angina), caused by coronary vasospasm, in which attacks occur at rest.

Management depends on the type of angina and may include drug treatment, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty.

### Stable Angina:

Drugs are used both for the relief of acute pain and for prophylaxis to reduce further attacks; they include organic nitrates, beta-adrenoceptor antagonists (beta-blockers) and calcium-channel blockers.

### Nitrates:

Organic nitrates have a vasodilating effect; they are sometimes used alone, especially in elderly patients with infrequent symptoms. Tolerance leading to reduced antianginal effect is often seen in patients taking prolonged-action nitrate formulations. Evidence suggests that patients should have a 'nitrate-free' interval to prevent the development of tolerance. Adverse effects such as flushing, headache and postural hypotension may limit nitrate therapy but tolerance to these effects also soon develops. The short-acting sublingual formulation of glyceryl trinitrate is used both for prevention of angina before exercise or other stress and for rapid treatment of chest pain. A sublingual tablet of isosorbide dinitrate is more stable in storage than glyceryl trinitrate and is useful in patients who require nitrates infrequently; it has a slower onset of action, but effects persist for several h.

### Beta-Blockers:

Beta-adrenoceptor antagonists (beta-blockers), such as atenolol, block beta-adrenergic receptors in the heart and thereby decrease heart rate and myocardial contractility and oxygen

consumption, particularly during exercise. Beta-blockers are first-line therapy for patients with effort-induced chronic stable angina; they improve exercise tolerance, relieve symptoms, reduce the severity and frequency of angina attacks and increase the anginal threshold.

Beta-blockers should be withdrawn gradually to avoid precipitating an anginal attack; they should not be used in patients with underlying coronary vasospasm (Prinzmetal's angina).

Beta-blockers may precipitate asthma and should not be used in patients with asthma or a history of obstructive airways disease. Some, including atenolol, have less effect on  $\beta_2$  (bronchial) receptors and are therefore relatively cardioselective. Although they have less effect on airways resistance they are not free of this effect and should be avoided.

Beta-blockers slow the heart and may induce myocardial depression, rarely, precipitating heart failure. They should not be given to patients who have incipient ventricular failure, second- or third-degree atrioventricular block, or peripheral vascular disease.

Beta-blockers should be used with caution in diabetes since they may mask the symptoms of hypoglycaemia, such as rapid heart rate. Beta-blockers enhance the hypoglycaemic effect of insulin and may precipitate hypoglycaemia.

### Calcium-Channel Blockers:

A calcium-channel blocker, such as verapamil, is used as an alternative to a beta-blocker to treat stable angina. Calcium-channel blockers interfere with the inward movement of calcium ions through the slow channels in heart and vascular smooth muscle cell membranes, leading to relaxation of vascular smooth muscle. Myocardial contractility may be reduced, the formation and propagation of electrical impulses within the heart may be depressed and coronary or systemic vascular tone may be diminished. Calcium-channel blockers are used to improve exercise tolerance in patients with chronic stable angina due to coronary atherosclerosis or with abnormally small coronary arteries and limited vasodilator reserve.

Calcium-channel blockers can also be used in patients with unstable angina with a vasospastic origin, such as Prinzmetal's angina and in patients in whom alterations in cardiac tone may influence the angina threshold.

### Unstable Angina:

Unstable angina requires prompt aggressive treatment to prevent progression to myocardial infarction.

Initial treatment is with acetylsalicylic acid to inhibit platelet aggregation, followed by heparin. Nitrates and beta-blockers are given to relieve ischaemia; if beta-blockers are contrain-

icated, verapamil is an alternative, provided left ventricular function is adequate.

### Prinzmetal's Angina:

Treatment is similar to that for unstable angina, except that a calcium-channel blocker is used instead of a beta-blocker.

### Acetylsalicylic Acid\* (Refer Page No. 4, 239 and 317)

#### Pregnancy Category-D

**Indications** *As an antiplatelet agent for prophylaxis of myocardial infarction, stable angina; stable angina pectoris; stroke prophylaxis.*

### Atenolol\*

#### Pregnancy Category-D

**Schedule H**

**Indications** *Angina and myocardial infarction; arrhythmias; hypertension; migraine prophylaxis.*

**Availability** **TABLETS** 12.5, 25, 50, and 100 mg; **INJECTION** ampoule 5 mg/ml (10 ml).

**Dose** **Oral**

**Adult-** 50 mg once daily, increased if necessary to 50 mg twice daily or 100 mg once daily. Angina: 50 mg daily administered alone or with a diuretic, dose can be increased to 100 mg (over 100 mg has no added advantage). May also be administered in combination with a mlodipine besylate 2.5 or 5 mg.

**Child-** 1 to 1.3 mg/kg body weight once daily or divided every 12 h.

#### **Intravenous injection**

2.5 mg at a rate of 1 mg/min, repeat at 5 min interval to a max. 10 mg.

**Contraindications** Asthma or history of obstructive airways disease (unless no alternative, then with extreme caution and under specialist supervision); uncontrolled heart failure, Prinzmetal angina, marked bradycardia, hypotension, sick sinus syndrome, second- and third-degree atrioventricular block, cardiogenic shock; metabolic acidosis; severe peripheral arterial disease; pheochromocytoma (unless used with alpha-blocker).

**Precautions**

Avoid abrupt withdrawal especially in angina; may precipitate or worsen heart failure; acute myocardial infarction, pregnancy (Appendix 7c), thyrotoxicosis, pheochromocytoma; lactation (Appendix 7b); first-degree atrioventricular block; liver function deteriorates in portal hypertension; reduce dose in renal impairment; diabetes mellitus (small decrease in glucose tolerance, masking of symptoms of hypoglycaemia); history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine (adrenaline)); myasthenia gravis; interactions (Appendix 6a, 6b, 6c).

**Adverse Effects**

Gastrointestinal disturbances (nausea, vomiting, diarrhoea, constipation, abdominal cramp); fatigue; cold hands and feet; exacerbation of intermittent claudication and Raynaud phenomenon; bronchospasm; bradycardia, heart failure, conduction disorders, hypotension; sleep disturbances, including nightmares; depression, confusion; hypoglycaemia or hyperglycaemia; exacerbation of psoriasis; rare reports of rashes and dry eyes (oculomucocutaneous syndrome-reversible on withdrawal).

**Diltiazem****Pregnancy Category-C****Schedule H****Indications**

*Angina pectoris due to coronary artery spasm; chronic stable angina; cardiac arrhythmia.*

**Availability**

**TABLETS/TABLETS (SR)** 30, 60, 90, 120, 180 and 240 mg; **CAPSULE** 60, 90, 120, 180 and 240 mg; **INJECTION** 5 ml (25 mg/5 ml).

**Dose****Oral**

**Adult**-30 mg 2 to 5 times a day before food and at night (bed time), increase gradually to 240 mg in 3 to 4 divided doses daily.

**Child**- Not recommended.

**Cardiac arrhythmia**

**Adult**-Initially 250 µg/kg by i.v. bolus over 2 min.

**Contraindications**

Severe bradycardia; left ventricular failure with pulmonary congestion; second- or third-degree AV block (unless pacemaker fitted); sick sinus syndrome; lactation.

**Precautions** Reduce dose in hepatic and renal impairment; heart failure or significantly impaired left ventricular function; bradycardia (avoid if severe); first degree AV block; or prolonged PR interval; interactions (Appendix 6c); sinoatrial nodal dysfunction; pregnancy (Appendix 7c).

**Adverse Effects** Bradycardia, sino-atrial block, AV block; palpitation; dizziness; hypotension, malaise; asthenia; headache; hot flushes; gastrointestinal disturbances; oedema (notably of ankles); rarely, rashes (including erythema multiforme and exfoliative dermatitis), photosensitivity; hepatitis; gynaecomastia; gum hyperplasia; extrapyramidal symptoms; depression reported; gastrointestinal haemorrhage; sinus arrest.

**Storage** Store protected from light.

**Esmolol\*** (Refer Page No. 296)

**Glyceryl Trinitrate\***

**Pregnancy Category-C**

**Schedule H**

**Indications** *Prophylaxis and treatment of angina, myocardial infarction; post operative hypertension; cardio-pulmonary edema.*

**Availability** **TABLETS** 0.5, 2.6 and 6.4 mg; **CAPSULES** 2.5 and 6.4 mg; **INJECTION** 5 and 10 ml (5 mg/ml); **SUBLINGUAL TAB** 500 µg. **SPRAY** 0.4 mg/puff (200 mdi)

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*Note: Glyceryl trinitrate tablets are unstable. They should therefore be dispensed in glass or stainless steel containers and closed with a foil-lined cap which contains no wadding. No more than 100 tablets should be dispensed at one time and any unused tablets should be discarded 8 weeks after opening the container.*

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**Dose**

**Sublingual**

**Adult-** 0.5 to 1 mg, repeated as required.

**Intravenous infusion**

10 to 200 µg/min.

**Contraindications**

Hypersensitivity to nitrates; hypotension; hypovolaemia; raised intracranial pressure; hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis; marked anaemia; head trauma; cerebral haemorrhage; angle-closure glaucoma.



<b>Precautions</b>	Severe hepatic or renal impairment; hypothyroidism; malnutrition; gastrointestinal hypermotility; malabsorption syndrome; hypothermia; recent history of myocardial infarction; interactions (Appendix 6b, 6c).
<b>Adverse Effects</b>	Throbbing headache; flushing; dizziness, postural hypotension; tachycardia (paradoxical bradycardia also reported); abdominal pain; collapse; neurological deficit.
<b>Storage</b>	Store protected from light and moisture in glass container of not more than 100 tablets at a temperature not exceeding 30°C. The container should be closed by means of screw cap lined with aluminium or tin foil. Cotton, wool wadding or other additional packing that absorbs glyceryl trinitrate should be avoided.

## Isosorbide-5-Mononitrate\*

Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Prophylaxis and treatment of angina, congestive heart failure.</i>
<b>Availability</b>	<b>TABLETS</b> 10, 20, 40, 50 and 60 mg; <b>TABLETS (SR)</b> 50 mg and 60 mg; <b>CAPSULE</b> 30, 40 and 60 mg.
<b>Dose</b>	<b>Oral</b> 20 mg 2 to 3 times a day initially, or 40 mg twice daily (max 120 mg daily individual dose).
<b>Contraindications</b>	Hypersensitivity to nitrates; hypotensive conditions and hypovolaemia; hypertrophic cardiomyopathy; aortic stenosis; cardiac tamponade; constrictive pericarditis; mitral stenosis; marked anaemia; glaucoma; obstructive cardiomyopathy; raised intracranial pressure.
<b>Precautions</b>	Hypothyroidism; malnutrition; hypothermia; head trauma; cerebral haemorrhage; gastrointestinal disease; recent history of myocardial infarction; hypoxaemia or other ventilation and perfusion abnormalities; susceptibility to angle-closure glaucoma; metal-containing transdermal systems should be removed before cardioversion or diathermy; avoid abrupt withdrawal; tolerance; severe hepatic impairment; severe renal impairment; pregnancy (Appendix 7c); lactation; interactions (Appendix 6a).

**Adverse Effects**

Postural hypotension, tachycardia (but paradoxical bradycardia also reported); throbbing headache; dizziness; less commonly nausea; vomiting; heartburn; flushing; temporary hypoxaemia; rash; application site reactions with transdermal patches; very rarely, angle-closure glaucoma; decreased cardiac output; urinary and faecal incontinence.

Specific side-effects following injection (particularly if given too rapidly) include severe hypotension, diaphoresis, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitation, abdominal pain, syncope; prolonged administration has been associated with methaemoglobinaemia.

**Storage**

Store at a temperature not exceeding 30°C.

**Isosorbide Dinitrate\*****Pregnancy Category-C****Schedule H****Indications**

*Prophylaxis and treatment of angina; heart failure.*

**Availability**

**TABLETS** (sublingual) 5 and 10 mg; **CAPSULES** (timed release) 20 and 40 mg.

**Dose****Sublingual**

**Adult-** Angina acute attack: 5 to 10 mg, repeated as required.

Angina prophylaxis: 120 mg daily in divided doses.

Angina prophylaxis: 20 to 120 mg.

**Contraindications**

Hypersensitivity to nitrates; hypotension; hypovolaemia; myocardial infarction; hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis; marked anaemia; head trauma; cerebral haemorrhage; angle-closure glaucoma.

**Precautions**

Severe hepatic or renal impairment; hypothyroidism; malnutrition; hypothermia; recent history of myocardial infarction; interactions (Appendix 6a, 6b, 6c, 6d); pregnancy (Appendix 7c).

Patients taking isosorbide dinitrate for the long-term management of angina may often develop tolerance to the antianginal effect; this can be avoided by giving the second of 2 daily doses of longer-acting oral presentations after an 8-h rather than a 12-h interval, thus ensuring a nitrate-free interval each day.

**Adverse Effects** Throbbing headache; flushing; dizziness, postural hypotension, tachycardia (paradoxical bradycardia also reported); palpitation, decreased cardiac output; confusion; increased intracranial pressure.

**Storage** Store at a temperature not exceeding 30°C.

## Metoprolol\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *Supraventricular arrhythmia, angina pectoris, hypertension, myocardial infarction; migraine prophylaxis; hyperthyroidism, heart failure.*

**Availability** **TABLETS** 10, 25, 50 and 100 mg; **CAPSULE** 12.5, 25, 50 and 100 mg; **INJECTION** 100 mg/2 ml, 250 mg/2 ml, 500 mg/2 ml.

**Dose** **Oral**

Heart failure: Initiating dose 12.5 - 25 mg once a day, Maximum dose: 200 mg once a day; Hypertension: initially 100 mg daily, increase if required to 200 mg in two divided doses (max 400 mg daily). Angina: 50 mg daily, up to 300 mg daily in 2 to 3 divided doses if necessary.

### ***Intravenous injection***

Arrhythmia: up to 5 mg at a rate of 1 to 2 mg per min, repeated after 5 min if necessary (max dose 10 to 15 mg). Arrhythmia developing during anaesthesia: 2 to 4 mg during induction.

**Contraindications** Asthma (important: see Bronchospasm below), uncontrolled heart failure, Prinzmetal's angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third- degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease; pheochromocytoma (apart from specific use with alpha-blockers).

Beta-blockers, including those considered to be cardioselective, should not be given to patients with a history of asthma or bronchospasm. However, in rare situations where there is no alternative cardioselective beta-blocker is given to these patients with extreme caution and under specialist supervision.

**Precautions**

Avoid abrupt withdrawal especially in ischaemic heart disease, first-degree AV block, portal hypertension (risk of deterioration in liver function); diabetes; history of obstructive airways disease (introduce cautiously and monitor lung function); myasthenia gravis; symptoms of hypoglycaemia and thyrotoxicosis may be masked; history of hypersensitivity may increase sensitivity to allergens and result in more serious hypersensitivity response; also may reduce response to adrenaline (epinephrine); reduce dose of oral propranolol in hepatic impairment; renal impairment; lactation; pregnancy (Appendix 7c).

**Adverse Effects**

Gastro-intestinal disturbances; bradycardia, heart failure, hypotension, conduction disorders; peripheral vasoconstriction (including exacerbation of intermittent claudication and Raynaud's phenomenon); bronchospasm; dyspnoea; headache; fatigue; sleep disturbances; paraesthesia; dizziness; vertigo; psychosis; sexual dysfunction; purpura; thrombocytopenia; visual disturbances; exacerbation of psoriasis; alopecia; rarely, rashes and dry eyes (reversible on withdrawal); on infusion venous irritation and thrombophlebitis; agranulocytosis; hyperglycemia; myocardial depression.

**Storage**

Store protected from light.

**Propranolol\*** (Refer Page No. 236)**Pregnancy Category-C****Schedule H****Indications**

*Cardiac arrhythmias; tachycardia; hypertrophic obstructive cardiac myopathy; pheochromocytoma; thrombosis; management of angina; essential and renal hypertension; prophylaxis of migraine.*

**Availability**

**TABLETS** 10, 20, 40, 60 and 80 mg plain; 40, 60 and 80 mg (SR); **CAPSULE** 40, 60 and 80 mg (SR); **INJECTION** 1 ml ampoule (1 mg/ml).

**Dose****Oral**

**Adult-** Hypertension: initially 40 mg twice a day or 80 mg once a day; increased at weekly intervals as required, maintenance 160 to 320 mg in three divided doses. Prophylaxis of variceal bleeding in portal hypertension: 40 mg twice daily, increased to 80 mg twice daily according to heart rate (max. 160g twice daily).

Angina: Initially 40 mg 3 times a day, maintenance 120 to 240 mg daily. Prophylaxis after myocardial infarction: 40 mg 4 times daily for 2 to 3 days, then 80 mg twice daily beginning 5 to 21 days after infarction.

### Contraindications

Asthma (important: see Bronchospasm below); uncontrolled heart failure, Prinzmetal's angina, marked bradycardia, hypotension; sick sinus syndrome, second- or third-degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease, pheochromocytoma (apart from specific use with alpha-blockers); haemorrhage.

Beta-blockers, including those considered to be cardioselective, should not be given to patients with a history of asthma or bronchospasm. However, in rare situations where there is no alternative a cardioselective beta-blocker is given to these patients with extreme caution and under specialist supervision.

### Precautions

Avoid abrupt withdrawal especially in ischaemic heart disease, first-degree AV block, portal hypertension (risk of deterioration in liver function), diabetes; history of obstructive airways disease (introduce cautiously and monitor lung function); myasthenia gravis; symptoms of hypoglycaemia and thyrotoxicosis may be masked; history of hypersensitivity may increase sensitivity to allergens and result in more serious hypersensitivity response; also may reduce response to adrenaline (epinephrine); reduce dose of oral propranolol in hepatic impairment; renal impairment; lactation (Appendix 7b); interactions (Appendix 6a, 6b, 6d); pregnancy (Appendix 7c).

### Adverse Effects

Gastro-intestinal disturbances; bradycardia; heart failure, hypotension, conduction disorders; peripheral vasoconstriction (including exacerbation of intermittent claudication and Raynaud's phenomenon); bronchospasm; dyspnoea; headache; fatigue; sleep disturbances; paraesthesia; dizziness; vertigo; psychosis; sexual dysfunction; purpura; thrombocytopenia; visual disturbances; exacerbation of psoriasis; alopecia; rarely, rashes and dry eyes (reversible on withdrawal); on infusion venous irritation and thrombophlebitis; eosinophilia; hyperglycemia; cardiogenic shock; visual hallucinations.

### Storage

Store protected from light and moisture. Injection: Store protected from light and moisture in a single dose container.

## Verapamil\*

Pregnancy Category-C

Schedule H

**Indications** *Angina, including stable, unstable and Prinzmetal angina; arrhythmias; ischaemic heart disease; migraine.*

**Availability** **TABLETS** 40, 80, 120 and 240 mg (SR);  
**INJECTION** 2 ml (5 mg/2 ml).

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*Note: Sustained-release (prolonged-release) tablets are available. A proposal to include such a product in a national list of essential drugs should be supported by adequate documentation*

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**Dose** **Oral**

**Adult-** 80 to 120 mg 3 times daily (120 mg 3 times daily usually required in Prinzmetal angina).

Supraventricular arrhythmias: 40 to 120 mg 3 times daily.

**Intravenous injection**

**Adult-** Supraventricular arrhythmias: 5 to 10 mg over 2 min (preferably with ECG monitoring).

**Elderly-** Paroxysmal tachyarrhythmias: 5 to 10 mg over 3 min, further 5 mg may be given after 5 to 10 min if required.

**Contraindications** Hypotension, bradycardia, second- and third-degree atrioventricular block, sinoatrial block, sick sinus syndrome; cardiogenic shock; history of heart failure or significantly impaired left ventricular function (even if controlled by therapy); atrial flutter or fibrillation complicating Wolff-Parkinson-White syndrome; porphyria; platelet dysfunction.

**Precautions** First-degree atrioventricular block; kidney impairment; cirrhosis patients; acute phase of myocardial infarction (avoid if bradycardia, hypotension, left ventricular failure); hepatic impairment (Appendix 7a); children (specialist advice only); lactation; pregnancy (Appendix 7c); interactions (Appendix 6b, 6c).

### Adverse Effects

Constipation; less commonly nausea, vomiting, flushing, headache, dizziness, fatigue, ankle oedema; rarely, allergic reactions (erythema, pruritus, urticaria, angioedema, Stevens-Johnson syndrome); myalgia; arthralgia, paraesthesia, increased prolactin concentration; gynaecomastia and gingival hyperplasia on long-term treatment; with high doses, hypotension, heart failure, bradycardia, heart block and asystole (due to negative inotropic effect), impotence; hepatotoxicity; hyperprolactinemia; myoclonic dystonia.

## 13.2 Antiarrhythmic Drugs

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Treatment of arrhythmias requires precise diagnosis of the type of arrhythmia and electrocardiography is essential; underlying causes such as heart failure require appropriate treatment.

Antiarrhythmic drugs must be used cautiously since most drugs that are effective in treating arrhythmias can provoke them in some circumstances; this arrhythmogenic effect is often enhanced by hypokalaemia. When antiarrhythmic drugs are used in combination, their cumulative negative inotropic effects may be significant, particularly if myocardial function is impaired.

### Atrial Fibrillation:

The increased ventricular rate in atrial fibrillation can be controlled with a beta-adrenoceptor antagonist (beta-blocker) or verapamil. Digoxin is often effective for controlling the rate at rest; it is also appropriate if atrial fibrillation is accompanied by congestive heart failure. Intravenous digoxin is occasionally required if the ventricular rate needs rapid control. If adequate control at rest or during exercise cannot be achieved readily verapamil may be introduced with digoxin, but it should be used with caution if ventricular function is impaired. Anticoagulants are indicated especially in valvular or myocardial disease and in the elderly. Warfarin is preferred to acetylsalicylic acid in preventing emboli. If atrial fibrillation began within the previous 48 h and there does not appear to be a danger of thromboembolism, antiarrhythmic drugs, such as procainamide or quinidine, may be used to terminate the fibrillation or to maintain sinus rhythm after cardioversion.

### Atrial Flutter:

Digoxin will sometimes slow the ventricular rate at rest. Reversion to sinus rhythm is best achieved by direct current electrical shock. If the arrhythmia is long-standing, treatment with an anticoagulant should be considered before cardioversion to prevent emboli. Intravenous verapamil reduces ventricular fibrillation during paroxysmal (sudden onset and intermittent) attacks of atrial flutter. An initial intravenous dose may be followed by oral treatment; hypotension may occur with high doses. It should not be used for tachyarrhythmias where the QRS complex is wide unless a supraventricular origin has been established beyond doubt. If the flutter cannot be restored to sinus rhythm, antiarrhythmics such as quinidine can be used.

### Paroxysmal Supraventricular Tachycardia:

In most patients this remits spontaneously or can revert to



sinus rhythm by reflex vagal stimulation. Failing this, intravenous injection of a beta-adrenoceptor antagonist (beta-blocker) or verapamil may be effective. Verapamil and a beta-blocker should never be administered concomitantly because of the risk of hypotension and asystole.

### Ventricular Tachycardia:

Very rapid ventricular fibrillation causes profound circulatory collapse and must be treated immediately with direct current shock. In more stable patients intravenous lidocaine or procainamide may be used. After sinus rhythm is restored, drug therapy to prevent recurrence of ventricular tachycardia should be considered; a beta-adrenoceptor antagonist (beta-blocker) or verapamil may be effective.

*Torsades de pointes* is a special form of ventricular tachycardia associated with prolongation of the QT interval. Initial treatment with intravenous infusion of magnesium sulphate (usual dose 2g over 10-15 min, repeated once if necessary) together with temporary pacing is usually effective; alternatively, isoprenaline infusion may be given with extreme caution until pacing can be instituted. Isoprenaline is an inotropic sympathomimetic; it increases the heart rate and therefore shortens the QT interval, but given alone it may induce arrhythmias.

### Bradycardias:

Sinus bradycardia (less than 50 beats/min) associated with acute myocardial infarction may be treated with atropine. Temporary pacing may be required in unresponsive patients. Drugs are of limited value for increasing the sinus rate long term in the presence of intrinsic sinus node disease and permanent pacing is usually required.

### Cardiac Arrest:

In cardiac arrest, epinephrine (adrenaline) is given by intravenous injection in a dose of 1 mg (10 ml of 1 in 10,000 solution) as part of the procedure for cardiopulmonary resuscitation.

## Adenosine\*

Pregnancy Category-C

Schedule H

#### Indications

*Coronary vasodilator; paroxysmal supraventricular tachycardia; cardiac imaging for coronary artery disease; angina pectoris.*

#### Availability

**TABLETS** 40, 80 and 120 mg (DT); **INJECTION** 2 ml ampoule (3 mg/ml).

<b>Dose</b>	<p><b>Oral</b></p> <p>40 to 80 mg, 3 to 4 times daily (Max. 480 mg/day).</p> <p><b>Rapid intravenous injection</b> (into central or large peripheral vein)</p> <p>3 mg every 2 seconds with regular cardiac monitoring, if necessary, followed by 6 mg every 1 to 2 min. Increment should not be given if higher level AV block occurs at any particular dose.</p>
<b>Contraindications</b>	Second- or third-degree AV block and sick sinus syndrome (unless pacemaker fitted), acute myocardial infarction, cardiovascular shock; asthma.
<b>Precautions</b>	Atrial fibrillation or flutter with accessory pathway (conduction down anomalous pathway may increase); heart transplant; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Transient facial flush, chest pain, dyspnoea, bronchospasm, choking sensation, nausea, light-headedness; severe bradycardia reported (requiring temporary pacing); ECG may show transient rhythm disturbances; edema; constipation.

## Amiodarone\*

Pregnancy Category-D

**Schedule H**

<b>Indications</b>	<i>Severe rhythmic disorder where other therapies cannot be used including tachyarrhythmia associated with Wolff-Parkinson-White syndrome, atrial flutter and fibrillation; all types of paroxysmal tachycardia.</i>
<b>Availability</b>	<b>TABLETS</b> 100 and 200 mg; <b>INJECTION</b> 3 ml ampoule (50 mg/ml).
<b>Dose</b>	<p><b>Oral</b></p> <p>200 mg three times a day for one week, reduced to 200 mg twice daily for further one week. Maintenance 200 mg daily or reduced to minimum required to control arrhythmia.</p> <p><b>Intravenous infusion</b> (with central venous catheter).</p> <p>Initially 5 mg/kg body weight over 20 to 120 min with ECG monitoring, subsequent infusion given if necessary according to response (up to max 1.2g in 24 h).</p>

### Contraindications

Sinus bradycardia, sino-atrial heart block; unless pacemaker fitted avoid in severe conduction disturbances or sinus node disease; thyroid dysfunction; iodine sensitivity; goitre; avoid intravenous use in severe respiratory failure, circulatory collapse, severe arterial hypotension, avoid bolus injection in congestive heart failure or cardiomyopathy; lactation; pregnancy (Appendix 7c).

### Precautions

Liver-function and thyroid-function tests required before treatment and then every 6 months; hypokalaemia (measure serum-potassium concentration before treatment); chest x-ray required before treatment; heart failure; elderly; severe bradycardia and conduction disturbances in excessive dosage; intravenous use may cause moderate and transient fall in blood pressure (circulatory collapse precipitated by rapid administration or overdosage) or severe hepatocellular toxicity (monitor transaminases closely); ECG monitoring and resuscitation facilities must be available during intravenous use; porphyria; interactions (Appendix 6d).

### Adverse Effects

Nausea, vomiting, taste disturbances, raised serum transaminases (may require dose reduction or withdrawal if accompanied by acute liver disorders), jaundice; bradycardia; pulmonary toxicity (including pneumonitis and fibrosis); tremor, sleep disorders; hypothyroidism, hyperthyroidism; reversible corneal microdeposits (sometimes with night glare); phototoxicity, persistent slate-grey skin discolouration; less commonly onset or worsening of arrhythmia, conduction disturbances, peripheral neuropathy and myopathy (usually reversible on withdrawal); very rarely, chronic liver disease including cirrhosis, sinus arrest, bronchospasm (in patients with severe respiratory failure), ataxia, benign intracranial hypertension, headache, vertigo, epididymo-orchitis, impotence, haemolytic or aplastic anaemia, thrombocytopenia, rash (including exfoliative dermatitis), hypersensitivity including vasculitis, alopecia, impaired vision due to optic neuritis or optic neuropathy (including blindness), anaphylaxis on rapid injection, also hypotension, respiratory distress syndrome, sweating and hot flushes.

### Storage

Store protected from light at temperature not exceeding 30°C.

### Atenolol\* (Refer Page No. 281)

## Digoxin\*

Pregnancy Category-C

**Schedule H**

**Indications** *Supraventricular arrhythmias, particularly atrial fibrillation; heart failure.*

**Availability** **TABLET** 0.25 mg; **INJECTION** 2 ml (0.5 mg/2 ml); **ELIXIR** 0.05 mg/ml (paediatric use); **SYRUP** 1.5 mg/30 ml.

**Dose** **Oral**

**Adult-** Atrial fibrillation and heart failure: 1 to 1.5 mg in divided doses over 24 h for rapid digitalization or 250 µg 1 to 2 times daily if digitalization less urgent; maintenance 62.5 to 500 µg daily (higher dose may be divided), according to renal function and heart rate response; usual range 125 to 250 µg daily.

**Elderly-** Lower dose more appropriate.

### **Intravenous infusion**

Emergency control of atrial fibrillation, over at least 2 h: 0.75 to 1 mg.

Emergency loading dose for heart failure, over at least 2 h: 0.75 to 1 mg.

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*Note: Infusion dose may need to be reduced if digoxin or other cardiac glycoside given in previous 2 weeks.*

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**Contraindications** Hypertrophic obstructive cardiomyopathy (unless also atrial fibrillation and heart failure); ventricular tachycardia; hypokalaemia; digitalis toxicity; arrhythmias; Wolff-Parkinson-White syndrome or other accessory pathway, particularly if accompanied by atrial fibrillation; intermittent complete heart block; second-degree atrioventricular block.

**Precautions** Recent myocardial infarction; sick sinus syndrome; severe pulmonary disease; thyroid disease; congestive cardiac myopathy; hypercalcaemia; aortic valve disease, heart block, cardiac dysrhythmias; elderly (reduce dose); renal impairment (Appendix 7d); avoid hypokalaemia; avoid rapid intravenous administration (nausea and risk of arrhythmias); lactation; interactions (Appendix 6c, 6d); pregnancy (Appendix 7c).

**Adverse Effects** Usually associated with excessive dosage and include anorexia, nausea, vomiting, diarrhoea, abdominal pain; visual disturbances, headache, fatigue, drowsiness, confusion, delirium, hallucinations, depression; arrhythmias, heart block; rarely, rash, intestinal ischaemia; gynaecomastia on long-term use; thrombocytopenia reported; sinus bradycardia; apathy; psychosis; malaise.

**Storage** Tablet: Store protected from light. Injection: Store protected from light in a single dose container. Solution: store protected from light at a temperature not exceeding 30°C.

**Diltiazem (Refer Page No. 282)**

**Esmolol\***

**Pregnancy Category-C**

**Indications** *Supraventricular arrhythmias (short term treatment); atrial fibrillation; flutter; tachycardia and hypertension in pre-operative period.*

**Availability** **INJECTION** 10 ml (100 and 250 mg).

**Dose** ***Intravenous infusion***

Usually with a range of 50 to 200 µg/kg body weight/min under strict professional supervision of cardiologist.

**Contraindications** Asthma (important: see Bronchospasm below), uncontrolled heart failure, Prinzmetal's angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third- degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease; pheochromocytoma (apart from specific use with alpha-blockers).

The Cardiovascular Society of Medicine has advised that beta-blockers, including those considered to be cardioselective, should not be given to patients with a history of asthma or bronchospasm. However, in rare situations where there is no alternative a cardioselective beta-blocker is given to these patients with extreme caution and under specialist supervision.

**Precautions**

Avoid abrupt withdrawal especially in ischaemic heart disease, first-degree AV block, portal hypertension (risk of deterioration in liver function); diabetes; history of obstructive airways disease (introduce cautiously and monitor lung function); myasthenia gravis; symptoms of hypoglycaemia and thyrotoxicosis may be masked; history of hypersensitivity-may increase sensitivity to allergens and result in more serious hypersensitivity response, also may reduce response to adrenaline (epinephrine); reduce dose of oral propranolol in hepatic impairment; renal impairment; lactation; pregnancy (Appendix 7c); interactions (Appendix 6c).

**Adverse Effects**

Gastro-intestinal disturbances; bradycardia, heart failure, hypotension, conduction disorders, peripheral vasoconstriction (including exacerbation of intermittent claudication and Raynaud's phenomenon); bronchospasm, dyspnoea; headache, fatigue, sleep disturbances, paraesthesia, dizziness, vertigo, psychoses; sexual dysfunction; purpura, thrombocytopenia; visual disturbances; exacerbation of psoriasis, alopecia; rarely, rashes and dry eyes (reversible on withdrawal); on infusion venous irritation and thrombophlebitis; asthenia.

**Isoprenaline****Pregnancy Category-C****Schedule H****Indications**

*Severe bradycardia, unresponsive to atropine; short-term emergency treatment of heart block; ventricular arrhythmias secondary to atrio-ventricular nodal block.*

**Availability**

**TABLETS** 20 mg; **INJECTION** 1 ml ampoule (2 mg/ml).

**Dose*****Slow intravenous injection***

2 mg/ml injection under strict professional supervision of cardiologist.

**Contraindications**

Angina pectoris; tachycardia.

**Precautions**

Ischaemic heart disease, diabetes mellitus or hyperthyroidism; pregnancy (Appendix 7c).

**Adverse Effects**

Arrhythmias, hypotension, sweating, tremor, headache, palpitations, tachycardia, nervousness, excitability, insomnia.

**Storage** Store protected from light at temperature not exceeding 30°C.

## Lidocaine (Lignocaine)\* (Refer Page No. 417)

### Pregnancy Category-B

**Indications** *Ventricular arrhythmias (especially after myocardial infarction); local anaesthesia.*

**Availability** **INJECTION** vial 30 ml (1, 2%w/v), 50 ml (21.3 mg/ml); 2%/50 ml; ampoule 5%/2 ml. **JELLY** 2% w/v **OINTMENT** 5% w/v

**Dose** **Adult-** Ventricular arrhythmias: loading dose of 50 to 100 mg (or 1 to 1.5 mg/kg) at a rate of 25 to 50 mg/min by intravenous injection, followed immediately by intravenous infusion of 1 to 4 mg/min, with ECG monitoring of all patients (reduce infusion dose if required for longer than 24 h).

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*Note: Following intravenous injection, lidocaine has a short duration of action (of 15 to 20 min). If it cannot be given by intravenous infusion immediately, the initial intravenous injection of 50 to 100 mg can be repeated if necessary once or twice at intervals of not less than 10 min.*

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**Contraindications** Sino-atrial disorder; any grade of atrioventricular block or any other type of conduction disturbances, severe myocardial depression, acute porphyria or hypovolaemia, bradycardia, cardiac decompensation.

**Precautions** Lower dosage in congestive heart failure, bradycardia, ECG monitoring must during therapy, pediatrics; hypotension; renal impairment; porphyria; debilitated patients; hepatic impairment (Appendix 7a); marked hypoxia; severe respiratory depression; following cardiac surgery and in elderly; lactation; interactions (Appendix 6c); pregnancy (Appendix 7c).

**Adverse Effects** Dizziness; paraesthesia; drowsiness, confusion; apnoea, respiratory depression; coma; seizures and convulsions; hypotension, arrhythmias, heart block; cardiovascular collapse and bradycardia (may lead to cardiac arrest); nystagmus often an early sign of lidocaine overdosage; blurred vision, disorientation.

**Storage** Store protected from light.

## Mexiletine

### Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Ventricular arrhythmias especially after myocardial infarction.</i>
<b>Availability</b>	<b>CAPSULES</b> 50, 100 and 150 mg; <b>INJECTION</b> 250 mg/10 ml.
<b>Dose</b>	<b>Oral</b>  Initial dose; 400 to 600 mg, followed by 200 to 250 mg after 2 h, 3 to 4 times a day.  <b>Intravenous infusion</b>  Slow i.v. infusion of 200 to 250 mg at the rate of 25 mg/min followed by i.v. infusion of 1 mg/min over 1 h.
<b>Contraindications</b>	Sinus node dysfunction; hepatic dysfunction; cardiogenic shock, myocardial infarction.
<b>Precautions</b>	Hepatic; cardiac or renal failure; hypotension, bradycardia; interactions (Appendix 6d); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Dizziness; confusion; ataxia; bradycardia, hypotension, nausea; vomiting; constipation; palpitations; jaundice; hepatitis; dysarthria.
<b>Storage</b>	Store protected from light. Store injection in single dose containers.

## Procainamide \*

Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Severe ventricular arrhythmias, especially those resistant to lidocaine or those appearing after myocardial infarction; atrial tachycardia, atrial fibrillation; maintenance of sinus rhythm after cardioversion of atrial fibrillation.</i>
<b>Availability</b>	<b>TABLET</b> 250 mg; <b>INJECTION</b> 10 ml ampoule/vial (100 mg/ml).
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> Ventricular arrhythmias: up to 50 mg/kg daily in divided doses every 3 to 6 h, preferably controlled by monitoring plasma-procainamide concentration (therapeutic concentration usually within range of 3 to 10 µg/ml).  Atrial arrhythmias: higher doses may be required.  <b>Slow intravenous injection</b>



Ventricular arrhythmias: 100 mg at a rate not exceeding 50 mg/min, with ECG monitoring; may be repeated at 5 min intervals until arrhythmias controlled (max 1g).

### **Intravenous infusion**

0.2 to 1g i.v.; 0.5 to 1g i.m. until oral therapy is possible.

Ventricular arrhythmias: 500 to 600 mg over 25 to 30 min with ECG monitoring, reduced to maintenance dose of 2 to 6 mg/min; if further treatment by mouth required, allow interval of 3 to 4 h after infusion.

**Contraindications** Asymptomatic ventricular premature contractions; *torsades de pointes*; systemic lupus erythematosus; heart block, heart failure, hypotension; lactation; children; myasthenia gravis.

**Precautions** Elderly, renal and hepatic impairment (Appendix 7a), asthma, myasthenia gravis; blood dyscrasias; heart failure, cardiomyopathy; cytopenia; digitalis intoxication; electrolyte imbalance; monitor blood count and ECG; pregnancy (Appendix 7c); lactation (Appendix 7b); use only under specialist supervision; interactions (Appendix 6d).

**Adverse Effects** Nausea, vomiting, diarrhoea, anorexia, rashes, pruritus, urticaria, flushing, fever, myocardial depression, heart failure, angioedema, depression, dizziness, psychosis; blood disorders include leukopenia, haemolytic anaemia and agranulocytosis after prolonged treatment; lupus erythematosus-like syndrome; high plasma procainamide concentration may impair cardiac conduction; hypotension, heart block; hallucinations.

**Storage** Store protected from light and moisture.

## **Quinidine**

**Pregnancy Category-C**

**Schedule H**

**Indications** *Suppression of supraventricular arrhythmias and ventricular arrhythmias; maintenance of sinus rhythm after cardioversion of atrial fibrillation.*

**Availability** **TABELTS** 100 and 200 mg.

**Dose** **Oral**

Initial test dose of 200 mg to detect hypersensitivity to quinidine.

**Adult-** Arrhythmias: 200 to 400 mg 3 to 4 times daily; increased if necessary in supraventricular tachycardia to 600 mg every 2 to 4 h (max. 3 to 4g daily); frequent ECG monitoring required.

**Contraindications** Complete heart block; myasthenia gravis; history of embolism.

**Precautions** Partial heart block, extreme care in uncompensated heart failure, myocarditis, severe myocardial damage; myasthenia gravis; acute infections or fever (symptoms may mask hypersensitivity reaction to quinidine); lactation (Appendix 7b); pregnancy (Appendix 7c).

**Adverse Effects** Hypersensitivity reactions, nausea, vomiting, diarrhoea, rashes, anaphylaxis, purpura, pruritus, urticaria, fever, thrombocytopenia, agranulocytosis after prolonged treatment, psychosis, angioedema, hepatotoxicity, respiratory difficulties; cardiac effects include myocardial depression, heart failure, ventricular arrhythmias and hypotension; cinchonism including tinnitus, impaired hearing, vertigo, headache, visual disturbances, abdominal pain and confusion; lupus erythematosus-like syndrome.

**Storage** Store protected from light.

**Verapamil\*** (Refer Page No. 289)

## 13.3 Antihypertensive Drugs

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### Management of Hypertension:

Treatment of hypertension should be integrated into an overall programme to manage factors that increase the risk of cardiovascular events (such as stroke and myocardial infarction). Treatment is often life-long. Hypertension was formerly classified as mild, moderate or severe, but a grading system is now preferred. Grade 1 hypertension is defined as 140-159 mmHg systolic blood pressure and 90-99 mmHg diastolic blood pressure, Grade 2 hypertension 160-179 mmHg systolic and 100-109 mmHg diastolic and Grade 3 hypertension more than 180 mmHg systolic and more than 110 mmHg diastolic. The goal of treatment is to obtain the max. tolerated reduction in blood pressure.

Lifestyle changes should be introduced for all patients; they include weight reduction, reduction in alcohol intake, reduction of dietary Sodium, stopping tobacco smoking and reduction in saturated fat intake. The patient should eat a healthy nutritious diet including adequate fruit and vegetables and should exercise regularly. These measures alone may be sufficient in mild hypertension, but patients with moderate to severe hypertension will also require specific antihypertensive therapy.

### Drug Treatment of Hypertension:

Three classes of drug are used for first-line treatment of hypertension: thiazide diuretics, beta-adrenoceptor antagonists (beta-blockers) and angiotensin-converting enzyme (ACE) inhibitors. Calcium-channel blockers are considered first-line in specific populations only e.g. Africans or the elderly. Other classes of drugs may be used in certain situations.

Thiazide diuretics, such as hydrochlorothiazide, have been used as first-line antihypertensive therapy and are particularly indicated in the elderly. They have few adverse effects in low doses, but in large doses they may cause a variety of unwanted metabolic effects (principally potassium depletion), reduced glucose tolerance, ventricular ectopic beats and impotence; they should be avoided in gout. These effects can be reduced by keeping the dose as low as possible; higher doses do not produce an increased reduction in blood pressure. Thiazides are inexpensive and, when used in combination, can enhance the effectiveness of many other classes of antihypertensive drugs.

Beta-adrenoceptor antagonists (beta-blockers) such as atenolol are effective in all grades of hypertension and are particu-

larly useful in angina and following myocardial infarction; they should be avoided in asthma, chronic obstructive pulmonary disease and heart block.

Angiotensin-converting enzyme inhibitors (ACE inhibitors) such as enalapril are effective and well tolerated by most patients. They can be used in heart failure, left ventricular dysfunction and diabetic nephropathy, but should be avoided in renovascular disease and in pregnancy. The most common adverse effect is a dry persistent cough.

Dihydropyridine calcium-channel blockers such as nifedipine are useful for isolated systolic hypertension, in populations unresponsive to other antihypertensives (e.g. Africans) and in the elderly when thiazides cannot be used. Short-acting formulations of nifedipine should be avoided as they may evoke reflex tachycardia and cause large variations in blood pressure.

Drugs acting on the central nervous system are also effective antihypertensive drugs. In particular, methyldopa is effective in the treatment of hypertension in pregnancy.

A single antihypertensive drug is often not adequate and other antihypertensive drugs are usually added in a stepwise manner until blood pressure is controlled.

### **Hypertensive Emergencies**

In situations where immediate reduction of blood pressure is essential and treatment by mouth is not possible, intravenous infusion of Sodium nitroprusside is effective. Over-rapid reduction in blood pressure is hazardous and can lead to reduced organ perfusion and cerebral infarction.

### **Hypertension in Pregnancy**

This is defined as a sustained diastolic blood pressure of 90 mmHg or more. Drug therapy for chronic hypertension during pregnancy remains controversial. If diastolic blood pressure is greater than 95 mmHg, methyldopa is the safest drug. Beta-blockers should be used with caution in early pregnancy, since they may retard fetal growth; they are effective and safe in the third trimester. ACE inhibitors are contraindicated in pregnancy since they may damage fetal and neonatal blood pressure control and renal function. Women who are taking these drugs and become pregnant should have their antihypertensive therapy changed immediately.

*Pre-eclampsia* and *eclampsia*: If pre-eclampsia or severe hypertension occurs beyond the 36th week of pregnancy, delivery is the treatment of choice. For acute severe hypertension in pre-eclampsia or eclampsia, intravenous hydralazine can be used. Magnesium sulphate is the treatment of choice to prevent eclamptic convulsions in eclampsia and severe pre-eclampsia.

## Amlodipine\*

Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Angina, hypertension, coronary artery disease.</i>
<b>Availability</b>	<b>TABLETS</b> 1.25, 2.5, 5, 7.5, 10 and 20 mg.
<b>Dose</b>	<b>Oral</b> <b>Angina:</b> <b>Adult-</b> Initially 5 mg once daily, increased if necessary; max. 10 mg once daily. <b>Hypertension:</b> <b>Adult-</b> Initially 5 mg once daily, increased if necessary; max. 10 mg once daily. <b>Elderly-</b> Initial dose- 2.5 mg once daily.
<b>Contraindications</b>	Significant aortic stenosis, sinoatrial node disease, hypersensitivity to dihydropyridines, cardiogenic shock, unstable angina; interactions (Appendix 6d).
<b>Precautions</b>	Hypotension, myocardial infarction, impaired renal function sick-sinus syndrome, severe ventricular dysfunction, hypertrophic cardiomyopathy, severe aortic stenosis, elderly, children, pregnancy (Appendix 7c); lactation; hepatic impairment (Appendix 7a).
<b>Adverse effects</b>	Arrhythmias, postural hypotension; dizziness, ankle edema, hypoesthesia, flatulence, dizziness, blurred vision, facial flushing, dyspnoea, asthenia, muscle cramps, conduction system delay, abdominal pain, headache; sleep disturbances, fatigue.
<b>Storage</b>	Store protected from moisture.

**Atenolol\*** (Refer Page No. 281)

**Clonidine** (Refer Page No. 546)

Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Hypertension of all grades except pheochromocytoma, glaucoma and migraine.</i>
<b>Availability</b>	<b>TABLETS</b> 100 and 150 µg.
<b>Dose</b>	<b>Oral</b> <b>Adult-</b> 75 to 225 µg/day in two divided doses, increase gradually every two weeks. <b>Child-</b> Not recommended.

<b>Contraindications</b>	Hypersensitivity; sinoarterial node disease, atrioventricular node disease.
<b>Precautions</b>	Depressive illness; concurrent antihypertensive therapy, cerebrovascular disease; porphyria; interactions (Appendix 6a, 6c); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Dry mouth; sedation; dizziness; nausea; nocturnal restlessness; occasionally rashes; cardiac arrhythmias; systemic lupus erythmatosus; anxiety; constipation; abdominal pain; hallucination; impotence and depression.
<b>Storage</b>	Store injection in a single dose container.

## Enalapril\*

Pregnancy Category-D

**Schedule H**

<b>Indications</b>	<i>Heart failure (with a diuretic); prevention of symptomatic heart failure and prevention of coronary ischaemic events in patients with left ventricular dysfunction; hypertension; renal hypertension.</i>
<b>Availability</b>	<b>TABLETS</b> 2.5, 5 and 10 mg; <b>INJECTION</b> 1 ml ampoule (1.25 mg/ml).
<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> Hypertension: initially 5 mg once daily; if used in addition to diuretic.</p> <p>Heart failure, asymptomatic left ventricular dysfunction: initially 2.5 mg daily under close medical supervision; usual maintenance dose 20 mg daily in 1 to 2 divided doses.</p> <p><b>Elderly-</b> Renal impairment: initially 2.5 mg daily. Usual maintenance dose 10 to 20 mg once daily; In severe hypertension may be increased to max. 40 mg once daily.</p>
<b>Contraindications</b>	Hypersensitivity to ACE inhibitors (including angioedema), renovascular disease, aortic stenosis; pregnancy (Appendix 7c).

**Precautions**

Use with diuretics; hypotension with first doses; especially in patients on diuretics; on a low-sodium diet; on dialysis; if dehydrated; or with heart failure; peripheral vascular disease or generalized atherosclerosis (risk of clinically silent renovascular disease); use with great care in severe or symptomatic aortic stenosis; monitor renal function before and during treatment; renal impairment (reduce dose; see also Appendix 7d); liver impairment (Appendix 7a); possibly increased risk of agranulocytosis in collagen vascular disease; history of idiopathic or hereditary angioedema (use with care or avoid); lactation; interactions (Appendix 6a, 6b, 6c); hypervolemia; patients with immunosuppression; hyperkalemia.

Risk of very rapid fall in blood pressure in volume-depleted patients; treatment should therefore be initiated with very low doses. High-dose diuretic therapy (furosemide dose greater than 80 mg) should be discontinued, or dose significantly reduced, at least 24 h before starting enalapril (may not be possible in heart failure-risk of pulmonary oedema). If high-dose diuretic cannot be stopped, medical supervision advised for at least 2 h after administration or until blood pressure stable.

Avoid enalapril during dialysis with high-flux polyacrylonitrile membranes and during low-density lipoprotein apheresis with dextran sulphate; also withhold before desensitization with wasp or bee venom.

**Adverse Effects**

Dizziness; headache; less commonly nausea; diarrhoea; hypotension (severe in rare cases); dry cough; fatigue; asthenia; muscle cramps; rash and renal impairment; rarely, vomiting; dyspepsia; abdominal pain; constipation; glossitis; stomatitis; ileus; anorexia; pancreatitis; liver damage; chest pain; palpitations; arrhythmias; angioedema; bronchospasm; rhinorrhoea; sore throat; pulmonary infiltrates; paraesthesia; vertigo; nervousness; depression; confusion; drowsiness or insomnia; pruritus; urticaria; alopecia; sweating; flushing; impotence; Stevens-Johnson syndrome; toxic epidermal necrolysis; exfoliative dermatitis; pemphigus; taste disturbance; tinnitus; blurred vision; electrolyte disturbances and hypersensitivity-like reactions (including fever; myalgia; arthralgia; eosinophilia and photosensitivity) reported; azotemia; acute renal failure; taste disturbances.

**Storage**

Store protected from light.

## Hydralazine

### Pregnancy Category-C

<b>Indications</b>	<i>In combination therapy in moderate to severe hypertension, hypertensive crisis; hypertension associated with pregnancy (including pre-eclampsia or eclampsia); heart failure.</i>
<b>Availability</b>	<b>TABLET</b> 25 mg; <b>INJECTION</b> 20 mg/ml.
<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> Hypertension: 25 mg twice daily, increased if necessary to max. 50 mg twice daily.</p> <p><b>Slow intravenous injection</b></p> <p><b>Adult-</b> Hypertensive crisis (including during pregnancy): 5 to 10 mg diluted with 10 ml Sodium Chloride 0.9%; if necessary may be repeated after 20 to 30 min.</p> <p><b>Intravenous infusion</b></p> <p><b>Adult-</b> Hypertensive crisis (including during pregnancy): initially 200 to 300 µg/min; maintenance usually 50 to 150 µg/min.</p>
<b>Contraindications</b>	Idiopathic systemic lupus erythematosus; severe tachycardia, high output heart failure, myocardial insufficiency due to mechanical obstruction; cor pulmonale; dissecting aortic aneurysm; porphyria; angina; mitral valvular heart disease; rheumatic disease.
<b>Precautions</b>	Hepatic impairment (Appendix 7a); renal impairment; coronary artery disease (may provoke angina, avoid after myocardial infarction until stabilized); cerebrovascular disease; check acetylase status before increasing dose above 100 mg daily; test for antinuclear factor and for proteinuria every 6 months; coronary artery disease; alcohol intake; lactation (Appendix 7b); occasionally over-rapid blood pressure reduction even with low parenteral doses; interactions (Appendix 6b, 6c); pregnancy (Appendix 7c).



<b>Adverse Effects</b>	Tachycardia, palpitations, postural hypotension; fluid retention; gastrointestinal disturbances including anorexia; nausea; vomiting; diarrhoea; rarely, constipation; dizziness; flushing; headache; abnormal liver function; jaundice; systemic lupus erythematosus-like syndrome; particularly in women and slow acetylators; nasal congestion; agitation; anxiety; polyneuritis; peripheral neuritis; rash; fever; paraesthesia; arthralgia; myalgia; increased lacrimation; dyspnoea; raised plasma creatinine; proteinuria; haematuria; blood disorders including haemolytic anaemia; leukopenia; thrombocytopenia; peripheral neuritis.
<b>Storage</b>	Store protected from light at temperature not exceeding 30°C.

## Hydrochlorothiazide\* (Refer Page No. 397)

### Pregnancy Category-B

<b>Indications</b>	<i>Alone in mild hypertension and in combination with other drugs in moderate to severe hypertension; heart failure; oedema; diabetes insipidus.</i>
<b>Availability</b>	<b>TABLETS</b> 12.5, 25 and 50 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> Hypertension: 12.5 to 25 mg daily. Heart failure: initially 25 mg daily on waking up, increasing to 50 mg daily if necessary.  <b>Elderly-</b> Initially 12.5 mg daily for hypertension as well as heart failure.
<b>Contraindications</b>	Severe renal or severe hepatic impairment; hyponatraemia; hypercalcaemia; refractory hypokalaemia; symptomatic hyperuricaemia; Addison's disease; gout; diabetes mellitus; persisting hypercalcaemia; anuria; sulphonamide allergy.
<b>Precautions</b>	Renal and hepatic impairment (Appendix 7a); lactation (Appendix 7b); elderly (reduce dose); may cause hypokalaemia; may aggravate diabetes mellitus and gout; may exacerbate systemic lupus erythematosus; porphyria; severe heart failure; edema; hyperlipidemia; interactions (Appendix 6a, 6b, 6c); pregnancy (Appendix 7c).

**Adverse Effects**

Fluid and electrolyte imbalance leading to dry mouth; thirst; gastrointestinal disturbances (including nausea; vomiting); weakness; lethargy; drowsiness; seizures; headache; muscle pains or cramps; hypotension (including postural hypotension); arrhythmias; hypokalaemia; oliguria; hypomagnesaemia; hyponatraemia; hypochloraemic alkalosis; hypercalcaemia; hyperglycaemia; hyperuricaemia; gout; rash; photosensitivity; altered plasma lipid concentration; rarely, impotence (reversible); blood disorders (including neutropenia; thrombocytopenia); pancreatitis; intrahepatic cholestasis; acute renal failure; hypersensitivity reactions (pneumonitis; pulmonary oedema; severe skin reactions); increased heart rate and ventricular ectopic activity.

**Losartan\*****Pregnancy Category-D****Schedule H****Indications**

*Congestive heart failure, hypertension (myocardial infarction along with stroke including reduction of stroke risk in hypertension) with left ventricular hypertrophy, diabetic nephropathy in type II diabetes.*

**Availability**

**TABLETS** 25, 50 and 100 mg.

**Dose****Hypertension and diabetic nephropathy:**

**Adult-** 50 mg once daily, increased to 100 mg daily as single dose or in two divided doses, if needed.

**Child-** ≥ 6 years, initially 700 µg/kg, increased to a max. of 50 mg once daily, if needed.

**Elderly** over 75 years initially 25 mg daily. Maintenance dose 25 to 100 mg orally in 1 to 2 divided doses.

**Contraindications**

Hyperaldosteronism, hypersensitivity, pregnancy (Appendix 7c), lactation, Not recommended in children <6yrs of age or GFR <30 ml/min/1.73msq.

**Precautions**

Pre-existing heart, liver or kidney diseases, diabetes, lactation, volume depleted patients, renal artery stenosis, monitor serum potassium concentration, elderly, interactions (Appendix 6a).

**Adverse effects**

Abdominal pain, edema, palpitation, back pain, dizziness, sinusitis, upper respiratory tract infection, rash, gastrointestinal disturbances, transient elevation of liver enzymes, impaired renal function, taste disturbances, hyperkalaemia, arthralgia, thrombocytopenia, vasculitis.

**Storage** Store protected from light and moisture.

## Methyldopa\*

**Pregnancy Category-B**

**Schedule H**

**Indications** *Hypertension in pregnancy.*

**Availability** **TABLET** 250 mg.

**Dose** **Oral**

**Adult-** Hypertension in pregnancy: initially 250 mg 2 to 3 times daily; if necessary, gradually increased at intervals of 2 or more days (max 3g daily).

**Contraindications** Depression; active liver disease; hypersensitivity; therapy with MAO inhibitors; pheochromocytoma; porphyria.

**Precautions** History of hepatic impairment (Appendix 7a); renal impairment; blood counts and liver-function tests advised; history of depression; positive direct Coomb test in up to 20% of patients (affects blood cross-matching); interference with laboratory tests; lactation; pregnancy (Appendix 7c); interactions (Appendix 6b, 6c).

May impair ability to perform skilled tasks; for example operating machinery; driving.

**Adverse Effects** Tend to be transient and reversible including sedation; dizziness; lightheadedness; postural hypotension; weakness; fatigue; headache; fluid retention and oedema; sexual dysfunction; impaired concentration and memory; depression; mild psychosis; disturbed sleep and nightmares; drug fever; influenza-like syndrome; nausea; vomiting; constipation; diarrhoea; dry mouth; stomatitis; sialadenitis; liver function impairment; hepatitis; jaundice; rarely, fatal hepatic necrosis; bone-marrow depression; haemolytic anaemia; leukopenia; thrombocytopenia; eosinophilia; parkinsonism; rash (including toxic epidermal necrolysis); nasal congestion; black or sore tongue; bradycardia; exacerbation of angina; myalgia; arthralgia; paraesthesia; Bell palsy; pancreatitis; hypersensitivity reactions including lupus erythematosus-like syndrome; myocarditis; pericarditis; gynaecomastia; hyperprolactinaemia; amenorrhoea; urine darkens on standing.

## Nifedipine\*

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Hypertension; angina prophylaxis; heart failure; Raynaud's phenomenon.</i>
<b>Availability</b>	<b>TABLETS</b> 5, 10, 20 and 30 mg plain and SR; <b>CAPSULES</b> 5, 10, 20 and 30 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> Hypertension (as sustained-release tablets): usual range 20 to 100 mg daily in 1 to 2 divided doses.
<b>Contraindications</b>	Cardiogenic shock, advanced aortic stenosis, within 1 month of myocardial infarction, unstable or acute attacks of angina, porphyria; hypersensitivity.
<b>Precautions</b>	Stop if ischaemic pain occurs or existing pain worsens shortly after starting treatment; poor cardiac reserve; heart failure or significantly impaired left ventricular function; monitor drug response in cirrhosis patients; blood pressure monitoring; calcium channel blockers; reduce dose in hepatic impairment; diabetes mellitus; may inhibit labour; lactation (Appendix 7b); pregnancy (Appendix 7c); interactions (Appendix 6b, 6c).
<b>Adverse Effects</b>	Headache; flushing; dizziness; lethargy; tachycardia; palpitations; gravitational oedema (only partly responsive to diuretics); rash (erythema multiforme reported); pruritus; urticaria; nausea; constipation or diarrhoea; increased frequency of micturition; eye pain; visual disturbances; gum hyperplasia; paraesthesia; myalgia; tremor; impotence; gynaecomastia; depression; telangiectasis; cholestasis; jaundice; exacerbated angina; cardiovascular collapse; ankle swelling; gastrointestinal upset; reversible gingival hyperplasia.
<b>Storage</b>	Store protected from light and moisture.

## Propranolol\* (Refer Page No. 236 and 287)

## Ramipril

Pregnancy Category-D

Schedule H

<b>Indications</b>	<i>Reduction in risk of myocardial infarction, stroke and death from cardiovascular causes; hypertension; heart failure post myocardial infarction.</i>
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<b>Availability</b>	<b>TABLETS AND CAPSULES</b> 1.25, 2.5, 5 and 10 mg.
<b>Dose</b>	<b>Reduction in risk of myocardial infarction, stroke, and death from cardiovascular causes:</b> Initial dose of 2.5 mg, once a day for 1 week, 5 mg, once a day for the next 3 weeks, and then increased as tolerated, to a maintenance dose of 10 mg once a day. <b>Hypertension:</b> The recommended initial dose for patients not receiving a diuretic is 2.5 mg once a day. The usual maintenance dosage range is 2.5 to 20 mg per day administered as a single dose or in two equally divided doses. <b>Heart failure post myocardial infarction:</b> Initial dose is 2.5 mg twice daily, after one week at the starting dose titrate to ( if tolerated) toward a target dose of 5 mg twice daily, with dosage increases being about 3 weeks apart.
<b>Contraindications</b>	Hypersensitivity to ramipril or any other ACE inhibitor, bilateral renal artery stenosis or a single kidney with unilateral renal artery stenosis.
<b>Precautions</b>	Impaired renal function, impaired liver function, diabetes mellitus (increased risk of hyperkalemia), patients undergoing surgery, history of angioedema; symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy; monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function; administration during pregnancy (Appendix 7c) can cause fetal/neonatal morbidity and death; when pregnancy is detected ACE inhibitors should be discontinued as soon as possible, interactions (Appendix 6a and 6c).
<b>Adverse Effects</b>	Hypotension, cough, asthenia, dizziness, headache, angioneurotic edema, hypersensitivity reactions, erythema multiforme, toxic epidermal necrolysis, Stevens Johnson syndrome, hepatic necrosis, pancreatitis, pancytopenia, thrombocytopenia.
<b>Storage</b>	Store protected from moisture at a temperature not exceeding 30°C.

## Sodium Nitroprusside\*

Pregnancy Category-C

Schedule H

**Indications** *Hypertensive crisis (when treatment by mouth not possible), congestive heart failure.*

**Availability** **INJECTION** ampoule/vial 5 ml (50 mg/ml).

**Dose** ***Intravenous infusion***

**Adult-** Hypertensive crisis: initially 0.3 µg/kg/min; usual maintenance dose 0.5 to 6 µg/kg/min; max. dose 8 µg/kg/min; stop infusion if response is unsatisfactory after 10 min at max. dose; lower doses in patients already being treated with antihypertensives.

**Contraindications** Compensatory hypertension; severe vitamin B<sub>12</sub> deficiency; Leber optic atrophy; arterial venous shunting; patients with acute CHF associated with reduced peripheral vascular resistance.

**Precautions** Impaired pulmonary function; hypothyroidism; renal impairment; ischaemic heart disease; impaired cerebral circulation; hyponatraemia; raised intracranial pressure; elderly; hypothermia; monitor blood pressure and blood-cyanide concentration; also blood-thiocyanate concentration if given for more than 3 days; avoid sudden withdrawal (reduce infusion over 15-30 min to avoid rebound effects); pregnancy (Appendix 7c); lactation; interactions (Appendix 6b); hepatic impairment (Appendix 7a).

**Adverse Effects** Severe hypotension; effects associated with over-rapid reduction in blood pressure include headache; dizziness; retching; abdominal pain; perspiration; palpitations; apprehension; retrosternal discomfort; rarely, reduced platelet count; acute transient phlebitis; muscle twitching; hypothyroidism; increased anaerobic metabolism.

Adverse effects associated with excessive concentration of cyanide metabolite include tachycardia; sweating; hyperventilation; arrhythmias; marked metabolic acidosis (discontinue infusion and give antidote).

**Storage** Store protected from light.

## Telmisartan

Pregnancy Category-C

Schedule H

**Indications** *Hypertension.*

<b>Availability</b>	<b>TABLETS</b> 20, 40 and 80 mg.
<b>Dose</b>	<b>Adult-</b> 40-80 mg once daily.
<b>Contraindications</b>	Renal artery stenosis, pregnancy (Appendix 7c), hyperkalemia.
<b>Precautions</b>	Interactions (Appendix 6c).
<b>Adverse Effects</b>	Cough, angioedema.

## Terazosin

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>Mild to moderate hypertension, benign prostatic hyperplasia.</i>
<b>Availability</b>	<b>TABLETS</b> 1, 2 and 5 mg.
<b>Dose</b>	<p><b>Hypertension:</b>  <b>Adult-</b>Initially 1 mg at bedtime (compliance with bedtime dose is important, see precautions), gradually increase at 7 day intervals. Maintenance dose- 2-10 mg once daily.</p> <p>Max. 20 mg daily in 1 or 2 divided doses.</p> <p><b>Benign prostatic hyperplasia:</b>  <b>Adult-</b> 1 mg at bedtime, gradually increase at 7-day interval. Maintenance dose- 5-10 mg once daily.</p> <p>Max. 20 mg daily.</p>
<b>Contraindications</b>	Hypersensitivity.
<b>Precautions</b>	First dose syncope (should be taken just before retiring to bed), kidney disease, liver disease, elderly, pregnancy (Appendix 7c), lactation, interactions (Appendix 6a).
<b>Adverse effects</b>	Dizziness, drowsiness, fatigue, dyspnoea, blurred vision, postural hypotension, asthenia, nasal congestion, miosis, chest pain, urinary frequency, weight gain, thrombocytopenia, decreased libido, back pain and pain in extremities.
<b>Storage</b>	Store protected from light and moisture.

## 13.4 Antithrombotic Drugs

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Anticoagulants prevent thrombus formation or the extension of an existing thrombus. Antiplatelet drugs also help to inhibit thrombus formation by decreasing platelet aggregation.

Thrombolytics (fibrinolytics) such as streptokinase are used to break up thrombi; they are used to treat acute myocardial infarction, extensive deep vein thrombosis, major pulmonary embolism and acute arterial occlusion.

### Myocardial Infarction:

Management of myocardial infarction includes two phases:

- initial management of the acute attack
- long-term management, including prevention of further attacks

#### 1. Initial Management:

Oxygen should be given to all patients, except those with severe chronic obstructive pulmonary disease.

Pain and anxiety are relieved by slow intravenous injection of an opioid analgesic such as morphine. Metoclopramide may also be given by intramuscular injection to prevent and treat nausea and vomiting caused by morphine.

Acetylsalicylic acid 150-300 mg by mouth (preferably chewed or dispersed in water) is given immediately for its antiplatelet effect.

Thrombolytic drugs such as streptokinase help to restore perfusion and thus relieve myocardial ischaemia; they should ideally be given within 1 h of infarction (use after 12 h requires specialist advice).

Nitrates may also be given to relieve ischaemic pain.

Early administration of beta-blockers such as atenolol have been shown to reduce both early mortality and the recurrence rate of myocardial infarction; initial intravenous administration is followed by long-term oral treatment (unless the patient has contraindications).

ACE inhibitors have also been shown to be beneficial in initial management (unless patient has contraindications) when given within 24 h and if possible continued for 5-6 weeks.

If arrhythmias occur, they should be treated aggressively, but the likelihood decreases rapidly over the first 24 h after infarction. Ventricular fibrillation should be treated immediately with a defibrillator; if this is ineffective alone, the antiarrhythmic drug lidocaine should be given.

All patients should be closely monitored for hyperglycaemia;



those with diabetes mellitus or raised blood-glucose concentration should receive insulin.

## 2. Long-term Management

Acetylsalicylic acid should be given to all patients in a dose of 75-150 mg daily by mouth, unless it is contraindicated. The prolonged antiplatelet effect has been shown to reduce the rate of reinfarction.

Treatment with beta-blockers should be continued for at least 1 year and possibly for up to 3 years.

ACE inhibitors such as enalapril should also be used since they reduce mortality, particularly in patients with left ventricular dysfunction.

Nitrates may be required for patients with angina.

The use of statins may also be considered in patients with high risk of recurrence.

### Stroke:

Stroke (cerebrovascular accident) may be ischaemic or haemorrhagic; precise diagnosis is essential, as management for the two types of stroke is quite different.

Primary prevention of both types of stroke includes reduction of high blood pressure, stopping smoking, weight reduction and cholesterol reduction. Atrial fibrillation, acute myocardial infarction and valvular disease may produce embolism and ischaemic stroke. Prophylaxis in patients at risk of ischaemic stroke includes oral anticoagulants such as warfarin and antiplatelet drugs such as acetylsalicylic acid. Treatment of acute ischaemic stroke includes use of acetylsalicylic acid, anticoagulants such as heparin and of thrombolytics, such as streptokinase. Streptokinase must be used with extreme caution due to risk of bleeding. Long-term therapy with acetylsalicylic acid reduces the risk of having another stroke.

Antiplatelet and thrombolytic drugs are not used in the management of haemorrhagic stroke, as they may exacerbate bleeding. The main treatment is to normalize blood pressure.

Acetylsalicylic acid is normally given for at least one year after coronary artery bypass surgery. It is also given to patients with prosthetic heart valves who have had cerebral embolism despite warfarin treatment.

## Abciximab

### Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Patients undergoing percutaneous coronary interventions.</i>
<b>Availability</b>	<b>INJECTION</b> 5 ml vial (2 mg/ml).
<b>Dose</b>	0.25 mg/kg bolus followed by infusion of 0.125 µg/kg per min (maximum 10 µg/min) for 12 to 24 h.
<b>Contraindications</b>	Surgery within 10 days, including organ biopsy, puncture of noncompressible vessels, serious trauma, cardiopulmonary resuscitation, active bleeding, serious gastrointestinal bleeding within 3 months, previous cerebrovascular accident or active intracranial process, thrombocytopenia, severe uncontrolled hypertension, aortic dissection, acute pericarditis.
<b>Precautions</b>	Monitor platelet count for thrombocytopenia; interactions (Appendix 6c); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Bleeding, thrombocytopenia.
<b>Storage</b>	Store between 2-8°C, do not freeze.

## Acetylsalicylic Acid\* (Refer Page No. 4, 239 and 281)

### Pregnancy Category-D

<b>Indications</b>	<i>Prophylaxis of cerebrovascular disease or myocardial infarction; pyrexia, pain, inflammation; arterial thromboembolism prophylaxis.</i>
<b>Dose</b>	<b>Oral</b>  <b>Adult</b> - Prophylaxis of cerebrovascular disease or myocardial infarction: 75 to 100 mg daily.
<b>Contraindications</b>	Hypersensitivity (including asthma; angioedema; urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; children and adolescents under 16 years (Reye's syndrome); active peptic ulceration; haemophilia and other bleeding disorders; hypoprothrombinemia.

**Precautions** Asthma; uncontrolled hypertension; history of blood coagulation defects; lactation (Appendix 7b); interactions (Appendix 6a, 6c, 6d), pregnancy (Appendix 7c), hepatic impairment and renal impairment (Appendix 7a and 7d).

**Adverse Effects** Bronchospasm; gastrointestinal haemorrhage (rarely, major); also other haemorrhage (for example subconjunctival); urticaria; hepatomegaly.

## Alteplase

**Pregnancy Category-C**

**Schedule H**

**Indications** *Acute myocardial infarction, acute massive pulmonary embolism, acute ischaemic stroke.*

**Availability** **INJECTION** 20 and 50 mg/vial.

**Dose** **Intravenous**

### **Acute myocardial infarction**

**Adult:** The recommended total dose is 100 mg. Administer as soon as possible after the onset of symptoms.

**Accelerated infusion (1.5 h):** Max 100 mg; as a 15 mg intravenous bolus, followed by 50 mg infused over the next 30 minutes, and then 35 mg infused over the next 60 minutes. Patients <67 kg: total dose should be  $\leq 1.5$  mg/kg; 15 mg as i.v bolus, then 0.75 mg/kg (up to a max of 50 mg) to be infused over 30 minutes, and then 0.50 mg/kg over the next 60 minutes not to exceed 35 mg.

**3-Hour Infusion:** Max 100 mg; 60 mg in the first hour (of which 6 to 10 mg is administered as a bolus) then 20 mg/h for 2 h. For patients < 65 kg, 0.75 mg/kg in 1st hour (including 0.045-0.075 mg/kg bolus in first 1-2 minutes), then 0.25 mg/kg/h x 2 hours.

### **Acute massive pulmonary embolism**

**Adult:** 100 mg (not >1.5 mg/kg for patients weighing < 65 kg).

First 10 mg as bolus followed by infusion of the remainder dose over 2 hours.

Heparin therapy to be instituted or reinstated near the end of or immediately following the alteplase infusion when the partial thromboplastin time returns to twice normal or less.

### **Acute ischemic stroke**

**Adult:** Use recommended within first 3 h of onset of the symptoms. Infuse 0.9 mg/kg (up to a max. of 90 mg) over 60 minutes with 10% of the dose as bolus over the first minute.

<b>Contraindications</b>	Uncontrolled hypertension with possible cerebrovascular haemorrhage, recent surgery or trauma, susceptibility to internal bleeding, uncontrolled hypertension, esophageal varices, heavy vaginal bleeding, bleeding diathesis, active peptic ulceration.
<b>Precautions</b>	Monitor for bleeding and BP in acute stroke. Caution in recent surgery or invasive procedures, diabetic hemorrhagic retinopathy, severe hepatic and renal impairment, pregnancy (Appendix 7c), lactation, children, elderly, interactions (Appendix 6c).
<b>Adverse Effects</b>	Hemorrhage including intracranial, gastrointestinal or genitourinary bleeding, transient hypotension, reperfusion dysrhythmias, cerebral edema, seizures, allergic-type reactions, nausea, vomiting.
<b>Storage</b>	Store protected from heat, light and moisture at room temperature (<30°C) or under refrigeration. Use reconstituted solution within 8 hours.

## Clopidogrel\*

**Pregnancy Category-B**

**Schedule H**

<b>Indications</b>	<i>Prophylaxis in thromboembolic disorders including myocardial infarction, peripheral arterial disease and stroke, acute coronary syndrome.</i>
<b>Availability</b>	<b>TABLETS</b> 75 and 150 mg.
<b>Dose</b>	<b>Adult-</b> 75 mg once daily.  <b>Non-ST segment elevation myocardial infarction:</b> loading dose 300 mg followed by 75 mg once daily.
<b>Contraindications</b>	Hypersensitivity, active pathological bleeding such as peptic ulcer or intracranial hemorrhage, coagulation disorders, lactation.
<b>Precautions</b>	Patient with increased risk of bleeding from trauma, surgery or other pathological conditions, ulcers, renal impairment, hepatic impairment, history of bleeding or haemostatic disorder, pregnancy (Appendix 7c); interactions (Appendix 6c).

**Adverse Effects** Bleeding, neutropenia, thrombocytopenia, other bone marrow toxicity, diarrhoea, epigastric pain, rashes, paraesthesia, vertigo.

## Heparin\* (Refer Page No. 331)

### Streptokinase\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *Life-threatening deep-vein thrombosis, pulmonary embolism, acute arterial thromboembolism; thrombosed arteriovenous shunts; acute myocardial infarction.*

**Availability** **INJECTION** (Powder for solution for injection) 7,50,000 and 15,00,000 units vial.

**Dose** ***Intravenous infusion.***

**Adult-** Thrombosis: 2,50,000 units over 30 min, followed by 1,00,000 units every h for 12 to 72 h according to condition with monitoring of clotting parameters.

Myocardial infarction: 15,00,000 units over 60 min.

**Contraindications** Recent haemorrhage; surgery (including dental); parturition; trauma; heavy vaginal bleeding; haemorrhagic stroke; history of cerebrovascular disease (especially recent or if residual disability); coma; severe hypertension; coagulation defects; bleeding diatheses; aortic dissection; risk of gastrointestinal bleeding such as recent history of peptic ulcer; oesophageal varices; ulcerative colitis; acute pancreatitis; severe liver disease; acute pulmonary disease with cavitation; previous allergic reactions; pregnancy (Appendix 7c).

**Precautions** Risk of bleeding from any invasive procedure; including injection; external chest compression; abdominal aneurysm or where thrombolysis may give rise to embolic complications such as enlarged left atrium with atrial fibrillation (risk of dissolution of clot and subsequent embolization); diabetic retinopathy (small risk of retinal haemorrhage); recent or concurrent anticoagulant treatment; platelet count; fibrinogen level; thrombin and prothrombin time.

**Adverse Effects**

Nausea and vomiting; bleeding; usually limited to site of injection but internal bleeding including intracranial haemorrhage may occur (if serious bleeding occurs; discontinue infusion-coagulation factors may be required); hypotension; arrhythmias (particularly in myocardial infarction); allergic reactions including rash; flushing; uveitis; anaphylaxis; fever; chills; back or abdominal pain; Guillain-Barré syndrome reported rarely.

**Storage**

Store in a sealed container protected from light in refrigerator (2 to 8°C). The container should be sterile and sealed so as to exclude micro-organisms. Under these conditions the contents may be expected to retain potency for 2 years.

**Urokinase\*****Pregnancy Category-C****Schedule H****Indications**

*Acute myocardial infarction; pulmonary embolism; deep vein thrombosis; peripheral vascular thrombosis; peripheral arterial thromboembolism; arterial thrombosis.*

**Availability**

**INJECTION** 20,000, 50,000, 2,50,000, 5,00,000, 7,50,000 and 10,00,000 IU/vial.

**Dose*****Intravenous infusion***

Deep vein thrombosis: 4,400 units/kg body weight in 15 ml Sodium Chloride (0.9%w/v) over 10 min followed by 4,400 units/kg body weight for 12 to 24 h.

Pulmonary embolism: 4,400 units/kg body weight in 15 ml Sodium Chloride (0.9%w/v) over 10 min followed by 4,400 units/kg body weight for 12 to 24 h, alternatively 15,000 units/kg body weight directly into the pulmonary artery initially, subsequent doses adjusted according to response, max. 3 doses in 24 h.

**Contraindications**

In recent haemorrhage; trauma; or surgery (including dental extraction); coagulation defects; bleeding diatheses; aortic dissection; coma; history of cerebrovascular disease especially recent events or with any residual disability; recent symptoms of possible peptic ulceration; heavy vaginal bleeding; severe hypertension; active pulmonary disease with cavitation; acute pancreatitis; pericarditis; bacterial endocarditis; severe liver disease and oesophageal varices.

### Precautions

Should be used with caution if there is a risk of bleeding including that from venepuncture or invasive procedures. They should also be used with caution in external chest compression; pregnancy (Appendix 7c); elderly; hypertension; abdominal aneurysm or other conditions in which thrombolysis might give rise to embolic complications such as enlarged left atrium with atrial fibrillation (risk of dissolution of clot and subsequent embolisation); diabetic retinopathy (very small risk of retinal bleeding) and recent or concurrent use of drugs that increase the risk of bleeding; hematocrit platelet count; thrombin and prothrombin time.

### Adverse Effects

Nausea; vomiting and bleeding. When used in myocardial infarction, reperfusion arrhythmias may occur. Hypotension can also occur and can usually be controlled by elevating the patient's legs or by reducing the rate of infusion or stopping it temporarily. Back pain; fever and convulsions have been reported. Bleeding is usually limited to the site of injection; but intracerebral haemorrhage or bleeding from other sites can occur. Serious bleeding calls for discontinuation of the thrombolytic and may require administration of coagulation factors and antifibrinolytic drugs (aprotinin or tranexamic acid). Rarely, further embolism may occur (either due to clots that break away from the original thrombus or to cholesterol crystal emboli). It causes allergic reactions (including rash; flushing and uveitis) and anaphylaxis has also been reported.

### Storage

Store in a sealed container protected from light in refrigerator (2 to 8°C). The container should be sterile, tamper evident and sealed so as to exclude micro-organisms.

## 13.5 Blood Products and Plasma Substitutes

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### 13.5.1 Plasma Substitutes

Dextran 70 and polygeline are macromolecular substances which are metabolized slowly; they may be used to expand and maintain blood volume in shock arising from conditions such as burns or septicaemia. They are rarely needed when shock is due to Sodium and water depletion as, in these circumstances, the shock responds to water and electrolyte repletion.

Plasma substitutes should not be used to maintain plasma volume in conditions such as burns or peritonitis where there is loss of plasma protein, water and electrolytes over periods of several days. In these situations, plasma or plasma protein fractions containing large amounts of albumin should be given.

Plasma substitutes may be used as an immediate short-term measure to treat massive haemorrhage until blood is available, but large volumes of some plasma substitutes can increase the risk of bleeding by depleting coagulation factors. Dextran may interfere with blood group cross-matching or biochemical measurements and these should be carried out before the infusion is started.

### Albumin\*

#### Pregnancy Category-C

**Indications** *Burns, hypoproteinaemia, shock, hypovolemia, acute liver failure, dialysis.*

**Availability** **SOLUTION** 5%, 10%, 20%.

**Dose** ***Intravenous infusion***

For hypovolemia: **Adult-** 25g,

**Child-** 1g/kg.

Max.- 2g of 20%/kg body weight.

For hypoproteinaemia: **Adult-** 2g/kg daily.

Usual rates of infusion: up to 5 ml/min (5%) or 1 to 2 ml/min (20%).

**Contraindications** Congestive heart failure, severe anaemia, history of allergic reactions to human albumin; pregnancy (Appendix 7c).



<b>Precautions</b>	If dehydration is present additional fluid must follow the administration of albumin. Administration of albumin should be supplemented or replaced by packed red blood cells, <b>history of cardiac or circulatory disease, increased capillary permeability.</b>
<b>Adverse effects</b>	Allergic (or) pyrogenic reactions, tachycardia, rash, anaphylactic shock, increased salivation.
<b>Storage</b>	Store protected from light at a temperature between 2-25°C. Human albumin stored at 2-8°C may be expected to continue to meet the requirements of the monograph for five years from the date on which it was heated at 60°C for 10 hours. Human albumin stored at a temperature not exceeding 25°C may be expected to meet the requirements of the monograph for three years from the date on which it was heated at 60°C for 10 hours.

## Dextran 40\*

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>Plasma volume expansion during hypovolemic shock when blood not available, Prophylaxis of thromboembolic disorders to improve local circulation in peripheral vascular occlusion.</i>
<b>Availability</b>	<b>INFUSION</b> 10% dextran 40 + 5% dextrose or 0.9% sodium chloride.
<b>Dose</b>	<p><b>Intravenous</b></p> <p><b>To improve local circulation in peripheral vascular occlusion: Adult-</b> 500-1000 ml (10-20 ml/kg) in first 24 hours; thereafter 500 ml every 1-2 days for up to 2 weeks.</p> <p><b>Thromboembolism prophylaxis: Adult-</b> 500-1000 ml (10-20 ml/kg) on day of surgery, then 500 ml daily for 2-3 days, then 500 ml every second or third day, for up to 2 weeks.</p> <p><b>Shock: Adult-</b> initially 500-1000 ml (10-20 ml/kg) infused as rapidly as needed; may follow with 500 ml (10 ml/kg) during the same 24 hour period; thereafter 500 ml (10 ml/kg) may be repeated daily for up to 5 days.</p>
<b>Contraindications</b>	Hypersensitivity, cardiac decompensation, oliguria or anuria, hemostatic defects, thrombocytopenia, blood coagulation disorder, pulmonary oedema, neonates.

<b>Precautions</b>	Renal and hepatic impairment, pregnancy (Appendix 7c), lactation, diabetes, cardiac patients, elderly, monitor urine output, monitor for signs of circulatory overload, interactions (Appendix 6c).
<b>Adverse Effects</b>	Nausea, vomiting, local injection site reaction, hypersensitivity and anaphylactoid reactions, increased serum SGOT and SGPT concentrations, osmotic nephrosis.
<b>Storage</b>	Store protected from light at a temperature not exceeding 30°C.

## Hydroxy Ethyl Starch\*

### Pregnancy Category-C

<b>Indications</b>	<i>Therapy for hypovolaemia, shock in surgery, trauma and infection to improve haemodynamics, macrocirculation, microcirculation and oxygen supply; improve organ function in blood loss.</i>
<b>Availability</b>	<b>INFUSION</b> 300 and 500 ml.
<b>Dose</b>	<b>Intravenous infusion</b> 500 to 1000 ml (daily max. 1500 ml).
<b>Contraindications</b>	Renal failure; haemorrhage; coagulation disorders; anuria; oligouria.
<b>Precautions</b>	Should be used with caution in patients with cardiac disease; liver disease; or renal impairment; urine output should be monitored. Care should be taken to avoid haematocrit concentration from falling below 25-30% and the patient should be monitored for hypersensitivity reactions; bleeding disorder; sufficient fluid should be administered to avoid dehydration; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Hypersensitivity reactions may occur including; rarely,; severe anaphylactoid reactions; transient increase in bleeding time may occur; headache; tachycardia; itching; fall in blood pressure.

### 13.5.2 Plasma Fraction for Specific Use

Factor VIII is essential for blood clotting and the maintenance of effective haemostasis; von Willebrand factor is a mediator in platelet aggregation and also acts as a carrier for factor VIII. Blood coagulation factors VII, IX and X are essential for the conversion of factor II (prothrombin) to thrombin. Deficiency in any of these factors results in haemophilia. Bleeding episodes in haemophilia

require prompt treatment with replacement therapy. Factor VIII, used for the treatment of haemophilia A, is a sterile freeze-dried powder containing the blood coagulation factor VIII fraction prepared from pooled human venous plasma. Standard factor VIII preparations also contain von Willebrand factor and may be used to treat von Willebrand disease. Highly purified preparations, including recombinant factor VIII, are available; they are indicated for the treatment of haemophilia A but do not contain sufficient von Willebrand factor for use in the management of von Willebrand disease.

Factor IX Complex is a sterile freeze-dried concentrate of blood coagulation factors II, VII, IX and X derived from fresh venous plasma. Factor IX complex which is used for the treatment of haemophilia B may also be used for the treatment of bleeding due to deficiencies of factor II, VII and X. High purity preparations of factor IX which do not contain clinically effective amounts of factor II, VII and X are available. A recombinant factor IX preparation is also available.

## Factor IX Complex (Coagulation Factors II, VII, IX, X) Concentrate\*

### Pregnancy Category-C

<b>Indications</b>	<i>Replacement therapy for factor IX deficiency in haemophilia; bleeding due to deficiencies of factors II, VII or X.</i>
<b>Availability</b>	<b>INFUSION</b> (Powder for solution for infusion), factor II, VII, IX and X 500 to1500 units.
<b>Dose</b>	<b>Slow intravenous infusion</b> <b>Adult and child-</b> Haemophilia B: according to patient's needs. Treatment of bleeding due to deficiencies in factor II, VII or X as well as IX: according to patient's need.
<b>Contraindications</b>	Disseminated intravascular coagulation; hypersensitivity to any component of the product.
<b>Precautions</b>	Risk of thrombosis (probably less risk with highly purified preparations); pregnancy (Appendix 7c); preexisting disease; check heart rate; interactions (Appendix 6c).
<b>Adverse Effects</b>	Allergic reactions including chills; fever; hepatitis; pulmonary embolism; disseminated intravascular coagulation.
<b>Storage</b>	Store protected from light.

## Factor VIII Concentrate\*

### Pregnancy Category-C

<b>Indications</b>	<i>Control of haemorrhage in haemophilia A.</i>
<b>Availability</b>	<b>INFUSION</b> (Powder for solution for infusion), factor VIII 250 to 1500 units.
<b>Dose</b>	<b>Slow intravenous infusion</b>  <b>Adult and child-</b> Haemophilia A; according to patient's needs.
<b>Contraindications</b>	Hypersensitivity to any component of the product.
<b>Precautions</b>	Intravascular haemolysis after large or frequently repeated doses in patients with blood groups A; B; or AB (less likely with high potency; highly purified concentrates); pregnancy (Appendix 7c); check heart rate.
<b>Adverse Effects</b>	Allergic reactions including chills; fever; hepatitis; anaphylaxis; fulminating hepatitis.
<b>Storage</b>	Store protected from light.

## Tranexamic Acid

### Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Prevention of hemorrhage due to dental procedures in hemophiliacs, cyclic heavy menstrual bleeding, hereditary angioedema, cone biopsy, epistaxis, traumatic hyphema.</i>
<b>Availability</b>	<b>TABLETS-</b> 250 mg, 500 mg and 1g. <b>INJECTION-</b> 100 mg/ml, 500 mg/5 ml.
<b>Dose</b>	<b>Dental extraction in Hemophiliacs:</b> Immediately before tooth extraction, 10 mg/kg intravenously. Following tooth extraction, intravenous therapy, at a dose of 10 mg/kg body weight three to four times daily, may be used for 2 to 8 days. <b>Menorrhagia:</b> 1300 mg orally 3 times daily up to 5 days during menstruation. <b>Cone biopsy:</b> 1000-1500 mg 2-3 times daily for 12 days postoperatively. <b>Epistaxis:</b> 1000 mg 3 times daily for 7 days. <b>Hyphema:</b> 1000-1500 mg 2-3 times daily for 7 days. <b>Hereditary angioedema:</b> 1000-1500 mg 2-3 times daily.
<b>Contraindications</b>	Hypersensitivity, acquired defective colour vision, subarachnoid hemorrhage, active intravascular clotting, pregnancy (Appendix 7c), interactions (Appendix 6c).

**Precautions**

Renal impairment, disseminated intravascular coagulation, thromboembolic history, coadministration with hormonal contraceptives may increase risk of thrombosis, stroke, or myocardial infarction; women using hormonal contraception should take tranexamic acid only if there is a strong medical need, and if the benefit of treatment outweighs risks. Ligneous conjunctivitis has been reported. Retinal venous and arterial occlusion has been reported in patients using tranexamic acid. Patients should be instructed to report visual and ocular symptoms promptly.

**Adverse Effects**

Nausea, vomiting, diarrhoea, disturbances in colour vision (discontinue), thromboembolic events, allergic skin reactions; giddiness and hypotension on rapid intravenous injection, headache, backache, musculoskeletal pain.

**Storage**

Store protected from light and moisture at a temperature not exceeding 30°C.

## 13.6 Drugs Affecting Coagulation

---

Anticoagulants are used to prevent thrombus formation or extension of an existing thrombus in the slower-moving venous side of the circulation, where the thrombus consists of a fibrin web enmeshed with platelets and red cells. They are therefore used widely in the prevention and treatment of deep-vein thrombosis in the legs, prophylaxis of embolization in rheumatic heart disease and atrial fibrillation and to prevent thrombi forming on prosthetic heart valves.

Heparin is a parenteral anticoagulant that initiates anticoagulation rapidly but has a short duration of action. The low molecular weight heparins have a longer duration of action.

For the treatment of deep venous thrombosis and pulmonary embolism heparin is given as an intravenous loading dose followed by continuous intravenous infusion (using an infusion pump) or by intermittent subcutaneous injection. An oral anticoagulant is started at the same time as heparin. The heparin needs to be continued for at least 5 days, until the oral anticoagulant has taken effect and the INR (international normalized ratio) has been in the therapeutic range for 2 consecutive days. Laboratory monitoring is essential, on a daily basis. Heparin is also used in regimens for the management of myocardial infarction, the management of unstable angina, acute peripheral arterial occlusion and in dialysis.

In patients undergoing general surgery, low-dose heparin by subcutaneous injection is used to prevent postoperative deep-vein thrombosis and pulmonary embolism in high risk patients (those with obesity, malignant disease, history of deep-vein thrombosis or pulmonary embolism, patients over 40 years, those with an established thrombophilic disorder or those undergoing major or complicated surgery). It is also of value in high-risk medical patients, for example obesity, heart failure, when confined to bed.

If haemorrhage occurs it is usually sufficient to withdraw heparin, but if rapid reversal of the effects of heparin is required, protamine sulphate is a specific antidote.

Oral anticoagulants take at least 48-72 h for the anticoagulant effect to develop fully; if an immediate effect is needed, heparin must be given concomitantly. Warfarin is indicated in deep-vein thrombosis, pulmonary embolism, for patients with atrial fibrillation who are at risk of embolization and for those with mechanical prosthetic heart valves (to prevent emboli developing on the valves); oral anticoagulants should not be used in cerebral thrombosis or peripheral arterial occlusion as first-line therapy. The main adverse effect of oral anticoagulants is

haemorrhage. Prothrombin time (usually reported as INR, international normalized ratio) should be checked on a daily basis initially then at longer intervals depending on response.

If severe haemorrhage occurs, stop warfarin and give phytonadione (vitamin K) by Slow intravenous injection

### **Anticoagulants in Pregnancy:**

Oral anticoagulants are teratogenic and should not be given in the first trimester of pregnancy. Women at risk of pregnancy should be warned of this danger since stopping warfarin before the sixth week of gestation may largely avoid the risk of fetal abnormality. Oral anticoagulants cross the placenta with the risk of placental or fetal haemorrhage, especially during the last few weeks of pregnancy and at delivery. Therefore, if at all possible, oral anticoagulants should be avoided in pregnancy, especially in the first and third trimester. Difficult decisions may have to be made, particularly in women with prosthetic heart valves or with a history of recurrent venous thrombosis or pulmonary embolism.

### **Haemophilia:**

Desmopressin by injection may aid haemostasis and be useful in mild forms of haemophilia. For minor procedures including dental surgery, it may circumvent the need for factor VIII.

## Heparin\*

Pregnancy Category-C

Schedule H

### Indications

*Treatment and prophylaxis of deep-vein thrombosis and pulmonary embolism; atrial fibrillation with embolism; treatment and prophylaxis of peripheral arterial embolism; prophylaxis of deep vein thrombosis in major surgery; lipemia clearing.*

### Availability

**INJECTION** vials 1000, 5000 and 25,000 IU/ml.

### Dose

#### ***Intravenous injection***

**Adult**-Treatment of deep-vein thrombosis and pulmonary embolism: loading dose of 5000 units (10,000 units in severe pulmonary embolism) followed by continuous intravenous infusion of 15 to 25 units/kg/h.  
**Child**- 50 to 100U/kg every 4 to 6 h.

#### ***Subcutaneous injection***

15,000 units every 12 h; laboratory monitoring is essential, preferably on a daily basis and dose adjusted accordingly.

Prophylaxis in general surgery: 5,000 units 2 h before surgery, then every 8 to 12 h for 7 days or until patient is ambulant (monitoring not needed); during pregnancy (with monitoring) 5,000-10,000 units every 12 h.

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*Note: Not intended to cover prosthetic heart valve management in pregnancy, which requires specialist management.*

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**Child**- 250 units/kg every 12 h.

Intravenous injection and continuous intravenous infusion.

**Child**- By intravenous injection: lower loading dose, then by continuous intravenous infusion; 15 to 25 units/kg/h.



<b>Contraindications</b>	Hypersensitivity to heparin; haemophilia and other haemorrhagic disorders; thrombocytopenia; peptic ulcer; recent cerebral haemorrhage; severe hypertension; severe liver or renal disease; after major trauma or recent surgery (especially to eye or nervous system); threatened abortion; piles; bacterial endocarditis; large malignancies; tuberculosis; lumbar puncture; chronic alcoholics; acetylsalicylic acid and other antiplatelet drugs.
<b>Precautions</b>	Hepatic impairment (Appendix 7a) and renal failure; hypersensitivity to low molecular weight heparins; spinal or epidural anaesthesia-risk of spinal haematoma; diabetes mellitus; acidosis; concomitant potassium-sparing drugs-increased risk of hyperkalaemia; lactation; paediatrics; elderly; interactions (Appendix 6c); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Immune-mediated thrombocytopenia usually developing 6 to 10 days after commencement of therapy (requires immediate withdrawal of heparin); haemorrhage; skin necrosis; hypersensitivity reactions including urticaria; angioedema and anaphylaxis; osteoporosis after prolonged use and rarely, alopecia; bleeding due to overdose.
<b>Storage</b>	Store at a temperature not exceeding 30°C.

## Menadione Sodium Sulphate

(Refer Phytomenadione below)

### Phytomenadione\*

Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Antagonist to warfarin; prophylaxis against haemorrhagic disease of the newborn; vit K deficiency, hematuria, menorrhagia.</i>
<b>Availability</b>	<b>TABLETS</b> 5 and 10 mg; <b>INJECTION</b> 10 mg/ml.
<b>Dose</b>	<b>Slow intravenous injection</b>  <b>Adult-</b> Warfarin-induced hypoprothrombinaemia, no bleeding or minor bleeding: 500 µg.  <b>Oral</b>  For vitamin K deficiency: 10 to 40 mg daily.

Warfarin-induced hypoprothrombinaemia, no bleeding or minor bleeding: 5 mg.

**Oral or intramuscular injection**

Less severe haemorrhage: 10 to 20 mg.

**Slow intravenous injection**

Severe haemorrhage: 2.5 to 5 mg; very rarely, up to 50 mg (but risk of over correction with high dosage).

**Intravenous or intramuscular injection**

**Child-** Neonates: Haemorrhagic disease of the newborn (treatment): 1 mg with further doses if necessary at 8 h intervals (prophylaxis).

**Intramuscular injection**

**Child-** 0.5 to 1 mg as single dose.

**Oral**

**Child-** 2 mg followed by a second dose after 4 to 7 days and for breastfed babies a third dose after 1 month.

**Contraindications**

Hypersensitivity.

**Precautions**

Reduce dose in elderly; hepatic impairment; not an antidote to heparin; can cause haemolysis in patients with G-6-PD; increased risk of severe haemolytic anaemia in neonates after large doses; premature neonates weighing < 2.5 kg; pregnancy (Appendix 7c).

**Adverse Effects**

Hypersensitivity reactions including flushing; dyspnoea; bronchospasm; dizziness; hypotension and respiratory or circulatory collapse which may be due to polyethoxylated castor oil surfactant in some injection formulations rather than due to phytomenadione.

**Storage**

Store protected from light.

**Protamine\***

**Pregnancy Category-C**

**Indications**

*Antidote to overdose with heparin; antidote for heparin in controlled bleeding.*

**Availability**

**SOLUTION** 5 ml (1%); **INJECTION** 5 ml ampoule (10 mg/ml).

**Dose****Intravenous injection**

Heparin overdose, over approximately 10 min; 1 mg neutralizes 80 to 100 units heparin when given within 15 min, if longer time, less protamine needed as heparin is rapidly excreted. 1 ml neutralises the effect of 1000 ml i.u. of circulating heparin; max. single dose 50 mg (5 ml).

**Precautions**

If used in excess protamine has an anticoagulant effect; allergic reactions increased in persons at risk including previous treatment with protamine or protamine insulin; fish allergies; men who are infertile or who have had a vasectomy; pregnancy (Appendix 7c); lactation; children.

**Adverse Effects**

Nausea; vomiting; lassitude; flushing; hypotension; bradycardia; dyspnoea; allergic reactions (including angioedema; anaphylaxis); allergy specially if previous exposure to protamine insulin; fish allergy; infertile or vasectomised men.

**Storage**

Store protected from light in a single dose container.

**Warfarin\*****Pregnancy Category-X****Schedule H****Indications**

*Prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation; prophylaxis after insertion of prosthetic heart valve; prophylaxis and treatment of venous thrombosis and pulmonary embolism; transient ischaemic attacks; myocardial infarction; vulvular heart disease.*

**Availability**

**TABLETS** 1, 2 and 5 mg.

**Dose****Oral**

**Adult-** Prophylaxis and treatment of thromboembolic disorders; usual induction dose is 10 mg daily for 2 days, according to the individual patient; the subsequent dose depends upon the prothrombin time; the usual daily maintenance dose is 3 to 9 mg administered at the same time each day.

Given as slow injection over 1 to 2 minutes into peripheral vein, initially 5 mg daily.  
For rapid anticoagulation: initially 10 mg daily for 2 days, maintenance dose 2 to 10 mg daily.

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*Note: Wherever possible, the base-line prothrombin time should be determined before the initial dose is given.*

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- Contraindications** Pregnancy (Appendix 7c); peptic ulcer; severe hypertension; bacterial endocarditis; hypersensitivity; blood dyscrasias; recent surgery; psychosis; pericardial effusion; cerebrovascular disorder; alcoholism; senility; aneurysm.
- Precautions** Heparin induced thrombocytopenia; surgery or trauma; Vit C, K; lactation; alcoholics; purple toes syndrome; discontinue if necrosis develops; elderly; hepatic impairment (Appendix 7a) or renal failure; recent surgery; lactation (Appendix 7b); interactions (Appendix 6a, 6b, 6c, 6d).
- Adverse Effects** Haemorrhage; hypersensitivity; rash; alopecia; diarrhoea; unexplained drop in haematocrit; 'purple toes'; skin necrosis; jaundice; hepatic dysfunction; nausea; vomiting and pancreatitis.
- Storage** Store protected from light.

## 13.7 Drugs Used in Heart Failure

---

Treatment of heart failure aims to relieve symptoms, improve exercise tolerance, reduce incidence of acute exacerbations and reduce mortality. Drugs used to treat heart failure due to left ventricular systolic dysfunction include ACE inhibitors, diuretics,  $\beta$ -blockers (metoprolol, carvedilol and bisoprolol), cardiac glycosides and vasodilators. In addition, measures such as weight reduction, moderate salt restriction and appropriate exercise should be introduced. The primary treatment of heart failure is with ACE inhibitors such as enalapril which can be used in all stages of chronic heart failure to prevent further deterioration and progression of heart disease.

A thiazide diuretic such as hydrochlorothiazide is used in the management of mild to moderate heart failure when the patient has mild fluid retention and severe pulmonary oedema is not present; however thiazides are ineffective if renal function is poor. In these patients and in more severe fluid retention, a loop diuretic such as furosemide is required. In severe fluid retention, intravenous furosemide produces relief from breathlessness and reduces preload sooner than would be expected from the time of onset of diuresis. Hypokalaemia may develop, but is less likely with the shorter-acting loop diuretics than with the thiazides; care is needed to avoid hypotension.

A combination of a thiazide and a loop diuretic may be required to treat refractory oedema. The combination often produces a synergistic effect on solute and water excretion, which relieves symptoms in the diuretic-resistant heart failure patient. However, the combination may produce excessive intravascular volume depletion and electrolyte disturbances including potentially life-threatening hypokalaemia.

The aldosterone antagonist spironolactone may be considered for patients with severe heart failure who are already receiving an ACE inhibitor and a diuretic; a low dose of spironolactone (usually 25 mg daily) reduces symptoms and mortality rate in these patients. Close monitoring of serum creatinine and potassium is necessary with any change in treatment or in the patient's clinical condition.

Digoxin, a cardiac glycoside, increases the strength of cardiac muscle contractions and increases cardiac output. In mild heart failure, digoxin inhibits the sympathetic nervous system and produces arterial vasodilation. It produces symptomatic improvement, increases exercise tolerance and reduces hospitalization, but it does not reduce mortality. It is considered for patients with atrial fibrillation and those who remain sympto-

matic despite treatment with an ACE inhibitor, a diuretic and a suitable beta-blocker.

Vasodilators are used in heart failure to reduce systemic vascular resistance. Isosorbide dinitrate produces mainly venous dilatation, which reduces left ventricular preload, leading to a reduction in pulmonary congestion and dyspnoea. Hydralazine produces mainly arterial vasodilation, which reduces left ventricular afterload and increases stroke volume and cardiac output. Isosorbide dinitrate and hydralazine can be used in combination when an ACE inhibitor cannot be used.

Dopamine, an inotropic sympathomimetic, may be given for short periods in the treatment of severe heart failure. Dosage is critical; at low doses it stimulates myocardial contractility and increases cardiac output, however, higher doses (more than 5 µg/kg per min) cause vasoconstriction, with a worsening of heart failure.

## Digoxin\* (Refer Page No. 295)

## Dobutamine\*

### Pregnancy Category-B

**Schedule H**

<b>Indications</b>	<i>Acute heart failure; acute myocardial infarction; cardiogenic shock following cardiac surgery; specific shock; acute decompensation of chronic CHF.</i>
<b>Availability</b>	<b>INJECTION</b> 250 mg/20 ml, 40 mg/ml, 12.5 mg/ml, 5 ml ampoule (50 mg/ml), vial 250 mg/20 ml, 50 mg/4 ml; 250 mg dry sterile lyophilised powder.
<b>Dose</b>	2.5 to 10 µg/kg/min which can be titrated to 40 µg/kg/min as per the individual requirement.
<b>Contraindications</b>	Hypersensitivity; idiopathic hypertrophic subaortic stenosis.
<b>Precautions</b>	Interactions (Appendix 6c); pregnancy (Appendix 7c); monitor heart rate and rhythm; arterial BP and infusion rate closely; correct hypovolemia prior to treatment; elderly; neonates; risk of rapid ventricular response in patients with atrial fibrillation; children.
<b>Adverse Effects</b>	Tachycardia and marked increase in systolic blood pressure indicate overdose; phlebitis; rarely, thrombocytopenia.

**Storage** Store protected from light.

## Dopamine\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *Cardiogenic shock in myocardial infarction or cardiac surgery; acute heart failure.*

**Availability** **INJECTIONS** 5 ml vial (40 mg/ml), 5 and 10 ml ampoule (200 mg/5 ml).

**Dose** **Intravenous infusion**

**Adult-** Cardiogenic shock: into large vein, initially 2 to 5 µg/kg/min; gradually increased by 5 to 10 µg/kg/min according to blood pressure, cardiac output and urine output; seriously ill patients up to 20 to 50 µg/kg/min. By intravenous route initially 1 to 5 µg/kg/min can be increased gradually to 5 to 10 µg/kg/min. max 20 to 50 µg/kg/min in serious patients.

**Contraindications** Hypersensitivity; tachyarrhythmias, ventricular fibrillation, ischaemic heart disease; pheochromocytoma; hyperthyroidism.

**Precautions** Correct hypovolaemia before and maintain blood volume during treatment; correct hypoxia; hypercapnia and metabolic acidosis before or at same time as starting treatment; low dose in shock due to myocardial infarction; history of peripheral vascular disease (increased risk of ischaemia of extremities); elderly; interactions (Appendix 6c); history of atherosclerosis; Raynaud's disease; diabetic endocarditis; disproportionate increase in diastolic pressure; pregnancy (Appendix 7c); lactation; paediatrics. Dopamine must be diluted before i.v. administration.

**Adverse Effects** Nausea and vomiting; peripheral vasoconstriction; hypotension with dizziness; fainting; flushing; tachycardia; ectopic beats; palpitations; anginal pain; headache; dyspnoea; hypertension particularly in overdose.

**Storage** Store in an airtight container protected from light.

## Enalapril\* (Refer Page No. 305)

## Furosemide\* (Refer Page No. 397)

### Pregnancy Category-C

<b>Indications</b>	<i>Oedema; mild to moderate hypertension.</i>
<b>Availability</b>	<b>TABLETS</b> 40, 100 and 500 mg; <b>INJECTION</b> ampoule 20 mg/ml, 10 mg/2 ml, 250 mg/25 ml, 20 mg/2 ml.
<b>Dose</b>	<b>Oral</b> <b>Adult-</b> Oedema: initially 40 mg daily on waking up. Maintenance. 20 to 40 mg daily; may be increased to 80 mg daily or more in resistant oedema: max 600 mg daily in severe cases. <b>Child-</b> 1 to 3 mg/kg daily (max. 40 mg daily). <b>Slow intravenous injection</b> <b>Adult-</b> Acute pulmonary oedema: 20 to 50 mg, if necessary increase by 20 mg step-by-step every 2 h; if effective single dose is more than 50 mg, at a rate not exceeding 4 mg/min. <b>Child-</b> 0.5 to 1.5 mg/kg daily (max. 20 mg daily). <b>Slow intravenous infusion</b> <b>Adult-</b> Oliguria (glomerular filtration rate less than 20 ml/min): at a rate not exceeding 4 mg/min, initially 250 mg over 1 h. If urine output not satisfactory during the h after first dose, infuse 500 mg over 2 h then; if no satisfactory response is there in an h after second dose, infuse 1g over 4 h. If no response is there after third dose, dialysis is probably necessary.
<b>Contraindications</b>	Renal failure with anuria; precomatose states associated with liver cirrhosis; severe sodium and water depletion; hypersensitivity to sulphonamides and furosemide; hypokalaemia; addison's disease; lactation.



### Precautions

Monitor electrolytes particularly potassium and Sodium; hypotension; elderly (reduce dose); pregnancy (Appendix 7c); lactation; correct hypovolaemia before using in oliguria; renal impairment; hepatic impairment (Appendix 7a); prostatic enlargement; porphyria; interactions (Appendix 6b, 6c); gout; impaired micturition; infusion rate should not exceed 4 mg/min to reduce the risk of ototoxicity; monitor serum levels for calcium or magnesium (may be lowered).

### Adverse Effects

Hypokalaemia; hypomagnesaemia; hyponatraemia; hypochloreaemic alkalosis (for symptoms of fluid and electrolyte imbalance; see introductory notes); increased calcium excretion; hypovolaemia; hyperglycaemia (but less often than with thiazide diuretics); temporary increase in plasma cholesterol and triglyceride concentration; less commonly hyperuricaemia and gout; rarely, rash; photosensitivity; bone marrow depression (withdraw treatment); pancreatitis (with large parenteral doses); tinnitus and deafness (with rapid administration of large parenteral doses and in renal impairment; deafness may be permanent if other ototoxic drugs taken); gastrointestinal upset; malaise; blood dyscrasias; vertigo; orthostatic hypotension; jaundice; tinnitus; renal calcification in premature infants.

### Storage

Store protected from light.

**Hydrochlorothiazide\*** (Refer Page No. 308 and 397)

**Spironolactone\*** (Refer Page No. 399)

## 13.8 Lipid Lowering Drugs

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Drug therapy to lower plasma lipids should be used in addition to dietary management and correction of other modifiable cardiovascular risk factors. Studies indicate that, 1% drop in serum cholesterol reduces the risk for Coronary heart disease (CHD) by 2%.

Various classes of drugs used as lipid lowering drugs are-

### H mg-CoA reductase inhibitors

They are the most efficacious and tolerable drugs like simvastatin, pravastatin, atorvastatin etc. They are primarily indicated in secondary prevention of myocardial infarction and stroke in patients who have symptomatic atherosclerotic disease following acute myocardial infarction or stroke and in primary prevention of arterial disease in patients who are at high risk because of elevated serum cholesterol concentration. Common adverse effects include mild gastrointestinal disturbances, rhabdomyolysis etc.

### Fibric acid derivatives

This class of drugs including fenofibrate, gemfibrozil etc are indicated in patients with mixed dyslipidemia (i.e. raised serum triglycerides and cholesterol), low high density lipoprotein (HDL) and high risk of atheromatous disease (often type 2 diabetic patients), and in severe treatment-resistant dyslipidemia. Major adverse effect include rhabdomyolysis and myoglobinuria. Fibrates are better avoided in alcoholics.

### Bile acid sequestrants

Drugs like cholestyramine, colestipol though are not clinically popular because of interference with absorption of many drugs like digoxin, warfarin etc and poor patient acceptability, but can be indicated in heterozygous familial hypercholesterolemia. Adverse effects include nausea, abdominal bloating, constipation or diarrhoea.

### Nicotinic acid

Nicotinic acid reduces serum cholesterol and triglycerides levels in types II, III, IV, and V hyperlipoproteinemias. Adverse effects include flushing, palpitations and gastrointestinal tract disturbances.

## Atorvastatin\*

Pregnancy Category-X

Schedule H

<b>Indications</b>	<i>Primary and secondary hypercholesterolemia, prevention of cerebrovascular accidents, primary prevention of coronary heart disease.</i>
<b>Availability</b>	<b>TABLETS</b> 5, 10, 20, 40 and 80 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> 10 mg daily, increased at 4 weeks interval. Max dose 80 mg.
<b>Contraindications</b>	Hypersensitivity; active liver diseases or unexplained persistent elevation of serum transaminase; pregnancy (Appendix 7c), lactation.
<b>Precautions</b>	Patients who consume substantial quantities of alcohol and have a history of liver diseases, Children below 10 years, premenarcheal females; interactions (Appendix 6a, 6c).
<b>Adverse Effects</b>	Myopathy is the serious adverse effect; headache; infrequent elevation of creatinine phosphokinase; rhabdomyolysis; insomnia; dizziness; abdominal pain, constipation, diarrhoea, dyspepsia, flatulence and nausea.
<b>Storage</b>	Store protected from moisture at a temperature not exceeding 30°C.

## Ezetimibe

Pregnancy Category-C

<b>Indications</b>	<i>Hypercholesterolemia, hyperlipidaemias, homozygous familial sitosterolaemia.</i>
<b>Availability</b>	<b>TABLETS</b> 10 mg.
<b>Dose</b>	<b>Adult-</b> 10 mg once daily. <b>10-18 years:</b> 10 mg once daily.
<b>Contraindications</b>	Hypersensitivity, children below 10 years, pregnancy (Appendix 7c), interactions (Appendix 6c, 6d), lactation, moderate to severe liver disease or unexplained serum transaminase elevation, acute pancreatitis.
<b>Precautions</b>	Renal or mild hepatic impairment, immediately discontinue ezetimibe and any H mg-CoA reductase inhibitor or fibrates if myopathy is diagnosed.

**Adverse Effects** Diarrhoea, sinusitis, pharyngitis, cough, arthralgia, myalgia, respiratory infection and fatigue, hepatitis/increased serum transaminases, increased creatinine phosphokinase, myopathy/rhabdomyolysis, headache, nausea, rash, dizziness, chest pain, abdominal pain with cramps, back pain, biliary calculus, thrombocytopenia.

**Storage** Store protected from light and moisture at a temperature not exceeding 30°C

## Fenofibrate

**Pregnancy Category-C**

**Schedule H**

**Indications** *Hypercholesterolemia, hypertriglyceridemia.*

**Availability** **CAPSULES** 67 and 200 mg, **TABLETS** 145 and 160 mg **INJECTIONS** 20, 40 and 60 mg/vial.

**Dose** **Hyperlipidemia:**  
**Adult-** Initial dose 67 mg 2-4 times a day (micronized) or 200 mg/day in divided doses (non-micronized).

**Child-** 5 mg/kg daily.

**Contraindications** Hypersensitivity, severe renal and hepatic impairment, preexisting gall bladder disease, primary biliary cirrhosis, pregnancy (Appendix 7c), lactation.

**Precautions** Pancreatitis; skeletal muscle effects; renal and hepatic impairment; monitor for LFT and blood counts regularly; interactions (Appendix 6c).

**Adverse Effects** Myalgia; hepatitis; rashes; cholelithiasis, rhabdomyolysis; increased SGPT and SGOT, abdominal pain, photosensitivity; rhinitis; sinusitis.

**Storage** Store protected from light.

## Nicotinic acid

**Pregnancy Category-C**

**Schedule H**

**Indications** *High risk hyperlipidaemia, nicotinic acid deficiency, peripheral vascular disease.*

**Availability** **Tablets** 375 and 500 mg Plain and 375 mg SR.

**Dose** **Oral**

**Treatment and prophylaxis of nicotinic acid deficiency:** Adult- 500 mg daily.

**Hyperlipidaemia: Adult-** 1-2 g, two to three times daily, maximum dose- 6 g per day; (As extended release tablets max. dose is 2 g). Niacin should be started at low doses and increased slowly over several weeks.

**Peripheral vascular disease:** Adult- 100-150 mg, three to five times daily; (Extended release preparation-) 300-400 mg 12 hourly.

**Contraindications** Hypersensitivity, liver disease, severe hypotension, diabetes, arterial bleeding.

**Precautions** Gout, hepatic dysfunction, children, pregnancy (Appendix 7c), lactation, myasthenia gravis, interactions (Appendix 6a and 6c).

**Adverse Effects** Headache, diarrhoea, vomiting, fainting, peptic ulcer, hyperuricaemia, gout, toxic amblyopia, flushing, hyperpigmentation, dry skin, muscle pain, jaundice, pruritus, atrial fibrillation. Flushing can be blocked by administering 300 mg of aspirin half an hour before taking niacin, or by taking one tablet of ibuprofen per day.

**Storage** Store protected from heat and moisture at room temperature.



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# 14. Dermatological Drugs

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## 14.1 Antibacterial Drugs

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Staphylococcal infections of the skin such as impetigo, folliculitis, and furunculi and streptococcal infections such as cellulitis and erysipelas are very common where the climate is hot and humid, where standards of hygiene are compromised, and in immunodeficient patients.

In all skin infections, an important part of treatment is cleansing and thorough drying. Washing with soap and water will often help to prevent infection. Light localized infections can often be treated effectively with an antiseptic solution such as chlorhexidine. Superficial crusts should be gently washed with soap and water or a weak solution of aluminium acetate or a 0.01% solution of potassium permanganate. Infected burns should be treated with silver sulfadiazine, which is bactericidal against both Gram-positive and Gram-negative organisms.

An ointment containing 2% mupirocin, which is active against Gram-positive bacteria, is of value, particularly in impetigo. To prevent the development of resistance, mupirocin should not be used for more than 10 days. Topical preparations containing neomycin and bacitracin are also widely used but these carry a risk of sensitization particularly with continued or repeated use.

Topical use of preparations containing antimicrobials which are widely used systemically should be avoided. These include penicillins, sulfonamides, streptomycin and gentamicin, which should be reserved for the systemic treatment of infections because of the possibility of inducing sensitivity and favouring the emergence of resistant organisms. Only widespread superficial or deep-seated infections associated with fever require treatment with a systemic antibiotic. Whenever possible, the choice of an antimicrobial should be based on the results of sensitivity tests.



## Gentian Violet\*

### Pregnancy Category-C

<b>Indications</b>	<i>Superficial fungal and bacterial infections.</i>
<b>Availability</b>	<b>SOLUTION</b> 0.5%; <b>TINCTURE</b> 0.5%.
<b>Dose</b>	Skin infections: apply 2 or 3 times daily for 2 to 3 days.
<b>Contraindications</b>	Sensitivity to gentian violet.
<b>Precautions</b>	External use only; avoid contact with eyes; it can dye skin; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Redness, swelling; irritation; allergic reaction.

## Neomycin + Bacitracin\*

### Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Superficial bacterial infections of the skin due to staphylococci and streptococci.</i>
<b>Availability</b>	<b>CREAM</b> 5, 10 and 15g (Aluminium tubes).
<b>Dose</b>	<b>Adult and child-</b> Bacterial skin infections over 2 years: apply as a thin layer 3 times daily.
<b>Contraindications</b>	<b>Neonates</b>
<b>Precautions</b>	Avoid application to substantial areas of skin or to broken skin (risk of significant systemic absorption); overgrowth of resistant organisms on prolonged use; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Sensitization; especially to neomycin; causing reddening and scaling; systemic absorption leading to irreversible ototoxicity; particularly in children; elderly; and in renal impairment; pregnancy (Appendix 7c).
<b>Storage</b>	Store protected from light at temperature not exceeding 30°C.

## Potassium Permanganate\*

<b>Indications</b>	<i>Wet dressings to assist healing of suppurating superficial wounds, tropical ulcers, tinea pedis infection, pemphigus, impetigo.</i>
<b>Availability</b>	<b>SOLUTION</b> 1:10,000 (0.01% solution).

<b>Dose</b>	Suppurating superficial wounds and tropical ulcers: wet dressings of 1:10,000 (0.01%) solution, changed 2 or 3 times daily; tropical ulcers also require treatment for 2 to 4 weeks with procaine benzylpenicillin.  <i>Tinea pedis</i> : soak severe weeping lesions in 1:10,000 (0.01%) solution every 8 h.  Pemphigus: soak compresses in 1:10,000 (0.01%) solution and apply every 4 h.  Impetigo: superficial crusts should be gently separated with a 1:10,000 (0.01%) solution.
<b>Contraindications</b>	Avoid occlusive dressings; interactions (Appendix 6d).
<b>Precautions</b>	Irritant to mucous membranes; redness of skin.
<b>Adverse Effects</b>	Local irritation; skin and fabrics stained brown.
<b>Storage</b>	Store protected from moisture.

## Silver Sulfadiazine\*

### Pregnancy Category-B

**Schedule H**

<b>Indications</b>	<i>Prophylaxis and treatment of infection in burns.</i>
<b>Availability</b>	<b>CREAM</b> 1%w/w.
<b>Dose</b>	Infection in burns: apply using aseptic technique daily (more frequently if volume of exudate is large) whilst there is a possibility of infection, or until healing is complete.
<b>Contraindications</b>	Hypersensitivity to sulfonamides; neonates; premature infants.
<b>Precautions</b>	Renal or hepatic impairment; G-6-PD deficiency; lactation (Appendix 7b); monitor serum sulphadiazine concentration and check urine for sulpha crystals; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Allergic reactions include rashes; burning and itching; argyria and sulfonamide-induced systemic toxicity; including blood disorders following application to large areas or prolonged use; transient leukopenia; skin necrosis; skin discolouration.
<b>Storage</b>	Store protected from light.

## 14.2 Antifungal Drugs

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### Ringworm:

Benzoic acid and methylrosanilinium chloride (gentian violet) solution are inexpensive and effective fungistatic compounds for the treatment of dermatophyte infections such as ringworm. Minor skin lesions due to ringworm can be cleared with repeated applications of compound benzoic acid ointment (Whitfield ointment), which combines the fungistatic action of benzoic acid with the keratolytic action of salicylic acid. However, the most effective topical treatment for dermatophyte infections is a cream containing an imidazole such as miconazole, which is effective for long-established lesions but is more expensive than compound benzoic acid ointment. Extensive and generalized infections of the skin, nails and scalp should be treated systemically for several weeks with griseofulvin or fluconazole.

Scalp ringworm (*Tinea capitis*) typically appears as a patch of scaling alopecia, or a swollen inflammatory area (*Tinea kerion*). Mild forms may remit spontaneously at puberty. Inflamed lesions should be treated systemically with griseofulvin. Application of miconazole cream may accelerate healing of scaly lesions.

Ringworm on the body (*Tinea corporis*) can also be cleared with compound benzoic acid ointment or a topical imidazole such as miconazole. In resistant cases a 4-week course of oral griseofulvin is required.

Foot ringworm (*Tinea pedis* or athlete's foot) is usually treated topically. Compound benzoic acid ointment should be applied twice daily to all infected areas and all toe clefts for at least 4 weeks. Systemic therapy with griseofulvin or fluconazole may be required if the foot is extensively infected. *Tinea pedis* commonly recurs and may be treated with miconazole cream. Severe weeping lesions respond to frequent soaking in solutions of 1:10,000 potassium permanganate and systemic antifungals may also be needed.

Nail infections (onychomycosis, *tinea unguium*) are difficult to treat; fingernails may require 6 months treatment with oral griseofulvin and toenails may require 12 months or more of this treatment. Approximately 60% of nail infections either do not respond or relapse after treatment with griseofulvin.

Ringworm of the groin (*Tinea cruris*) is usually limited to the skin of the inner thigh in contact with the scrotum. Flexural eczema, often superinfected with candida or bacteria, occurs in the same site. The latter is frequently treated with

combined antifungal/corticosteroid preparations, but must not be treated with a corticosteroid alone, which will worsen the condition. An imidazole cream such as miconazole applied daily for 2 weeks is usually effective. Lesions unresponsive to topical preparations can usually be cleared with a 4-week course of griseofulvin.

### Candidosis:

*Candida* can infect the oral cavity, the vagina or the skin. Cutaneous lesions tend to occur in patients with diabetes mellitus and some chronic debilitating conditions, including hypoparathyroidism and various congenital disorders of the immune system. The most severe infections of candida are now seen in patients with HIV infection.

Cutaneous candidosis usually responds to miconazole cream as a twice daily application. Chronic candida paronychia, which can result ultimately in nail dystrophy, is more difficult to treat. Treatment should be based on determination of the underlying cause and its reduction or elimination; hands and folds of the nail must be kept dry and daily application of an imidazole cream for several months may be required, ensuring penetration of the cleft between the nail plate and the swollen skin around the nail.

### Pityriasis Versicolor:

Pityriasis (*tinea*) versicolor is caused by a commensal yeast. Application of Sodium thiosulfate twice daily for 4 weeks is usually effective although areas of depigmentation on darker skins remain after completion of treatment. Relapses can be frequent, however, probably because much of the infected area may appear normal and be left untreated. Better results have been reported with topical applications of miconazole or selenium sulphide.

## Benzoic Acid + Salicylic Acid

### Salicylic Acid Pregnancy Category-C

<b>Indications</b>	<i>Mild dermatophyte infections, particularly caused by Tinea pedis and Tinea corporis.</i>
<b>Availability</b>	<b>CREAM</b> 25 and 50g (Aluminium tubes, jars).
<b>Dose</b>	Fungal skin infections: apply twice daily until the infected skin is shed (usually at least 4 weeks).
<b>Precautions</b>	Avoid contact with eye, nose and mouth, pregnancy (Appendix 7c).

**Adverse Effects** Occasionally localized; mild inflammatory reaction; swelling of face, lips and tongue; difficulty in breathing.

**Storage** Store at a temperature not exceeding 30°C.

## Miconazole\* (Refer Page No. 553)

**Pregnancy Category-C**

**Schedule H**

**Indications** *Superficial fungal infections due to dermatophytes and yeasts, and secondary infections caused by Gram-positive cocci, including ringworm, intertrigo, candida napkin rash, paronychia, and pityriasis versicolor.*

**Availability** **CREAM** 10 and 15g (2%); **GEL** 2% w/w.

**Dose** **Skin infections:** apply twice daily to clean dry lesions, continuing for at least 10 days after the condition has cleared.

**Nail infections:** apply 1 to 2 times daily.

**Precautions** Contact with eyes and mucous membranes should be avoided; pregnancy (Appendix 7c).

**Adverse Effects** Occasional local irritation and burning; also contact dermatitis; discontinue if sensitization occurs.

**Storage** Store protected from light and moisture at a temperature not exceeding 30°C. If it is packed in aluminates; the inner surface of tubes should be coated with suitable lacquer.

## Sodium Thiosulphate\* (Refer Page No. 95)

**Pregnancy Category-C**

**Indications** *Pityriasis versicolor; cyanide poisoning.*

**Availability** **SOLUTION** 15%.

**Dose** Pityriasis versicolor: apply twice daily for 4 weeks.

**Precautions** Pregnancy (Appendix 7c).

**Adverse Effects** Mild temporary burning or stinging at site of application.

**Storage** Store protected from light and moisture.

## 14.3 Anti-Inflammatory and Antipruritic Drugs

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### Contact Dermatitis:

Contact dermatitis can result from an allergic or irritant skin reaction. Removal of the substance provoking the reaction is the first step in treating this condition. Mild cases of contact dermatitis can be treated with topical hydrocortisone which suppresses inflammation. A short course of oral prednisolone or a topical corticosteroid such as betamethasone should be considered for more severe cases and for suppression of severe acute reactions associated with blistering, exudation and oedema. Soaking in clean water or mild saline solution is recommended in the acute stages of severe dermatitis.

### Pruritus:

Pruritus or itching is a common symptom of many skin diseases. However, contact with certain substances, conditions that dry the skin, stress, and extremes of temperature may also be a cause. Thus, an important part of treatment is to eliminate or minimize the reason for the irritation.

Corticosteroids, such as hydrocortisone or betamethasone applied topically, can give relief. Soothing baths or the application of an emollient cream may also be helpful. Systemic antihistamines, such as oral chlorpheniramine, may relieve generalized pruritus.

### Atopic Dermatitis:

Atopic dermatitis (or eczema) is a common skin disorder, which mainly occurs in infants and children; it is associated with intense itching, with areas of red skin. Pruritus may be partially relieved by applying astringent aluminium acetate lotion to exudative lesions and emollients to lichenified plaques. Topical hydrocortisone should be applied in short courses of 1-2 weeks to treat even mild areas of involvement. The use of betamethasone should be considered in the treatment of persistent localized dermatitis in adults. Topical antihistamines are not effective and should be avoided because of the risk of sensitization. However, a sedative antihistamine can be given at night to calm pruritus and facilitate sleep. A secondary infection, often involving *Staphylococcus aureus*, may be responsible for exacerbations; in such cases, an oral antibiotic such as erythromycin can be given for 7-10 days.

### Seborrhoeic Dermatitis:

Use of a keratolytic shampoo and exposure to ultraviolet light reduce both the inflammation and the scaling resulting from seborrhoeic dermatitis of the scalp (dandruff). The shampoo

should be massaged into the scalp, immediately rinsed off and then reapplied until a foam is produced, leaving the second application in contact with the scalp for at least 5 min. Selenium sulfide, which has both antifungal and keratolytic properties, is widely used in many proprietary shampoos. A combination of sulphur and salicylic acid, which has an additional antimicrobial action, is also effective.

### Ichthyosis:

In ichthyosis, emollients such as aqueous creams and emulsifying creams should be applied daily (or more frequently in severe cases) to affected skin. The addition of a keratolytic, such as salicylic acid 5% can be helpful.

### Lichen Planus:

Lichen planus is a chronic, papular, pruritic skin eruption that occurs typically in middle age and later life; the condition is often mild and may need no treatment. In more severe cases, when the underlying cause cannot be identified, a topical corticosteroid offers the only prospect of remission.

### Pityriasis Rosea:

In pityriasis rosea, a common self-limiting dermatosis that is probably of infective origin, calamine lotion helps to relieve pruritus in most cases. If it does not, topical application of hydrocortisone in a concentration not exceeding 1% is worth trying.

## Betamethasone\*

Pregnancy Category-C

Schedule H

### Indications

*Severe inflammatory skin conditions including contact dermatitis, atopic dermatitis (eczema), seborrhoeic dermatitis, lichen planus, psoriasis of the scalp, hands and feet, intractable pruritus; Addison's disease, Simmond's disease, bursitis.*

### Availability

**TABLETS** 0.5 mg; **INJECTION** 1 ml ampoule (4 mg/ml); **CREAM** 0.1%; **OINTMENT** 0.1%.

### Dose

**Adult and child-** Inflammatory skin conditions, over 2 years of age: apply small quantity to the affected area 1 to 2 times daily until improvement occurs, then less frequently.

### Contraindications

Untreated skin infections or broken skin; rosacea; acne; perioral dermatitis; systemic infections unless specific anti-infective therapy is employed.

**Precautions** Children (avoid prolonged use); adrenal suppression if used on a large area of the body or for a long time; particularly with an occlusive dressing or on broken skin; avoid use on the face for more than 7 days; secondary infection requires treatment with an appropriate antimicrobial; may impair the ability to resist and counteract infections; diabetes mellitus; pregnancy (Appendix 7c); elderly; lactation (Appendix 7b).

**Adverse Effects** Exacerbation of local infection; local atrophic changes particularly on the face and in skinfolds; characterized by thinning of the dermis; depigmentation; dilatation of superficial blood vessels and formation of striae; perioral dermatitis; acne at site of application; suppression of the hypothalamic-pituitary-adrenal axis with prolonged or widespread use (particularly under occlusion); subcapsular cataract; osteoporosis; glaucoma; intracranial hypertension; psychic instability.

**Storage** Store protected from light.

## Calamine\*

**Indications** *Mild pruritus.*

**Availability** **LOTION** 50 and 100 ml (8%); **CREAM** 1g.

**Dose** Mild pruritus: apply liberally 3 to 4 times daily.

**Storage** For lotion and Cream: Store at a temperature not exceeding 30°C. Do not freeze.

## Hydrocortisone\* (Refer Page No. 32, 429 and 479)

**Pregnancy Category-C**

**Schedule H**

**Indications** *Contact dermatitis, atopic dermatitis (eczema), lichen planus; intractable pruritus and phototoxic reactions, including polymorphic light eruptions and actinic prurigo; short-term treatment of psoriasis of the face and flexures; ulcerative colitis.*

**Availability** **CREAM** 10 and 15g (1%).

**Dose** Inflammatory skin conditions: apply a small quantity to the affected area 1 to 2 times daily until improvement occurs, then less frequently.

**Contraindications** Untreated skin infections or broken skin; rosacea; acne; perioral dermatitis.



### Precautions

Children (avoid prolonged use); occlusive dressings increase penetration into keratinized lesions (use occlusive dressings only at night and for no longer than 2 days; avoid use on weeping lesions); secondary infection requires treatment with an appropriate antimicrobial; latent peptic ulcer; hypertension; hypothyroidism; psychic derangement; lactation (Appendix 7b); interactions (Appendix 6d); pregnancy (Appendix 7c).

### Adverse Effects

Exacerbation of local infection; atrophic changes (see under Betamethasone) less likely with mild corticosteroids; but infants and children particularly susceptible; fluid retention; hypokalaemia; osteoporosis; impaired wound healing; increased intracranial and intraocular pressure; negative nitrogen balance.

## 14.4 Astringent Drugs

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Aluminum acetate is a topical astringent used as an antiseptic for various skin conditions including suppurating superficial wounds and tropical ulcers, and the lesions produced by pemphigus and impetigo. Potassium permanganate may be used in the same way.

### Zinc Oxide\*

It is astringent antiseptic available in the form of powder.

## 14.5 Drugs Affecting Skin Differentiation and Proliferation

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### Acne Vulgaris:

Acne is a disorder of the pilosebaceous follicles and typically first appears during puberty when androgenic stimulation triggers excessive production of sebum. *Mild acne* is characterized by comedones and a few pustules which heal without scarring, and usually responds to topical therapy alone. In *moderate acne*, where there are more extensive pustules causing mild scarring, oral antibiotics such as a tetracycline or erythromycin are commonly used. In *severe acne*, widespread pustules are accompanied by nodular abscesses and cysts, requiring treatment with estrogens, antiandrogens, or retinoids. Since scarring of the skin resulting from severe nodular acne causes major distress, acne should always be treated as soon as possible. Exposure to substances suspected of causing or aggravating the condition should be avoided. Systemic treatment must be continued for several months before a response can be anticipated. During this time, topical preparations should be applied to the affected areas to prevent the development of new lesions.

Benzoyl peroxide is a keratolytic drug with bacteriostatic activity against *Propionibacterium acnes*; treatment is usually started at a lower strength and increased as tolerance develops to the initial irritant reaction.

Preparations containing sulphur, which is bactericidal and promotes desquamation, are often used, and may be combined with salicylic acid, which is a keratolytic agent.

Topical antibiotics such as clindamycin are widely used in inflammatory acne. However, treatment must be maintained for 2 to 3 months before any benefit is seen and this prolonged course carries the risk of selection and spread of antibiotic-resistant organisms.

### Psoriasis:

Psoriasis, which affects people of all ages in all countries, is one of the most common chronic dermatoses in industrialized countries, and is characterized by epidermal thickening and scaling. Considerable local variations in its prevalence have been variously attributed to genetic, climatic, nutritional and ecological factors. Various biological events may trigger psoriasis, such as streptococcal or viral infection, an emotional crisis or pregnancy. Occasionally psoriasis may be provoked or exacerbated by drugs such as ACE inhibitors, beta-adrenoceptor antagonists (beta-blockers), chloroquine, lithium, and

non-steroidal anti-inflammatory drugs.

Psoriasis vulgaris (chronic plaque psoriasis) is the most common form of the condition, usually affecting extensor surfaces of the limbs and the scalp. Guttate psoriasis, commonly seen in children, is often caused by a streptococcal infection; lesions may disappear following antimicrobial treatment. The condition is also known to resolve spontaneously but more commonly transforms into chronic plaque psoriasis. No treatment is known to assure remission, although sunlight often clears lesions.

Dithranol restores the normal rate of epidermal cell proliferation and keratinization, and localized psoriasis vulgaris can frequently be cleared by daily applications for a period of 2 to 4 weeks. A short contact method of application causes little, if any, irritation or staining of normal skin, and is particularly useful for outpatient management. There is a risk of severe conjunctivitis if dithranol enters the eye.

Crude coal tar is also effective in the treatment of psoriasis. Some preparations additionally contain salicylic acid as a keratolytic. Good results are often obtained when daily applications or baths are combined with exposure to ultraviolet light or sunlight.

Emollients containing low concentrations of salicylic acid (1-2%) are a useful adjunct to treatment, particularly where there is thick scaling. A preparation containing urea 10%, which has moisturizing, keratolytic and antimitotic properties, may prove more effective than an emollient.

Topical corticosteroids have a limited role in psoriasis. A mild corticosteroid such as hydrocortisone may be used on the face and flexures, whereas a potent corticosteroid such as betamethasone is most appropriate for the scalp, hands and feet. However, when extensive areas of the body surface are involved or when there is erythrodermic psoriasis, sufficient may be absorbed to cause adrenal suppression; also rebound often occurs after stopping treatment, resulting in a more unstable form of psoriasis.

### **Actinic Keratosis:**

The lesions of actinic keratosis are distributed primarily over sun-exposed areas. Horny growths, which are often covered by light brown scales, are usually asymptomatic but can be disfiguring. They respond to light cautery and cryosurgery or topical application of 5-fluorouracil over a three-week period. Simple emollients may be satisfactory for people with many lesions.

## Warts:

Warts most commonly affect the hands, feet (plantar warts, verrucas), and anogenital region (condylomata acuminata); all are caused by the human papilloma virus. They may regress spontaneously at any time within months or years of their first appearance; however, particularly in immunosuppressed patients, they may spread and be difficult to cure. Many common, plane and plantar warts can reasonably be left untreated, but painful or unsightly lesions generally respond to application of preparations containing salicylic acid. Where available, cryotherapy using liquid nitrogen applied with a cotton-tip or a spray is highly effective; however, freezing the skin can produce temporary or permanent depigmentation (particularly on dark skin), and should be used with caution.

*Anogenital warts* are usually transmitted by sexual contact; they should always be treated, although they frequently recur, because of the increased risk of cervical cancer. Podophyllum resin, a caustic antimitotic agent, may be applied to small external lesions. The risk of extensive local necrosis and of systemic toxicity excludes the use of podophyllum resin on larger surfaces. When available, podophyllotoxin is a less toxic alternative. Where podophyllum is contraindicated or ineffective surgical removal, electrocautery, cryosurgery and laser therapy are possible options. Topical application of 5-fluorouracil has been reported to be of value in resistant cases but the treatment is expensive and efficacy is still under investigation.

## Coaltar\*

### Pregnancy Category-C

<b>Indications</b>	<i>Chronic psoriasis, either alone or in combination with exposure to ultraviolet light; eczema.</i>
<b>Availability</b>	<b>CREAM</b> 20g (1 - 6% w/w); <b>LOTION</b> 50 ml (1 - 6 %w/v).
<b>Dose</b>	Psoriasis: apply 1 to 4 times daily, preferably starting with lower strength preparation.  Coal tar bath; use 100 ml in bath of tepid water and soak for 10 to 20 min; use once daily to once every 3 days for at least 10 baths; often alternated with ultraviolet (UV) rays, allowing at least 24 h between exposure and treatment with coal tar.
<b>Contraindications</b>	Inflamed, broken or infected skin.

**Precautions** Skin protection possibly required to reduce photosensitivity reactions; avoid contact with eyes; pregnancy (Appendix 7c).

**Adverse Effects** Irritation; photosensitivity reactions; rarely, hypersensitivity, skin; hair and fabrics discoloured; stinging.

## Dithranol\*

### Pregnancy Category-C

**Indications** *Moderately severe psoriasis.*

**Availability** **OINTMENT** 30g (0.25, 0.5 and 1% w/w).

**Dose** Psoriasis: initiate under medical supervision starting with 0.1%, carefully apply to lesions only, leave in contact for 30 min, then wash off thoroughly; repeat application daily, gradually increasing strength to 2% and contact time to 60 min at weekly intervals; wash hands thoroughly after use.

**Contraindications** Hypersensitivity; avoid use on face; acute eruptions; excessively inflamed areas.

**Precautions** Irritant-avoid contact with eyes and healthy skin; not to be used in acute psoriasis; pregnancy (Appendix 7c).

**Adverse Effects** Local irritation; discontinue use if excessive erythema or spread of lesions; conjunctivitis following contact with eyes; staining of skin; hair; and fabrics; stains skin.

**Storage** Store protected from light.

## 5-Fluorouracil\* (Refer Page No. 255)

### Pregnancy Category-D

**Schedule H**

**Indications** *Actinic keratosis; genital warts unresponsive to podophyllum resin; malignant disease.*

**Availability** **CREAM** 5%w/w.

**Dose** Actinic keratosis, genital warts: apply thinly 1 to 2 times daily until marked inflammatory response occurs (usually 3 to 4 weeks); healing may require further 2 months after completion of treatment.

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*Note: Avoid use of metal applicator.*

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<b>Contraindications</b>	Haemorrhagic ulcerated tissue; patients with dihydropyrimidine dehydrogenase enzyme deficiency; pregnancy (Appendix 7c); hypersensitivity.
<b>Precautions</b>	Avoid mucous membranes and eyes; since UV light intensifies the inflammatory reaction; avoid prolonged exposure to sunlight; inflamed ulcerated skin; hepatic impairment (Appendix 7a); lactation (Appendix 7b); interactions (Appendix 6c).
<b>Adverse Effects</b>	Local inflammatory and allergic reactions; rarely, erythema multiforme; photosensitivity reactions during and for up to 2 months after treatment; eye irritation.
<b>Storage</b>	Store protected from light. For injection: store protected from light in a single dose container at a temperature not exceeding 30°C. Injection should not be allowed to freeze.

## Isotretinoin

### Pregnancy Category-X

<b>Indications</b>	<i>Resistant and severe nodulocystic acne, dry scaly surface, mottling, wrinkles, rough and leathery texture, acute promyelocytic leukemia, actinic keratoses.</i>
<b>Availability</b>	<b>TABLET</b> 20 mg; <b>CAPSULES</b> 5, 10, 20, 30 and 40 mg; <b>CREAM</b> 15 and 20 g (0.025 & 0.05%w/w); <b>GEL</b> 10 and 20 mg (0.05 & 0.025% w/w); <b>OINTMENT</b> 20 g (0.05% w/w).

### Dose **Oral**

#### **Acne**

**Adult:** 0.5-1 mg/kg daily in 2 divided doses. Duration of treatment: 15-20 week; may be discontinued if number of cysts is reduced by >70% (whichever is sooner). Patients intolerant to initial dose: Treatment continued at a lower dose. Patients with very severe acne or acne evident on the body instead of face: max dose of 2 mg/kg daily. There should be a 2-month drug-free interval if a 2nd course is necessary.

#### **Topical/Cutaneous**

#### **Acne**

**Adult:** As 0.05% gel: Apply sparingly once or twice daily. Effect may not be evident for 6-8 week.

**Contraindications** Female patients who are or may become pregnant (Appendix 7c), lactation, hypersensitivity, acute eczematous, sunburnt or abraded skin, hypervitaminosis of Vitamin A, hyperlipidemia, pancreatitis.

**Precautions** Contraceptive measures must be followed for any subsequent course of therapy, concomitant application with keratolytic agents, avoid exposure to sunlight and UV light, renal and hepatic impairment, patients and their relatives should be informed of the depressive symptoms and the same may be actively assessed during each visit and appropriate action taken, interactions (Appendix 6c).

**Adverse Effects** Dryness of skin and mucous membranes, pruritus, epistaxis, cheilitis, erythema, sometimes Stevens-Johnson syndrome, paresthesias, anxiety, conjunctivitis, paronychia, rise in serum lipids, pancreatitis, hypervitaminosis (however it is less than that of tretinoin), edema, hair thinning and intracranial tension leading to nausea and vomiting, hearing impairment, hepatotoxicity, visual impairment. Psychiatric side effects such as depression, suicidal tendencies and psychotic symptoms can occur frequently in adolescents and young adults.

**Storage** Store protected from moisture, light and at a temperature 15-30°C.

## Salicylic Acid\*

### Pregnancy Category-C

**Indications** *Hyperkeratotic conditions.*

**Availability** **TOPICAL SOLUTION** 2%w/w, **OINTMENT** 6%, 12%w/w.

**Dose** Hyperkeratotic skin disorders: apply once daily, starting with lower strength preparations; gradually increase strength until satisfactory response obtained.

**Contraindications** Broken or inflamed skin; children under 2 years.

**Precautions** Diabetes mellitus or if peripheral blood circulation impaired; avoid contact with eyes; mouth; and mucous membranes; avoid application to large areas; irritated; loose/infected skin; pregnancy (Appendix 7c).



**Adverse Effects** Local irritation; dermatitis; salicylism on excessive application or treatment of large areas; particularly in children; salicylic acid poisoning; confusion; dizziness; headache; rapid breathing; ringing/buzzing in ears.

**Storage** Store protected from light.

## Urea

### Pregnancy Category-D

**Indications** *Hydrating agent and keratolytic for dry, scaling and itching skin conditions.*

**Availability** **CREAM** 10% in combination with other drugs (Aluminium tubes/jars) 20, 30 and 50g.

**Dose** Dry, scaling skin disorders: apply twice daily, preferably to damp skin.

**Precautions** Avoid application to face or broken skin; avoid contact with eyes; pregnancy (Appendix 7c).

**Adverse Effects** Transient stinging and local irritation; irritation to eyes; skin and respiratory tract.

**Storage** Store protected from moisture. Store cream in accordance with the instructions of the manufacturer.

## 14.6 Scabicides and Pediculicides

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### Scabies:

Scabies is caused by a mite, *Sarcoptes scabiei*, that burrows into the skin. It is readily transmitted from person to person; therefore the entire household must be treated at the same time to prevent reinfection. It is not necessary to take a bath before treatment with an acaricide, but all clothing and bedding should be washed to prevent reinfection.

Benzyl benzoate is an inexpensive scabicide. It must be applied to all skin surfaces, from the scalp to the soles of the feet, avoiding contact with the eyes; it is too irritant for use on children. Permethrin is less irritant and more effective than benzyl benzoate, but also more expensive; it may be used on children. Young infants can be treated with a cream containing precipitated sulphur 6-10% applied once daily for one week.

### Pediculosis:

Pediculosis of the head and body is caused by *Pediculus humanus capitis* and *Pediculus humanus corporis* respectively; pubic lice (crab lice) infestations are caused by *Pthirus pubis*, which may also affect the eye lashes and brows. All are transmitted by person to person contact, and may also contaminate clothing and bedding. All members of the affected household (and sexual contacts) must be treated at the same time, and clothing and bedding should be washed or exposed to the air; in head lice infestations, hair brushes and combs should also be disinfected.

Head and body lice are readily treated with permethrin; malathion is effective against pubic lice. Benzyl benzoate may be used for all lice infestations.

### Benzyl Benzoate\*

<b>Indications</b>	<i>Scabies; head, body and pubic lice; pediculosis.</i>
<b>Availability</b>	<b>LOTION</b> 100 ml (25% w/v); <b>OINTMENT</b> 25% w/w (25g).
<b>Dose</b>	<b>Adult-</b> Scabies: apply from neck down at night for 2 nights; on each occasion wash off after at least 24 h.  Pediculosis: apply to affected area and wash off 24 h later; further applications possibly needed after 7 and 14 days.
<b>Contraindications</b>	Irritated skin; neonates; pregnancy.

- Precautions** Do not use on inflamed or broken skin; avoid contact with eyes and mucous membranes; not recommended for children; lactation (withhold during treatment); apply below neck only; elderly.
- Adverse Effects** Local irritation; particularly in children.
- Storage** Store protected from light and air in well filled containers.

## Gamma Benzene Hexachloride

### Pregnancy Category-B

- Indications** *Pediculosis (but use for head lice is restricted by resistance), scabies.*
- Availability** **LOTION** 1%w/v; **OINTMENT** 1%w/w; **CREAM** 1%w/w; **SHAMPOO** 1%w/v.
- Dose** **For pediculosis:** As 1% preparation, apply to scalp and hair (taking care not to enter eyes), it should be massaged for 4 minutes and rinsed thoroughly.
- For scabies:** Take a proper bath and dry your skin then apply lotion in a thin layer below the neck upto the sole of feet. Leave it for 8-12 hour and then take bath.
- Contraindications** Seizure; hypersensitivity; skin inflammation; broken skin; premature infants; lactation; pregnancy (Appendix 7c).
- Precautions** Seizure disorder; open wound or sores; neonates, infants below 2 years; avoid contact with face, eyes; mucus membranes urethral meatus, psoriasis, elderly.
- Adverse effects** Insomnia; paresthesia; giddiness, agranulocytosis, aplastic anaemia, skin irritation, contact dermatitis; ataxia; alopecia; severe neurologic toxicities; symptoms of acute poisoning include nausea, vomiting, tremors, coma, convulsions and respiratory failure. Liver, kidney and myocardial toxicity have been reported.
- Storage** Store protected from light.

### Ivermectin (Refer Page No. 153)



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# 15. Diagnostic Agents

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## 15.1 Immunologicals

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The tuberculin test has limited diagnostic value. A positive tuberculin test indicates previous exposure to mycobacterial antigens through infection with one of the tubercle bacilli, or BCG vaccination. The tuberculin test does not distinguish between tuberculosis and other mycobacterial infection, between active and quiescent disease, or between acquired infection and seroconversion induced by BCG vaccination.

### Tuberculin Purified Protein Derivative\* (Tuberculin PPD)

**Indications** *Used for test of hypersensitivity to tuberculo-protein.*

**Availability** Available at special clinics or by specialists.

**Dose** *Intradermal injection*

**Adult and Child-** 5 to 10 units (1 unit may be used in hypersensitive patients or if tuberculosis is suspected).

**Contraindications** Should not be used within 3 weeks of receiving a live viral vaccine.

**Precautions** Elderly; malnutrition; viral or bacterial infections (including HIV and severe tuberculosis), malignant disease, corticosteroid or immunosuppressant therapy-diminished sensitivity to tuberculin; avoid contact with open cuts, abraded or diseased skin, eyes or mouth.

**Adverse Effects** Occasionally nausea, headache, malaise, rash; immediate local reactions (more common in atopic patients); rarely, vesicular or ulcerating local reactions, regional adenopathy and fever; necrosis, pruritis, pain.

## 15.2 Ophthalmics

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Fluorescein is used in ocular diagnostic procedures and for locating damaged areas of the cornea due to injury or disease.

Tropicamide is a short-acting relatively weak mydriatic that dilates the pupil and paralyzes the ciliary muscle. It facilitates the examination of the fundus of the eye.

### Fluorescein\*

#### Pregnancy Category-B

**Indications** *Detection of lesions and foreign bodies in the eye.*

**Availability** **EYE DROPS** 5 and 10 ml (2% w/v).

**Dose** **Ocular instillation**

**Adult and Child-** Detection of lesions and foreign bodies in eye: instill sufficient solution dropwise to stain damaged area.

**Contraindications** Hypersensitivity; avoid use with soft contact lenses.

**Precautions** History of allergy or bronchial asthma; lactation; pregnancy (Appendix 7c).

**Adverse effects** Gastrointestinal distress; hypotension; syncope; cardiac arrest; thrombophlebitis.

**Storage** Store protected from light.

### Lidocaine\* (Refer Page No. 298 and 417)

### Tropicamide\*

#### Pregnancy Category-C

**Indications** *Dilatation of the pupil to examine the fundus; cycloplegia.*

**Availability** **EYE DROPS** 5 and 10 ml vial (0.08 & 1.0 % w/v).

**Dose** **Ocular instillation**

**Adult and Child-** Dilatation of pupil to examine the fundus: 1 drop, 15 to 20 min before examination of eye.

**Precautions**

Patients aged over 60 years and hypermetropic (long-sighted)-may precipitate acute angle-closure glaucoma; darkly pigmented iris; more resistant to pupillary dilatation-exercise caution to avoid overdosage; hyperthyroidism; pregnancy (Appendix 7c); hypertension.

Avoid operating machinery or driving for 1-2 h after mydriasis.

**Adverse Effects**

Transient stinging and raised intraocular pressure; on prolonged administration-local irritation; hyperaemia; oedema and conjunctivitis; eczematous dermatitis; photophobia; parasympathetic stimulation.

**Storage**

Store protected from light and moisture. For eye drops: store in a refrigerator (8 to 15°C). It should not be allowed to freeze.



## 15.3 Radiocontrast Media

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Radiographic contrast media are needed for delineating soft tissue structures such as blood vessels, stomach, bowel loops and body cavities not otherwise visualized by standard X-ray examination. The contrast media in this group containing heavy atoms (metal or iodine) absorb a significantly different amount of X-rays than the surrounding soft tissue, thereby making the examined structures visible on radiographs.

Barium sulphate is a metal salt which is used to delineate the gastrointestinal tract. It is not absorbed by the body and does not interfere with stomach or bowel secretion or produce misleading radiographic artefacts. Barium sulphate may be used in either single- or double-contrast techniques or computer-assisted axial tomography. For double contrast examination gas can be introduced into the gastrointestinal tract by using suspensions of barium sulphate containing carbon dioxide or by using separate gas-producing preparations based on Sodium bicarbonate. Air administered through a gastrointestinal tube can be used as an alternative to carbon dioxide to achieve a double-contrast effect.

Amidotriozates (meglumine amidotriozate and Sodium amidotriozate) are iodinated ionic monomeric organic compounds. Both salts have been used alone in diagnostic radiography including computer-assisted axial tomography but a mixture of both is often preferred to minimize adverse effects and to improve the quality of the examination. Amidotriozates are used in a wide range of procedures including urography and examination of the gallbladder, biliary ducts and spleen. Owing to their high osmolality and the resulting hypertonic solutions, they are associated with a high incidence of adverse effects. Radiodensity depends on iodine concentration, and osmolality depends on number of particles in a given weight of solvent. The osmolality for a given radiodensity can be reduced by using an ionic dimeric medium such as meglumine iotroxate which contains twice the number of iodine atoms in a molecule or by using a non-ionic medium such as iohexol. Low osmolality media such as iohexol are associated with a reduction in some adverse effects (see below), but they are generally more expensive. Iohexol is used for a wide range of diagnostic procedures including urography, angiography and arthrography and also in computer-assisted axial tomography. Iopanoic acid is an oral iodinated ionic monomeric organic compound. It is absorbed from the gastrointestinal tract, excreted into the bile and concentrated in the gallbladder thus making it ideal for cholecystography. Propylidone is an iodinated organic compound which is used for the examination of the bronchial tract. Meglu-

mine iotroxate is excreted into the bile after intravenous administration and used for cholecystography and cholangiography.

### Hypersensitivity:

Anaphylactoid reactions to iodinated radiocontrast media are more common with ionic, high osmolality compounds. Patients with a history of asthma or allergy, drug hypersensitivity, adrenal suppression, heart disease, previous reaction to contrast media, and those receiving beta-adrenoceptor antagonists (beta-blockers) are at increased risk. Non-ionic media are preferred for these patients and beta-blockers should be discontinued if possible.

### Barium Sulphate\*

<b>Indications</b>	<i>Radiographic examination of the gastrointestinal tract.</i>
<b>Availability</b>	<b>DRY POWDER</b> (to be administered with water before procedure); <b>SUSPENSIONS</b> 100%w/v, 250%w/v.
<b>Dose</b>	<b>Adult and Child-</b> Radiographic examination of gastrointestinal tract: route and dosage depend on procedure and preparation used (consult literature).
<b>Contraindications</b>	Intestinal obstruction; conditions such as pyloric stenosis or lesions which predispose to obstruction; intestinal perforation or conditions with risk of perforation; such as acute ulcerative colitis; diverticulitis; or after rectal or colonic biopsy; sigmoidoscopy or radiotherapy; hypersensitivity; gastrointestinal haemorrhage; inflammation.
<b>Precautions</b>	Adequate hydration after procedure to prevent severe constipation.
<b>Adverse Effects</b>	Constipation or diarrhoea; abdominal cramps and bleeding; perforation of bowel resulting in peritonitis; adhesions; granulomas and high mortality rate; electrocardiographical changes-may occur with rectal administration; pneumonitis or granuloma formation-following accidental aspiration into lungs; bloating; constipation; stomach pain; ringing in ears; nausea; vomiting; pale skin; weakness.

### Iopanoic Acid\*

<b>Indications</b>	<i>Examination of gall bladder and biliary tract.</i>
<b>Availability</b>	<b>TABLET</b> 500 mg.
<b>Dose</b>	<b>Oral</b>

**Adult-** 3g with plenty of water 10 to 14 h before examination; if examination needs to be repeated, a further 3g on the same day. Alternatively, repeat examination carried out after 5 to 7 days with single 6g dose. Avoid dose over 3g in case of renal impairment.

**Contraindications** Severe renal disease and hepatic disease; jaundice caused by biliary-tract obstruction; impaired absorption due to acute gastrointestinal disorders.

**Precautions** Hypersensitivity to iodine-containing compounds or other contrast media; severe hyperthyroidism; hyperuricaemia or cholangitis; may interfere with thyroid-function tests; adequate resuscitation facilities must be immediately available when radiographic procedures are carried out; interactions (Appendix 6c).

**Adverse Effects** Nausea and vomiting; abdominal pain and diarrhoea; mild stinging on micturition; rashes and flushing; acute renal failure; thrombocytopenia and hypersensitivity reactions reported; also uricosuric and anticholinesterase effects.

**Storage** Store protected from light.

## Meglumine Iotroxate\*

**Pregnancy Category-D**

**Indications** *Examination of the gallbladder and biliary tract.*

**Availability** **INJECTION** 30 and 50 ml; **SOLUTION** 5-8g iodine in 100-250 ml.

**Dose** ***Intravenous injection***

**Adult-** Examination of gallbladder and biliary tract: 100 ml of meglumine iotroxate 10.5% solution over at least 15 min (consult literature).

**Contraindications** Hypersensitivity to iodine-containing compounds.

**Precautions**

History of allergy; atopy or asthma; severe hepatic impairment; renal impairment; dehydration-correct fluid and electrolyte balance before administration; multiple myeloma (risk if dehydrated; may precipitate fatal renal failure); cardiac disease; hypertension; pheochromocytoma; sickle-cell disease; hyperthyroidism; elderly; debilitated or children-increased risk of adverse effects; pregnancy; lactation; may interfere with thyroid-function tests; biguanides (withdraw 48 h before administration; restart when renal function stabilized); because of risk of hypersensitivity reactions; adequate resuscitation facilities must be immediately available during radiographic procedures; pregnancy (Appendix 7c).

**Adverse Effects**

Nausea, vomiting, metallic taste; flushing; sensations of heat; weakness; dizziness; headache; cough; rhinitis; sweating; sneezing; lacrimation; visual disturbances; pruritus; salivary gland enlargement; pallor; cardiac disorders, haemodynamic disturbances and hypotension or hypertension; convulsions; paralysis; coma; rigors; arrhythmias; pulmonary oedema; circulatory failure and cardiac arrest; occasionally anaphylactoid or hypersensitivity reactions; hyperthyroidism; pain on injection; extravasation may result in tissue damage; thrombophlebitis; thrombosis; venospasm and embolism.

**Propylidone\*****Indications**

*Examination of the bronchial tract.*

**Availability**

**SUSPENSION** 20 ml ampoule (600 mg/ml).

**Dose**

***Instillation into the lungs***

**Adult-** Examination of bronchial tract: consult literature.

**Contraindications**

Hypersensitivity to iodine-containing compounds; severe heart disease.

**Precautions**

Asthma; bronchiectasis; pulmonary emphysema or reduced pulmonary function; use of excessive volume or too rapid administration may result in lobar collapse; may interfere with thyroid-function tests; important: because of risk of hypersensitivity reactions; adequate resuscitation facilities must be immediately available when radiographic procedures are carried out.

**Adverse Effects**

Pyrexia; malaise; arthralgia; cough; occasionally; dyspnoea; atelectasis; pneumonia; rarely,; hypersensitivity reactions.

## 16. Dialysis Fluids

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## 16. Dialysis Fluids

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Solutions for peritoneal dialysis are preparations for intraperitoneal use which contain electrolytes in a similar concentration to that in plasma, and also contain glucose or another suitable osmotic agent. Peritoneal dialysis solutions always contain sodium, chloride, and hydrogen carbonate or a precursor; they may also contain calcium, magnesium, and potassium.

In renal failure haemodialysis is the preferred method to correct the accumulation of toxins, electrolytes and fluid. Peritoneal dialysis is less efficient than haemodialysis, but it is preferred in children, diabetic patients, and patients with unstable cardiovascular disease; it is also used in patients who can manage their condition, or those who live far from a dialysis centre. It is unsuitable for patients who have had significant abdominal surgery.

In peritoneal dialysis, the solution is infused into the peritoneal cavity, where exchange of electrolytes takes place by diffusion and convection, and excess fluid is removed by osmosis, using the peritoneal membrane as an osmotic membrane. There are two forms of peritoneal dialysis:

- *continuous ambulatory peritoneal dialysis* (CAPD), in which dialysis is performed manually by the patient several times each day
- *automated peritoneal dialysis* (APD), in which dialysis is performed by machine overnight.

The main complication of peritoneal dialysis is peritonitis, which often results from poor exchange technique; infections of the catheter exit site may also occur, again because of poor technique. With long-term dialysis progressive structural changes to the peritoneal membrane occur, ultimately resulting in dialysis failure.

## Intraperitoneal Dialysis Solution\*

### Indications

*Haemodialysis and peritoneal dialysis in renal failure; acute pulmonary oedema with renal insufficiency, cardiac dropsy.*

### **Peritoneal dialysis**

It is preferred in children, diabetic patients, and patients with unstable cardiovascular disease; also used in patients who can manage their condition, or those who live far from a dialysis centre. Unsuitable for patients who have had significant abdominal surgery.

### **The two forms of peritoneal dialysis**

a) Continuous Ambulatory Peritoneal Dialysis (CAPD), in which dialysis is performed manually by the patient several times each day.

b) Automated Peritoneal Dialysis (APD), in which dialysis is performed by machine overnight.

### Availability

**Intraperitoneal dialysis solution with Dextrose** - 1.5% w/v, 2.5% w/v and 4.25% w/v.

### Contraindications

Abdominal sepsis; previous abdominal surgery; severe inflammatory bowel disease; pregnancy, excessive obesity; behavioural disturbances.

### Precautions

Care required with technique to reduce risk of infection; warm dialysis solution to body temperature before use; some drugs may be removed by dialysis; generalised peritonitis; traumatic abdominal lesions.

### Adverse Effects

Infection including peritonitis; hernia; haemoperitoneum; hyperglycaemia, protein malnutrition; blocked catheter; fluid and electrolyte imbalance, disequilibrium syndrome, muscle cramp.





<b>17.</b>	<b>Disease Modifying Anti-Rheumatic Drugs (DMARDs) and Drugs for Gout</b>	<b>381</b>
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# 17. Disease Modifying Anti-Rheumatic Drugs (DMARDs) and Drugs for Gout

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## 17.1 Disease Modifying Anti Rheumatic Drugs (DMARDs)

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The process of cartilage and bone destruction which occurs in rheumatoid arthritis may be reduced by the use of a diverse group of drugs known as DMARDs (disease-modifying antirheumatic drugs). DMARDs include antimalarials (chloroquine, hydroxychloroquine), penicillamine, sulfasalazine, immunosuppressants (azathioprine, cyclophosphamide, methotrexate) and gold compounds.

Treatment should be started early in the course of the disease, before joint damage starts. Treatment is usually initiated with a NSAID when the diagnosis is uncertain and the disease course unpredictable. However, when the diagnosis, progression and severity of rheumatic disease have been confirmed, a DMARD should be introduced.

DMARDs do not produce an immediate improvement but require 4-6 months of treatment for a full response. Their long-term use is limited by toxicity and loss of efficacy. If one drug does not lead to objective benefit within 6 months, it should be discontinued and another DMARD substituted. Adverse reactions with DMARDs occur frequently and may be life threatening; careful monitoring is needed to avoid severe toxicity. Blood disorders (bone marrow suppression) can occur during treatment with many DMARDs; blood counts should be carried out before and during treatment, and patients should be advised to report without delay any unexplained symptom such as bleeding, bruising, purpura, infection, sore throat or fever. It has been suggested that combinations of DMARDs may be more effective than single drug but increased toxicity may be a problem; whether used alone or in combination, they should be prescribed only by specialists to ensure that they are used safely and to best advantage.

The antimalarial chloroquine is less effective than most other DMARDs, but as it is generally better tolerated it may be preferred in the treatment of mild rheumatoid arthritis. Chloroquine should not be used for psoriatic arthritis. Because long-term therapy can result in retinopathy ophthalmological examinations should be conducted before and during treatment.

Sulfasalazine has a beneficial anti-inflammatory effect and is considered by some rheumatologists to be a first-line DMARD, but it is poorly tolerated by about 25% of patients. Adverse reactions include blood disorders (bone marrow suppression), hepatotoxicity, skin reactions and gastrointestinal disturbances.

Methotrexate, an immunosuppressant, is considered to be a first-line DMARD; at the low doses used for rheumatoid arthritis it is well tolerated but there remains the risk of blood disorders (bone marrow suppression) and of hepatic and pulmonary toxicity. Other immunosuppressant drugs, including azathioprine, are generally reserved for use in patients with severe disease who have failed to respond to other DMARDs, especially in those with extra-cellular manifestations such as vasculitis. Immunosuppressants are used in psoriatic arthritis. Adverse reactions include blood disorders, alopecia, nausea and vomiting.

Penicillamine is not a first-line drug and its use is limited by a significant incidence of adverse effects including blood disorders (bone marrow suppression), proteinuria and rash.

Corticosteroids are potent anti-inflammatory drugs but their place in the treatment of rheumatoid arthritis remains controversial. Their usefulness is limited by adverse effects and their use should be controlled by specialists. Corticosteroids are usually reserved for use in patients with severe disease which has failed to respond to other antirheumatic drugs, or where there are severe extra-articular effects such as vasculitis. Corticosteroids are also used to control disease activity during initial therapy with DMARDs. Although corticosteroids are associated with bone loss this appears to be dose-related; recent studies have suggested that a low dose of a corticosteroid started during the first two years of moderate to severe rheumatoid arthritis may reduce the rate of joint destruction. The smallest effective dose should be used, such as oral prednisolone 7.5 mg daily for 2-4 years only, and at the end of treatment the dose should be tapered off slowly to avoid possible long term adverse effects. Relatively high doses of a corticosteroid, with cyclophosphamide, may be needed to control vasculitis.

## Azathioprine\* (Refer Page No. 266 and 434)

**Pregnancy Category-D**

**Schedule H**

### Indications

*Rheumatoid arthritis in cases that have failed to respond to chloroquine or penicillamine; psoriatic arthritis; transplant rejection; inflammatory bowel disease.*

### Availability

**TABLET 50 mg.**

<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> Rheumatoid arthritis and ankylosing spondylitis: 1.2g daily in 2 to 4 divided doses. Acute gout: 1.8g daily in divided doses until acute symptoms are resolved.</p> <p><b>Elderly over 60 years-</b> Rheumatoid arthritis and ankylosing spondylitis: 300 mg twice daily. Acute gout: 1.8g daily in divided doses for the first 24 h, reduce to 600 mg daily in divided doses as soon as possible.</p> <p><b>Child-</b> Not recommended.</p>
<b>Contraindications</b>	Hypersensitivity to azathioprine or mercaptopurine.
<b>Precautions</b>	<p>Monitor throughout treatment including blood counts; hepatic impairment (Appendix 7a); renal impairment; elderly (reduce dose); lactation (Appendix 7b); interactions (Appendix 6c, 6d); pregnancy (Appendix 7c).</p> <p>Patients should be warned to report immediately any signs or symptoms of bone marrow suppression; for example unexplained bruising or bleeding; purpura; infection; sore throat.</p>
<b>Adverse Effects</b>	Hypersensitivity reactions requiring immediate and permanent withdrawal include malaise; dizziness; vomiting; diarrhoea; fever; rigors; myalgia; arthralgia; rash; hypotension and interstitial nephritis; dose-related bone marrow suppression; liver impairment; cholestatic jaundice; hair loss and increased susceptibility to infections and colitis in patients also receiving corticosteroids; nausea; rarely, pancreatitis and pneumonitis. hepatic veno-occlusive disease; herpes zoster infection.
<b>Storage</b>	Store protected from light.

## Chloroquine\* (Refer Page No. 178)

**Pregnancy Category-D**

**Schedule H**

<b>Indications</b>	<i>Rheumatoid arthritis (including juvenile arthritis); malaria.</i>
<b>Availability</b>	<b>TABLETS</b> 150, 250 and 500 mg; <b>SYRUP</b> 100 mg/5 ml; <b>INJECTION</b> 5 ml ampoule and 30 ml vial (40 mg/ml).
<b>Dose</b>	<p><b>Oral</b></p> <p>Acute rheumatoid arthritis including juvenile idiopathic arthritis: 150 mg/day (max. 2.5 mg/kg/day).</p>
<b>Contraindications</b>	Psoriatic arthritis.

**Precautions** Monitor visual acuity throughout treatment; warn patient to report immediately any unexplained visual disturbances; hepatic impairment; renal impairment (Appendix 7d); lactation (Appendix 7b); neurological disorders including epilepsy; severe gastrointestinal disorders; G-6-PD deficiency; elderly; may exacerbate psoriasis and aggravate myasthenia gravis; porphyria; interactions (Appendix 6c, 6d).

**Adverse Effects** Gastrointestinal disturbances; headache; skin reactions (rash; pruritus); less frequently ECG changes; convulsions; visual changes; retinal damage; keratopathy; ototoxicity; hair depigmentation; alopecia; discolouration of skin; nails and mucous membranes; rarely, blood disorders (including thrombocytopenia; agranulocytosis; aplastic anaemia); mental changes (including emotional disturbances; psychosis); myopathy (including cardiomyopathy and neuromyopathy); acute generalized exanthematous pustulosis; exfoliative dermatitis; erythema multiforme (Stevens-Johnson syndrome) and hepatic damage; arrhythmias and convulsions in overdose.

**Storage** Store protected from light.

## Leflunomide\*

**Pregnancy Category-X**

**Schedule H**

**Indications** *Active rheumatoid arthritis, psoriatic arthritis.*

**Availability** **Tablet-** 10 and 20 mg.

**Dose** **Oral**  
**Active rheumatoid arthritis: Adults-** 100 mg once daily as loading dose for 3 days. Maintenance dose- 10-20 mg daily.

**Contraindications** Pregnancy (Appendix 7c), interactions (Appendix 6a and 6c).

**Precautions** Liver disease, kidney disease, heart disease, women of child bearing age, monitor blood counts and blood pressure regularly. May impair the ability to drive or operate machinery.

**Adverse Effects** Diarrhoea occurs in approximately 25% of patients, other adverse effect associated are mild alopecia, weight gain, increased blood pressure. Leukopenia and thrombocytopenia occur rarely.

**Storage** Store protected from heat, light and moisture at room temperature.

**Methotrexate\*** (Refer Page No. 259)**Pregnancy Category-X****Schedule H**

**Indications** *Rheumatoid arthritis which has failed to respond to penicillamine or chloroquine; malignant disease.*

**Availability** **TABLETS** 2.5, 5.0 and 7.5 mg; **INJECTION** vial/ampoule 25 mg/ml and 100 mg/ml.

**Dose** **Oral**

Severe active rheumatoid arthritis: 7.5 mg once weekly, adjusted according to response (max. weekly dose 20 mg).

Intramuscular, subcutaneous or intravenous route in severe attack under expert medical supervision at a dose of 7.5 mg once weekly.

**Contraindications** Lactation (Appendix 7b); pregnancy (Appendix 7c); immunodeficiency syndromes; significant pleural effusion or ascites.

**Precautions** Monitor throughout treatment including blood counts and hepatic and renal function tests; renal and hepatic impairment (avoid if severe; see also Appendices 7a); reduce dose or withdraw if acute infection develops; for woman or man; during contraception and for at least 6 months after treatment; peptic ulceration; ulcerative colitis; diarrhoea; ulcerative stomatitis; advise patient to avoid self-medication with salicylates or other NSAIDs; warn patient with rheumatoid arthritis to report cough or dyspnoea; interactions (Appendix 6a, 6c, 6d).

Patients should be warned to report immediately any signs or symptoms of bone marrow suppression; for example unexplained bruising or bleeding; purpura; infection; sore throat.

**Adverse Effects** Blood disorders (bone marrow suppression); liver damage; pulmonary toxicity; gastrointestinal disturbances-if stomatitis and diarrhoea occur; stop treatment; renal failure; skin reactions; alopecia; osteoporosis; arthralgia; myalgia; ocular irritation; precipitation of diabetes.

**Storage** Tablet: Store protected from light and moisture. Injection: store protected from light.

**D-Penicillamine\*** (Refer Page No. 90)**Pregnancy Category-D****Schedule H**

**Indications** *Severe rheumatoid arthritis; copper and lead poisoning.*

**Availability****CAPSULE/TABLET** 250 mg.**Dose****Oral**

**Adult-** Severe active rheumatoid arthritis: initially 125 to 250 mg daily for one month, increased by increments of similar amount at intervals of not less than 4 weeks to usual maintenance dose of 500 to 750 mg daily in divided doses (max 1.5g daily). If remission sustained for 6 months, reduce daily dose (125 to 150 mg every 12week may be attempted).

**Elderly-** Severe active rheumatoid arthritis: initially usual 125 mg daily for 1 month. Increase by increments of similar amount at intervals of not less than 4 weeks (max. 1g daily).

**Child-** Severe active rheumatoid arthritis: maintenance dose of 15 to 20 mg/kg daily, initial amount at intervals of 4 weeks over a period of 3 to 6 months.

**Contraindications**

Hypersensitivity; lupus erythematosus; pregnancy (Appendix 7c).

**Precautions**

Monitor throughout treatment including blood counts and urine tests; renal impairment; avoid concurrent gold; chloroquine or immunosuppressive treatment; avoid oral iron within 2 h of a dose.

Patients should be warned to report immediately any signs or symptoms of bone marrow suppression; for example unexplained bruising or bleeding; purpura; infection; sore throat.

**Adverse Effects**

Initially nausea (less of a problem if taken before food or on retiring; and if initial dose is only gradually increased); anorexia; fever; taste loss (mineral supplements not recommended); blood disorders including thrombocytopenia; neutropenia; agranulocytosis and aplastic anaemia; proteinuria; rarely, haematuria (withdraw immediately); haemolytic anaemia; nephrotic syndrome; lupus erythematosus-like syndrome; myasthenia-like syndrome; polymyositis (rarely, with cardiac involvement); dermatomyositis; mouth ulcers; stomatitis; alopecia; bronchiolitis and pneumonitis; pemphigus; glomerulonephritis (Goodpasture syndrome) and erythema multiforme (Stevens-Johnson syndrome); male and female breast enlargement; rash (early rash disappears on withdrawing treatment-reintroduce at lower dose and increase gradually; late rash is more resistant-either reduce dose or withdraw treatment).

**Storage**

Store protected from moisture.

**Sulfasalazine\*** (Refer Page No. 430)**Pregnancy Category-B****Schedule H**

<b>Indications</b>	<i>Severe rheumatoid arthritis; ulcerative colitis; Crohn's disease.</i>
<b>Availability</b>	<b>TABLETS</b> 500 and 1000 mg Enteric coated.
<b>Dose</b>	<b>Oral</b>  Acute rheumatoid arthritis: <b>Adult-</b> initially 500 mg daily increase by 500 mg at interval of one week (max. 2 to 3g in divided doses). <b>Child-</b> 40-50 mg/kg/day.
<b>Contraindications</b>	Hypersensitivity to salicylates and sulfonamides; severe renal impairment; child under 2 years; porphyria.
<b>Precautions</b>	Monitor during first 3 months of treatment including blood counts and hepatic and renal function tests; lactation (Appendix 7b); history of allergy; G-6-PD deficiency; slow acetylator status; interactions (Appendix 6c, 6d); pregnancy (Appendix 7c).  Patients should be warned to report immediately any signs or symptoms of bone marrow suppression; for example unexplained bruising or bleeding; purpura; infection; sore throat.
<b>Adverse Effects</b>	Nausea; diarrhoea; headache; loss of appetite; fever; blood disorders (including Heinz body anaemia; megaloblastic anaemia; leukopenia; neutropenia; thrombocytopenia); hypersensitivity reactions (including rash; urticaria; erythema multiforme (Stevens-Johnson syndrome); exfoliative dermatitis; epidermal necrolysis; pruritus; photosensitization; anaphylaxis; serum sickness; interstitial nephritis; lupus erythematosus-like syndrome); lung complications (including eosinophilia; fibrosing alveolitis); ocular complications (including periorbital oedema); stomatitis; parotitis; ataxia; aseptic meningitis; vertigo; tinnitus; alopecia; peripheral neuropathy; insomnia; depression; hallucinations; kidney reactions (including proteinuria; crystalluria; haematuria); oligospermia; rarely, acute pancreatitis; hepatitis; urine may be coloured orange.
<b>Storage</b>	Store protected from light.



## 17.2 Drugs for Gout

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### Acute Gout:

Acute attacks of gout are usually treated with high doses of a NSAID such as indomethacin (150-200 mg daily in divided doses); ibuprofen has weaker anti-inflammatory properties than other NSAIDs and is therefore less suitable for treatment of gout. Salicylates, including acetylsalicylic acid are also not suitable because they may increase plasma-urate concentrations. Colchicine is an alternative for those patients in whom NSAIDs are contraindicated. Its use is limited by toxicity with high doses. It does not induce fluid retention and can therefore be given to patients with heart failure; it can also be given to patients receiving anticoagulants.

### Chronic Gout:

For long-term control of gout in patients who have frequent attacks, the xanthine oxidase inhibitor allopurinol may be used to reduce production of uric acid. It should not be used to treat an acute attack since it may prolong it indefinitely. Treatment for chronic gout should not be started until after an acute attack has completely subsided, usually 2-3 weeks. The initiation of allopurinol treatment may precipitate an acute attack therefore colchicine or a suitable NSAID should be used as a prophylactic and continued for at least one month after the hyperuricaemia has been corrected. If an acute attack develops during treatment for chronic gout, then allopurinol should continue at the same dosage and the acute attack should be treated in its own right. Treatment for chronic gout must be continued indefinitely to prevent further attacks of gout.

## Allopurinol\*

Pregnancy Category-C

Schedule H

**Indications** *Prophylaxis of gout; prophylaxis of hyperuricaemia associated with cancer chemotherapy.*

**Availability:** TABLET 100 mg.

**Dose** *Oral*

**Adult-** Initially 100 mg daily after food, thereafter adjust according to uric acid concentration. (Usual maintenance dose in mild conditions: 100 to 200 mg daily, in moderately severe condition: 300 mg daily given in divided doses).

**Child-** Neoplastic conditions and enzyme disorders: 10 to 20 mg/kg daily (max. 400 mg).

**Contraindications** Acute gout; if an acute attack occurs while receiving allopurinol; continue prophylaxis and treat attack separately.

**Precautions** Ensure adequate fluid intake of 2-3 litres daily; lactation (Appendix 7b); renal and hepatic impairment (Appendices 7d and 7a); withdraw treatment if rash occurs; reintroduce if rash is mild but discontinue immediately if it recurs; interactions (Appendix 6c, 6d); pregnancy (Appendix 7c).

**Adverse Effects** Rash (see precautions above); hypersensitivity reactions occur rarely, and include fever; lymphadenopathy; arthralgia; eosinophilia; erythema multiforme (Stevens-Johnson syndrome) or toxic epidermal necrolysis; vasculitis; hepatitis; renal impairment.

## Colchicine\*

Pregnancy Category-C

Schedule H

**Indications** *Acute gout; short-term prophylaxis during initial therapy with allopurinol.*

**Availability** TABLET 0.5 mg.

**Dose** *Oral*

Acute gout: 1-2 tablets (0.5 mg each) can be given every 6-8 hours over several days with subsequent tapering. The drug must be stopped promptly at the first sign of loose stools and symptomatic treatment must be given for diarrhoea.

Prophylaxis: 0.5 mg once or twice daily.

<b>Contraindications</b>	Pregnancy (Appendix 7c).
<b>Precautions</b>	Elderly; gastrointestinal disease; cardiac impairment; hepatic impairment; renal impairment; lactation (Appendix 7b).
<b>Adverse Effects</b>	Nausea; vomiting; abdominal pain; excessive doses may cause severe diarrhoea; gastrointestinal haemorrhage; rash; renal and hepatic damage; rarely, peripheral neuritis; myopathy; alopecia; inhibition of spermatogenesis with prolonged treatment; blood disorders.
<b>Storage</b>	Store protected from light.



## 18. Diuretics

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## 18. Diuretics

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Diuretics increase urinary excretion of water and electrolytes and are used to relieve oedema associated with heart failure, nephrotic syndrome or hepatic cirrhosis. Some diuretics are used at lower doses to reduce raised blood pressure. Osmotic diuretics are mainly used to treat cerebral oedema, and also to lower raised intraocular pressure.

Most diuretics increase urine volume by inhibiting the reabsorption of Sodium and chloride ions in the renal tubule; they also modify renal handling of potassium, calcium, magnesium and urate. Osmotic diuretics act differently; they cause an increase in urine volume by an osmotic effect.

Although loop diuretics are the most potent their duration of action is relatively short, whilst thiazide diuretics are moderately potent but produce diuresis for a longer period. Potassium-sparing diuretics are relatively weak. Carbonic anhydrase inhibitors are weak diuretics which are rarely, used for their diuretic effect and are principally used to lower intraocular pressure in glaucoma.

### Electrolyte Imbalance:

The adverse effects of diuretic therapy are mainly due to the fluid and electrolyte imbalance induced by the drugs. *Hyponatraemia* is an adverse effect of all diuretics. The risk of *hypokalaemia*, which may occur with both thiazide and loop diuretics, depends more on the duration of action than on potency and is thus greater with thiazides than with loop diuretics (when given in equipotent doses). Potassium-sparing diuretics can cause *hyperkalaemia*. Other electrolyte disturbances include *hypercalcaemia* (thiazides), *hypocalcaemia* (loop diuretics) and *hypomagnesaemia* (thiazide and loop diuretics).

Symptoms of fluid and electrolyte imbalance include dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, restlessness, seizures, confusion, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, arrhythmias.

### Elderly:

The elderly are more susceptible to electrolyte imbalance than younger patients. Treatment should begin with a lower initial dose of the diuretic (commonly about 50% of the adult dose) and then adjusted carefully according to renal function, plasma electrolytes and diuretic response.

## Thiazide Diuretics:

Thiazide diuretics, such as hydrochlorothiazide, are moderately potent and act by inhibiting Sodium and chloride reabsorption at the beginning of the distal convoluted tubule. They produce diuresis within 1-2 h of oral administration and most have a duration of action of 12-24 h.

Thiazide diuretics are used in the management of oedema associated with mild to moderate congestive heart failure, renal dysfunction or hepatic disease; however, thiazides are not effective in patients with poor renal function (creatinine clearance of less than 30 ml per min). In severe fluid retention a loop diuretic may be necessary.

In hypertension, a thiazide diuretic is used at a low dose to lower blood pressure with very little biochemical disturbance; the max. therapeutic effect may not be seen for several weeks. Higher doses should not be used because they do not necessarily increase the hypotensive response but may cause marked changes in plasma potassium, magnesium, uric acid, glucose and lipids. If a thiazide alone does not lower blood pressure adequately, it may be used in combination with another anti-hypertensive such as a beta-adrenoceptor antagonist.

Urinary excretion of calcium is reduced by thiazide diuretics and this property is occasionally utilized in the treatment of idiopathic hypercalciuria in patients with calcium-containing calculi. Paradoxically, thiazide diuretics are used in the treatment of diabetes insipidus, since in this disease they reduce urine volume.

Thiazide diuretics, especially in high doses, produce a marked increase in potassium excretion which may cause hypokalaemia; this is dangerous in patients with severe coronary artery disease and those being treated with cardiac glycosides. In hepatic failure hypokalaemia can precipitate encephalopathy, particularly in alcoholic cirrhosis. Potassium-sparing diuretics are used as a more effective alternative to potassium supplements for prevention of hypokalaemia induced by thiazide diuretics; however supplementation with potassium in any form is seldom necessary with the smaller doses of diuretics used to treat hypertension.

## Loop Diuretics:

Loop diuretics, or high-ceiling diuretics, such as furosemide, are the most potent and rapidly produce an intense dose-dependent diuresis of relatively short duration. Oral furosemide produces diuresis within 30-60 min of administration, with the max. diuretic effect in 1-2 h. The diuretic action lasts for 4-6 h. Intravenous furosemide produces diuresis within 5 min, with the max. diuretic effect in 20-60 min and diuresis completes within 2 h.

Loop diuretics inhibit reabsorption from the ascending loop of Henlé in the renal tubule and are useful, particularly in situations where rapid and effective diuresis is needed such as reduction of acute pulmonary oedema due to left ventricular failure. They are also used to treat oedema associated with renal and hepatic disorders and are used in high doses in the management of oliguria due to chronic renal insufficiency. Loop diuretics may be effective in patients unresponsive to thiazide diuretics.

Because of their shorter duration of action, the risk of hypokalaemia may be less with loop diuretics than with thiazide diuretics; if required, potassium-sparing diuretics may be used for prevention of hypokalaemia. Loop diuretics may cause hypovolaemia and excessive use can produce severe dehydration with the possibility of circulatory collapse. Furosemide may cause hyperuricaemia and precipitate attacks of gout. Rapid high-dose injection or infusion of furosemide may cause tinnitus and even permanent deafness.

### **Potassium-Sparing Diuretics:**

Potassium-sparing diuretics include amiloride and spironolactone; they are weak diuretics and reduce potassium excretion and increase Sodium excretion in the distal tubule. Amiloride acts about 2 h after oral administration, reaching a peak in 6-10 h and persisting for about 24 h. Spironolactone, which acts by antagonising aldosterone, has a relatively slow onset of action requiring 2-3 days to achieve max. diuretic effect, and a similar period of 2-3 days for diuresis to cease after discontinuation of treatment.

Amiloride may be used alone, but its principal use is in combination with a thiazide or a loop diuretic to conserve potassium during treatment of congestive heart failure or hepatic cirrhosis with ascites.

Spironolactone is used in the treatment of refractory oedema due to heart failure, hepatic cirrhosis (with or without ascites), nephrotic syndrome and ascites associated with malignancy. It is frequently given with a thiazide or a loop diuretic, helping to conserve potassium in those at risk from hypokalaemia. A low dose of spironolactone is beneficial in severe heart failure in patients who are already taking an ACE inhibitor and a diuretic. Spironolactone is used in the diagnosis and treatment of primary hyperaldosteronism; presumptive evidence for diagnosis is provided by correction of hypokalaemia and of hypertension.

The most dangerous adverse effect of potassium-sparing diuretics, such as amiloride or spironolactone, is hyperkalaemia, which can be life-threatening. These diuretics are thus best avoided or used very carefully in patients who have or may develop hyperkalaemia, such as those with renal failure,



patients receiving other potassium-sparing diuretics and patients taking ACE inhibitors or potassium supplements.

## Osmotic Diuretics:

Osmotic diuretics, such as mannitol, are administered in sufficiently large doses to raise the osmolarity of plasma and renal tubular fluid. Osmotic diuretics are used to reduce or prevent cerebral oedema, to reduce raised intraocular pressure or to treat disequilibrium syndrome. Mannitol is also used to control intraocular pressure during acute attacks of glaucoma. Reduction of cerebrospinal and intraocular fluid pressure occurs within 15 min of the start of infusion and lasts for 3-8 h after the infusion has been discontinued; diuresis occurs after 1-3 h. Circulatory overload due to expansion of extracellular fluid is a serious adverse effect of mannitol; as a consequence, pulmonary oedema can be precipitated in patients with diminished cardiac reserve, and acute water intoxication may occur in patients with inadequate urine flow.

## Amiloride

Pregnancy Category-B

Schedule H

<b>Indications</b>	<i>Oedema associated with heart failure or hepatic cirrhosis (with ascites), usually with thiazide or loop diuretic; hypertension.</i>
<b>Availability</b>	<b>TABLETS</b> 5 mg (Amiloride) + 50 mg (Hydrochlorothiazide), 5 mg (Amiloride) + 40 mg (furosemide).
<b>Dose</b>	<b>Oral</b>  Oedema: used alone initially 10 mg daily in 1 or 2 divided doses, adjusted according to response (max. 20 mg daily).  Combined with a thiazide or a loop diuretic: initially 5 mg daily, increasing to 10 mg if necessary (max. 20 mg daily).
<b>Contraindications</b>	Hyperkalaemia; renal failure; potassium supplementation.
<b>Precautions</b>	Monitor electrolytes; particularly potassium; hypochloremia, hepatic cirrhosis, renal impairment (Appendix 7d); diabetes mellitus; elderly (reduce dose); lactation; interactions (Appendix 6b, 6c); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Hyperkalaemia; hyponatraemia (for symptoms of fluid and electrolyte imbalance see introductory notes); diarrhoea; constipation; anorexia; paraesthesia; dizziness; minor psychiatric or visual disturbances; rash; pruritus; rise in blood urea nitrogen; headache; abdominal pain, flatulence.

**Storage** Store protected from light.

## **Furosemide\*** (Refer Page No. 339)

**Pregnancy Category-C**

**Indications** *Oedema; oliguria due to renal failure; pulmonary oedema; hypertension.*

**Availability** **TABLETS** 40, 100, 200 and 500 mg; **INJECTION** 2 ml (20 mg/ml).

**Dose** **Oral**

**Adult-** Oedema: initially 40 mg daily on waking up; maintenance dose 20 to 40 mg daily; may be increased to 80 mg daily or more in resistant oedema.

**Child-** 1 to 3 mg/kg daily (max. 40 mg daily).

**Contraindications** Renal failure with anuria; precomatose states associated with liver cirrhosis; hypersensitivity.

**Precautions** Monitor electrolytes particularly potassium and Sodium; hypotension; asymptomatic hyperuricaemia, systemic lupus erythmatosus, elderly (reduce dose); pregnancy (Appendix 7c); lactation; correct hypovolaemia before using in oliguria; renal impairment; hepatic impairment (Appendix 7a); prostatic enlargement; porphyria; interactions (Appendix 6b, 6c).

**Adverse Effects** Hypokalaemia; hypomagnesaemia; hyponatraemia; hypochloroemic alkalosis (for symptoms of fluid and electrolyte imbalance; see introductory notes); increased calcium excretion; hypovolaemia; hyperglycaemia (but less often than with thiazide diuretics); temporary increase in plasma cholesterol and triglyceride concentration; less commonly hyperuricaemia and gout; rarely, rash; photosensitivity; bone marrow depression (withdraw treatment); pancreatitis (with large parenteral doses); tinnitus and deafness (with rapid administration of large parenteral doses and in renal impairment; deafness may be permanent if other ototoxic drugs taken); hepatic encephalopathy, anorexia, orthostatic hypotension.

## **Hydrochlorothiazide\*** (Refer Page No. 308)

**Pregnancy Category-B**

**Indications** *Oedema; diabetes insipidus; hypertension; heart failure.*

**Dose** **Oral**

**Adult-** Hypertension: 12.5 to 25 mg daily. Oedema: initially 25 mg daily on waking up, increased to 50 mg daily if necessary. Severe oedema in patients unable to tolerate loop diuretics: up to 100 mg either daily or on alternate days (max. 100 mg daily). Nephrogenic diabetes insipidus: initially up to 100 mg daily.

**Elderly-** Hypertension: initially 12.5 mg daily. Oedema: initially 12.5 mg daily.

### Contraindications

Same as in chapter 13.4.

### Precautions

Same as in chapter 13.4.

### Adverse Effects

Hypokalaemia; hypomagnesaemia; hyponatraemia; hypochloreaemic alkalosis (for symptoms of fluid and electrolyte imbalance see introductory notes); hypercalcaemia; hyperglycaemia; hyperuricaemia; gout; rash; photosensitivity; altered plasma lipid concentration; rarely, impotence (reversible); blood disorders (including neutropenia; thrombocytopenia); pancreatitis; intrahepatic cholestasis and hypersensitivity reactions (including pneumonitis; pulmonary oedema; severe skin reactions) also reported; acute renal failure.

## Mannitol\*

### Pregnancy Category-C

### Indications

*Cerebral edema, impending acute renal failure, acute poisonings, raised intraocular pressure (emergency treatment or before surgery).*

### Availability

**INFUSION** 5, 10 and 20%.

### Dose

**Test dose** (if patient is oliguric or if renal function is inadequate), By intravenous infusion as a 20% solution infused over 3–5 minutes, **Adult and Child-** 200 mg/kg; repeat test dose if urine output is less than 30–50 ml/h; if response is inadequate after a second test dose, re-evaluate the patient.

**Raised intracranial or intraocular pressure:** By i.v infusion as a 20% solution infused over 30–60 minutes, **Adult-** 0.25–2g/kg; **Child-** 0.5–1.5g/kg.

**Cerebral oedema:** By i.v infusion as a 20% solution infused rapidly, **Adult and Child-** 1g/kg.

### Contraindications

Acidosis, congestive heart failure, pulmonary oedema (particularly in diminished cardiac reserve), dehydration, inadequate urine flow, acute tubular necrosis, anuria, acute left ventricular failure, intracranial bleeding.

<b>Precautions</b>	Patients with cardiovascular disease; hypervolemia; urinary tract obstruction; should not be given with whole blood; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Headache, nausea, vomiting, dehydration, edema, hypernatraemia, inflammation, skin necrosis, urticaria, chills, convulsions, fluid and electrolyte imbalance, acidosis, circulatory overload, visual disturbance.
<b>Storage</b>	Store at temperatures between 20° and 30°C. Exposure to lower temperatures may cause the deposition of crystals, which should be dissolved by warming before use.

## Spirolactone\*

**Pregnancy Category-D**

**Schedule H**

<b>Indications</b>	<i>Refractory oedema in congestive heart failure; adjunct to ACE inhibitor and loop or thiazide diuretic in severe congestive heart failure; nephrotic syndrome; hepatic cirrhosis with ascites and oedema; ascites associated with malignancy; primary hyperaldosteronism.</i>
<b>Availability</b>	<b>TABLETS</b> 25 and 100 mg.
<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> Oedema: 100 to 200 mg daily, increased if necessary to 400 mg daily in resistant oedema; usual maintenance dose 75-200 mg daily.</p> <p>Primary hyperaldosteronism (diagnosis): 400 mg daily for 3 to 4 weeks. Preoperative management: 100 to 400 mg daily. If not suitable for surgery; lowest effective dose for long-term maintenance.</p> <p>Adjunct in severe heart failure: usually 25 mg daily.</p> <p><b>Child-</b> Initially 3 mg/kg daily in divided doses.</p>
<b>Contraindications</b>	Pregnancy (Appendix 7c); lactation; hyperkalaemia; hyponatraemia; severe renal impairment; Addison's disease; anuria.
<b>Precautions</b>	Monitor blood urea nitrogen and plasma electrolytes (discontinue if hyperkalaemia); concomitant administration of potassium sparing diuretics and its inhibitors and NSAIDs, elderly (reduce dose); diabetes mellitus; renal impairment; hepatic impairment; porphyria; high doses carcinogenic in rodents; interactions (Appendix 6b, 6d).

**Adverse Effects**

Hyperkalaemia; hyponatraemia; hyperchloraemic acidosis; dehydration (for symptoms of fluid and electrolyte imbalance see introductory notes); transient increase in blood urea nitrogen; diarrhoea; gynaecomastia; menstrual irregularities; impotence; hirsutism; deepening of voice; rash; ataxia; fever; hepatotoxicity; gastric bleeding, ulceration; agranulocytosis.

**Storage**

Store protected from light and moisture.



## 19. Drugs in Osteoporosis

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## 19. Drugs in Osteoporosis

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Osteoporosis is defined as a reduction in the strength of bone leading to increased risk of fractures. It occurs more frequently with increasing age as bone tissue is progressively lost. If diagnosed early, the fractures associated can often be prevented. Attempt should be made to prevent it by taking measures such as balanced diet rich in calcium and vitamin D, weight bearing exercises, adequate exposure to sunlight, adopting a healthy lifestyle with no smoking and alcohol consumption. Pharmacotherapy is recommended only when not controlled by above measures.

**Bisphosphonates (BPNs)** are structurally related to pyrophosphates, compounds that are incorporated into bone matrix. They specifically impair osteoclast function and reduce osteoclast number, in part by the induction of apoptosis. BPNs can be grouped into 3 different categories. The first category of drugs, like etidronate, have simpler side chains, are the least potent and are seldom used now. The second and third categories of drugs have an amino or nitrogenous ring substitution in the side chain; are more potent and have higher efficacy, eg. pamidronate, alendronate and risedronate, zoledronate respectively.

BPNs are poorly absorbed on oral administration. The most common side effect associated with bisphosphonates is stomach upset. These drugs are also known to cause esophageal inflammation, which can lead to erosion of the esophagus and increase the risk of esophageal cancer. Esophageal irritation can be minimized by taking the drug with a full glass of water and remaining upright for 30 minutes. Other serious but rare side effect associated with bisphosphonates include osteonecrosis (death of bone cells) of the jaw. This complication is more frequently seen in individuals who have taken high IV doses of zoledronate.

**Estrogens** have been found to reduce bone turnover, prevent bone loss, and induce small increases in bone mass of the spine, hip, and total body. The effects of estrogen are seen in women with natural or surgical menopause and in late postmenopausal women with or without established osteoporosis. Estrogens are efficacious when administered orally or transdermally.

Calcium and vitamin D are needed to increase bone mass in addition to estrogen replacement therapy. A daily intake of



1,000-1,200 mg of calcium (through diet and supplements) is recommended. A daily intake of 200-600 IU of vitamin D is also recommended.

**Selective estrogen receptor modulators (SERMs)** such as raloxifene is a non-hormonal drug recommended for the prevention of vertebral fractures in women with osteoporosis who are not at high risk of non-vertebral fractures and who do not have a past history of venous thromboembolism. It is slightly less potent than BPNs with regard to hip fracture reduction. However it reduces the risk of new vertebral fractures and also the risk of cardiovascular events.

**Calcitonin-salmon** is a synthetic version of the body's natural hormone, calcitonin, which is produced by the thyroid gland. The hypocalcaemic hormone is also used in osteoporosis and paget's disease. It may be administered via nasal spray and injection.

**Strontium ranelate** appears to block osteoclast differentiation while promoting their apoptosis and thus inhibiting bone resorption. At the same time, strontium ranelate appears to promote bone formation. It is therefore regarded as a "dual action bone agent" (DABA). This results in a rebalance of bone turnover in favour of bone formation.

## Alendronate

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Treatment and prevention of postmenopausal osteoporosis, glucocorticoid-induced osteoporosis, Paget's disease.</i>
<b>Availability</b>	<b>Tablet-</b> 5, 10, 35, and 70 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult</b> <b>Treatment of postmenopausal osteoporosis:</b> 5-10 mg daily or 35-70 mg weekly. <b>Paget's disease:</b> 40 mg once daily for six months. <b>Glucocorticoid-induced osteoporosis:</b> 5 mg once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dose is 10 mg once daily.
<b>Contraindications</b>	Esophageal dysmotility, esophageal obstruction, esophageal ulcer, hypocalcaemia, hypersensitivity, lactation, pregnancy (Appendix 7c), interactions (Appendix 6c, 6d).
<b>Precautions</b>	History of ulcers, hypocalcaemia, severe renal insufficiency, should be taken on an empty stomach and remain upright for not less than 30 minutes.

**Adverse Effects** Oesophagitis, abdominal pain with cramps, abdominal swelling, constipation, diarrhoea, dysphagia, headache, myalgia, nausea, vomiting, peptic ulcer, flatulence, retrosternal pain, bodyache.

**Storage** Store protected from heat, light and moisture at room temperature not exceeding 30°C.

## Raloxifene\*

**Schedule H**

**Indications** *Prevention and treatment of postmenopausal osteoporosis.*

**Availability** **TABLET** 60 mg.

**Dose** Prevention of post menopausal osteoporosis: **Adult-** 60 mg daily.

**Contraindications** Active or past history of venous thromboembolism including deep vein thrombosis; pulmonary embolism; retinal vein thrombosis; pregnancy (Appendix 7c), lactation.

**Precautions** Not to be used for primary or secondary prevention of cardiovascular disease; prolonged immobilisation; CHF, active malignancy; prior stroke or transient ischemic attack, premenopausal women, moderate/severe renal impairment, liver disease; history of estrogen-induced hypertriglyceridaemia; interactions (Appendix 6c).

**Adverse Effects** Hot flushes; leg cramps; peripheral oedema, influenza-like symptoms; less commonly venous thromboembolism, thrombophlebitis; rarely, rashes, gastro-intestinal disturbances, hypertension, arterial thromboembolism, headache (including migraine); breast discomfort; thrombocytopenia; weight gain; endometrial carcinoma.

**Storage** Store protected from light and moisture between 20-25°C.

## Strontium Ranelate

**Indications** *To reduce risk of fractures in postmenopausal osteoporosis.*

**Availability** **Granules-** 2g sachet.

**Dose**

**Oral**

**Adult-** 2g once daily at bedtime preferably 2 hours after meals. Mix the granules in a glass of water and administer the suspension immediately after preparation.

**Contraindications**

Hypersensitivity, phenylketonuria, severe renal impairment (creatinine clearance <30 ml/min), patients at increased risk of venous thromboembolism.

**Precautions**

Pregnancy, lactation, children and elderly, interactions (Appendix 6c).

**Adverse Effects**

Nausea and diarrhoea are common; headache, eczema, transient reversible increase in creatine kinase activity, memory loss on long term use, venous thromboembolism, dermatitis are also reported.

**Storage**

Store protected from light and moisture.



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## 20. Drugs for Anaesthesia

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During the use of Anaesthetics special precautions and close monitoring of the patient are required. These drugs may be fatal if used inappropriately and should be used by non-specialized personnel only as a last resort. Irrespective of whether a general or conduction (regional or local) anaesthetic technique is used; it is essential that facilities for intubation and mechanically assisted ventilation are available. A full preoperative assessment is required including; if necessary; appropriate fluid replacement.

### Long-Term Medication

The risk of stopping long-term medication before surgery may be greater than the risk of continuing it. It is essential that the anaesthetist is told of all drugs that the patient is (or has been) taking; in case of oral anticoagulants; corticosteroids; hormonal contraceptives and diabetic patients.

## 20.1 General Anaesthetics

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### Intravenous Agents:

Intravenous anaesthetics may be used alone to produce anaesthesia for short surgical procedures but are more commonly used for induction only. They can produce apnoea and hypotension and thus facilities for adequate resuscitation must be available. Before intubation is attempted; a muscle relaxant must be given. Individual requirements vary considerably; lesser dosage is indicated in the elderly; debilitated or hypovolaemic patients.

Intravenous induction using thiopental is rapid and excitement does not usually occur. Anaesthesia persists for about 4–7 min; large or repeated doses severely depress respiration and delay recovery.

Anaesthesia with ketamine persists for up to 15 min after a single intravenous injection and is characterized by profound analgesia. It may be used as the sole agent for diagnostic and minor surgical interventions. Subanaesthetic concentrations of ketamine may be used to provide analgesia for painful procedures of short duration such as the dressing of burns; radiotherapeutic procedures; marrow sampling and minor orthopaedic procedures. Recovery from ketamine anaesthesia is associated with a high incidence of hallucinations and other emergence reactions. Ketamine is of particular value in children; in whom hallucinations are believed to be less significant.

### Volatile Inhalational Agents:

One of the volatile anaesthetics; ether; halothane (with or without nitrous oxide); must be used for induction when intravenous agents are contraindicated and particularly when intubation is likely to be difficult.

Full muscle relaxation is achieved in deep anaesthesia with ether. Excess bronchial and salivary secretion can be avoided by premedication with atropine. Laryngeal spasm may occur during induction and intubation. Localized capillary bleeding can be troublesome and postoperative nausea and vomiting are frequent; recovery time is slow particularly after prolonged administration.

**If intubation is likely to be difficult; halothane is preferred.**

It does not augment salivary or bronchial secretions and the incidence of postoperative nausea and vomiting is low. Severe hepatitis; which may be fatal; sometimes occurs; it is more likely in patients who are repeatedly anaesthetized with halothane within a short period of time.

## Inhalational Gases:

Nitrous oxide is used for the maintenance of anaesthesia. It is too weak to be used alone; but it allows the dosage of other anaesthetic agents to be reduced. It has a strong analgesic action.

Oxygen should be added routinely during anaesthesia with inhalational agents; even when air is used as the carrier gas; to protect against hypoxia.

Oxygen is also used in the management of anaphylaxis; myocardial infarction and severe acute asthma.

## Halothane\*

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>Induction and maintenance of anaesthesia.</i>
<b>Availability</b>	<b>VOLATILE LIQUID</b> 30, 50, 200, and 250 ml.
<b>Dose</b>	Induction of anaesthesia using specially calibrated vaporiser; in oxygen or oxygen–nitrous oxide. Introductory dose: 0.5 to 3%. Maintenance dose: 0.5 to 1.5%.  <b>Adult-</b> Increase gradually 2 to 4%.  <b>Child-</b> 1.5 to 2%.  Maintenance of anaesthesia using specially calibrated vaporiser; oxygen; oxygen–nitrous oxide 0.5 to 2%.
<b>Contraindications</b>	History of unexplained jaundice or pyrexia following previous exposure to halothane; family history of malignant hyperthermia; raised cerebrospinal fluid pressure; porphyria; not recommended for obstetrical anaesthesia, interactions (Appendix 6c).
<b>Precautions</b>	Anaesthetic history should be carefully taken to determine previous exposure and previous reactions to halothane (at least 3 months should be allowed to elapse between each re-exposure); avoid for dental procedures in patients under 18 years unless treated in hospital (high risk of arrhythmias); pregnancy (Appendix 7c); lactation (Appendix 7b); renal failure; hyperkalaemia.
<b>Adverse Effects</b>	Arrhythmias; bradycardia; respiratory depression; hepatic damage; malignant hyperthermia; cyanosis; post operative nausea and vomiting.
<b>Storage</b>	Store protected from light at a temperature not exceeding 25°C.



## Ketamine\*

Pregnancy Category-B

Schedule H

**Indications** *Induction and maintenance of anaesthesia; analgesia for painful procedures of short duration especially for patients at the risk of hypotension and bronchospasm.*

**Availability** **INJECTIONS** 2 ml ampoule (50 mg/ml); 10 ml vial (10 and 50 mg/ml).

**Dose** ***Intravenous injection***

Short Procedures: Initially 6.5 to 13 mg/kg adjusted according to response (10 mg/kg usually produces 12 to 25 min. of surgical anaesthesia).

Procedures not involving intense pain: initially 4 mg/kg; (usual dose is 1 to 4.5 mg/kg).

Short procedure over at least 60 min: initially 4 mg/kg (2 mg/kg usually produces 5 to 10 min. of surgical anaesthesia).

Longer Procedure: induction by intravenous injection using solution containing 1 mg/ml.

Longer procedure: induction dose 0.5 to 2 mg/kg; maintenance 10 to 45 mg/kg/min. rate adjusted according to response.

**Contraindications** Thyrotoxicosis; hypertension (including pre-eclampsia); history of cerebrovascular accident; cerebral trauma; intracerebral mass or haemorrhage or other cause of raised intracranial pressure; open eye injury and increased intraocular pressure; psychiatric disorders; particularly hallucinations; hypersensitivity to the drug.

**Precautions** Supplementary analgesia often required in surgical procedures involving visceral pain pathways (morphine may be used but addition of nitrous oxide will often suffice); during recovery; patient must remain undisturbed but under observation; lactation; children; alcohol intoxicated patients; increased CSF pressure; cardiac decompensation; pregnancy (Appendix 7c).

Warn patient not to perform skilled tasks; for example operating machinery or driving; for 24 h and also to avoid alcohol for 24 h.

**Adverse Effects** Hallucinations and other emergence reactions during recovery possibly accompanied by irrational behaviour (effects rarely, persist for more than few hour but can recur at any time within 24 h); transient elevation of pulse rate and blood pressure common; arrhythmias have occurred; hypotension and bradycardia occasionally reported; confusion; delirium; morbilliform rash; transient erythema; diplopia; increased intraocular pressure; anorexia; nausea; vomiting; local pain and exanthema at injection site; apnoea; laryngospasm.

**Storage** Store protected from light at a temperature not exceeding 30°C.

## Nitrous Oxide\*

### Pregnancy Category-C

**Indications** *Maintenance of anaesthesia in combination with other anaesthetic agents (halothane; ether; or ketamine) and muscle relaxants; analgesia for obstetric practice; for emergency management of injuries; during postoperative physiotherapy and for refractory pain in terminal illness.*

**Availability** **INHALATIONAL GAS**

**Dose** Maintenance of anesthesia using suitable equipment up to 66% in oxygen.

Analgesic use: 50% in oxygen or according to patient's need.

**Contraindications** Demonstrable collection of air in pleural; pericardial or peritoneal space; intestinal obstruction; occlusion of middle ear; arterial air embolism; decompression sickness; chronic obstructive airway disease; emphysema.

**Precautions** Minimize exposure of staff; interactions (Appendix 6c); pregnancy (Appendix 7c).

**Adverse Effects** Nausea and vomiting; after prolonged administration megaloblastic anaemia; depressed white cell formation; peripheral neuropathy.

**Storage** Store under pressure in metal cylinders of the type conforming to the appropriate safety regulations and at temperature not exceeding 37°C.

## Oxygen\*

**Indications** *To maintain an adequate oxygen tensio in inhalational anaesthesia.*

**Availability** **INHALATIONAL GAS**

**Dose** (Oxygen is treated as drug since it is prescribed for hypoxemic patient to support alveolar oxygen in emergencies).

40 to 60% oxygen using special oxygen therapy equipment.

**Adverse Effects** Concentrations greater than 80% have a toxic effect on the lungs leading to pulmonary congestion; exudation and atelectasis.

**Storage** Store under pressure in metal cylinder of the type conforming to appropriate safety regulations. Valves and taps should not be lubricated with oil or grease.

## Propofol\*

**Pregnancy Category-B**

**Schedule H**

**Indications** *Induction and maintenance of general anaesthesia, sedation.*

**Availability** **INJECTIONS** 10, 20 and 50 ml vials (10 mg/ml), 10 and 20 ml vials (20 mg/ml); Ampoule 12, 20 and 50 ml (1%)

**Dose** ***Intravenous***

**Induction and maintenance of general anaesthesia:**

**Adult:** Induction: 40 mg by injection or infusion every 10 seconds. Usual dose: 2-2.5 mg/kg. Maintenance: Infusion- 6-12 mg/kg/h, intermittent bolus injection - 20-50 mg as needed.

**Child:** >3 years: Induction dose of 2.5-3.5 mg/kg. Maintenance dose: 7.5-18 mg/kg/h by i.v infusion

**Elderly:** Including debilitated patients: Infuse at a rate of 20 mg every 10 seconds. Maintenance: 3-6 mg/kg/h.

**Sedation:**

**Adult:** In diagnostic and surgical procedures: Initially, 6-9 mg/kg/h by infusion given for 3-5 minutes or an alternative dose of 0.5 mg/kg by slow injection over 3-5 minutes. Maintenance: 1.5-4.5 mg/kg/h infusion. Reduce maintenance dose by 20% for high-risk patients needing sedation. For ventilated patients: 0.3 mg/kg/h by infusion, subsequent maintenance dose: 0.3 – 3 mg/kg/h.

**Contraindications** Sedation in children and adolescents ≤16 years, Known hypersensitivity to propofol.

**Precautions** Cardiac impairment; respiratory impairment; elderly; hypovolaemia; epilepsy; hypotension; patients with high intracranial pressure; monitor blood-lipid concentration if risk of fat overload or if sedation longer than 3 days; hepatic impairment; renal impairment, pregnancy (Appendix 7c), interactions (Appendix 6c).

**Adverse Effects** Apnoea, bradycardia, arrhythmias, hypotension, anaphylaxis, rash, pruritus, involuntary muscle movements, headache, pain, burning or stinging at injection site.

**Storage** Store at a temperature not exceeding 30°C. It should not be allowed to freeze.

## Thiopental

**Pregnancy Category-C**

**Schedule H**

**Indications** *Induction of anaesthesia prior to administration of inhalational anaesthetic; anaesthesia of short duration. Preferred if cerebral ischemia is expected.*

**Availability** **STERILE POWDER** 500 mg and 1g/vial.

**Dose** **Slow intravenous injection**

3 to 5 mg/kg as 2.5% solution.

**Adult-** over 18 year fit and premeditated: 10 to 150 mg.

**Child-** 4 to 7 mg/kg.

**Contraindications** Inability to maintain airway; hypersensitivity to barbiturates; cardiovascular disease; dyspnoea or obstructive respiratory disease; porphyria; hypotension or shock; Addison's disease; hepatic or renal dysfunction; increased blood urea; severe anaemia; asthma; myasthenia gravis.

**Precautions** Local extravasation can result in extensive tissue necrosis and sloughing; intra-arterial injection causes intense pain and may result in arteriospasm; hepatic impairment (Appendix 7a); interactions (Appendix 6a); pregnancy (Appendix 7c); patients with advanced cardiac disease; increased intracranial pressure; asthma; myasthenia gravis; endocrine insufficiency.

Warn patient not to perform skilled tasks; for example operating machinery; driving for 24 h and also to avoid alcohol for 24 h.

**Adverse Effects** Respiratory depression; myocardial depression; cardiac arrhythmias; somnolence; bronchospasm; urticaria; vasodilation; apnoea; emergence delirium; headache; nausea; oedema.

**Storage** Store in single dose container.

## 20.2 Local Anaesthetics

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Drugs used for conduction anaesthesia (also termed local or regional anaesthesia) act by causing a reversible block to conduction along nerve fibres. Local anaesthetics are used very widely in dental practice; for brief and superficial interventions; for obstetric procedures and for specialized techniques of regional anaesthesia calling for highly developed skills. Facilities and equipment for resuscitation should be readily available at all times. Local anaesthetic injections should be given slowly in order to detect inadvertent intravascular injection. Hypersensitivity testing should be done in all patients before administrations of local anaesthetics.

### Local Infiltration

Many simple surgical procedures that neither involve the body cavities nor require muscle relaxation can be performed under local infiltration anaesthesia. Lower-segment caesarean section can also be performed under local infiltration anaesthesia. The local anaesthetic drug of choice is lidocaine 0.5% with or without epinephrine. No more than 4 mg/kg of plain lidocaine or 7 mg/kg of lidocaine with epinephrine should be administered on any one occasion. The addition of epinephrine (adrenaline) diminishes local blood flow; slows the rate of absorption of the local anaesthetic and prolongs its effect. **Care is necessary when using epinephrine for this purpose since; in excess; it may produce ischaemic necrosis. It should not be added to injections used in digits or appendages.**

### Surface Anaesthesia

Topical preparations of lidocaine are available and topical eye drop solutions of tetracaine (chapter 19.2) are used for local anaesthesia of the cornea and conjunctiva.

### Regional Block

A regional nerve block can provide safe and effective anaesthesia but its execution requires considerable training and practice. Nevertheless; where the necessary skills are available; techniques such as axillary or ankle blocks can be invaluable. Either lidocaine 1% or bupivacaine 0.5% is suitable. Bupivacaine has the advantage of a longer duration of action.

### Spinal Anaesthesia

This is one of the most useful of all anaesthetic techniques and can be used widely for surgery of the abdomen and the lower limbs. It is a major procedure requiring considerable training and practice. Either lidocaine 5% in glucose or bupivacaine 0.5% in glucose can be used but the latter is often chosen because of its longer duration of action.

## Bupivacaine\*

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Infiltration anaesthesia; peripheral and sympathetic nerve block; spinal anaesthesia; postoperative pain relief.</i>
<b>Availability</b>	<b>INJECTION</b> 20 ml vial (0.25%; 0.5% and 1%).
<b>Dose</b>	<p><b>Adult-Local:</b> Infiltration using 2.5 mg/ml solution (max. 60 ml).</p> <p>Peripheral nerve block: 2.5 mg/ml solution (max. 20 ml) or 5.0 mg/ml solution (max. 30 ml).</p> <p>Epidural block: Lubricant surgery 5 mg/ml solution (max. 20 ml).</p> <p>Sympathetic nerve block: 2.5 mg/ml solution (max. 50 ml).</p>
<b>Contraindications</b>	Adjacent skin infection; inflamed skin; concomitant anticoagulant therapy; severe anaemia or heart disease; spinal or epidural anaesthesia in dehydrated or hypovolaemic patient.
<b>Precautions</b>	Respiratory impairment; hepatic impairment (Appendix 7a); epilepsy; porphyria; myasthenia gravis; lactation; interactions (Appendix 6c); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	With excessive dosage or following intravascular injection; light-headedness; dizziness; blurred vision; restlessness; tremors and occasionally convulsions rapidly followed by drowsiness; unconsciousness and respiratory failure; cardiovascular toxicity includes hypotension; heart block and cardiac arrest; hypersensitivity and allergic reactions also occur; epidural anaesthesia occasionally complicated by urinary retention; faecal incontinence; headache; backache or loss of perineal sensation; transient paraesthesia and paraplegia very rare.
<b>Storage</b>	Store in single dose or multi-dose containers preferably of Type-I glass.

## Lignocaine\* (Refer Page No. 298)

Pregnancy Category-B

<b>Indications</b>	<i>Surface anaesthesia of mucous membranes; infiltration anaesthesia; peripheral and sympathetic nerve block; dental anaesthesia; spinal anaesthesia; intravenous regional anaesthesia; arrhythmias.</i>
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<b>Availability</b>	<b>INJECTIONS</b> 30 ml vial (1%) and 10 ml (5%/2 ml) ampoule and 30 ml vial (2%); <b>TOPICAL</b> 30 ml vial (4%); 30 ml vial (lignocaine 20 mg and adrenaline 5 mg/ml); <b>GEL</b> 2% and 4%; <b>OINTMENT</b> 5% w/w; <b>SPRAY</b> 15% w/w.  <b>INJECTIONS</b> 2 ml ampoule (Lignocaine HCl 53.3 mg and Dextrose 75 mg/ml) for spinal anaesthesia.
<b>Dose</b>	Induction of anaesthesia: By injection according to patient weight and nature of procedure. (max. 200 mg lignocaine or 500 mg with adrenaline).  Local application: Rub gently on the affected area.
<b>Contraindications</b>	Adjacent skin infection; inflamed skin; concomitant anticoagulant therapy; severe anaemia or heart disease; spinal or epidural anaesthesia in dehydrated or hypovolaemic patient; hypersensitivity.
<b>Precautions</b>	Respiratory impairment; hepatic impairment (Appendix 7a); epilepsy; porphyria; myasthenia gravis; avoid (or use with great care) solutions containing epinephrine (adrenaline) for ring block of digits or appendages (risk of ischaemic necrosis); lactation; pregnancy (Appendix 7c); interactions (Appendix 6c).
<b>Adverse Effects</b>	Same as Bupivacaine (above).
<b>Storage</b>	Store in a cool place.

## 20.3 Preoperative Medication

Pre-anaesthetic medication is often advisable prior to both conduction and general anaesthetic procedures.

Sedatives improve the course of subsequent anaesthesia in apprehensive patients. Diazepam and promethazine are effective. Diazepam can be administered by mouth; by rectum; or by intravenous injection. Promethazine; which has antihistaminic and antiemetic properties as well as a sedative effect; is of particular value in children.

A potent analgesic such as morphine should be administered preoperatively to patients in severe pain or for analgesia during and after surgery.

Anticholinergic (more correctly antimuscarinic) drugs such as atropine are also used before general anaesthesia. They inhibit excessive bronchial and salivary secretions induced; in particular; by ether and ketamine. Intramuscular administration is most effective; but oral administration is more convenient in children. Lower doses should be used in cardiovascular disease or hyperthyroidism.

### Atropine\* (Refer Page No. 88 and 560)

Pregnancy Category-C

Schedule H

#### Indications

*To inhibit salivary secretions; to inhibit arrhythmias resulting from excessive vagal stimulation; to block the parasympathomimetic effects of anticholinesterases such as neostigmine; organophosphate poisoning; antispasmodic; mydriasis and cycloplegia.*

#### Availability

**INJECTION** 10 ml (0.6 mg/ml).

#### Dose

##### **Intravenous injection**

**Adult-** 0.3 to 0.6 mg immediately before induction of anaesthesia. Intra-operative bradycardia: 300 to 600 µg (longer dose in emergency). Inhibition of bradycardia: 0.4 to 1 mg. Reversal of neuromuscular block; 0.6 to 1.2 mg.

**Child-** Premedication: 20 µg/kg; Inhibition of bradycardia: 10 to 30 µg/kg. Reversal of neuromuscular block: 20 µg/kg.

##### **Intramuscular route or subcutaneous**

Premedication (30 to 60 min before induction of anaesthesia): 300 to 600 µg.

**Child-** 20 µg/kg (max. 60 µg). Intra operative bradycardia: (1 to 12 years) 10 to 20 µg/kg.



**Contraindications** Angle-closure glaucoma; myasthenia gravis; paralytic ileus; pyloric stenosis; prostatic enlargement.

**Precautions** Down syndrome; children; elderly; ulcerative colitis; diarrhoea; hyperthyroidism; heart failure; hypertension; patients with atrial fibrillation or flutter; lactation (Appendix 7b); interactions (Appendix 6a); pregnancy (Appendix 7c).

Since atropine has a shorter duration of action than neostigmine; late unopposed bradycardia may result; close monitoring of the patient is necessary.

**Adverse Effects** Dry mouth; blurred vision; photophobia; flushing and dryness of skin; rash; difficulty in micturition; less commonly arrhythmias; tachycardia; palpitations; confusion (particularly in elderly); heat prostration and convulsions; ventricular fibrillation; hallucinations; dilated pupils; psychosis.

**Storage** Store protected from light.

## Diazepam\* (Refer Page No. 57 and 567)

**Pregnancy Category-D**

**Schedule H**

**Indications** *Premedication before major or minor surgeries; sedation with amnesia for endoscopic procedures and surgeries under local anaesthesia; emergency reduction of fractures (in combination with pethidine when anaesthetics are not available); epilepsy; anxiety disorders.*

**Availability** **TABLETS** 2, 5 and 10 mg; **CAPSULE** 10 mg; **INJECTION** 2 ml ampoule (5 mg/ml).

**Dose** **Oral**

**Adult-** 5 mg on night before surgery or minor procedure; thereafter 5 mg for 2h before procedures.

**Elderly-** Half of adult dose.

### ***Intravenous injection***

10 to 20 mg over 2 to 4 min immediately before procedure. Premedication: 100 to 200 µg/kg.

**Child-** 2.5 to 10 mg over 2 to 4 min.

0.1 to 0.3 mg/kg in divided doses over 24 h; every 4 to 8 h (adjust according to response).

**Contraindications** Central nervous system depression or coma; shock; respiratory depression; acute pulmonary insufficiency; acute narrow angle glaucoma; sleep apnoea; acute alcohol intoxication; severe hepatic impairment; myasthenia gravis; pregnancy (Appendix 7c).

**Precautions** Respiratory disease; muscle weakness; history of alcohol or drug abuse; marked personality disorder; elderly or debilitated patients (adverse effects more common in these groups); hepatic impairment (Appendix 7a) or renal failure; lactation (monitoring for adverse effects required Appendix 7b); porphyria; interactions (Appendix 6a, 6c); organic cerebral changes; epileptic patients.

Warn patient not to perform skilled tasks; for example operating machinery; driving for 24 h.

**Adverse Effects** Central nervous system effects common and include drowsiness; sedation; confusion; amnesia; vertigo and ataxia; hypotension; bradycardia; or cardiac arrest; particularly in elderly or severely ill patients; also paradoxical reactions; including irritability; excitability; hallucinations; sleep disturbances; pain and thromboembolism on intravenous injection.

**Storage** Store protected from light.

## Metoclopramide\* (Refer Page No. 98)

## Midazolam\*

Pregnancy Category-D

**Schedule H**

**Indications** *Intravenous sedative administered before or during minor surgical procedures; sedative administered by intravenous route in intensive care induction of anaesthesia.*

**Availability** **INJECTION** 1 ml ampoule (5 mg/ml); 5 and 10 ml vial (1 mg/ml).

**Dose** ***Slow intravenous injection***

**Adult-** Conscious sedation: approximately 2 mg/min; 5 to 10 min before procedure; initially 2 to 2.5 mg. Usual total dose 3.5 to 5 mg (Max. 7.5 mg).

**Elderly-** 0.5 to 1.0 mg. Increase if necessary in steps of 1 mg.

***Intravenous injection (Over 2 to 3 min)***

**Child-** 6 months to 7 years: initially 50 to 100 µg/kg; increase if necessary in steps (max. total dose 6.0 mg). 6 to 12 years: initially 25 to 50 µg/kg increase in steps if necessary (max. total dose 10 mg).

#### ***Intramuscular injection***

**Adult-** Sedation in combined anaesthesia: 30 to 100 µg/kg repeated as required by continuous intravenous infusion 30 to 100 µg/kg/h (lower doses in elderly). Premedication: 70 to 100 µg/kg.

1 to 15 years: 50 to 150 µg/kg (max.1 mg).

**Elderly and debilitated-** 25 to 50 µg/kg. (20 to 60 min induction).

#### **Contraindications**

Acute narrow angle glaucoma; comatose patients; shock; acute alcohol intoxication; for intrathecal and epidural use; acute pulmonary insufficiency; myasthenia gravis.

#### **Precautions**

Chronic renal failure; cardiac disease; open angle glaucoma; respiratory disorders; neonates; prolonged use and abrupt withdrawal should be avoided; hepatic impairment; pregnancy (Appendix 7c) and lactation; interactions (Appendix 6a, 6c).

#### **Adverse Effects**

Hypersensitivity; cardiac arrest; laryngospasm; apnoea; headache; hiccups; nausea; vomiting; cough; kernicterus; nystagmus; skin rash; CNS symptoms like euphoria; hallucination; ataxia.

## **Morphine\*** (Refer Page No. 11)

**Pregnancy Category-C**

**Schedule H, X**

#### **Indications**

*In severe pain (acute and chronic); myocardial infarction; acute pulmonary oedema; adjunct during major surgery and postoperative analgesia.*

#### **Availability**

**INJECTION** 10 ml ampoule (1 mg/ml, 10 mg/ml and 15 mg/ml); **TABLETS** 10, 20, 30 and 60 mg.

#### **Dose**

#### ***Subcutaneous or intramuscular injection***

**Adult-** Preoperative medication before procedure: up to 10 mg; 60 to 90 min before procedure; 20 to 30 mg per 12 h depending on patient weight. Postoperative analgesia: 150 to 300 µg/kg every 4 h.

**Child-** (By intramuscular injection) Preoperative medication before procedure: 150 µg/kg. Postoperative analgesia: 100 to 200 µg/kg.

#### ***Intravenous injection***

**Adult-** Intra-operative analgesia: 100 µg/kg; repeated every 40 to 60 min as required. Postoperative analgesia: 8 to 10 mg over 30 min (slow intravenous infusion); then 2 to 2.5 mg/h.

**Child-** Intra-operative analgesia: 100 µg/kg; repeated every 40 to 60 min as required.

### Contraindications

Patients with acute respiratory depression and when there is risk of paralytic ileus; conditions associated with raised intracranial pressure and in head injury (they interfere with pupillary responses vital for neurological assessment); comatose patients; acute asthma; acute liver disease; acute alcoholism; pulmonary oedema; interactions (Appendix 6a, 6c, 6d); lactation (Appendix 7b); hepatic impairment (Appendix 7a).

### Precautions

Patients with impaired respiratory function (avoid in chronic obstructive pulmonary disease) and asthma (avoid during an acute attack); hypotension; myasthenia gravis; prostatic hypertrophy and hyperplasia; obstructive or inflammatory bowel disorders; disease of the biliary tract and convulsive disorders; pancreatitis; cardiac arrhythmias; hypothyroidism; head injury; circulatory shock; lactation; pregnancy (Appendix 7c).

### Adverse Effects

Nausea and vomiting (particularly in initial stages); constipation; dry mouth and biliary spasm; larger doses produce muscle rigidity; hypotension and respiratory depression; bradycardia; paralytic ileus; abdominal pain; anorexia; dyspepsia; exacerbation of pancreatitis; taste disturbance; hypertension; hypothermia; syncope; bronchospasm; inhibition of cough reflex; restlessness; seizures; paraesthesia; asthenia; malaise; disorientation; excitation; agitation; delirium; raised intracranial pressure; amenorrhoea; myoclonus; muscle fasciculation and rhabdomyolysis.

### Storage

Store protected from light.

## Omeprazole\* (Refer Page No. 20)

## Promethazine\* (Refer Page No. 102)

### Pregnancy Category-C

**Schedule G**

### Indications

*Premedication prior to surgery; antiemetic.*

### Availability

**TABLETS** 10 and 25 mg; **SYRUP** 60 ml (5 mg/5 ml); **INJECTION** 2 ml ampoule (25 mg/ml).

### Dose

**Oral**

**Adult-** Premedication: 25 mg at night and increase to 25 mg twice daily; if necessary; alternately 10 to 20 mg 2 to 3 times daily.

**Child-** 2 to 5 years: not recommended.  
5 to 10 years: 20 to 25 mg.

***Deep intramuscular route***

**Adult-** 50 mg (max. 100 mg). Premedication: 25 to 60 mg 1 h before operation.

**Child-** 5 to 10 years: 6.25 to 12.5 mg.  
Premedication, 5 to 10 years: 6.5 to 12.5 mg.

***Slow intravenous injection***

In emergencies: 25 to 50 mg as solution containing 2.5 mg/ml in water for injection (max. 100 mg).

**Contraindications** Child under 1 year; impaired consciousness due to cerebral depressants or of other origin; porphyria.

**Precautions** Prostatic hypertrophy; urinary retention; glaucoma; epilepsy; hepatic impairment (Appendix 7a); lactation (Appendix 7b); interactions (Appendix 6a); pregnancy (Appendix 7c).

Warn patient not to perform skilled tasks; for example operating machinery, driving for 24 h.

**Adverse Effects** Drowsiness (rarely, paradoxical stimulation in children); headache; anticholinergic effects such as dry mouth; blurred vision; urinary retention.

**Storage** Store protected from light and moisture.

**Ranitidine\*** (Refer Page No. 21)



<b>21. Drugs for Inflammatory Bowel Disease</b>	<b>427</b>
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## 21. Drugs for Inflammatory Bowel Disease

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Ulcerative colitis and Crohn's disease are inflammatory diseases of the intestinal tract.

### Ulcerative Colitis:

Acute attacks of ulcerative colitis require treatment with local corticosteroids such as **hydrocortisone** in the form of suppositories or retention enemas. Because of the risk of intestinal perforation, rectal administration of hydrocortisone must be used with extreme caution in patients with severe ulcerative disease and should not be given to such patients without conducting a thorough proctological examination. More extensive disease requires oral corticosteroid treatment and severe extensive or fulminant disease needs hospital admission and intravenous corticosteroid administration; other therapy may include intravenous fluid and electrolyte replacement, blood transfusion and possibly parenteral nutrition and antibiotics.

The aminosalicylate **sulfasalazine** is useful in the treatment of symptomatic disease. It also has value in the maintenance of remission in ulcerative colitis for which corticosteroid treatment is unsuitable because of adverse effects. In resistant or frequently relapsing cases azathioprine 2–2.5 mg/kg daily (chapter 12.1) given under close supervision may be helpful. Laxatives are required to facilitate bowel movement when proctitis is present. Antimotility drugs such as codeine and antispasmodic drugs should not be used in active ulcerative colitis because they can precipitate paralytic ileus and megacolon. Diarrhoea resulting from reduced bile salt absorption may improve with cholestyramine. General nutritional care and appropriate supplements are essential. High-fibre or low-residue diets should be used as appropriate. Irritable bowel syndrome during remission of ulcerative colitis requires avoidance of a high-fibre diet and possibly treatment with an antispasmodic.

### Crohn's Disease:

Treatment of Crohn's disease of the colon is similar to that of ulcerative colitis. In small bowel disease **sulfasalazine** may have marginal benefit. Symptoms and inflammation associated with disease exacerbation are suppressed by oral corticosteroids such as prednisolone. **Metronidazole** may be beneficial in the treatment of active Crohn disease particu-



larly with perianal involvement, possibly through its antibacterial activity. Other antibacterials should be given if specifically indicated (for example, sepsis associated with fistulas and perianal disease) and for managing bacterial overgrowth in the small bowel. General nutritional care and appropriate supplements are essential.

## Dicyclomine\*

Pregnancy Category-B

**Schedule H**

<b>Indications</b>	<i>Infantile colic, gastrointestinal tract spasm.</i>
<b>Availability</b>	<b>TABLETS</b> 10 and 20 mg. <b>DROPS</b> 10 mg/ml; <b>INJECTION</b> 10 mg/ml.
<b>Dose</b>	<b>Oral</b> <b>Adult-</b> 10-20 mg three times a day. <b>Parenteral</b> IM injection: 80 mg daily in 4 divided doses.
<b>Contraindications</b>	Glaucoma, reflux oesophagitis, myasthenia gravis, lactation, intestinal obstruction.
<b>Precautions</b>	Patients with mental depression and mental disturbances, hepatic or kidney disease, angle closure glaucoma, hyperthyroidism, CHF, elderly, pregnancy, may impair the ability to drive or operate machinery; interactions (Appendix 6c); pregnancy (Appendix 7c).
<b>Adverse effects</b>	Dry mouth; nausea; vomiting; constipation; taste loss; anorexia; dizziness; dyskinesia; lethargy, respiratory arrest; drowsiness; photophobia, blurred vision; increased ocular pressure; tachycardia; urinary retention.
<b>Storage</b>	Injection: Store protected from light, in single dose or multiple dose containers. Tablets: Store protected from light.

## Hydrocortisone\* (Refer Page No. 32, 355 abd 479)

Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Ulcerative colitis, proctitis, proctosigmoiditis; anaphylaxis; skin; adrenocortical insufficiency.</i>
<b>Availability</b>	<b>INJECTION</b> 100 mg/vial; <b>SUPPOSITORIES</b> 25 mg; <b>RETENTION ENEMA</b> 60 ml (Rectal solution 100 mg/60 ml); <b>CREAM</b> 0.1% w/w.
<b>Dose</b>	<b>Rectal (suppositories)</b> <b>Adult-</b> Ulcerative colitis, proctitis: 25 mg twice daily for 2 weeks; may be increased to 25 mg 3 times daily or 50 mg twice daily in severe cases; in factitial proctitis treatment may be required for 6 to 8 weeks. <b>Rectal (retention enema)</b>

**Adult-** Ulcerative colitis, ulcerative proctitis, ulcerative proctosigmoiditis: 100 mg at night for 21 days or until clinical and proctological remission; if no clinical and proctological improvement after 21 days, discontinue; treatment for 2 to 3 months may be required for proctological remission; when used for more than 21 days, discontinue gradually using 100 mg every other night for 2 to 3 weeks.

**Contraindications** Use of enemas in bowel obstruction, bowel perforation, or extensive fistulas; untreated infections.

**Precautions** Proctological examination required before treatment; systemic absorption may occur; prolonged use should be avoided; lactation (Appendix 7b); interactions (Appendix 6d); pregnancy (Appendix 7c).

**Adverse Effects** Local pain or burning sensation; rectal bleeding (reported with use of enema); exacerbation of untreated infections; suppositories may stain fabrics; systemic adverse effects.

**Storage** Store protected from light.

## Sulfasalazine\* (Refer Page No. 387)

**Pregnancy Category-B**

**Schedule H**

**Indications** *Ulcerative colitis; Crohn's disease; severe rheumatoid arthritis; inflammatory bowel disease.*

**Availability** **TABLETS** 500 and 1000 mg.

**Dose** **Oral**

**Adult-** Ulcerative colitis: 1 to 2g 4 times daily in acute attack until remission, reducing to maintenance dose of 500 mg 4 times daily. Active Crohn's disease: 1 to 2g four times daily in acute attack until remission occurs.

**Child-** Ulcerative colitis: over 2 years; 40 to 60 mg/kg daily in acute attack, reducing to maintenance dose of 20–30 mg/kg daily. Active Crohn disease: over 2 years, 40–60 mg/kg daily in acute attack.

**Contraindications** Hypersensitivity to salicylates or sulfonamides; child under 2 years; porphyria; intestinal or urinary obstruction; severe renal impairment; G-6-PD deficiency; blood dyscrasias.

### Precautions

Renal impairment; hepatic impairment; G-6-PD deficiency; slow acetylator status; monitor blood counts and liver function initially and at monthly intervals for first 3 months; monitor kidney function initially and at intervals during treatment; history of allergy; lactation (Appendix 7b); interactions (Appendix 6c, 6d).

Patients should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise occurring during treatment; blood count should be performed and sulfasalazine stopped immediately if there is suspicion or evidence of blood disorder; pregnancy (Appendix 7c).

### Adverse Effects

Nausea, exacerbation of colitis; diarrhoea, loss of appetite, fever; blood disorders (including Heinz body anaemia, megaloblastic anaemia, leukopenia, neutropenia, thrombocytopenia); hypersensitivity reactions (including rash, urticaria, Stevens-Johnson syndrome (erythema multiforme), exfoliative dermatitis, epidermal necrolysis, pruritus, photosensitization, anaphylaxis, serum sickness, interstitial nephritis, lupus erythematosus-like syndrome); lung complications (including eosinophilia, fibrosing alveolitis); ocular complications (including periorbital oedema); stomatitis, parotitis; ataxia, aseptic meningitis, vertigo, tinnitus, alopecia, peripheral neuropathy, insomnia, depression, headache, hallucinations; kidney reactions (including proteinuria, crystalluria, haematuria); oligospermia; rarely, acute pancreatitis, hepatitis; urine may be coloured orange; some soft contact lenses may be stained.

### Storage

Store protected from light.

## **22. Drugs for Myasthenia Gravis 433**

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## 22. Drugs for Myasthenia Gravis

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Myasthenia gravis is a rare autoimmune neuromuscular disorder of peripheral nerves characterized by variable weakness of voluntary muscles. It is caused by a defect in the transmission of nerve impulses to muscles. It occurs when normal communication between the nerve and the muscle is interrupted at the neuromuscular junction. In this autoimmune disorder antibodies are formed against Acetylcholine (ACh.) nicotinic postsynaptic receptors at the myoneural junction. A reduction in the number of ACh receptors results in a characteristic pattern of progressively reduced muscle strength and recovery of muscle strength following a period of rest. The bulbar muscles are affected severely.

## Azathioprine\* (Refer Page No. 266 and 382)

Pregnancy Category-D

**Schedule H**

<b>Indications</b>	<i>Long term immunosuppression in Myasthenia gravis.</i>
<b>Availability</b>	<b>TABLET</b> 50 mg.
<b>Dose</b>	<b>Adult-</b> 1 to 3 mg/kg per day, discontinue if no improvement after 12 weeks. <b>Child-</b> 1 to 2 mg/kg/day.
<b>Contraindications</b>	Hypersensitivity, pregnancy (Appendix 7c); lactation (Appendix 7b).
<b>Precautions</b>	Monitor liver function; hepatic impairment (Appendix 7a); WBC and platelets; interactions (Appendix 6c, 6d).
<b>Adverse Effects</b>	Nausea, fatigue; hair loss; rash; liver dysfunction; flu-like reaction.
<b>Storage</b>	Store protected from light.

## Cyclosporine\* (Refer Page No. 267)

Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Long term immunosuppression, treatment of Myasthenia gravis when prednisolone is ineffective.</i>
<b>Availability</b>	<b>CAPSULES</b> 25, 50 and 100 mg; <b>INJECTION</b> 50 ml ampoule (100 mg/5 ml) (50 mg/5 ml).
<b>Dose</b>	<b>Adults-</b> 2.5 mg/kg twice daily.
<b>Contraindications</b>	Hypersensitivity.
<b>Precautions</b>	Monitor renal function and blood pressure; liver or kidney disease; blood disorders; diabetes; pregnancy (Appendix 7c), lactation (Appendix 7b); hepatic impairment (Appendix 7a), interactions (Appendix 6b, 6c).
<b>Adverse Effects</b>	Nephrotoxicity; stomach upset, nausea, diarrhoea; hypertension; swollen gums; blurred vision; fever, chest pain; unusual bleeding.

## Mycophenolate Mofetil

Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Long term immunosuppression, treatment of cases resistant to prednisolone or where prednisolone is contraindicated.</i>
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<b>Availability</b>	<b>TABLETS/CAPSULES</b> 250 and 500 mg.
<b>Dose</b>	1g twice daily.
<b>Contraindications</b>	Hypersensitivity; allergy to polysorbate 80.
<b>Precautions</b>	Renal impairment; active disorders of gastrointestinal tract; neutropenia; interactions (Appendix 6c, 6d); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Anaemia; electrolyte disturbances; dizziness; disturbances of blood lipids; gastrointestinal disturbances.

## Neostigmine\* (Refer Page No. 537)

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>Treatment of Myasthenia gravis.</i>
<b>Availability</b>	<b>TABLET</b> 15 mg; <b>INJECTION</b> 0.5 mg/ml.
<b>Dose</b>	<b>Oral</b> <b>Adult-</b> 15 mg every 3 to 4 hrs. Total daily dose 75 to 300 mg in divided doses. <b>Child-</b> 2 mg/kg daily in divided doses every 3 to 4 hrs. Total daily dose 15 to 90 mg. <b>Neonate-</b> 1 to 5 mg every 4 hour. <b>Intramuscular</b> <b>Adult-</b> 0.02 mg/kg as a single dose. <b>Child-</b> 0.04 mg/kg as a single dose.

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*Note: Discontinue all other anticholinesterase medications for at least 8 hours prior to administration.*

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	<b>Intravenous</b> <b>Adult-</b> 0.5 to 2.5 mg to a total daily dose of 5-20 mg. <b>Child-</b> 200 to 500 µg as single daily dose. <b>Neonate-</b> 50 to 250 µg every 4 hour.
<b>Contraindications</b>	Mechanical gastrointestinal or urinary tract obstruction; peritonitis.
<b>Precautions</b>	Renal impairment; peptic ulcer; lactation (Appendix 7b); heart blockage, slow heart-beat; bradycardia, hypotension; urinary tract infection; epilepsy; asthma; interactions (Appendix 6c); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Abdominal cramps, diarrhoea; pupil dilatation; excess saliva; headache; joint pain; severe allergic reactions; fainting; interrupted breathing; irregular heart beat; seizures; vision changes; anxiety.



**Storage**                      Tablets: Store protected from light and moisture. Injection: Store protected from light.

## Prednisolone\* (Refer Page No. 35, 481 and 557)

**Pregnancy Category-C**

**Schedule H**

**Indications**                      *Effective long term immunosuppression in pyridostigmine resistant patient, refractory ocular Myasthenia gravis.*

**Availability**                      **TABLETS** 4, 8, 5, 10, 16, 20 and 40 mg; **SYRUP** 30, 40 and 60 ml; **INJECTION** vial 40 mg/ml; **EYE DROPS** 1% w/v.

**Dose**                                      Initially 20 mg four times daily.

Maximum dose 50 mg four times daily.

**Contraindications**                      Hypersensitivity; systemic infections including tuberculosis.

**Precautions**                      Monitor weight; blood pressure, blood glucose and electrolytes, antibiotic coverage may be required, doses should be tapered and not withdrawn suddenly; hepatic impairment (Appendix 7a); lactation (Appendix 7b); pregnancy (Appendix 7c); interactions (Appendix 6c, 6d).

**Adverse Effects**                      Initial transient exacerbation; elevation of intraocular pressure; optic nerve damage; posterior subcapsular cataract formation; delayed wound healing; weight gain; moon face; avascular necrosis; osteoporosis; psychosis and mood change, increased chance of opportunistic infections.

**Storage**                                      Tablets: Store protected from light. Injection: Store protected from light, in a single dose or in multi dose containers.

## Pyridostigmine\* (Refer Page No. 539)

**Pregnancy Category-C**

**Schedule H**

**Indications**                      *Treatment of Myasthenia gravis, neonatal Myasthenia gravis.*

**Availability**                      **TABLETS** 30 and 60 mg Plain; 180 mg SR; **INJECTIONS** 10 mg/2 ml.

**Dose**                                      **Oral**

**Adult-** 0.3 to 1.2g daily in divided doses.

**Children under 6 yrs-** Initially 30 mg.

**Children 6-12 yrs-** Initially 60 mg. Increase by 15 to 30 mg daily until control.

**Neonate-** 5 to 10 mg given every 4 to 6 hours.

***Intramuscular***

**Child-** 50 to 150 µg/kg every 4 to 6 hours.

**Contraindications**

Recent intestinal or bladder surgery; gastrointestinal or urinary tract obstruction; after suxamethonium; pneumonia; peritonitis.

**Precautions**

Asthma; urinary tract infection; cardiovascular disease including arrhythmias (especially bradycardia or atrioventricular block); hyperthyroidism; hypotension; peptic ulcer; epilepsy; parkinsonism; avoid intravenous injection; renal impairment; pregnancy (Appendix 7c); lactation.

**Adverse Effects**

Muscarinic effects generally weaker than with neostigmine: increased salivation, nausea, salivation, vomiting, abdominal cramps, diarrhoea; signs of overdose include bronchoconstriction, increased bronchial secretions; lacrimation, excessive sweating, involuntary defecation and micturition, miosis, nystagmus; bradycardia, heart block, arrhythmias, hypotension; agitation, excessive dreaming, weakness eventually leading to fasciculation and paralysis, thrombophlebitis; rash associated with bromide salt; diaphoresis, increased peristalsis.

**Storage**

Store protected from light and moisture.

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## 23. Drugs for Respiratory Diseases

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### 23.1 Antiasthmatics and Drugs for Chronic Obstructive Pulmonary Disease (COPD)

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#### **Asthma:**

Asthma is a chronic inflammatory disease characterized by episodes of reversible airways obstruction due to bronchial hyperresponsiveness; inflammation may lead to irreversible obstruction in few patients. A classification based on severity before the start of treatment and disease progression is of importance when decisions have to be made about management. It can be divided by severity into intermittent, mild persistent, moderate persistent and severe persistent. Antiasthmatics are useful in the management of the disease since therapy has a stepwise approach which must be discussed with the patient before commencing therapy. The level of therapy is increased as the severity of the asthma increases with stepping-down if control is sustained (see tables on treatment below).

#### **Inhalation:**

Medications for asthma can be administered in several different ways, including inhalation, oral and parenteral (subcutaneous, intramuscular or intravenous routes). The main advantage of delivering drugs directly into the airways via inhalation is that high concentrations can be delivered more effectively and rapidly to the airways, and systemic adverse effects avoided or minimized.

It is important that patients receive careful instruction in the use of pressurized (aerosol) inhalation (using a metered-dose inhaler) to obtain optimum results. Before use, the inhaler should be shaken well. After exhaling as completely as possible, the mouthpiece of the inhaler should be placed well into the mouth and the lips firmly closed around it. The patient should inhale deeply through the mouth while actuating the inhaler. After holding the breath for 10 seconds or as long as is comfortable, the mouthpiece should be removed and the patient should exhale slowly.

It is important to check that patients continue to use their inhalers correctly as inadequate technique may be mistaken for drug failure. Spacing devices provide a space between the

inhaler and the mouth. They may be of benefit for patients such as the elderly, small children and the asthmatic who find inhalers difficult to use or for those who have difficulty synchronizing their breathing with administration of the aerosol. A large volume spacing device is also recommended for inhalation of high doses of corticosteroids to reduce oropharyngeal deposition which can cause candidosis. The use of metered-dose inhalers with spacers is less expensive and may be as effective as use of nebulizers, although drug delivery may be affected by choice of spacing device.

Breath-actuated devices including dry powder inhalers are also available.

Solutions for nebulization are available for use in acute severe asthma. They are administered over a period of 5-10 min from a nebulizer, usually driven by oxygen in hospital.

### Oral:

The oral route is used when administration by inhalation is not possible. Systemic adverse effects occur more frequently when a drug is given orally rather than by inhalation. Drugs given by mouth for the treatment of asthma include  $\beta_2$ -agonists, corticosteroids and theophylline.

### Parenteral:

Drugs such as corticosteroids, aminophylline etc. may be given by injection in acute severe asthma when administration by nebulization is inadequate or inappropriate. If the patient is being treated in the community, urgent transfer to hospital should be arranged.

### Pregnancy:

Poorly controlled asthma in pregnant women can have an adverse effect on the fetus, resulting in perinatal mortality, increased prematurity and low birth-weight. For this reason using medications to obtain optimal control of asthma is justified. Administration of drugs by inhalation during pregnancy has the advantage that plasma drug concentrations are not likely to be high enough to have an effect on the fetus. Acute exacerbations should be treated aggressively in order to avoid fetal hypoxia.

### Acute Exacerbation of Asthma:

Severe asthma can be fatal and must be treated promptly and energetically. Acute severe asthma attacks require hospital admission where resuscitation facilities are immediately available.

Severe asthma is characterized by persistent dyspnoea

poorly relieved by bronchodilators, exhaustion, a high pulse rate (usually more than 110/min) and a very low peak expiratory flow.

As asthma becomes more severe, wheezing may be absent. Patients should be given oxygen 40-60% (if available). Patients should also be given salbutamol or terbutaline via a nebulizer. In emergencies where a nebulizer is not available, salbutamol 100 µg by aerosol inhalation can be repeated 10-20 times preferably using a large-volume spacing device. Patients should also be given a corticosteroid ; for adults, prednisolone 30-60 mg by mouth or hydrocortisone 200 mg intravenously; for children, prednisolone 1-2 mg/kg by mouth (1-4 years, max. 20 mg, 5-15 years, max. 40 mg) or hydrocortisone 100 mg intravenously; if the patient experiences vomiting the parenteral route may be preferred for the first dose.

If response is inadequate, ipratropium by nebulizer should be considered. Most patients do not benefit from the addition of intravenous aminophylline or a parenteral  $\beta_2$ -agonist; both cause more adverse effects than nebulized  $\beta_2$ -agonists. Nevertheless, an occasional patient who has not been taking theophylline, may benefit from a slow intravenous infusion of aminophylline.

The use of epinephrine (adrenaline) in asthma has generally been superseded by  $\beta_2$ -selective adrenoceptor agonists.

Treatment should never be delayed for investigations, patients should never be sedated and the possibility of pneumothorax should be considered. Patients who deteriorate further despite treatment may need intermittent positive pressure ventilation.

## Treatment of Chronic Asthma: Infants and Young Childrens under 5 Years

Preferred treatments are in bold print

	<b>Long-term Preventive</b>	<b>Quick Relief</b>
STEP 4 Severe Persistent	Daily medications <ul style="list-style-type: none"> <li>• Inhaled corticosteroid, beclomethasone dipropionate MDI with spacer and face mask &gt; 1 mg daily or nebulized beclomethasone &gt; 1 mg twice daily. Consider short course of soluble prednisolone tablets, regular inhaled long-acting <math>\beta_2</math>-agonist or modified-release theophylline. Also, nebulized <math>\beta_2</math>-agonist.</li> </ul>	<ul style="list-style-type: none"> <li>• Inhaled short-acting bronchodilator: inhaled <math>\beta_2</math>-agonist or ipratropium bromide as needed for symptoms, not to exceed 3-4 times daily.</li> </ul>
STEP 3 Moderate Persistent	Daily medications <ul style="list-style-type: none"> <li>• Inhaled corticosteroid, beclomethasone dipropionate MDI with spacer and face mask 400-800 <math>\mu\text{g}</math> daily or nebulized beclomethasone <math>\leq</math> 1 mg twice daily. Consider short course of soluble prednisolone tablets, regular inhaled long-acting <math>\beta_2</math>-agonist or modified-release theophylline.</li> </ul>	<ul style="list-style-type: none"> <li>• Inhaled short-acting bronchodilator: inhaled <math>\beta_2</math>-agonist or ipratropium bromide as needed for symptoms, not to exceed 3-4 times daily.</li> </ul>
STEP 2 Mild Persistent	<ul style="list-style-type: none"> <li>• Either inhaled corticosteroid, beclomethasone dipropionate, 400-800 <math>\mu\text{g}</math>, or cromoglicate (use MDI with a spacer and face mask or use a nebulizer).</li> </ul>	<ul style="list-style-type: none"> <li>• Inhaled short-acting bronchodilator: inhaled <math>\beta_2</math>-agonist or ipratropium bromide as needed for symptoms, not to exceed 3-4 times daily.</li> </ul>
STEP 1 Intermittent	<ul style="list-style-type: none"> <li>• None needed.</li> </ul>	<ul style="list-style-type: none"> <li>• Inhaled short-acting bronchodilator: inhaled <math>\beta_2</math>-agonist or ipratropium bromide as needed for symptoms, but not more than once daily.</li> <li>• Intensity of treatment will depend on severity of attack.</li> </ul>

Step down Review treatment every 3 to 6 months. If control is sustained for at least 3 months, a gradual stepwise reduction in treatment may be possible.

Step up If control is not achieved, consider step up. But first: review patient medication technique, compliance and environmental control.

## Treatment of Chronic Asthma: Adults and Childrens Over 5 Years Old

Preferred treatments are in bold print

	<b>Long-term Preventive</b>	<b>Quick Relief</b>
STEP 4 Severe Persistent	Daily medications <ul style="list-style-type: none"> <li>• Inhaled corticosteroid, beclomethasone dipropionate 0.8-2 mg +</li> <li>• Long-acting bronchodilator: either long-acting inhaled <math>\beta_2</math>-agonist, and/or modified-release theophylline, and/or long-acting <math>\beta_2</math>-agonist tablets or syrup +</li> <li>• corticosteroid tablets or syrup long term.</li> </ul>	<ul style="list-style-type: none"> <li>• Short-acting bronchodilator: inhaled <math>\beta_2</math>-agonist as needed for symptoms.</li> </ul>
STEP 3 Moderate Persistent	Daily medications <ul style="list-style-type: none"> <li>• Inhaled corticosteroid, beclomethasone dipropionate 0.8-2 mg daily in divided doses + if needed</li> <li>• Long-acting bronchodilator: either long-acting inhaled <math>\beta_2</math>-agonist, modified-release theophylline, or long-acting <math>\beta_2</math>-agonist tablets or syrup.</li> </ul>	<ul style="list-style-type: none"> <li>• Short-acting bronchodilator: inhaled <math>\beta_2</math>-agonist as needed for symptoms, not to exceed 3-4 times daily.</li> </ul>
STEP 2 Mild Persistent	Daily medications <ul style="list-style-type: none"> <li>• Either inhaled corticosteroid, beclomethasone dipropionate 100-400 <math>\mu</math>g twice daily, Sodium cromoglicate or modified-release theophylline.</li> </ul>	<ul style="list-style-type: none"> <li>• Short-acting bronchodilator: inhaled <math>\beta_2</math>-agonist as needed for symptoms, not to exceed 3-4 times daily.</li> </ul>



STEP 1  
Intermittent

- None needed.

- Short-acting bronchodilator: inhaled  $\beta_2$ -agonist as needed for symptoms (up to once daily)
- Intensity of treatment will depend on severity of attack
- Inhaled  $\beta_2$ -agonist or Sodium cromoglicate before exercise or exposure to allergen.

Step down Review treatment every 3 to 6 months. If control is sustained for at least 3 months, a gradual stepwise reduction in treatment may be possible.

Step up If control is not achieved, consider step up. But first: review patient medication technique, compliance and environmental control.

## Chronic Obstructive Pulmonary Disease:

Chronic obstructive pulmonary disease (chronic bronchitis and emphysema) may be helped by an inhaled short-acting  $\beta_2$ -adrenoceptor agonist used as required or when the airways obstruction is more severe, by an inhaled anticholinergic (antimuscarinic) bronchodilator or both if necessary. Although many patients are treated with an inhaled corticosteroid its role in chronic obstructive pulmonary disease is not clear at present. A limited trial of high-dose inhaled corticosteroid or an oral corticosteroid is recommended for patients with moderate airflow obstruction to determine the extent of the airway reversibility and to ensure that asthma has not been overlooked.

Long-term oxygen therapy prolongs survival in some patients with chronic obstructive pulmonary disease.

## $\beta_2$ -Adrenoceptor Agonists ( $\beta_2$ -Adrenoceptor Stimulants):

The adrenoceptors in bronchi are mainly  $\beta_2$  type and their stimulation causes bronchial muscles to relax. The  $\beta_2$ -adrenoceptor agonists include salbutamol, terbutaline, and fenoterol.

When salbutamol is given by inhalation (100-200  $\mu\text{g}$ ) the effect can last as long as 4 h thus making it suitable for both the treatment (see tables) and prevention of asthma. Salbutamol can also be taken orally in a dose of 2-4 mg up to 4 times daily but is less effective and causes more adverse effects. It can also be given by injection for severe bronchospasm.

### Adverse Effects

Cardiovascular adverse effects (arrhythmias, palpitations and tachycardia) may occur with salbutamol, but are infrequent with inhaled preparations. Hypokalaemia may result from  $\beta_2$ -adrenoceptor agonist therapy. Particular caution is required in severe asthma because this effect may be potentiated by concomitant treatment with xanthines (for example theophylline), corticosteroids, diuretics and hypoxia. Plasma potassium concentrations should be monitored in severe asthma.

### Xanthines:

Xanthines include theophylline and aminophylline. They relax bronchial smooth muscle relieving bronchospasm and also stimulate respiration. Absorption of theophylline from the gastrointestinal tract is usually rapid and complete. It is metabolized by the liver but its half-life can vary considerably in certain diseases including hepatic impairment and cardiac failure, with some coadministered drugs (see Appendix 5) as well as by factors such as age, smoking and alcohol intake. The half-life variation can be important because theophylline has a narrow margin between therapeutic and toxic effects. At therapeutic doses some patients experience nausea and diarrhoea and when plasma concentrations exceed the recommended range of 10-20 mg/litre (55-110 micromol/litre) arrhythmias and convulsions which may be fatal can occur. Monitoring of plasma concentrations is therefore recommended. Theophylline is used to treat chronic asthma, usually in the form of modified-release preparations which produce adequate plasma concentrations for up to 12 h. It is used as an adjunct to  $\beta_2$ -agonist or corticosteroid therapy when additional bronchodilation is required but there is an increased risk of adverse effects with  $\beta_2$ -agonists (see

above). When given as a single dose at night, modified-release preparations may be useful in controlling nocturnal asthma and early morning wheezing.

The absorption characteristics of modified-release theophylline preparations vary considerably and therefore it is important to keep the patient on the same brand-name formulation.

Theophylline is given by injection as aminophylline (a mixture of theophylline with ethylenediamine) which is 20 times more soluble in water than theophylline alone. It is administered by slow intravenous injection in severe asthma attacks.

## Corticosteroids:

### Inhaled Corticosteroids:

Inhaled corticosteroids, such as beclomethasone, are the most effective anti-inflammatory medications for the treatment of asthma. They are recommended for the long-term control of asthma in patients using a  $\beta_2$ -adrenoceptor agonist more than once a day. *Regular use* of inhaled corticosteroids reduces the risk of exacerbations of asthma.

Corticosteroids must be used regularly to obtain max. benefit. Symptom control is usually effective after 3 to 7 days treatment. Long-term high-dose regimens of inhaled corticosteroids are useful for the treatment of severe persistent asthma because they both reduce the need for the long-term use of oral corticosteroids and have fewer systemic adverse effects.

Local adverse effects from inhaled corticosteroids include oropharyngeal candidosis, dysphonia and occasional coughing from upper airway irritation. The use of spacing devices reduces oropharyngeal deposition and thus reduces the incidence of candidosis. The risk for systemic effects of inhaled corticosteroids is small and is dependent upon the dose and potency of the corticosteroid as well as its bioavailability and the plasma half-life of its systemically absorbed fraction. Systemic effects are rare and include skin thinning and easy bruising, a small increased risk of glaucoma and cataracts, adrenal suppression, decrease of bone metabolism and growth retardation in children.

### Systemic Corticosteroids

Oral corticosteroids may be used as 'max. therapy' to achieve control of a patient's asthma. This may be useful either when initiating long-term therapy for a patient with uncontrolled asthma or as a short 'rescue' course at any stage for acute exacerbation.

Long-term oral corticosteroid therapy may be required to

control severe persistent asthma, but its use is limited by the risk of significant adverse effects. In these cases high-dose inhaled corticosteroids should be continued so that oral requirements are reduced to a minimum. Oral doses should be given as a single dose in the morning to reduce the disturbance to the circadian cortisol secretion. Dosage should always be adjusted to the lowest dose which controls symptoms.

### Anticholinergic (Antimuscarinic) Bronchodilators:

Ipratropium can provide short-term relief in chronic asthma, but short-acting  $\beta_2$ -agonists work more quickly. Ipratropium is also used as a bronchodilator in chronic obstructive pulmonary disease.

## Aminophylline

### Pregnancy Category-C

<b>Indications</b>	<i>Status asthmaticus, chronic obstructive pulmonary disease (COPD), reversible airway obstruction, chronic bronchitis, pulmonary edema, adjunct in treating CHF, apnoea in premature infants.</i>
<b>Availability</b>	<b>TABLETS</b> 100, 200, 225, and 350 mg; <b>INJECTION</b> 10 ml (250 mg/2 ml, 25 mg/ml); <b>ORAL LIQUID</b> 105 mg/5 ml; <b>SUPPOSITORY</b> 250 mg, 500 mg.
<b>Dose</b>	<b>Parenteral/Oral</b>  <b>Adult-</b> 250-500 mg orally or by slow i.v. injection. Loading dose- 5 mg/kg.  Maintainance dose- 0.5 mg/kg/h.  <b>Child-</b> (6 months – 9 years) 1 mg/kg/h. (10 – 16 years) 800 $\mu$ g/kg/h
<b>Contraindications</b>	Hypersensitivity to theophyllines.
<b>Precautions</b>	Alcohol dependence; hyperthyroidism; peptic ulcer; febrile illness; patients with severe heart, liver or kidney disease; lactation (Appendix 7b); renal impairment (Appendix 7d); interactions (Appendix 6c); congestive heart failure; neonates and elderly patients; epilepsy; high blood pressure; glaucoma; diabetes; allergies, pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Convulsions; hypokalemia; dizziness, headache; palpitation, tachycardia, diarrhoea; anxiety; urinary retention; restlessness; tremors; abdominal pain; exfoliative dermatitis; erythema.

**Storage** Store protected from light and from atmospheric carbon dioxide. Injection: Store in single dose containers, from which carbon dioxide has been excluded. Do not allow contact with metals. Tablets: Store protected from light.

## Beclomethasone\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *Chronic asthma not controlled by short-acting  $\beta_2$ -adrenoceptor agonists.*

**Availability** **INHALER** 100 and 200  $\mu\text{g}$  per actuation; **CREAM** 5, 10, 15 (0.025%) and 20g (0.0125%); **OINTMENT** 20g.

**Dose** **Aerosol inhalation**

**Adult-** Metered dose inhaler: 200  $\mu\text{g}$  twice daily or 100  $\mu\text{g}$  3 to 4 times daily (in more severe cases, initially 600 to 800  $\mu\text{g}$  daily).

High dose inhaler: 500  $\mu\text{g}$  twice daily or 250  $\mu\text{g}$  4 times daily; if necessary may be increased to 500  $\mu\text{g}$  4 times daily.

**Child-** Metered dose inhaler: 50 to 100  $\mu\text{g}$  2 to 4 times daily or 100 to 200  $\mu\text{g}$  twice daily.

High dose inhaler: not recommended.

**Contraindication** Acne; respiratory tract infection; pulmonary tuberculosis; ulcer; perioral dermatitis.

**Precautions** See notes above; active or quiescent tuberculosis; systemic therapy may be required during periods of stress or when airway obstruction or mucus prevent drug access to smaller airways; not for relief of acute symptoms; monitor height of children receiving prolonged treatment-if growth slowed; review therapy; untreated fungal, bacterial and systemic viral infection, lactation (Appendix 7b); pregnancy (Appendix 7c).

**Adverse Effects** Oropharyngeal candidosis; cough and dysphonia (usually only with high doses); adrenal suppression; growth retardation in children and adolescents; impaired bone metabolism; glaucoma and cataract (with high doses; but less frequent than with systemic corticosteroids); paradoxical bronchospasm-requires discontinuation and alternative therapy (if mild; may be prevented by inhalation of  $\beta_2$ -adrenoceptor agonist or by transfer from aerosol to powder inhalation); rarely,; urticaria; rash; angioedema; telangiectasia; increased intraocular pressure; dermal thinning.

Candidosis can be reduced by use of a spacing device (see notes above); rinsing the mouth with water after inhalation may help to prevent candidosis.

**Storage**

Store protected from moisture at a temperature not exceeding 30°C.

## Budesonide

**Preganacy Category-B**

**Schedule H**

**Indications**

*Nasal allergy, prophylaxis and treatment of seasonal and perennial allergic or vasomotor rhinitis, nasal polyposis, asthma.*

**Availability**

**INHALER** 100 and 200 µg, **ROTACAP** 100, 200 and 400 µg, **NASAL SPRAY** 0.02% w/v.

**Dose**

**Asthma**

**Adult-** 200-400 µg Meter Dose Inhaler twice daily by inhalation, as dry powder inhaler 200-800 µg in single or two divided doses, as nebulised solution 0.5-1 mg twice daily.

**Child-** 50-400 µg Meter Dose Inhaler twice daily, as nebulised solution 0.25-0.5 mg twice daily.

**Nasal polyps and allergic rhinitis:** 200-400 µg/day by intranasal spray.

**Contraindications**

Hypersensitivity; presence of infections or nasal ulcers.

**Precautions**

Paradoxical bronchospasm; children, elderly, pregnancy (Appendix 7c), lactation; active or quiescent tuberculosis, interactions (Appendix 6c).

**Adverse Effects**

Inhalation leads to hoarseness of voice, opportunistic fungal infection in oropharynx, respiratory infection, headache.

## Epinephrine\* (Refer Page No. 28 and 561)

## Formoterol + Fluticasone propionate

**Preganacy Category-B**

**Schedule H**

**Indications**

*Asthma, severe chronic obstructive pulmonary disease (COPD).*

**Availability**

**Inhalation Aerosol-**  
 Formoterol + Fluticasone Propionate  
 6 µg + 125 µg  
 6 µg + 250 µg

<b>Dose</b>	<p><b>Inhalation</b></p> <p><b>Asthma: Adults-</b> 1-2 inhalations twice daily.  <b>Child-</b> 1 rotacap twice daily.  <b>(Rotacaps to be used with a rotahaler device only. Do not swallow the capsules).</b></p> <p><b>COPD: Adults-</b> 2 inhalations twice daily.                      Not recommended for children below 4 years of age.</p>
<b>Contraindications</b>	Hypersensitivity, acute asthma symptoms.
<b>Precautions</b>	Severe cardiovascular disorders, cardiac rhythm abnormalities, seizure disorder, diabetes, thyrotoxicosis, hypokalemia, pulmonary tuberculosis, pregnancy (Appendix 7c), lactation, interactions (Appendix 6c).
<b>Adverse Effects</b>	Headache, pharyngitis, throat irritation, upper respiratory tract infections, pneumonia, bronchitis, oral candidiasis, nausea, vomiting, diarrhea, chest pain, musculoskeletal pain, back pain, allergic reactions, wheezing, cough, skin rash, tremors, paradoxical bronchospasm, insomnia, adrenal suppression.
<b>Storage</b>	Store protected from light and moisture at a temperature not exceeding 30°C.

## Hydrocortisone\* (Refer Page No. 32, 355, 429 and 479)

### Ipratropium\*

Pregnancy Category-B

**Schedule H**

<b>Indications</b>	<i>Chronic asthma; chronic obstructive pulmonary disease; bronchospasm; rhinorrhoea, rapid reversal of sinus rhythm.</i>
<b>Availability</b>	<b>METERED DOSE INHALER</b> 200 doses (200 µg per actuation); <b>CAPSULE</b> 40 mg.
<b>Dose</b>	<p><b>Aerosol inhalation</b></p> <p><b>Adult-</b> Metered dose inhaler; 20 to 40 µg, in early treatment up to 80 µg at a time, 3 to 4 times daily.</p> <p><b>Child-</b> Metered dose inhaler; up to 6 years; 20 µg 3 times daily. 6 to 12 years; 20 to 40 µg 3 times daily.</p>
<b>Contraindications</b>	Glaucoma; hypersensitivity; bladder obstruction; urinary retention.

**Precautions** Prostatic hypertrophy; pregnancy (Appendix 7c); glaucoma (standard doses unlikely to be harmful; reported with nebulized drug; particularly in association with nebulized salbutamol); lactation; allergy to atropine or *Atropa belladonna* leaves.

**Adverse Effects** Occasionally dry mouth; constipation; angina; tremors; palpitation; nasal congestion.

**Storage** Store protected from light and moisture.

## Mometasone

**Pregnancy Category-C**

**Schedule H**

**Indications** *Dermatoses, prophylaxis and treatment of allergic rhinitis, nasal polyps, prophylaxis of asthma.*

**Availability** **CREAMS** 0.1% w/w; **LOTIONS** 0.1 % w/v; **OINTMENTS** 0.1% w/v; **NASAL SPRAY** 0.05% w/v.

**Dose** **Dermatoses: Adult** 0.1% cream or ointment or lotion.

**Allergic rhinitis:** 100 µg in each nostril once daily. Usual maintenance dose 50 µg in each nostril daily.

**Asthma: Adult-** 200-400 µg daily in 1-2 divided doses.

**Child-** 100 µg once daily.

**Contraindications** Hypersensitivity.

**Precautions** Hepatic and renal disease; myasthenia gravis, cardiovascular disease; ocular diseases; osteoporosis, glucocorticosteroid insufficiency; discontinue if irritation or sensitization occurs; interactions (Appendix 6c); pregnancy (Appendix 7c).

**Adverse Effects** Adrenal suppression; immunosuppression; anaphylaxis; musculoskeletal pain; depression; fatigue; sinusitis; oropharyngeal infections; upper respiratory tract infection; gastrointestinal disturbances; conjunctivitis; otitis media; local irritation and sensitization; bacterial skin infection; skin depigmentation; cataract; growth suppression.



## Montelukast

Pregnancy Category-B

Schedule H

<b>Indications</b>	<i>Prophylaxis of mild to moderate asthma.</i>
<b>Availability</b>	<b>TABLETS</b> 5 and 10 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> 10 mg once a day.  <b>Child-</b> 2-5yrs: 4 mg once daily; 6-14 yrs: 5 mg once daily; ≥ 15 yrs: 10 mg once daily.
<b>Contraindications</b>	Hypersensitivity.
<b>Precautions</b>	History of liver disease, pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Headache; rashes; eosinophilia; neuropathy; Churg-strauss syndrome.
<b>Storage</b>	Store protected from light and moisture.

## Salbutamol\*

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Prophylaxis and treatment of asthma; premature labour; reversible airway obstruction.</i>
<b>Availability</b>	<b>TABLETS</b> 2 and 4 mg; <b>SYRUP</b> 2 mg/5 ml (100 ml); <b>CAPSULES</b> 4 mg; <b>INHALER</b> 100, 200 doses (100 µg per actuation).
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> Chronic asthma (when inhalation is ineffective): 2 to 4 mg, 3 or 4 times daily; in some patients up to max. of 8 mg, 3 or 4 times daily.  <b>Child-</b> Chronic asthma (when inhalation is ineffective): under 2 years; 100 µg/kg, 4 times daily. 2 to 6 years; 1 to 2 mg, 3 to 4 times daily.  <b>Slow intravenous injection</b>  <b>Adult-</b> Severe acute bronchospasm: 250 µg, repeated if necessary.  <b>Aerosol inhalation and intramuscular or subcutaneous injection</b>

**Adult-** Relief of acute bronchospasm: 100 to 200 µg (1 to 2 puffs) by aerosol inhalation and 500 µg by intramuscular or subcutaneous injection; repeated every 4 h if necessary.

**Child-** Relief of acute bronchospasm: 100 µg (1 puff) increased to 200 µg (2 puffs); if necessary.

### ***Aerosol inhalation***

**Adult-** Prophylaxis of exercise-induced bronchospasm: 200 µg (2 puffs).

Chronic asthma (as adjunct in stepped treatment): 100 to 200 µg (1 to 2 puffs), up to 3 to 4 times daily.

**Child-** Prophylaxis of exercise-induced bronchospasm: 100 µg (1 puff) increased to 200 µg (2 puffs); if required.

Chronic asthma (as adjunct in stepped treatment): 100 µg (1 puff) 3 to 4 times daily, increased to 200 µg (2 puffs) 3 to 4 times daily; if necessary.

### ***Inhalation of nebulized solution***

**Adult-** Severe acute asthma or chronic bronchospasm unresponsive to conventional treatment: 2.5 mg repeated up to 4 times daily; may be increased to 5 mg, if necessary- medical assessment should be considered since alternative therapy may be indicated.

**Child-** Severe acute asthma or chronic bronchospasm unresponsive to conventional treatment, over 18 months: 2.5 mg repeated up to 4 times daily; may be increased to 5 mg, if necessary- medical assessment should be considered since alternative therapy may be indicated. Under 18 months: clinical efficacy uncertain (transient hypoxaemia may occur- consider oxygen supplementation).

### **Contraindications**

β<sub>2</sub> agonists are contraindicated in cardiac disease; antepartum haemorrhage; intrauterine infection; intrauterine fetal death; placenta praevia; abruptio placenta; threatened miscarriage; cord compression; eclampsia or severe pre-eclampsia; diabetes mellitus; thyrotoxicosis.

**Precautions**                    Hyperthyroidism; myocardial insufficiency; arrhythmias; susceptibility to QT-interval prolongation; hypertension; pregnancy (Appendix 7c) (but appropriate to use; see also notes above); lactation (Appendix 7b); diabetes mellitus-especially intravenous administration (monitor blood glucose; ketoacidosis reported); interactions (Appendix 6c).

**Adverse Effects**                Hypokalaemia after high doses; arrhythmias; tachycardia; palpitations; peripheral vasodilation; fine tremor (usually hands); muscle cramps; headache; insomnia; behavioural disturbances in children; hypersensitivity reactions including paradoxical bronchospasm; urticaria and angioedema; slight pain on intramuscular injection.

**Storage**                         Store protected from light and moisture at a temperature not exceeding 30°C.

## Terbutaline\* (Refer Page No. 502)

### Theophylline

**Pregnancy Category-C**

**Indications**                    *Chronic asthma including nocturnal asthma; acute severe asthma; apnoea of prematurity.*

**Availability**                    **TABLETS** 100, 150, 200, 250, 300, 400 and 600 mg; **CAPSULES** 125, 200, 250 and 400 mg; **SYRUP** 5 mg/5 ml (100 ml) Aminophylline, 100 ml (50 mg/5ml), 200 ml (80 mg/5ml), (125 mg/5ml); **INJECTION** 10 ml ampoule (25 mg/ml).

(Theophylline tablets available in combination with aminophylline).

**Dose**                                **Oral**

**Adult-** Chronic asthma (as tablets): 100 to 200 mg, 3 to 4 times daily after food.

Chronic asthma (as modified-release tablets): 300 to 450 mg every 12 h.

Nocturnal asthma (as modified-release tablets): total daily requirement as single evening dose.

**Child-** Chronic asthma (as tablets); over 12 years: 100 to 200 mg, 3 to 4 times daily after food.

**Slow intravenous injection and infusion**

**Adult-** Acute severe asthma; by slow intravenous injection (over at least 20 min): 5 mg/kg. Maintenance by intravenous infusion: 500 µg/kg/hr.

**Child-** Acute severe asthma; by slow intravenous injection (over at least 20 min): 5 mg/kg. Maintenance by intravenous infusion; 6 months to 9 years: 1 mg/kg/h. 10 to 16 years: 800 µg/kg/h, adjusted according to plasma concentration.

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*Note: Patients taking oral theophylline (or aminophylline) should not normally receive intravenous aminophylline unless plasma-theophylline concentration is available to guide dosage and vice versa.*

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<b>Contraindications</b>	Porphyria; known hypersensitivity to ethylenediamine (for aminophylline).
<b>Precautions</b>	Cardiac disease; hypertension; hyperthyroidism; peptic ulcer; epilepsy; hepatic impairment; pregnancy (Appendix 7c); lactation (Appendix 7b); elderly; fever; smokers may require larger or more frequent doses; interactions (6b, 6c).
<b>Adverse Effects</b>	Nausea vomiting and other gastrointestinal disturbances; restlessness; anxiety; tremor; palpitations; headache; insomnia; dizziness; convulsions; arrhythmias and hypotension—especially if given by rapid injection; urticaria; erythema and exfoliative dermatitis—resulting from hypersensitivity to ethylenediamine component of aminophylline; neurotoxicity; hypokalemia; metabolic acidosis; gastrointestinal haemorrhage.
<b>Storage</b>	Store protected from moisture.

## 23.2 Antitussives (Cough suppressants)

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Cough acts as protective reflex. It is helpful in the expulsion of respiratory secretion and other foreign particles from respiratory tract. Cough is of non-productive and productive type. Non-productive cough should be suppressed, whereas productive cough should not be suppressed. Cough suppressants are used only for the control of non-productive cough.

**Codeine\*** (Refer Page No. 10 and 72)

**Dextromethorphan\***

**Pregnancy Category-C**

<b>Indications</b>	<i>Dry cough.</i>
<b>Availability</b>	<b>TABLET</b> 10 mg; <b>SYRUP</b> 15 mg/5 ml and 30 mg/5 ml.
<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> 10 – 20 mg every 4 hour or 30 mg every 6 – 8 hours.</p> <p><b>Child-</b> 6 – 12 years: 5 – 10 mg every 4 hours or 15 mg every 6 – 8 hours.</p> <p>2 – 6 years: 2.5 – 5 mg every 4 hours or 7.5 mg every 6 – 8 hours.</p>
<b>Contraindications</b>	Patients at risk of developing respiratory failure; persistent or chronic cough; patients receiving monoamine oxidase inhibitors (with or within 2 weeks).
<b>Precautions</b>	Moderate/severe renal impairment; liver disease, atopic children; patients confined to supine position; debilitated patients; third trimester of pregnancy (Appendix 7c); asthma; interactions (Appendix 6a, 6c).
<b>Adverse effects</b>	Dependency; dizziness; restlessness; mental confusion; excitation; gastrointestinal disturbance.



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# 24. Hormones, Contraceptives and Related Drugs

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## 24.1 Contraceptives

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### 24.1.1 Oral Hormonal Contraceptives

Hormonal contraception is one of the most effective methods of reversible fertility control.

#### Combined Oral Contraceptives:

Estrogen plus progestogen combinations are the most widely used hormonal contraceptives. They produce a contraceptive effect mainly by suppressing the hypothalamic-pituitary system resulting in prevention of ovulation; in addition, changes in the endometrium make it unreceptive to implantation.

Endometrial proliferation is usually followed by thinning or regression of the endometrium resulting in reduced menstrual flow. Ovulation usually resumes within three menstrual cycles after oral contraception has been discontinued; anovulation and amenorrhoea persisting for six months or longer requires investigation and appropriate treatment if necessary.

Potential non-contraceptive benefits of combined oral contraceptives include improved regularity of the menstrual cycle, decreased blood loss, less iron-deficiency anaemia and significant decrease in dysmenorrhoea. Long-term use is associated with reduced risk of endometrial and ovarian cancer and of some pelvic infections.

An association between the amount of estrogen and progestogen in oral contraceptives and an increased risk of adverse cardiovascular effects has been observed. The use of oral contraceptive combinations containing the progestogens, desogestrel or gestodene are associated with a slightly increased risk of venous thromboembolism compared with oral contraceptives containing the progestogens, levonorgestrel or norethisterone.

#### Risk Factors for Venous Thromboembolism or Arterial Disease:

Risk factors for venous thromboembolism include family history of venous thromboembolism in first-degree relative aged under 45 years, obesity, long-term immobilization and varicose veins.

Risk factors for arterial disease include family history of arterial



disease in first-degree relative aged under 45 years, diabetes mellitus, hypertension, smoking, age over 35 years (avoid if over 50 years), obesity and migraine.

If any one of the factors is present, combined oral contraceptives should be used with caution; if 2 or more factors for either venous thromboembolism or arterial disease are present, combined oral contraceptives should be avoided. Combined oral contraceptives are contraindicated in migraine with aura, in severe migraine without aura regularly lasting over 72 h despite treatment and in migraine treated with ergot derivatives.

### **Surgery:**

Estrogen-containing oral contraceptives should preferably be discontinued (and adequate alternative contraceptive arrangements made) 4 weeks before major elective surgery and all surgery to the legs or surgery which involves prolonged immobilization of a lower limb. They should normally be restarted at the first menses occurring at least 2 weeks after full mobilization. When discontinuation is not possible thromboprophylaxis (with heparin and graduated compression hosiery) is advised.

### **Reasons to Stop Combined Oral Contraceptives Immediately:**

Combined estrogen-containing oral contraceptives should be stopped immediately if any of the following symptoms occur and resumed only after consultation with a health care provider:

- Sudden severe chest pain (even if not radiating to left arm);
- Sudden breathlessness (or cough with blood-stained sputum);
- Severe pain in calf of one leg;
- Severe stomach pain;
- Serious neurological effects including unusual, severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptual disorders or dysphagia or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body;
- Hepatitis, jaundice, liver enlargement;
- Blood pressure above 160 mmHg systolic and 100 mmHg diastolic;
- Detection of 2 or more risk factors for venous thromboembolism or arterial disease, see notes above

### Progestogen-Only Contraceptives:

Progestogen-only contraceptives, such as oral levonorgestrel may offer a suitable alternative when estrogens are contraindicated but the oral progestogen-only preparations do not prevent ovulation in all cycles and have a higher failure rate than combined estrogen-containing preparations. Progestogen-only contraceptives carry less risk of thromboembolic and cardiovascular disease than combined oral contraceptives and are preferable for women at increased risk of such complications, for example smokers over 35 years. They can be used as an alternative to estrogen-containing combined preparations prior to major surgery. Oral progestogen-only contraceptives may be started 3 weeks after birth; lactation women should preferably start at least 6 weeks after birth. Menstrual irregularities (oligomenorrhoea, menorrhagia, amenorrhoea) are common. Injectable preparations of medroxyprogesterone acetate or norethisterone enantate may be given intramuscularly. They have prolonged action and should only be given with full counselling and manufacturer's information leaflet.

### Emergency Contraception:

Levonorgestrel is used for emergency contraception. Levonorgestrel 1.5 mg should be taken as a single dose within 72 h of unprotected intercourse; alternatively, levonorgestrel 750 µg can be taken within 72 h of unprotected intercourse followed 12 h later by another 750 µg. Under these circumstances levonorgestrel prevents about 86% of pregnancies that would have occurred if no treatment had been given. Adverse effects include nausea, vomiting, headache, dizziness, breast discomfort, and menstrual irregularities. If vomiting occurs within 2-3 h of taking the tablets, replacement tablets can be given with an antiemetic.

It should be explained to the woman that her next period may be early or late; that she needs to use a barrier contraceptive method until her next period, and that she should return promptly if she has any lower abdominal pain or if the subsequent menstrual bleed is abnormally light, heavy, brief or absent. There is no evidence of harmful effects to the fetus if pregnancy should occur.

## Centchroman (Non-steroidal oral contraceptive)

Pregnancy Category-X

Schedule H

**Indications** *Contraception.*

**Availability** **TABLET** 30 mg.

**Dose** **Oral**

30 mg tablets. A single tablet should be taken twice a week (on a sunday and a wednesday) for the first three months and then weekly (every sunday) thereafter.

**Contraindications** Medical history of liver disease, jaundice; ovarian disease (polycystic ovaries); cervical hyperplasia; cervicitis; chronic renal disorders.

**Precautions** Prolongation of menstrual cycles may be experienced by some individuals. Delayed menstruation is inconsequential if dosages have not been missed. In case of delay exceeding 15 days, pregnancy should be ruled out with routine investigations. Administration should be discontinued immediately if pregnancy is confirmed (Appendix 7c).

**Adverse Effects** Water retention; tender breasts; acne; heavy menstruation.

## 'Ethinylestradiol + Levonorgestrel'\* and 'Ethinylestradiol + Norethisterone'\*

Pregnancy Category-X

Schedule H

**Indications** *Contraception; menstrual symptoms; endometriosis.*

**Availability** **TABLETS**  
 Levonorgestrel + Ethinylestradiol  
     0.15 mg + 0.03 mg  
     0.25 mg + 0.05 mg  
 Levonorgestrel 0.15 mg + Ethinylestradiol  
 0.03 mg + Ferrous fumarate 60 mg.  
 Norethisterone + Ethinylestradiol  
     0.5 mg + 0.03 mg  
     1.0 mg + 0.03 mg

**Dose** **Oral**

**Adult-** Contraception: 1 tablet (pill) daily for 21 days; subsequent courses repeated after 7-day pill-free interval (during which withdrawal bleeding occurs).

Each tablet (pill) should be taken at approximately the same time each day; if delayed by longer than 24 h contraceptive protection may be lost. It is important to bear in mind that the critical time for loss of protection is when a pill is omitted at the beginning or end of a cycle (which lengthens the pill-free interval).

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*Note: Ethinylestradiol with levonorgestrel and ethinylestradiol with norethisterone are representative combined oral contraceptive preparations. Various combinations can serve as alternatives.*

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### Contraindications

Use within 3 weeks of birth; lactation until weaning or for first 6 months after birth (Appendix 7b); personal history of 2 or more risk factors for venous or arterial thrombosis (see notes above); heart disease associated with pulmonary hypertension or risk of embolism; migraine (see below); history of sub-acute bacterial endocarditis; ischaemic cerebrovascular disease; liver disease (Appendix 7a), including disorders of hepatic secretion such as Dubin-Johnson or Rotor syndromes, infectious hepatitis (until liver function normal); porphyria; systemic lupus erythematosus; liver adenoma; history of cholestasis with oral contraceptives; gallstones; estrogen-dependent neoplasms; neoplasms of breast or genital tract; undiagnosed vaginal bleeding; history of pruritus during pregnancy, chorea, herpes, deteriorating otosclerosis, cholestatic jaundice; diabetes mellitus (if either retinopathy, neuropathy or if more than 20 years duration); after evacuation of hydatidiform mole (until return to normal of urine and plasma gonadotrophin values).

Migraine with typical focal aura; migraine without aura regularly lasting over 72 h duration despite treatment; migraine treated with ergot derivatives; migraine without focal aura or controlled with 5-HT<sub>1</sub> agonist.

### Precautions

Risk factors for venous thromboembolism and arterial disease (see notes above); migraine (see below); hyperprolactinaemia (seek specialist advice); some types of hyperlipidaemia; gallbladder disease; severe depression; long-term immobilization (see also Travel below); sickle-cell disease; inflammatory bowel disease including Crohn's disease, interactions (Appendix 6c, 6d).

Patients should report any increase in headache frequency or onset of focal symptoms (discontinue immediately and refer urgently to neurology expert if focal neurological symptoms not typical of aura persist for more than one hour).

Women taking oral contraceptives may be at increased risk of deep-vein thrombosis during travel involving long periods of immobility (over 5 h). The risk may be reduced by appropriate exercise during the journey and possibly by wearing elastic hosiery; pregnancy (Appendix 7c).

### Adverse Effects

Nausea, vomiting, headache; breast tenderness; increase in body weight; thrombosis; changes in *libido*; depression; chorea; skin reactions; chloasma; hypertension; impairment of liver function; 'spotting' in early cycles; absence of withdrawal bleeding; breast cancer (small increase in risk of breast cancer during use which reduces during the 10 years after stopping; risk factor seems related to age at which contraceptive is stopped rather than total duration of use; small increase in risk of breast cancer should be weighed against the protective effect against cancers of the ovary and endometrium which persists after stopping); dizziness, stomach upset, bloating, mental and mood changes.

## Levonorgestrel

### Pregnancy Category-X

**Schedule H**

### Indications

*Emergency hormonal contraception.*

### Availability

**TABLETS** 0.75 and 1.5 mg.

### Dose

**Oral**

**Adult-** Contraception: 1 tablet ('pill') (30 µg) daily, starting on the first day of the cycle and then continuously.

### Contraindications

Progestogen-only oral contraceptives; undiagnosed vaginal bleeding; severe arterial disease; liver tumours; breast cancer; thromboembolic disorders; sickle-cell anaemia; porphyria; after evacuation of hydatidiform mole (until return to normal urine and plasma gonadotrophin values); progestogen-only emergency hormonal contraceptives; severe liver disease.

### Precautions

Possible small increase in risk of breast cancer; cardiac disease; sex-steroid dependent cancer; past ectopic pregnancy; malabsorption syndrome; ovarian cysts; active liver disease, recurrent cholestatic jaundice, history of jaundice in pregnancy (Appendix 7c); increase in frequency or severity of headache (discontinue pending investigation); lactation (Appendix 7b); pregnancy (Appendix 7c).

**Adverse Effects** Menstrual irregularities (including oligomenorrhoea and menorrhagia); nausea, vomiting, headache, dizziness; breast discomfort, depression; skin disorders; disturbances of appetite; weight increase; change in *libido*.

## 24.1.2 Injectable Hormonal Contraceptives

### Medroxyprogesterone

**Pregnancy Category-X**

**Schedule H**

**Indications** *Parenteral progestogen-only contraception (short-term or long-term); menstrual symptoms and endometriosis; dysmenorrhoea.*

**Availability** **TABLETS** 2.5, 5 and 10 mg; **INJECTION** 150 mg (1 ml VIAL/PREFILLED SYRINGE).

**Dose** **Deep intramuscular injection**

**Adult-** Contraception (short-term): 150 mg within first 5 days of cycle or within first 5 days after parturition (delay until 6 weeks after parturition if lactating). Contraception (long-term); as for short-term, repeated every 3 months.

Mild to moderate endometriosis: 10 mg 3 times daily for 90 consecutive days, beginning on day 1 of cycle. Dysfunctional uterine bleeding; 2.5 to 10 mg daily for 5 to 10 days beginning on day 16 to 21 of cycle for 2 cycles. Secondary amenorrhoea; 5 to 10 mg daily for 5 to 10 days beginning on day 16 to 21 of cycle for 3 cycles.

If interval between injections is greater than 3 months and 14 days, exclude pregnancy before next injection and advise patient to use additional contraceptive measures (for example barrier) for 7 days after the injection.

**Contraindications** Pregnancy (Appendix 7c); hormone-dependent breast or genital neoplasms; undiagnosed vaginal bleeding; hepatic impairment or active liver disease (Appendix 7a); severe arterial disease; porphyria; active thrombophlebitis; lactation (Appendix 7b).

**Precautions** Small increase in possible risk of breast cancer; migraine; liver disease; thromboembolic or coronary vascular disease; diabetes mellitus; trophoblastic disease; hypertension; renal disease; fluid retention, CNS disorder and convulsions.

**Adverse Effects** Menstrual irregularities; delayed return to fertility; reduction in bone mineral density; weight gain; depression; rarely, anaphylaxis; abdominal pain, asthenia, breast pain, bloating, insomnia, vaginitis.

**Storage** Store protected from light and moisture.

## Norethisterone\* (Refer Page No. 496)

**Pregnancy Category-X**

**Schedule H**

**Indications** *Parenteral progestogen-only contraception (short-term).*

**Availability** **TABLETS** 1 and 5 mg **INJECTION** 1 ml ampoule (200 mg/ml).

**Dose** **Deep intramuscular injection** (into the gluteal muscle).

**Adult-** Short-term contraception: 200 mg within 5 days of cycle or immediately after parturition; repeated after 2 months.

If interval between injections is greater than 2 months and 14 days, exclude pregnancy before next injection and advise patient to use additional contraceptive measures (for example barrier) for 7 days after the injection.

**Contraindications** Pregnancy (Appendix 7c); breast or endometrial cancer; severe liver disease (Dubin-Johnson or Rotor's syndromes) (Appendix 7a); history of jaundice, pruritus, herpes or of deteriorating otosclerosis during pregnancy; severe diabetes mellitus with vascular changes; hypertension; 12 weeks before planned surgery and during immobilization; thromboembolic disease; disturbances of lipid metabolism; undiagnosed vaginal bleeding; porphyria; epilepsy, hepatitis, amenorrhoea, herpes gestation.

**Precautions** Possible small increase in risk of breast cancer; migraine; liver dysfunction; depression; diabetes mellitus; previous ectopic pregnancy; cardiac and renal disease; interactions (Appendix 6b); vaginal bleeding; blood clots; seizures, lactation (Appendix 7b).

**Adverse Effects** Bloating; breast discomfort; headache; dizziness, depression; nausea; menstrual irregularities; rarely; weight gain; hepatitis; cataract; optic neuritis; mental discomfort.

**Storage**

Tablets: Store protected from light and moisture. Injection: Store protected from light.

### 24.1.3 Intrauterine Devices

Copper-bearing intrauterine contraceptive devices consist of a plastic carrier wound with copper wire or fitted with copper bands; some also have a central core of silver to prevent fragmentation of copper. Smaller devices have been introduced to minimize adverse effects and the replacement time for these devices is normally between 3 and 8 years. Fertility declines with age and therefore a copper intrauterine device fitted in a woman over 40 years of age, may remain in the uterus until menopause.

The intrauterine device is appropriate for women who expect to use it for continuous long-term contraception. It is suitable for older parous women; intrauterine devices should be used with caution in young nulliparous women because of the increased risk of expulsion. Young women at risk of sexually transmitted infections are also at risk of pelvic inflammatory disease.

The timing and technique of fitting an intrauterine device play a critical role in its subsequent performance and call for proper training and experience. Patients should receive full counselling backed by the manufacturer's approved leaflet. For routine contraception the device can be inserted between 4 and 12 days after the start of menstruation; for emergency contraception the device can be inserted at any time in the menstrual cycle within 5 days of unprotected intercourse. There is an increased risk of infection for 20 days after insertion and this may be related to existing lower genital tract infection. Pre-screening (at least for chlamydia and gonorrhoea) should if possible be performed. If sustained pelvic or lower abdominal pain occur during the following 20 days after insertion of the device, the woman should be treated as having acute pelvic inflammatory disease. An intrauterine device should not be removed in mid-cycle unless an additional contraceptive was used for the previous 7 days. If removal is essential (for example to treat severe pelvic infection) post-coital contraception should be considered. If the woman becomes pregnant, the device should be removed in the first trimester and the possibility of ectopic pregnancy considered; if the threads of the intrauterine device are already missing on presentation, the pregnancy is at risk of second trimester abortion, haemorrhage, pre-term delivery and infection.



## Emergency Contraception:

Insertion of a copper intrauterine contraceptive device is a highly effective method of emergency contraception and is more effective than hormonal methods of emergency contraception. Sexually transmitted diseases should be tested for and insertion of the device should usually be covered by anti-bacterial prophylaxis.

### Hormone Releasing IUD\*

<b>Indications</b>	<i>For contraception.</i>
<b>Availability</b>	At Family Welfare clinics or speciality centres.
<b>Dose</b>	For contraception, the device can be inserted at any time between day 4 and day 12 after the start of menstrual bleeding; not to be fitted during heavy menstrual bleeding.  Emergency contraception, the device may be inserted up to 120 h (5 days) after unprotected intercourse, at any time of menstrual cycle; if intercourse has occurred more than 5 days previously, device can still be inserted up to 5 days after the earliest likely calculated day of ovulation; device can be removed at the beginning of menstruation if no longer required.
<b>Contraindications</b>	Abnormal pap smear or abnormal vaginal bleeding.
<b>Adverse Effects</b>	Heavy bleeding, perforation of uterus; cramps.

### IUD Containing Copper\*

<b>Indications</b>	<i>Contraception; emergency contraception.</i>
<b>Availability</b>	Single IUD in pouch pack.
<b>Dose</b>	For contraception, the device can be inserted at any time between day 4 and day 12 after the start of menstrual bleeding; not to be fitted during heavy menstrual bleeding.  Emergency contraception, the device may be inserted up to 120 h (5 days) after unprotected intercourse, at any time of menstrual cycle; if intercourse has occurred more than 5 days previously, device can still be inserted up to 5 days after the earliest likely calculated day of ovulation; device can be removed at the beginning of menstruation if no longer required.

### Contraindications

Pregnancy; 48h-4 weeks post partum; puerperal sepsis; postseptic abortion; cervical or endometrial cancer; pelvic inflammatory disease; recent sexually transmitted disease (if not fully investigated and treated); pelvic tuberculosis; unexplained uterine bleeding; malignant gestational trophoblastic disease; distorted or small uterine cavity; copper allergy; Wilson's disease; medical diathermy; abnormal pap smear or abnormal vaginal bleeding.

### Precautions

Anaemia; heavy menstrual bleeding, endometriosis, severe primary dysmenorrhoea, history of pelvic inflammatory disease, history of ectopic pregnancy or tubal surgery, fertility problems, nulliparity and young age, severely scarred uterus or severe cervical stenosis, valvular heart disease (requires antibacterial cover)-avoid if prosthetic valve or history of endocarditis; HIV infection or immunosuppressive therapy (risk of infection-avoid if marked immunosuppression); joint and other prostheses; increased risk of expulsion if inserted before uterine involution; gynaecological examination before insertion and 4-6 weeks afterwards-counsel women to see doctor promptly if significant symptoms such as pain; anticoagulant therapy; remove if pregnancy occurs (consider possibility of ectopic pregnancy).

### Adverse Effects

Uterine or cervical perforation, displacement, expulsion; pelvic infection exacerbated; heavy menstrual bleeding; dysmenorrhoea; pain and bleeding and occasionally epileptic seizure or vasovagal attack on insertion.

## 24.1.4 Estrogens

Estrogens are necessary for the development of female secondary sexual characteristics; they also stimulate myometrial hypertrophy with endometrial hyperplasia. They affect bone by increasing calcium deposition. They are secreted at varying rates during the menstrual cycle throughout the period of activity of the ovaries. During pregnancy, the placenta becomes the main source of estrogens. At the menopause, ovarian secretion declines at varying rates.

Estrogen therapy is given cyclically or continuously principally for contraception and for the alleviation of menopausal symptoms. If long-term therapy is required for menopausal hormone therapy a progestogen should be added to prevent cystic hyperplasia of the endometrium (or of endometrial foci in women who have had a hysterectomy) and possible transformation to cancer.

The palliative care of advanced inoperable, metastatic carcinoma of the breast in both men and postmenopausal women is another indication for estrogen therapy.

## Hormone Therapy (HT):

Estrogens are used for replacement therapy in perimenopausal and menopausal women for the treatment of vasomotor instability, vulvar and vaginal atrophy associated with the menopause and for the prevention of osteoporosis. HT should not be prescribed with the aim of reducing the incidence of heart disease. HT may be used for menopausal women whose lives are unduly inconvenienced by vaginal atrophy or vasomotor instability. Vaginal atrophy may respond to a short course of a vaginal estrogen preparation. Systemic treatment is needed for vasomotor and other symptoms of estrogen deficiency and can be given for up to 2-3 years; Medroxyprogesterone acetate (see also chapter 21.4.2) may be given in a dose of 10 mg daily for the last 12-14 days of each estrogen HT cycle. Alternatively, norethisterone 1 mg daily may be given on the last 12-14 days of each 28-day estrogen cycle.

HT should be considered for women with early natural or surgical menopause (before age 45 years) because they have a high risk of osteoporosis. Small doses of estrogen given systemically in the perimenopausal and postmenopausal period also diminish osteoporosis, but the slight increased risk of breast cancer needs to be taken into account. For early menopause, HT can be given until the approximate age of natural menopause (until age 50 years).

For longer-term use of HT in postmenopausal women (with a uterus or without a uterus), women must be made aware of the increased incidence of breast cancer and other adverse effects. Each decision to start HT should be made on an individual basis, and treatment should be regularly reappraised (at least once a year). Factors such as corticosteroid therapy, family history of osteoporosis, thinness, lack of exercise, alcoholism or smoking, early menopause, fractures to the hip or forearm before age 65 years should be taken into account when considering the use of HT; women of African origin appear to be less susceptible to osteoporosis than those who are white or of Asian origin.

There is an increased risk of deep-vein thrombosis and of pulmonary embolism in women taking HT. In women who have predisposing factors such as a personal or family history of deep venous thrombosis or pulmonary embolism, severe varicose veins, obesity, surgery, trauma or prolonged bed-rest, the overall risk may outweigh the benefit.

Using HT increases the risk of breast cancer slightly. The increased risk is related to the duration of HT use and this excess risk disappears within about 5 years of stopping. The risk of breast cancer is greater with combined HT (an estrogen

and a progestogen) than with estrogen-only HT (but estrogen alone may not be suitable for women with intact uterus).

Epidemiological studies indicate that in women aged between 50 and 65 years not using HT, about 32 cases of breast cancer will be diagnosed in every 1000 women. In those using HT, the risk of breast cancer is increased as follows:

- Women using *combined HT* with an estrogen and a progestogen for 5 years, about 6 additional cases in 1000; in those using combined HT for 10 years, about 19 additional cases in 1000
- Women using *estrogen-only HT* for 5 years, about 2 additional cases in 1000; in those using estrogen-only HT for 10 years, about 5 additional cases in 1000.

HT does not provide contraception. If a potentially fertile woman needs to use HT, non-hormonal contraceptive measures are necessary.

Precautions for patients on HT undergoing surgery and reasons to stop HT are the same as those for hormonal contraceptives.

## Ethinylestradiol\*

Pregnancy Category-X

Schedule H

### Indications

*Hormone replacement for menopausal symptoms; osteoporosis prophylaxis; palliation in breast cancer in men and postmenopausal women; contraception in combination with a progestogen; dysfunctional uterine bleeding, prostatic carcinoma.*

### Availability

**TABLETS** 0.01, 0.05 and 1 mg; **INJECTION** 1 ml ampoule (10 mg/ml).

### Dose

**Oral**

**Adult-** Hormone replacement: 10 to 20 µg daily. Palliation in breast cancer in postmenopausal women: 0.1 to 1 mg 3 times daily.

### Contraindications

Pregnancy (Appendix 7c); estrogen-dependent cancer; active thrombophlebitis or thromboembolic disorders or history of recent venous thromboembolism (unless already on anticoagulant therapy); undiagnosed vaginal bleeding; lactation (Appendix 7b); liver disease (where liver function tests have failed to return to normal), Dubin-Johnson and Rotor syndromes (or monitor closely); jaundice; cerebrovascular disease; hepatic carcinoma; CV disease; estrogen dependent cancer.

**Precautions** Progestogen may need to be added to regimen to reduce risk of endometrial cancer due to unopposed estrogen (see notes above); migraine (or migraine-like headache); history of breast nodules of fibrocystic disease-closely monitor breast status (risk of breast cancer, see notes above); uterine fibroids may increase in size; symptoms of endometriosis may be exacerbated; predisposition to thromboembolism (see notes above); presence of antiphospholipid antibodies; increased risk of gallbladder disease; hypophyseal tumours; porphyria; interactions (Appendix 6c, 6d); hepatic impairment (Appendix 7a).

**Adverse Effects** Nausea and vomiting, abdominal cramps and bloating, weight increase; breast enlargement and tenderness; premenstrual-like syndrome; Sodium and fluid retention; thromboembolism (see notes above); altered blood lipids; cholestatic jaundice; rashes and chloasma; changes in *libido*; depression, headache, migraine, dizziness, leg cramps (rule out venous thrombosis); contact lenses may irritate; impotence; hypertension.

**Storage** Store protected from light.

## Tamoxifen\*

**Pregnancy Category-D**

**Schedule G**

**Indications** *Adjuvant treatment for estrogen receptor positive breast cancer, metastatic breast cancer, male infertility, anovulatory infertility.*

**Availability** TABLETS 10, 20, 25, 40 and 100 mg.

**Dose**  
**Breast cancer:**  
**Adult-** 20 mg daily as a single dose or in 2 divided doses. max. 40 mg/day.

**Anovulatory infertility:**  
**Adult-** 20 mg daily on second- fifth day of the menstrual cycle. max.- 80 mg/day.

**Contraindications** Hypersensitivity, deep vein thrombosis, pulmonary embolism, pregnancy (Appendix 7c) (exclude before treatment and advise non-hormonal contraception if appropriate), lactation (Appendix 7b).

**Precautions** If patient experiences swelling around ankles or legs, decrease salt intake, cystic ovarian swellings in premenopausal woman.

### Adverse Effects

Hypersensitivity reactions such as angioedema, Steven's Johnson syndrome and bullous pemphigoid. Hot flushes, nausea, vomiting; vaginal discharge and bleeding, menstrual irregularities, increased risk of venous thromboembolism; distaste of food; depression; hair thinning; hypercalcaemia; peripheral oedema; decreased platelet count; increased pain and hypercalcaemia with bony metastasis; tumor flare; liver enzyme changes (rarely, cholestasis); hepatitis; hepatic necrosis; hypertriglyceridaemia (sometimes with pancreatitis).

### Storage

Store protected from light and moisture.

## 24.2 Hormones

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### 24.2.1 Adrenal Hormones and synthetic Substitutes

Corticosteroids include hormones secreted by the adrenal cortex and synthetic analogues of these hormones. The adrenal cortex normally secretes hydrocortisone which has glucocorticoid activity and weak mineralocorticoid activity. It also secretes the mineralocorticoid aldosterone. Synthetic glucocorticoids include betamethasone, dexamethasone and prednisolone. Fludrocortisone has glucocorticoid properties but it has potent mineralocorticoid properties and is used for its mineralocorticoid effects.

Pharmacology of the corticosteroids is complex and their actions are wide-ranging. In physiological (low) doses, they replace deficient endogenous hormones. In pharmacological (high) doses, glucocorticoids decrease inflammation and suppress the immune response.

In therapeutic doses glucocorticoids suppress release of corticotrophin (adrenocorticotrophic hormone, ACTH) from the pituitary thus the adrenal cortex ceases secretion of endogenous corticosteroids. If suppressive doses are given for prolonged periods, the adrenal cortex may undergo atrophy and this leads to a deficiency on sudden withdrawal or dosage reduction or situations such as stress or trauma where corticosteroid requirements are increased. After high dosage or prolonged therapy, withdrawal should be gradual, the rate depending on various factors including patient response, corticosteroid dose, duration of treatment and disease state. The suppressive action of a corticosteroid on cortisol secretion is least when given in the morning. Corticosteroids should normally be given in a single morning dose to attempt to minimize pituitary-adrenal suppression. Because the therapeutic effects of corticosteroids are of longer duration than the metabolic effects, intermittent therapy may allow the body's normal metabolic rhythm and the therapeutic effects to be maintained. Alternate day dosing is, however, suitable only in certain disease states and with corticosteroids with small mineralocorticoid effects and a relatively short duration of action.

Hydrocortisone is used in adrenal replacement therapy and on a short-term basis by intravenous injection for the emergency management of some conditions. Its mineralocorticoid activity is too high for it to be used on a long-term basis for disease suppression. The mineralocorticoid activity of fludrocortisone is also high and its anti-inflammatory activity is of no clinical relevance. It is used together with glucocorticoids in adrenal insufficiency. Prednisolone has predominantly gluco-

corticoid activity and is the corticosteroid most commonly administered for long-term disease suppression. It is the active metabolite of prednisone, conversion of which is variable and prednisone should not be used interchangeably with prednisolone. Dexamethasone has very high glucocorticoid activity in conjunction with insignificant mineralocorticoid activity making it particularly suitable for high-dose therapy in conditions where water retention would be a disadvantage such as cerebral oedema. It also has a long duration of action and this, together with its lack of mineralocorticoid activity makes it particularly suitable for conditions requiring suppression of corticotrophin secretion such as congenital adrenal hyperplasia.

### **Adverse Effects of Corticosteroids:**

Overdosage or prolonged use may exaggerate some of the normal physiological actions of corticosteroids leading to mineralocorticoid and glucocorticoid adverse effects.

Mineralocorticoid adverse effects include hypertension, sodium and water retention and potassium loss. These effects are most marked with fludrocortisone but are significant with hydrocortisone, occur slightly with prednisolone and are negligible with dexamethasone.

Glucocorticoid adverse effects include diabetes mellitus and osteoporosis which is of particular importance in the elderly since it may result in osteoporotic fractures of the hip or vertebrae. High doses may also be associated with avascular necrosis of the femoral neck. Muscle wasting may also occur and there is a weak link with peptic ulceration. Mental disturbances can occur, including serious paranoid state or depression with risk of suicide, particularly in patients with a history of mental disorders; euphoria is also common. High doses may cause Cushing syndrome (typical moon face, striae and acne), which is usually reversible on withdrawal of treatment, but this should always be tapered gradually to avoid symptoms of acute adrenal insufficiency (see also Withdrawal). In children, corticosteroids may result in suppression of growth and corticosteroids administered during pregnancy can affect adrenal development in the fetus. Any adrenal suppression in the neonate following prenatal exposure usually resolves spontaneously after birth and is rarely, clinically important. Healing of wounds may be impaired and infections and thinning of the skin may occur; spread of infections may result from modification of tissue reactions.

### **Adrenal Suppression**

Adrenal suppression occurs during prolonged therapy with corticosteroids, with development of adrenal atrophy which



may persist for years after stopping. Abrupt withdrawal after a prolonged period may lead to acute adrenal insufficiency, hypotension or death (see Withdrawal of Systemic Corticosteroids, below). Withdrawal may also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss.

### Corticosteroid Cover During Stress:

To compensate for a diminished adrenocortical response caused by prolonged corticosteroid treatment, any significant intercurrent illness, trauma, or surgery requires a temporary increase in corticosteroid dose, or if already stopped, a temporary re-introduction of corticosteroid treatment. Anaesthetists must therefore know whether a patient is taking or has been taking a corticosteroid, to avoid a precipitous fall in blood pressure during anaesthesia or in the immediate postoperative period. A suitable regimen for corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of surgery, is:

- *Minor surgery under general anaesthesia*-usual oral corticosteroid dose on the morning of surgery or hydrocortisone 25-50 mg intravenously at induction; the usual oral corticosteroid dose is recommenced after surgery.
- *Moderate or major surgery*-usual oral corticosteroid dose on the morning of surgery and hydrocortisone 25-50 mg intravenously at induction, followed by hydrocortisone 25-50 mg 3 times a day by intravenous injection for 24 h after moderate surgery or for 48-72 h after major surgery; the usual preoperative oral corticosteroid dose is recommenced on stopping hydrocortisone injections.

### Infections:

Prolonged courses of corticosteroids increase susceptibility to infections and increase their severity; clinical presentation of infections may also be atypical. Serious infections, for example septicaemia and tuberculosis, may reach an advanced stage before being recognised, and amoebiasis or strongyloidiasis may be activated or exacerbated (exclude before initiating a corticosteroid in those at risk or with suggestive symptoms). Fungal or viral ocular infections may also be exacerbated.

### Chickenpox

Unless they have had chickenpox, patients receiving oral or parenteral corticosteroids for purposes other than replacement should be regarded as being at risk of severe chickenpox on exposure. Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation;

rash is not necessarily a prominent feature.

Passive immunization with varicella-zoster immunoglobulin is needed for exposed non-immune patients receiving systemic corticosteroids or for those who have used them within the previous 3 months; varicella-zoster immunoglobulin should preferably be given within 3 days of exposure and no later than 10 days. Confirmed chickenpox warrants specialist care and urgent treatment. Corticosteroids should not be stopped and dosage may need to be increased.

Topical, inhaled or rectal corticosteroids are less likely to be associated with an increased risk of severe chickenpox.

## Measles

Patients taking corticosteroids should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.

## Dosage and Administration:

Adverse effects of systemic glucocorticoids, including suppression of the Hypothalamo-Pituitary-Adrenal (HPA) axis, are dose- and duration-dependent; thus patients should be given treatment for the shortest period at the lowest dose that is clinically necessary. Patient response is variable and doses should therefore be individualized. In life-threatening diseases, high doses may be needed because the complications of therapy are likely to be less serious than the disease. In long-term therapy in relatively benign chronic conditions such as rheumatoid arthritis, adverse effects often outweigh the advantages. In order to minimize the adverse effects, the maintenance dose should be kept as low as possible and if possible, single morning doses or alternate day therapy should be used. Glucocorticoids can improve the prognosis of serious conditions such as systemic lupus erythematosus, temporal arteritis and polyarteritis nodosa; in such disorders the effects of the disease process may be suppressed and symptoms relieved but the underlying condition is not cured.

Glucocorticoids are used both topically and systemically. In emergency situations, hydrocortisone may be given intravenously; in the treatment of asthma, inhalation therapy with beclomethasone may be used (chapter 20.1). Whenever possible, local treatment with creams, intra-articular injections, inhalations, eye-drops or enemas should be used in preference to systemic therapy.

## Withdrawal of Systemic Corticosteroids:

The rate of withdrawal of systemic glucocorticoids is dependent upon several factors including size of dose, dura-

tion of treatment, individual patient's response and the likelihood of relapse of the underlying disease. If there is uncertainty about suppression of the HPA axis, withdrawal should be gradual to enable the adrenal gland to recover. Patients should be advised not to stop taking glucocorticoids abruptly unless permitted by their doctor.

Gradual withdrawal should be considered in those whose disease is unlikely to relapse and who have:

- recently received repeated courses (particularly if taken for longer than 3 weeks)
- taken a short course within 1 year of stopping long-term therapy
- other possible causes of adrenal suppression
- received more than 40 mg daily prednisolone (or equivalent)
- been given repeat doses in the evening
- received more than 3 weeks' treatment

Abrupt withdrawal may be considered in those whose disease is unlikely to relapse and who have received treatment for 3 weeks or less and who are not included in the patient groups described above.

During corticosteroid withdrawal the dose may be reduced rapidly down to the physiological dosage (equivalent to 7.5 mg prednisolone daily) and then reduced more slowly. Assessment of the disease may be needed during withdrawal to ensure that relapse does not occur.

## Dexamethasone\* (Refer Page No. 30)

Pregnancy Category-C

Schedule H

### Indications

*Suppression of inflammatory and allergic disorders; shock; diagnosis of Cushing syndrome; congenital adrenal hyperplasia; cerebral oedema; respiratory distress syndrome.*

### Availability

**TABLETS** 0.5, 2 and 4 mg; **INJECTION** 2 ml vial (4 mg/ml). **CREAM** 5 and 15 gm (0.1% w/w).

### Dose

#### Oral

**Adult-** 0.5 to 10 mg daily.

#### *Intramuscular injection or slow intravenous injection or intravenous infusion*

**Adult-** Initially 0.5 to 20 mg daily.

**Child-** 200 to 500 µg/kg daily.

**Adult- Cerebral oedema:** 10 mg initially by intravenous injection, then 4 mg by intramuscular injection every 6 h, as required for 2-10 days.

### Contraindications

See notes above; systemic infection (unless life-threatening or specific antimicrobial therapy given); avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished); diabetes, hypertension, psychosis, osteoporosis, gastric ulceration.

### Precautions

Adrenal suppression during prolonged treatment which persists for years after stopping treatment (see notes above); ensure patients understand importance of compliance with dosage and have guidance on precautions to reduce risks; monitor weight, blood pressure, fluid and electrolyte balance and blood glucose levels throughout prolonged treatment; infections (greater susceptibility, symptoms may be masked until advanced stage); clinical presentation may be atypical; risk of chickenpox and measles increased (see notes above); quiescent tuberculosis-chemoprophylactic therapy during prolonged corticosteroid treatment; elderly; children and adolescents (growth retardation possibly irreversible); hypertension, recent myocardial infarction (rupture reported), congestive heart failure, liver failure, renal impairment, diabetes mellitus including family history, osteoporosis (may be manifested as back pain, postmenopausal women at special risk), glaucoma including family history, epilepsy, psoriasis, peptic ulcer, hypothyroidism, history of steroid myopathy; lactation (Appendix 7b); interactions (Appendix 6c); pregnancy (Appendix 7c).

### Adverse Effects

Refer adverse effects of corticosteroids.

## Hydrocortisone\* (Refer Page No. 32, 355 and 429)

Pregnancy Category-C

**Schedule H**

### Indications

*Adrenocortical insufficiency; hypersensitivity reactions including anaphylactic shock; inflammatory bowel disease; asthma; perineal trauma; joint inflammation; seborrheic dermatitis.*

### Availability

**TABLETS** 5, 10 and 20 mg, **CREAM** 10g (1% w/w), **OINTMENT** 1%, 2.5% w/w **INJECTION** 100, 200 and 400 mg vial (25 mg/5 ml).

### Dose

#### Oral

**Adult**-20 to 30 mg daily in divided doses (usually 20 mg in the morning and 10 mg in early evening).

**Child**-400-800 µg/kg/day in 2-3 divided doses.

***Slow intravenous injection or intravenous infusion***

**Adult**- Acute adrenocortical insufficiency: 100 to 500 mg, 3 to 4 times in 24 h or as required.

**Child**- Up to 1 year: 25 mg; 1 to 5 years: 50 mg; 6 to 12 years: 100 mg.

**Contraindications** See notes above; systemic infection (unless life-threatening or specific antimicrobial therapy given); avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished); ulcers.

**Precautions** Refer corticosteroids; lactation (Appendix 7b); interactions (Appendix 6b, 6c, 6d); pregnancy (Appendix 7c).

**Adverse Effects** Refer adverse effects of corticosteroids.

## Methyl Prednisolone\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *Corticosteroid responsive conditions such as severe allergic rhinitis, asthma, rheumatoid arthritis, osteoarthritis, collagen disease, dermatoses.*

**Availability** **TABLETS** 4, 8, 16 and 24 mg; **INJECTION** vials 40, 125, 500 and 1000 mg, 2 ml ampoule (80 mg/2 ml).

**Dose** **Oral**

**Adult**- Asthma, allergies and dermatological conditions: 40 and 120 mg.

Dose should be regulated in accordance with severity of condition; large joints- 20 to 80 mg; medium joints- 10 to 40 mg; small joints- 4 to 10 mg directly in bursae.

**Contraindications** Systemic fungal infection (unless specific antimicrobial therapy given); avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished); hypersensitivity.

**Precautions** Refer notes above; interactions (Appendix 6c, 6d); pregnancy (Appendix 7c).

**Adverse Effects** Refer adverse effects of corticosteroids.

**Storage** Store protected from light at a temperature not exceeding 30°C. The injection should not be allowed to freeze.

**Prednisolone\*** (Refer Page No. 35, 436 and 557)**Pregnancy Category-C****Schedule H**

<b>Indications</b>	<i>Suppression of inflammatory and allergic reactions; with antineoplastic drugs for acute leukaemias and lymphomas; asthma; rheumatic disorder; hematologic disorder.</i>
<b>Availability</b>	<b>TABLETS</b> 5, 10, 20 and 40 mg; <b>INJECTION</b> 1 ml vial (40 mg/ml); <b>SYRUP</b> 60 ml (5 mg/5 ml and 15 mg/5 ml).
<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult-</b> Suppression of inflammatory and allergic disorders: initially up to 10 to 20 mg daily (severe disease, up to 60 mg daily), preferably taken in the morning after breakfast; dose can often be reduced within a few days, but may need to be continued for several weeks or months. Maintenance dose 2.5 to 15 mg daily or higher; cushingoid features are increasingly likely with doses above 7.5 mg daily.</p> <p>Myasthenia gravis: initially 10 mg on alternate days, increased in steps of 10 mg on alternate days to 1-1.5 mg/kg (max. 100 mg) on alternate days or initially 5 mg daily increased in steps of 5 mg daily to usual dose of 60-80 mg daily (0.75-1 mg/kg daily).</p> <p><b>Child-</b> Fractions of adult dose may be used (At 1 year: 25% of adult dose; at 7 years: 50%; and at 12 years: 75%) but clinical factors must be given due weight.</p>
<b>Contraindications</b>	See notes above; systemic infection (unless life-threatening or specific antimicrobial therapy given); avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished).
<b>Precautions</b>	Refer notes above; hepatic impairment (Appendix 7a); lactation (Appendix 7b); interactions (Appendix 6c, 6d); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Refer Adverse effects of Corticosteroids.

## 24.2.2 Androgens

Androgens are secreted by the testes and weaker androgens by the adrenal cortex and ovaries. In the male, they are responsible for the development and maintenance of the sex organs and the secondary sexual characteristics, normal reproductive function, and sexual performance ability in addition to stimulating the growth and development of the skeleton and skeletal muscle during puberty. At high doses in the normal male androgens inhibit pituitary gonadotrophin secretion and depress spermatogenesis. Testosterone is used as replacement therapy in those who are hypogonadal due to either pituitary (secondary hypogonadism) or testicular disease (primary hypogonadism). Androgens are useless as a treatment of impotence and impaired spermatogenesis unless there is associated hypogonadism; they should not be given until the hypogonadism has been properly investigated and treatment should always be under expert supervision. When given to patients with hypopituitarism they can lead to normal sexual development and potency but not fertility. If fertility is desired, the usual treatment is with gonadotrophins or pulsatile gonadotrophin-releasing hormone which will stimulate spermatogenesis as well as androgen production. Androgens cannot induce fertility in men with primary hypogonadism. Caution should be used in treating boys with delayed puberty with excessive doses of testosterone since the fusion of epiphyses is hastened and may result in short stature. Androgens, including testosterone have also been used in postmenopausal women for the palliative treatment of androgen-responsive, advanced, metastatic breast cancer; care is required to prevent masculinizing effects.

### Danazol\*

Pregnancy Category-X

Schedule H

#### Indications

*Endometriosis, fibrocystic mastitis, hereditary angioedema, menorrhagia, gynaecomastia, precocious puberty.*

#### Availability

**TABLETS/CAPSULES** 50, 100 and 200 mg.

#### Dose

Endometriosis: **Adult-** 200 to 600 mg daily in 2 divided doses.

Fibrocystic mastitis: **Adult-** 100 to 400 mg daily in 2 divided doses.

Hereditary angioedema: **Adult-** 200 mg twice or thrice daily.

Gynaecomastia: **Adult-** Initially 400 mg daily in 4 divided doses for 6 months.

**Child-** Initially 200 mg daily, may increase to 400 mg after 2 months.

Menorrhagia: **Adult**- 200 mg once daily.

**Contraindications** Hepatic dysfunction; undiagnosed vaginal bleeding; porphyria; thromboembolic complication; hypersensitivity; pregnancy (Appendix 7c), lactation.

**Precautions** Use with caution in patients with migraine, headache, heart, liver or kidney disease. History of seizures; abnormal bleeding; previous strokes; severe hypertension; diabetes mellitus, polycythaemia; interactions (Appendix 6c).

**Adverse effects** Androgen like effects including weight gain, acne, deepening of voice; seborrhoea; edema; hair loss; amenorrhoea; hirsutism; benign intracranial hypertension; dizziness.

**Storage** Store protected from light.

## Testosterone\*

**Pregnancy Category-X**

**Schedule H**

**Indications** *Hypogonadism; palliative treatment of advanced breast cancer in women.*

**Availability** **INJECTION** 10 ml ampoule (25 mg/ml, 50 mg/ml, 100 mg/ml).

**Dose** ***Slow intramuscular injection***

**Adult**- Hypogonadism: initially 200 to 250 mg every 2 to 3 weeks; maintenance dose 200 to 250 mg every 3 to 6 weeks. Breast cancer: 250 mg, every 2 to 3 weeks.

**Contraindications** Breast cancer in men; prostate cancer; hypercalcaemia; pregnancy (Appendix 7c), lactation (Appendix 7b); nephrosis; history of primary liver tumours.

**Precautions** Cardiac, renal or hepatic impairment (Appendix 7a), elderly; ischaemic heart disease; hypertension, epilepsy; migraine; diabetes mellitus; skeletal metastases (risk of hypercalcaemia); regular examination of prostate during treatment; prepubertal boys; breathing disturbance.



<b>Adverse Effects</b>	Prostate abnormalities and prostate cancer; headache, depression, gastrointestinal bleeding, nausea; polycythaemia; cholestatic jaundice; changes in <i>libido</i> ; gynaecomastia, anxiety, asthenia; generalized paraesthesia; electrolyte disturbances including sodium retention with oedema and hypercalcaemia; increased bone growth; androgenic effects such as hirsutism, male-pattern baldness, seborrhoea, acne, priapism, precocious sexual development and premature closure of epiphyses in pre-pubertal males, virilism in females, and suppression of spermatogenesis in men.
<b>Storage</b>	Store protected from light.

### 24.2.3 Drugs for Erectile dysfunction

#### Sildenafil

**Schedule H**

<b>Indications</b>	<i>Erectile dysfunction.</i>
<b>Availability</b>	<b>TABLETS</b> 25, 50 and 100 mg.
<b>Dose</b>	50 mg about 1 hour before sexual intercourse, maximum 100 mg per dose and not more than once in 24 hours.  <b>Elderly</b> (greater than 65 yrs)- lower initial dose at 25 mg.
<b>Contraindications</b>	Hypersensitivity; coronary heart disease; patients on nitrates.
<b>Precautions</b>	Liver or kidney disease; peptic ulcer; bleeding disorder; leukemia, sickle cell anaemia, myeloma predisposing priapism; recent history of stroke, myocardial infarction, arrhythmias, unstable angina; anatomical deformation of penis; interactions (Appendix 6c); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Headache, nasal congestion, dizziness, flushing; fall in blood pressure; diarrhoea; impairment of colour vision; AV-block, angina pectoris, cardiac arrest, myocardial infarction, cerebral thrombosis, abnormal LFT, hypoglycaemia; retinal vascular disease; photosensitivity, paresthesia; tremor; depression.

## 24.3 Insulin and Other Anti-Diabetic Agents

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Diabetes mellitus is characterized by hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism. There are 2 principal types of diabetes.

Type-1 diabetes or insulin-dependent diabetes mellitus is due to a deficiency of insulin caused by autoimmune destruction of pancreatic  $\beta$ -cells. Patients require administration of insulin.

Type-2 diabetes or non-insulin dependent diabetes mellitus is due to reduced secretion of insulin or to peripheral resistance to the action of insulin. Patients may be controlled by diet alone, but often require administration of oral antidiabetic drugs or insulin. The energy and carbohydrate intake must be adequate but obesity should be avoided. In type 2 diabetes, obesity is one of the factors associated with insulin resistance. Diets high in complex carbohydrate and fibre and low in fat are beneficial. Emphasis should be placed on exercise and increased activity.

The aim of treatment is to achieve the best possible control of plasma glucose concentration and prevent or minimize complications including microvascular complications (retinopathy, albuminuria, neuropathy). Diabetes mellitus is a strong risk factor for cardiovascular disease; other risk factors such as smoking, hypertension, obesity and hyperlipidaemia should also be addressed.

### Insulin

Appropriate insulin regimens should be worked out for each patient. Insulin requirements may be affected by variations in lifestyle (diet and exercise)-drugs such as corticosteroids, infections, stress, accidental or surgical trauma, puberty and pregnancy (second and third trimesters) may increase insulin requirements; renal or hepatic impairment and some endocrine disorders (for example Addison's disease, hypopituitarism) or coeliac disease may reduce requirements. In pregnancy insulin requirements should be monitored frequently.

If possible patients should monitor their own blood-glucose concentration using blood glucose strips. Since blood-glucose concentration varies throughout the day, patients should aim to maintain blood-glucose concentration between 4 and 9 mmol/litre (4-7 mmol/L before meals, <9 mmol/L) for most of the day while accepting that on occasions it will be higher; strenuous efforts should be made to prevent blood-glucose concentrations falling below 4 mmol/litre because of the risk of hypoglycaemia. Patients should be advised to look for troughs and peaks of blood glucose and to adjust their insulin dosage only once or twice a week. Insulin doses are

determined on an individual basis, by gradually increasing the dose to optimise blood-glucose concentration while avoiding hypoglycaemia.

In the absence of blood-glucose monitoring strips, urine-glucose monitoring strips can be used; in fact this is the method of personal choice for many patients with Type 2 diabetes mellitus. It is less reliable than blood glucose but is easier and costs much less. All patients should monitor either blood- or urine-glucose concentration daily.

Hypoglycaemia is a potential complication in all patients treated with insulin or oral hypoglycaemic agents. The consequences of hypoglycaemia include confusion, seizures, coma and cerebral infarction.

Loss of warning of hypoglycaemia is common among insulin-treated patients and can be a serious hazard especially for drivers and those in dangerous occupations. Very tight control lowers the blood glucose concentration needed to trigger hypoglycaemic symptoms; increase in the frequency of hypoglycaemic episodes reduces the warning symptoms experienced by patients. Beta-blockers can also blunt hypoglycaemic awareness (and delay recovery). Some patients report loss of hypoglycaemic warning after transfer to human insulin. Clinical studies do not confirm that human insulin decreases hypoglycaemic awareness. If a patient believes that human insulin is responsible for loss of warning it is reasonable to revert to animal insulin. To restore warning signs, episodes of hypoglycaemia must be reduced to a minimum; this involves appropriate adjustment of insulin dose and frequency, and suitable timing and quantity of meals and snacks.

Drivers need to be particularly careful to avoid hypoglycaemia. They should check their blood-glucose concentration before driving and, on long journeys, at intervals of approximately two hours; they should ensure that a supply of sugar is always readily available. If hypoglycaemia occurs, the driver should stop the vehicle in a safe place, ingest a suitable sugar supply and wait until recovery is complete (may be 15 min or longer). Driving is particularly hazardous when hypoglycaemic awareness is impaired.

For sporadic physical activity, extra carbohydrate may need to be taken to avert hypoglycaemia. Blood glucose should be monitored before, during and after exercise. Hypoglycaemia can develop in patients taking oral antidiabetics, notably the sulfonylureas, but this is uncommon and usually indicates excessive dosage. Sulfonylurea-induced hypoglycaemia may persist for several hours and must be treated in hospital.

Diabetic ketoacidosis is a potentially lethal condition caused by

an absolute or relative lack of insulin; it commonly occurs when adjustments to insulin dosage fail to compensate for increases in insulin requirements, for example during severe infection or major intercurrent illness. Diabetic ketoacidosis occurs mostly in patients with Type 1 diabetes mellitus. It also occurs in Type 2 diabetics who have a temporary need for insulin. Diabetic ketoacidosis is characterized by hyperglycaemia, hyperketonaemia and acidaemia with dehydration and electrolyte disturbances. It is essential that soluble insulin (and intravenous fluids) is readily available for its treatment.

Infections are more likely to develop in patients with poorly controlled diabetes mellitus. These should be treated promptly and effectively to avoid diabetic ketoacidosis.

**Surgery:** Particular attention should be paid to insulin requirements when a patient with diabetes undergoes surgery that is likely to need an intravenous infusion of insulin for longer than 12 h. Soluble insulin should be given in intravenous infusion of glucose and potassium chloride (provided the patient is not hyperkalaemic), and adjusted to provide a blood-glucose concentration of between 7 and 12 mmol/litre. The duration of action of intravenous insulin is only a few min therefore the infusion must not be stopped unless the patient becomes frankly hypoglycaemic. For non-insulin dependent diabetics, insulin treatment is almost always required during surgery (oral hypoglycaemic drugs having been omitted).

Insulin must be given by injection because it is inactivated by gastrointestinal enzymes. Generally, insulin is given by subcutaneous injection into the upper arms, thighs, buttocks, or abdomen. There may be increased absorption from a limb, if the limb is used in strenuous exercise following the injection. It is essential to use only syringes calibrated for the particular concentration of insulin administered.

There are three main types of insulin preparations, classified according to duration of action after subcutaneous injection:

- those of short duration which have a relatively rapid onset of action, for example soluble or neutral insulin;
- those with an intermediate action, for example isophane insulin and insulin zinc suspension;
- those with a relatively slow onset and long duration of action, for example crystalline insulin zinc suspension.

Soluble insulin, when injected subcutaneously, has a rapid onset of action (after 30-60 min), a peak action between 2 and 4 h, and a duration of action up to 8 h. Soluble insulin by the intravenous route is reserved for urgent treatment and fine control in serious illness and perioperative state. When injected

intravenously, soluble insulin has a very short half-life of only about 5 min.

When injected subcutaneously, intermediate-acting insulins have an onset of action of approximately 1-2 h, a maximal effect at 4-12 h and a duration of action of 16-24 h. They can be given twice daily together with short-acting insulin or once daily, particularly in elderly patients. They can be mixed with soluble insulin in the syringe, essentially retaining properties of each component.

The duration of action of different insulin preparations varies considerably from one patient to another and this needs to be assessed for every individual. The type of insulin used and its dose and frequency of administration depend on the needs of each patient. For patients with acute onset diabetes mellitus, treatment should be started with soluble insulin given 3 times daily with medium-acting insulin at bedtime. For those less seriously ill, treatment is usually started with a mixture of pre-mixed short- and medium-acting insulins (for example 30% soluble insulin with 70% isophane insulin) given twice daily. The proportions of soluble insulin can be increased in patients with excessive post-prandial hyperglycaemia.

### Oral Antidiabetic Drugs

Oral antidiabetic (hypoglycaemic) drugs are used for non-insulin-dependent diabetes mellitus in patients who do not respond to dietary adjustment and an increase in physical exercise. They are used to supplement the effect of diet and exercise. There are various types of oral antidiabetic agents. The most commonly used are the sulfonylureas and the biguanide, metformin.

Sulfonylureas act mainly by augmenting insulin secretion and are therefore only effective if there is some residual pancreatic beta-cell activity. They may occasionally lead to hypoglycaemia 4 h or more after food. This may be dose-related and usually indicates excessive dose and it occurs more frequently with long-acting sulfonylureas such as glibenclamide and occurs particularly in the elderly. The sulfonylureas have the disadvantage that they may encourage weight gain. They should not be used during lactation and caution is required in the elderly and those with renal or hepatic insufficiency because of the risk of hypoglycaemia. Insulin therapy is generally required during intercurrent illness such as myocardial infarction, coma, infection, and trauma, during surgery and also during pregnancy.

Metformin exerts its effect by decreasing gluconeogenesis and by increasing peripheral utilization of glucose. Metformin can only act in the presence of endogenous insulin therefore is effective only in diabetics with some residual functioning pancreatic islet cells. It is used as a first-line treatment in over-

weight non-insulin-dependent diabetic patients and in others when strict dieting and sulfonylureas have failed to control the disease. Gastrointestinal adverse effects are common on initial treatment and may persist, particularly when very high doses (such as 3g daily) are given. In order to reduce gastrointestinal effects, treatment should be initiated with a low dose which may be gradually increased. Metformin may provoke lactic acidosis which is most likely to occur in patients with renal impairment; it should not be used in patients with even mild renal impairment. One major advantage of metformin is that it does not usually cause hypoglycaemia. It may be used together with insulin (but weight gain and hypoglycaemia can be problem) or sulfonylureas (but possibility of increased adverse effects with such combinations). During medical and surgical emergencies insulin treatment is almost always required; insulin should be substituted for metformin before elective surgery and in pregnancy.

## Glibenclamide\*

**Pregnancy Category-C**

**Schedule G**

<b>Indications</b>	<i>Type II diabetes mellitus.</i>
<b>Availability</b>	<b>TABLETS</b> 1.25, 2.5 and 5 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> initially 5 mg once daily with or immediately after breakfast; max. 15 mg daily.  <b>Elderly-</b> 2.5 mg, but it should preferably be avoided, adjusted according to response (max. 15 mg daily).
<b>Contraindications</b>	Ketoacidosis; porphyria; lactation (Appendix 7b).
<b>Precautions</b>	Renal impairment; hepatic impairment (Appendix 7a); elderly; substitute insulin during severe infection, trauma, surgery (see notes above); interactions (Appendix 6b, 6c); diabetic coma; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Mild and infrequent, including gastrointestinal disturbances and headache; liver disorders; hypersensitivity reactions usually in first 6-8 weeks; rarely; erythema multiforme, exfoliative dermatitis, fever and jaundice; hypoglycaemia, particularly in the elderly; rarely, blood disorders including leukopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, and aplastic anaemia; cholestatic jaundice.

## Gliclazide

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Type II diabetes mellitus.</i>
<b>Availability</b>	<b>TABLETS</b> 20, 30, 40, 80 and 160 mg; <b>MODIFIED RELEASE TABLETS</b> 30 and 60 mg; <b>CAPSULES</b> 30, 40, 60 and 80 mg.
<b>Dose</b>	40- 320 mg daily, doses >160 mg daily may be given in 2 divided doses.  Modified release tablets 30-120 mg daily.
<b>Contraindications</b>	Type I diabetes mellitus, severe renal and hepatic impairment, diabetic ketoacidosis, pregnancy (Appendix 7c), lactation.
<b>Precautions</b>	Monitor blood glucose concentration, increased risk of hypoglycaemia in elderly; debilitated patients; renal and hepatic impairment, metabolic stressful situations; interactions (Appendix 6c).
<b>Adverse Effects</b>	Cutaneous reactions; blood dyscrasias, gastrointestinal disturbances; cholestatic jaundice.

## Glimepiride

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Type II diabetes mellitus.</i>
<b>Availability</b>	<b>TABLETS</b> 1, 2, 3 and 4 mg.
<b>Dose</b>	<b>Adult</b> 1-2 mg daily.  Max dose 8 mg daily.
<b>Contraindications</b>	Hypersensitivity; pregnancy (Appendix 7c); diabetic ketoacidosis.
<b>Precautions</b>	Elderly; hepatic and renal impairment; interactions (Appendix 6b, 6c); monitor blood-glucose concentration; lactation.
<b>Adverse Effects</b>	Hypoglycaemia; weight gain.
<b>Storage</b>	Store protected from moisture at temperature not exceeding 30°C.

## Glipizide

Pregnancy Category-C

<b>Indications</b>	<i>Type II diabetes mellitus.</i>
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<b>Availability</b>	<b>TABLETS</b> 2.5, 5, 7.5 and 10 mg.
<b>Dose</b>	2.5-20 mg once or twice daily. Maximum 40 mg daily.
<b>Contraindications</b>	Hypersensitivity; type I diabetes mellitus, ketoacidosis with or without coma; severe hepatic or renal insufficiency; pregnancy (Appendix 7c), lactation.
<b>Precautions</b>	Stress; fever; trauma; infection or surgery; elderly; thyroid impairment; monitor blood glucose concentration.
<b>Adverse Effects</b>	Hypoglycemia, nausea, diarrhoea, allergic skin reactions, thrombocytopenia, leucopenia, agranulocytosis, jaundice, hemolytic anaemia.
<b>Storage</b>	Store protected from moisture.

## Glucagon\*

Pregnancy Category-B

**Schedule H**

<b>Indications</b>	<i>Severe hypoglycaemia and radiological examination of gastrointestinal tract.</i>
<b>Availability</b>	<b>INJECTION</b> (powder for reconstitution)- 1 mg vial with pre-filled syringe containing water for injection.
<b>Dose</b>	<p><b>Parenteral</b></p> <p><b>Severe hypoglycaemia:</b>  <b>Adult and child over 8 years (or body weight over 25 kg)-</b> 1 mg by s.c, i.m or i.v route.</p> <p><b>Child under 8 years (or body weight under 25 kg)-</b> 500 µg, if no response within 10 minutes i.v glucose must be given.</p> <p><b>As diagnostic aid in gastrointestinal examination: Adult-</b> 1-2 mg by i.m or 0.2-2 mg by i.v. injection.</p> <p><b>Diagnosis of pheochromocytoma:</b> 1 mg i.v.</p>
<b>Contraindications</b>	Pheochromocytoma; hypersensitivity.
<b>Precautions</b>	Patients with insulinoma, glucagonoma, monitor prothrombin time, starvation and adrenal insufficiency, ineffective in chronic hypoglycaemia, alcohol-induced hypoglycaemia, pregnancy (Appendix 7c), lactation, interactions (Appendix 6b, 6c).
<b>Adverse effects</b>	Hypokalemia; nausea, vomiting, abdominal pain; rarely, hypersensitivity.



## Insulin\*

### Pregnancy Category-B

**Schedule H, G**

<b>Indications</b>	<i>Diabetes mellitus; diabetic emergencies and at surgery; diabetic ketoacidosis or coma.</i>
<b>Availability</b>	<b>INJECTION</b> (multi-dose vials/prefilled syringes/cartridges) - 40 and 100 IU/ml.
<b>Dose</b>	<b><i>Subcutaneous, intramuscular, intravenous injection or intravenous infusion.</i></b>  <b>Adult and Child-</b> Diabetes mellitus: according to individuals requirement.
<b>Precautions</b>	See notes above; reduce dose in renal impairment, lactations; interactions (Appendix 6a, 6b, 6c); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Hypoglycaemia in overdose; localized, and rarely, generalized allergic reactions; lipodystrophy at injection site.
<b>Storage</b>	Store in multi dose container in a refrigerator (2 to 8°C). It should not be allowed to freeze.

## Intermediate Acting Insulin\*

### Insulin Zinc

**Schedule G**

<b>Indications</b>	<i>Diabetes mellitus.</i>
<b>Availability</b>	<b>INJECTION</b> 40 and 80 IU/ml.
<b>Dose</b>	<b><i>Subcutaneous injection</i></b>  <b>Adult and Child-</b> Diabetes mellitus: according to individuals requirement.
<b>Precautions</b>	See notes above; reduce dose in renal impairment; lactation.
<b>Adverse Effects</b>	Hypoglycaemia in overdose; localized, and rarely, generalized allergic reactions; lipodystrophy at injection site.
<b>Storage</b>	Store in multi dose containers in a refrigerator (2 to 8°C). It should not be allowed to freeze.

## Isophane Insulin

**Schedule G**

<b>Indications</b>	<i>Diabetes mellitus.</i>
<b>Availability</b>	<b>INJECTION</b> 40 and 80 IU/ml.
<b>Dose</b>	<b><i>Subcutaneous injection</i></b>

**Adult and Child-** Diabetes mellitus: according to individual's requirement.

- Precautions** See notes above; reduce dose in renal impairment; lactation.
- Adverse Effects** Hypoglycaemia in overdose; localized and rarely, generalized allergic reactions; lipodystrophy at injection site.
- Storage** Store in multi dose containers in a refrigerator (2 to 8°C). It should not be allowed to freeze.

## Metformin\*

**Pregnancy Category-B**

**Schedule H**

- Indications** *Diabetes mellitus.*
- Availability** **TABLETS** 250, 500, 850 mg, and 1g.
- Dose** **Oral**
- Adult-** Diabetes mellitus: initially 500 mg with breakfast for at least 1 week, then 500 mg with breakfast and evening meal for at least 1 week, then 500 mg with breakfast, lunch and evening meal or 850 mg every 12 h with or after food (max. 2g daily in divided doses).
- Contraindications** Renal impairment (withdraw if renal impairment suspected; Appendix 7d); withdraw if tissue hypoxia likely (for example sepsis, respiratory failure, recent myocardial infarction, hepatic impairment), use of iodine-containing X-ray contrast media (do not restart metformin until renal function returns to normal) and use of general anaesthesia (suspend metformin 2 days beforehand and restart when renal function returns to normal); alcohol dependence; pregnancy (Appendix 7c); anaemia; ketosis.
- Precautions** Measure serum creatinine before treatment and once or twice annually during treatment; substitute insulin during severe infection; trauma, surgery (see notes above and contraindications); lactation (Appendix 7b); interactions (Appendix 6a, 6b, 6c); hepatic or renal disease (Appendix 7a); heart disease.
- Adverse Effects** Anorexia, nausea and vomiting, diarrhoea (usually transient), abdominal pain, metallic taste; lactic acidosis most likely in patients with renal impairment (discontinue); decreased vitamin B<sub>12</sub> absorption.
- Storage** Store protected from light and moisture.

## Pioglitazone

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Type 2 diabetes mellitus.</i>
<b>Availability</b>	<b>TABLETS</b> 15 and 30 mg.
<b>Dose</b>	<b>Oral</b>  <b>Type 2 diabetes mellitus: Adult-</b> 15-30 mg once daily. Max. dose- 45 mg per day.
<b>Contraindications</b>	Hypersensitivity, type 1 diabetes, diabetic ketoacidosis, symptomatic or history of heart failure, children, lactation.
<b>Precautions</b>	Oedema, congestive heart failure, hepatic dysfunction, anaemia, concomitant oral contraceptives and hormone replacement therapy, pregnancy (Appendix 7c), interactions (Appendix 6c).
<b>Adverse Effects</b>	Oedema, headache, upper respiratory tract infection, GI disturbances, nausea, shortness of breath, weight gain, blurred vision, dizziness, arthralgia, impotence.
<b>Storage</b>	Store protected from heat, light and moisture at a temperature not exceeding 30°C.

## 24.4 Ovulation Inducers and Progestogens

### 24.4.1 Drugs for Ovulation Induction

The anti-estrogen, clomifene is used in the treatment of female infertility due to disturbances in ovulation. It induces gonadotrophin release by occupying estrogen receptors in the hypothalamus, thereby interfering with feedback mechanisms. Patients should be carefully counselled and should be fully aware of the potential adverse effects, including a risk of multiple pregnancy (rarely, more than twins), of this treatment. Most patients who are going to respond will do so to the first course; 3 courses should be adequate; long-term cyclical therapy (more than 6 cycles) is not recommended as it may increase risk of ovarian cancer.

#### Clomifene\*

Pregnancy Category-X

Schedule H

<b>Indications</b>	<i>Anovulatory infertility.</i>
<b>Availability</b>	<b>TABLETS</b> 25, 50 and 100 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> Anovulatory infertility: 50 mg daily for 5 days, starting within 5 days of onset of menstruation, preferably on the second day, or at any time if cycles have ceased; a second course of 100 mg daily for 5 days may be given in the absence of ovulation.
<b>Contraindications</b>	Hepatic impairment (Appendix 7a); ovarian cysts; hormone dependent tumours or uterine cysts; bleeding of undetermined cause; pregnancy (exclude before treatment, Appendix 7c); hyperprolactinaemia; depression.
<b>Precautions</b>	Visual disturbances (discontinue and initiate eye examination) and ovarian hyperstimulation syndrome (discontinue treatment immediately); polycystic ovary syndrome (cysts may enlarge during treatment); uterine fibroids, ectopic pregnancy, incidence of multiple births increased (consider ultrasound monitoring); lactation (Appendix 7b).
<b>Adverse Effects</b>	Visual disturbances; ovarian hyperstimulation; hot flushes; abdominal discomfort; occasional nausea and vomiting; depression; insomnia; breast tenderness; headache; intermenstrual spotting; menorrhagia; endometriosis; convulsions; weight gain; rashes; dizziness and hair loss.

## 24.4.2 Progestogens

Progesterone is a hormone secreted by the corpus luteum whose actions include induction of secretory changes in the endometrium, relaxation of uterine smooth muscle and production of changes in the vaginal epithelium. Progesterone is relatively inactive following oral administration and produces local reactions at site of injection. This has led to the development of synthetic progestogens including levonorgestrel, norethisterone and medroxyprogesterone. Where endometriosis requires drug treatment, it may respond to synthetic progestogens on a continuous basis. They may also be used for the treatment of severe dysmenorrhoea. In postmenopausal women receiving long-term estrogen therapy for hormone replacement, a progestogen needs to be added for women with an intact uterus to prevent hyperplasia of the endometrium.

Progestogens are also used in combined oral contraceptives and progestogen-only contraceptives.

### Medroxyprogesterone\* (Refer Page No. 465)

### Norethisterone\* (Refer Page No. 466)

#### Pregnancy Category-X

**Schedule H**

<b>Indications</b>	<i>Endometriosis; menorrhagia; severe dysmenorrhoea; contraception; premenstrual tension.</i>
<b>Availability</b>	<b>TABLET</b> 5 mg; <b>INJECTION</b> 1 ml ampoule (200 mg/ml).
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> Endometriosis: 10 mg daily starting on fifth day of cycle (increased if spotting occurs to 20 to 25 mg daily, reduce once bleeding has stopped). Menorrhagia: 5 mg three times daily for 10 days to stop bleeding; to prevent bleeding 5 mg twice daily from day 19 to 26 of cycle. Dysmenorrhoea: 5 mg, 2 to 3 times daily from day 5 to 24 for 3 to 4 cycles.
<b>Contraindications</b>	Pregnancy (Appendix 7c); undiagnosed vaginal bleeding; hepatic impairment or active liver disease (Appendix 7a); severe arterial disease; breast or genital tract cancer; porphyria; history in pregnancy of idiopathic jaundice, severe pruritus.
<b>Precautions</b>	Epilepsy; migraine; diabetes mellitus; hypertension; cardiac or renal disease and those susceptible to thromboembolism; depression; lactation (Appendix 7b).

### Adverse Effects

Acne, urticaria; fluid retention; weight increase, gastrointestinal disturbances; changes in *libido*, breast discomfort, premenstrual symptoms, irregular menstrual cycles; depression; insomnia, somnolence; headache; dizziness; alopecia; hirsutism; anaphylactoid-like reactions; exacerbation of epilepsy and migraine; rarely, jaundice.

## 24.5 Oxytocics and Antioxytocics

Drugs may be used to modify uterine contractions. These include oxytocic drugs used to stimulate uterine contractions both in induction of labour and to control postpartum haemorrhage and  $\beta_2$ -adrenoceptor agonists used to relax the uterus and prevent premature labour.

### Postpartum Haemorrhage:

Ergometrine and oxytocin differ in their actions on the uterus. In moderate doses oxytocin produces slow generalized contractions with full relaxation in between; ergometrine produces faster contractions superimposed on a tonic contraction. High doses of both substances produce sustained tonic contractions. Oxytocin is now recommended for routine use in postpartum and post-abortion haemorrhage since it is more stable than ergometrine. However, ergometrine may be used if oxytocin is not available or in emergency situations.

### Premature Labour:

Salbutamol is a  $\beta_2$ -adrenoceptor agonist which relaxes the uterus and can be used to prevent premature labour in uncomplicated cases between 24 and 33 weeks of gestation. Its main purpose is to permit a delay in delivery of at least 48 h. The greatest benefit is obtained by using this delay to administer corticosteroid therapy or to implement other measures known to improve perinatal health. Prolonged therapy should be avoided since the risk to the mother increases after 48 h and the response of the myometrium is reduced.

### 24.5.1 Oxytocics

#### Ergometrine

Pregnancy Category-C

Schedule H

#### Indications

*Prevention and treatment of postpartum and post-abortion haemorrhage in emergency situations and where oxytocin not available.*

#### Availability

**TABLETS** 0.125, 0.25 and 0.5 mg; **INJECTION** 5 ml ampoule (0.2 mg/ml).

#### Dose

**Oral**

**Adult and adolescent**-Secondary postpartum haemorrhage: 400  $\mu$ g 3 times daily for 3 days.

**Intramuscular injection**

**Adult and adolescent-** Prevention and treatment of postpartum haemorrhage: when oxytocin is not available, 200 µg when the anterior shoulder is delivered or immediately after birth.

***Slow intravenous injection***

**Adult and adolescent-** Excessive uterine bleeding: 250 to 500 µg when the anterior shoulder is delivered or immediately after birth.

<b>Contraindications</b>	Induction of labour, first and second stages of labour; vascular disease, severe cardiac disease especially angina pectoris; severe hypertension; hepatic impairment (Appendix 7a) and renal impairment; sepsis; eclampsia.
<b>Precautions</b>	Cardiac disease, hypertension; multiple pregnancy (Appendix 7c); porphyria.
<b>Adverse Effects</b>	Nausea, vomiting; headache; dizziness; tinnitus, abdominal pain; chest pain; palpitations; dyspnoea; bradycardia, transient hypertension, vasoconstriction; stroke, myocardial infarction and pulmonary oedema also reported.
<b>Storage</b>	Tablets: Store protected from light at a temperature not exceeding 30°C. Injection: Store protected from light in a single dose container at a temperature not exceeding 30°C.

## Oxytocin\*

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>Routine prevention and treatment of postpartum and post-abortion haemorrhage; induction of labour.</i>
<b>Availability</b>	<b>INJECTION</b> 2 IU/2 ml and 5 IU/ml.
<b>Dose</b>	<b><i>Intravenous infusion</i></b>

**Adult and adolescent-** Induction of labour: initially 0.001 to 0.002 units/min increased in 0.001 to 0.002 units/min increments at intervals of 30 min until a max. of 3 to 4 contractions occur every 10 min; max. recommended rate 0.02 units/min.

***Slow intravenous injection***

**Adult and adolescent-** Prevention of postpartum haemorrhage: 5 units when the anterior shoulder is delivered or immediately after birth. Treatment of postpartum haemorrhage: 5-10 units.



***Intramuscular injection***

**Adult and adolescent-** Prevention of postpartum haemorrhage: 10 units when the anterior shoulder is delivered or immediately after birth.

10 units, followed in severe cases by slow intravenous infusion, a total of 40 units should be infused at a rate of 0.02-0.04 units/min; this should be started after the placenta is delivered.

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*Note: The dose shown above is suitable for use in hospital where equipment to control the infusion rate is available; alternative recommendations may be suitable for other settings. Careful monitoring of fetal heart rate and uterine motility essential for dose titration (never give intravenous bolus injection during labour); discontinue immediately in uterine hyperactivity or fetal distress.*

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**Contraindications**

Hypertonic uterine contractions, mechanical obstruction to delivery, fetal distress; any condition where spontaneous labour or vaginal delivery inadvisable; avoid prolonged administration in oxytocin-resistant uterine inertia, in severe pre-eclamptic toxemia or in severe cardiovascular disease; uterine hyperactivity; major cephalopelvic disproportion, placental previa.

**Precautions**

Induction or enhancement of labour in presence of borderline cephalopelvic disproportion (avoid if significant); mild to moderate pregnancy (Appendix 7c)-associated hypertension or cardiac disease; age over 35 years; history of low-uterine segment caesarean section; avoid tumultuous labour if fetal death or meconium-stained amniotic fluid (risk of amniotic fluid embolism); water intoxication and hyponatraemia (avoid large volume infusions and restrict fluid intake); caudal block anaesthesia (risk of severe hypertension due to enhanced vasopressor effect of sympathomimetics); interactions (Appendix 6a).

**Adverse Effects**

Uterine spasm, uterine hyperstimulation (usually with excessive doses-may cause fetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions, soft-tissue damage or uterine rupture); water intoxication and hyponatraemia associated with high doses and large-volume infusions; nausea, vomiting, arrhythmias, rashes and anaphylactoid reactions also reported; hypotension; sinus bradycardia; hematoma; fetal asphyxia.

**Storage**

Store at a temperature not exceeding 30°C. Do not freeze.

## Mifepristone + Misoprostol

Pregnancy Category-X

Schedule H

<b>Indications</b>	<i>Medical termination of pregnancy of upto 49 days, cervical dilatation prior to surgical termination of pregnancy in the first trimester, therapeutic termination of pregnancy for medical reasons beyond the first trimester, labor induction in case of fetal death in utero.</i>
<b>Availability</b>	<b>TABLET KIT</b> mifopristone 200 mg, misoprostol 200 µg.
<b>Dose</b>	Mifepristone 200 mg orally followed 1 to 3 days latter by misoprostol 800 µg vaginally. Patients should return for followup visit after approximately 14 days after administration of mifepristone.
<b>Contraindications</b>	Hypersensitivity to Mifepristone, Misoprostol or other prostaglandin; confirmed or suspected ectopic pregnancy (Appendix 7c); chronic adrenal failure; haemorrhagic disorders or concurrent anticoagulant therapy; inherited porphyria.
<b>Precautions</b>	IUD in place; asthma, chronic obstructive pulmonary disease; alcoholism; prosthetic heart valve; infective endocarditis; interactions (Appendix 6c), pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Abdominal pain, diarrhoea, nausea, vomiting; fever, chills, uterine cramping; vaginal bleeding or spotting; Pelvic inflammatory disease.

## 24.5.2 Antioxytocics (Tocolytics)

### Isoxsuprine

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Cerebral and peripheral vascular disorder; threatened abortion and premature labour; night cramps; habitual abortion.</i>
<b>Availability</b>	<b>TABLETS</b> 10 and 20 mg; <b>INJECTION</b> 2 ml ampoule (5 mg/ml).
<b>Dose</b>	<b>Oral</b>

Premature labour and threatened abortion: initially 20 mg 6 hly after food, maintenance dose after improvement 10 mg thrice a day.

#### ***Intravenous injection/infusion***

Premature labour and threatened abortion: 0.2 to 0.5 mg/min, adjust according to response, monitor BP and heart rate.

<b>Contraindications</b>	Anaemia; heart disease, arterial hemorrhage; postpartum; premature detachment of placenta; hypersensitivity.
<b>Precautions</b>	Blood disorders, bleeding episodes or allergies, pregnancy (Appendix 7c), lactation.
<b>Adverse Effects</b>	Dizziness, nausea and vomiting; tachycardia, Irregular heart beat, hypotension, chest pain; flushed skin, rashes.

## **Terbutaline\***

**Pregnancy Category-B**

**Schedule H**

<b>Indications</b>	<i>Bronchial spasm in bronchial asthma and chronic bronchitis; emphysema; premature labour; lymphoma.</i>
<b>Availability</b>	<b>TABLETS</b> 2.5 and 5 mg; <b>INJECTION</b> 1 ml ampoule (0.5 mg/ml), <b>NEBULISING SOLUTION</b> 10 mg/ml, <b>METERED DOSE INHALER (MDI)</b> 250 µg/puff .
<b>Dose</b>	<p><b>Oral</b></p> <p>Premature abortion: 2.5 to 5 mg thrice daily.</p> <p>Acute bronchospasm: <b>Adult-</b> 2.5 to 5 mg thrice daily.</p> <p><b>Subcutaneous, intramuscular or intravenous injection</b></p> <p>Uncomplicated premature labour: <b>Adult-</b> 5 µg/min for 20min, increased every 20min in steps of 2.5 µg/min until contractions have ceased continue for 1 h then decreased every 20 min in steps of 205 µg/min to lowest dose that maintain suppression, max. dose 20 µg/min.</p> <p>Severe bronchospasm: <b>Adult-</b> 250-500 µg, 4 times daily. <b>Child:</b> &gt;2 years-10 µg/kg, max. dose- 300 µg.</p>

#### ***Inhalation***

*Acute bronchospasm: Adult/Child-* MDI- 250 or 500 µg every 4-6 h, max. dose- 2000 µg/24 h; As nebuliser- 5-10 mg inhaled 2-4times.  
**Child-** As nebuliser- 2-5 mg inhaled 2-4 times.

### Contraindications

Cardiac disease; antepartum haemorrhage; intrauterine infection; intrauterine fetal death; placenta praevia; abruptio placenta; threatened miscarriage; cord compression; and eclampsia or severe pre-eclampsia; thyrotoxicosis; toxæmia.

### Precautions

Suspected cardiovascular disease (such patients should be assessed by a cardiologist before initiating therapy), hypertension, mild to moderate pre-eclampsia, hyperthyroidism, and hypokalaemia (particular risk with potassium-depleting diuretics). It is important to monitor pulse rate (should not exceed 140 beats per min) and the patient's fluid and electrolyte status (avoid over-hydration-discontinue drug immediately and initiate diuretic therapy if pulmonary oedema occurs). It should also be used with caution in diabetes-monitor blood glucose (risk of hyperglycaemia and ketoacidosis, especially with intravenous  $\beta_2$  agonist); pregnancy (Appendix 7c).

### Adverse Effects

Nausea, vomiting; pulmonary oedema; palpitation; tachycardia, arrhythmias, peripheral vasodilation; headache, tremor, hyperglycaemia, hypokalaemia, muscle cramps and tension and hypersensitivity reactions (including angioedema, urticaria, rash, bronchospasm, hypotension, and collapse).

### Storage

Tablet: Store protected from light and moisture. Injection: Store protected from light in a single dose container.

## 24.6 Thyroid Hormones and Antithyroid Drugs

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### Thyroid Drugs:

Thyroid agents are natural or synthetic agents containing levothyroxine (thyroxine) or liothyronine (tri-iodothyronine). The principal effect is to increase the metabolic rate. They also exert a cardiostimulatory effect which may be the result of a direct action on the heart. Thyroid hormones are used in hypothyroidism (myxoedema) and also in diffuse non-toxic goitre, Hashimoto thyroiditis (lymphadenoid goitre) and thyroid carcinoma. Neonatal hypothyroidism requires prompt treatment for normal development.

Levothyroxine Sodium (thyroxine Sodium) is the treatment of choice for maintenance therapy. It is almost completely absorbed from the gastrointestinal tract but the full effects are not seen for up to 1 to 3 weeks after beginning therapy; there is a slow response to dose change and effects may persist for several weeks after withdrawal. Dosage of levothyroxine in infants and children for congenital hypothyroidism and juvenile myxoedema should be titrated according to clinical response, growth assessment and measurement of plasma thyroxine and thyroid-stimulating hormone.

### Antithyroid Drugs:

Antithyroid drugs such as propylthiouracil and carbimazole are used in the management of thyrotoxicosis. They are also used to prepare the patient for thyroidectomy. They are usually well-tolerated, with mild leukopenia or rashes developing in a few percent of cases, usually during the first 6-8 weeks of therapy. During this time the blood count should be checked every 2 weeks or if a sore throat or other signs of infection develop. The drugs are generally given in a high dose in the first instance until the patient becomes euthyroid, the dose may then be gradually reduced to a maintenance dose which is continued for 12-18 months, followed by monitoring to identify relapse. There is a lag time of some 2 weeks between the achievement of biochemical euthyroidism and clinical euthyroidism. Beta-adrenoceptor antagonists (beta-blockers) (usually propranolol) may be used as a short-term adjunct to antithyroid drugs to control symptoms but their use in heart failure associated with thyrotoxicosis is controversial. Treatment can be given, if necessary, in pregnancy but antithyroid drugs cross the placenta and in high doses may cause fetal goitre and hypothyroidism. The lowest dose that will control the hyperthyroid state should be used (requirements in Graves disease tend to fall during pregnancy). Propylthiouracil appears in breast milk but does not

preclude lactation as long as neonatal development is closely monitored and the lowest effective dose is used.

If surgery (partial thyroidectomy) is contemplated, it may be necessary to give iodine for 10 to 14 days in addition to antithyroid drugs to assist control and reduce vascularity of the thyroid. Iodine should not be used for long-term treatment since its antithyroid action tends to diminish. In patients in whom drug therapy fails to achieve long-term remissions definitive treatment with surgery or (increasingly) radioactive iodine is preferable.

## Carbimazole\*

**Pregnancy Category-D**

**Schedule H**

<b>Indications</b>	<i>Thyrotoxicosis; Grave's disease.</i>
<b>Available:</b>	<b>TABLETS</b> 5 and 10 mg.
<b>Dose</b>	<b>Oral</b>  Initially 15 to 45 mg daily in 4 divided doses depending upon severity. Maintenance dose 25 to 50 mg for 1 year.
<b>Contraindications</b>	Nodular goitre; subacute thyroiditis, postpartum painless thyroiditis.
<b>Precautions</b>	Liver disorders; pregnancy (Appendix 7c), lactation; neutropenia.
<b>Adverse Effects</b>	Nausea, mild gastro-intestinal disturbances; headache; rashes and pruritus, arthralgia; rarely, myopathy, alopecia, bone marrow suppression (including pancytopenia and agranulocytosis); vasculitis; cholestatic jaundice, hepatic necrosis.
<b>Storage</b>	Store protected from light and moisture at a temperature not exceeding 30°C.

## Iodine\* (Refer Page No. 608)

**Pregnancy Category-D**

<b>Indications</b>	<i>Hypothyroidism; sporotrichosis.</i>
<b>Available:</b>	<b>COLLOIDAL IODINE</b> 8 mg/5 ml.
<b>Dose</b>	5 to 10 ml diluted in water 3 times a day.
<b>Contraindications</b>	Lactation (Appendix 7b), tuberculosis, bronchitis, asthma, hyperkalaemia, acne vulgaris.

**Precautions** Pregnancy (Appendix 7c), children; not for long-term treatment; cardiac disease, interactions (Appendix 6c).

**Adverse Effects** Hypersensitivity reactions including coryza-like symptoms; headache; lacrimation; conjunctivitis, pain in salivary glands; laryngitis, bronchitis, rashes; on prolonged treatment depression, insomnia, impotence; goitre in infants of mothers taking iodides; eosinophilia, hypothyroidism, abdominal pain, arrhythmia.

**Storage** Store in ground glass stoppered container or earthenware container with waxed bungs.

## Levothyroxine\*

**Pregnancy Category-A**

**Schedule H**

**Indications** *Hypothyroidism.*

**Availability** **TABLETS** 50 and 100 µg.

**Dose** **Oral**

**Adult- Hypothyroidism:** Initially 50 to 100 µg daily (25 to 50 µg for those over 50 years) before breakfast, increased by 25 to 50 µg every 3 to 4 weeks until normal metabolism maintained (usual maintenance dose, 100 to 200 µg daily); where there is cardiac disease, initially 25 µg daily or 50 µg on alternate days, adjusted in steps of 25 µg every 4 weeks.

**Child- Congenital hypothyroidism and juvenile myxoedema;** Up to 1 month: initially 5 to 10 µg/kg daily. Over 1 month: initially 5 µg/kg daily, adjusted in steps of 25 µg every 2 to 4 weeks, until mild toxic symptoms appear, then reduce dose slightly.

**Contraindications** Thyrotoxicosis.

**Precautions** Cardiovascular disorders (myocardial insufficiency or ECG evidence of myocardial infarction); hypopituitarism or predisposition to adrenal insufficiency (must be corrected by corticosteroid prior to initial levothyroxine); elderly; long-standing hypothyroidism, diabetes insipidus, diabetes mellitus (may need to increase dose of insulin or oral antidiabetic drug); pregnancy (Appendix 7c), lactation; interactions (Appendix 6c, 6d).

**Adverse Effects**

Anginal pain, arrhythmias, palpitations, tachycardia, skeletal muscle cramps; diarrhoea, vomiting; tremors; restlessness excitability, insomnia, headache, flushing, sweating; excessive loss of weight and muscular weakness; heat intolerance.

**Storage**

Store protected from light and moisture.



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## 25. Immunologicals

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### Active Immunity:

Active immunity may be induced by the administration of micro-organisms or their products which act as antigens to induce antibodies to confer a protective immune response in the host. Vaccination may consist of (a) a live attenuated form of a virus or bacteria, (b) inactivated preparations of the virus or bacteria, or (c) extracts of or detoxified exotoxins. Live attenuated vaccines usually confer immunity with a single dose which is of long duration. Inactivated vaccines may require a series of injections in the first instance to produce an adequate antibody response and in most cases, require reinforcing (booster) doses. The duration of immunity varies from months to many years. Extracts of or detoxified exotoxins require a primary series of injections followed by reinforcing doses.

### Passive Immunity:

Passive immunity is conferred by injecting preparations made from the plasma of immune individuals with adequate levels of antibody to the disease for which protection is sought. Treatment has to be given soon after exposure to be effective. This immunity lasts only a few weeks but passive immunization can be repeated where necessary.

### Sera and Immunoglobulins

Antibodies of human origin are usually termed immunoglobulins. Material prepared from animals is called antiserum. Because of serum sickness and other allergic-type reactions that may follow injections of antisera, this therapy has been replaced wherever possible by the use of immunoglobulins.

All immunoglobulins and antisera should comply with WHO requirements for blood and plasma products.

### Contraindications and Precautions

Anaphylaxis, although rare, can occur and epinephrine (adrenaline) must always be immediately available during immunization.

Immunoglobulins may interfere with the immune response to live virus vaccines which should normally be given *either at least 3 weeks before or at least 3 months after the administration of the immunoglobulin.*

### **Adverse Reactions:**

Intramuscular injection; Local reactions including pain and tenderness may occur at the injection site. Hypersensitivity reactions may occur including, rarely, anaphylaxis.

Intravenous injection; Systemic reactions including fever, chills, facial flushing, headache and nausea may occur, particularly following high rates of infusion. Hypersensitivity reactions may occur including, rarely, anaphylaxis.

### **Anti-D Immunoglobulin (Human):**

Anti-D immunoglobulin is prepared from plasma with a high titre of anti-D antibody. It is available to prevent a rhesus-negative mother from forming antibodies to fetal rhesus-positive cells which may pass into the maternal circulation. The aim is to protect any subsequent child from the hazard of haemolytic disease of the newborn. It should be administered following any potentially sensitizing episode (for example abortion, miscarriage, still-birth) immediately or within 72 h of the episode but even if a longer period has elapsed it may still give protection and should be used. The dose of anti-D immunoglobulin given depends on the level of exposure to rhesus-positive blood. The injection of anti-D immunoglobulin is not effective once the mother has formed anti-D antibodies. It is also given following Rh0 (D) incompatible blood.

### **Antitetanus Immunoglobulin (Human):**

Antitetanus immunoglobulin of human origin is a preparation containing immunoglobulins derived from the plasma of adults immunized with tetanus toxoid. It is used for the management of tetanus-prone wounds in addition to wound toilet and if appropriate antibacterial prophylaxis and adsorbed tetanus vaccine.

### **Diphtheria Antitoxin:**

Diphtheria antitoxin is prepared from the plasma or serum of healthy horses immunized against diphtheria toxin or diphtheria toxoid. It is used for passive immunization in suspected cases of diphtheria without waiting for bacterial confirmation of the infection. A test dose should be given initially to exclude hypersensitivity. Diphtheria antitoxin is not used for prophylaxis of diphtheria because of the risk of hypersensitivity.

### **Rabies Immunoglobulin (Human):**

Rabies immunoglobulin is a preparation containing immunoglobulins derived from the plasma of adults immunized with rabies vaccine. It is used as part of the management of potential rabies following exposure of an unimmunized indi-

vidual to an animal in or from a high-risk country. It should be administered as soon as possible after exposure without waiting for confirmation that the animal is rapid. The site of the bite should be washed with soapy water and the rabies immunoglobulin should be infiltrated round the site of the bite and also given intramuscularly. In addition rabies vaccine should be administered at a different site.

## 25.1 Immunoglobulins

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### Anti-D Immunoglobulin (Human)\*

**Indications** *Prevention of formation of antibodies to rhesus-positive blood cells in rhesus-negative patients.*

**Availability** **INJECTIONS** 150 µg/vial and 300 µg/vial.

**Dose** *Intramuscular injection*

**Adult and Child-** Following birth of a rhesus-positive infant in rhesus-negative mother: 250 µg immediately or within 72 h.

Following any potentially sensitizing episode like amniocentesis, still birth, up to 20 weeks gestation: 250 µg per episode, after 20 weeks: 500 µg immediately or within 72 h.

Following Rho (D) incompatible blood transfusion: 10 to 20 µg/ml transfused rhesus-positive blood.

**Contraindications** See introductory notes; known hypersensitivity.

**Precautions** See introductory notes; caution in rhesus-positive patients for treatment of blood disorders; caution in rhesus-negative patients with anti-D antibodies in their serum; patients should be observed for 20 min after injection.

**Rubella Vaccine.** Rubella vaccine may be administered in the postpartum period at the same time as anti-D immunoglobulin injection, but only using separate syringes and separate contralateral sites. If blood is transfused, the antibody response to the vaccine may be inhibited and a test for antibodies should be performed after 8 weeks and the subject revaccinated if necessary.

**Adverse Effects** See introductory notes; local pain and tenderness, fever, headache; cutaneous reaction; tachycardia, hypotension.

**Storage** For liquid preparations: Store protected from light at temperature stated on the label. For freeze dried preparation: Store protected from light in a colourless glass container at a temperature not exceeding 30°C.

## Antitetanus Immunoglobulin (Human)\*

### Pregnancy Category-C

**Indications** *Passive immunisation against tetanus as part of the management of tetanus-prone wounds.*

**Availability** **INJECTIONS** 250, 500 and 1000 I.U./vial.

**Dose** ***Intramuscular injection***

**Adult and Child**-250 units, increased to 500 units if wound older than 12 h or there is risk of heavy contamination or if patient weighs more than 90 kg. Second dose of 250 µg given after 3 to 4 weeks if patient is immunosuppressed or if active immunisation with tetanus vaccine contraindicated.

**Contraindications** See introductory notes.

**Precautions** See introductory notes; must not be administered i.v and patient must be observed for 20 min after administration; pregnancy (Appendix 7c).

**Tetanus Vaccine.** If schedule requires tetanus vaccine and antitetanus immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites.

**Adverse Effects** See introductory notes; chest pain; dyspnoea; facial oedema.

**Storage** Store as stated In the label.

## Diphtheria Antitoxin\*

**Indications** *Passive immunisation in suspected cases of diphtheria.*

**Availability** **INJECTION** 10000 IU/10 ml.

**Dose** ***Intramuscular injection***

**Adult and Child**- 10,000 to 30,000 units in mild to moderate cases; 40,000 to 1,00,000 units in severe cases.

***Both intramuscular and intravenous injection***

For doses more than 40,000 units, a portion should be given by intramuscular injection followed by the bulk of the dose intravenously after an interval of 0.5 to 2 h.

<b>Contraindications</b>	Hypersensitivity.
<b>Precautions</b>	Initial test dose to exclude hypersensitivity; observation required after full dose [epinephrine (adrenaline) and resuscitation facilities should be available]; history of asthma.
<b>Adverse Effects</b>	Anaphylaxis with urticaria, hypotension, dyspnoea and shock; serum sickness up to 12 days after injection; fever, respiratory distress.
<b>Storage</b>	Refer antivenom serum.

## Rabies Immunoglobulin\*

### Pregnancy Category-C

<b>Indications</b>	<i>Passive immunisation either post-exposure or in suspected exposure to rabies in high-risk countries in unimmunised individuals (in conjunction with rabies vaccine).</i>
<b>Availability</b>	<b>INJECTION</b> 150 IU/2 ml; 300 IU/ml; 200-400 IU/5 ml; 1000 IU/ml; 1000 IU/5 ml; 1500 IU/5 ml.
<b>Dose</b>	<b><i>Intramuscular injection and wound infiltration</i></b>  <b>Adult and Child-</b> 20 units/kg (half by intramuscular injection and half by wound infiltration).
<b>Contraindications</b>	See introductory notes; avoid repeat doses after vaccine treatment initiated; intravenous administration.
<b>Precautions</b>	Epinephrine should be available for management of anaphylactic reaction.  If schedule requires rabies vaccine and rabies immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites.; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	See introductory notes; soreness at injection site; fever; chest pain; tremor; dyspnoea.
<b>Storage</b>	Refer antivenom serum.

## 25.2 Sera

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### Antivenom Sera:

The snake bite may cause local and systemic effects.

Local effects include pain, swelling, bruising and tender enlargement of regional lymph nodes. Wounds should be cleaned and pain may be relieved by analgesics.

If significant amounts of toxin are absorbed after a snake bite, this may result in early anaphylactoid symptoms such as transient hypotension, angioedema, abdominal colic, diarrhoea and vomiting, followed by persistent or recurrent hypotension and ECG abnormalities. Spontaneous systemic bleeding, coagulopathy, adult respiratory distress syndrome and acute renal failure may occur. Early anaphylactoid symptoms may be treated with epinephrine (adrenaline). Snake antivenom sera are the only specific treatment available but they can produce severe adverse reactions. They are generally only used if there is a clear indication of systemic involvement or severe local involvement or, if supplies are not limited, in patients at high risk of systemic or severe local involvement.

Spider bites may cause either necrotic or neurotoxic syndromes depending on the species involved. Supportive and symptomatic treatment is required and in the case of necrotic syndrome, surgical repair may be necessary. Spider antivenom sera, suitable for the species involved, may prevent symptoms if administered as soon as possible after envenomation.

### Antivenom Sera\*

<b>Indications</b>	<i>Treatment of snake bites.</i>
<b>Availability</b>	<b>INJECTION</b> 10 ml ampoule.
<b>Dose</b>	60-100 ml in 5% dextrose or normal saline intravenously over one hour; start at 1 ml of diluted solution per minute initially, watching for reaction. Skin sensitivity test is not recommended; In hemotoxic snake bites, may repeat a second dose at 6 h. if bleeding/clotting abnormalities continue, or whole blood clotting time is still prolonged at 6 h; In neurotoxic snake bites, may repeat at 1-2 h.
<b>Precautions</b>	Resuscitation facilities should be immediately available; antihistamine and treatment for anaphylactic shock should be kept ready.
<b>Adverse Effects</b>	Serum sickness; anaphylaxis with hypotension, dyspnoea, urticaria and shock.
<b>Storage</b>	Store liquid vaccines at a temperature below 2 to 8°C. Should not be allowed to freeze.

## 25.3 Vaccines

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Vaccines may consist of a live attenuated form of a virus (for example, rubella or measles) or bacteria (for example, BCG vaccine); an inactivated preparation of a virus (for example, influenza vaccine) or bacteria; an extract of or detoxified exotoxin produced by a micro-organism (for example, tetanus vaccine).

### Contraindications and Precautions

Recipients of any vaccine should be observed for an adverse reaction. Anaphylaxis though rare, can occur and epinephrine (adrenaline) must always be immediately available whenever immunization is given. If a serious adverse event (including anaphylaxis, collapse, shock, encephalitis, encephalopathy, or non-febrile convulsion) occurs following a dose of any vaccine, a subsequent dose should not be given. In the case of a severe reaction to Diphtheria, Pertussis, and Tetanus vaccine, the pertussis component should be omitted and the vaccination completed with Diphtheria and Tetanus vaccine.

Immunization should be postponed in acute illness which may limit the response to immunization, but minor infections without fever or systemic upset are not contraindications. A definite reaction to a preceding dose is a definite contraindication.

If alcohol or other disinfecting agent is used to wipe the injection site it must be allowed to evaporate, otherwise inactivation of a live vaccine may occur.

The intramuscular route must not be used in patients with bleeding disorders such as haemophilia or thrombocytopenia.

Some viral vaccines contain small quantities of antibacterials such as polymyxin B or neomycin; such vaccines may need to be withheld from individuals who are extremely sensitive to the antibacterial. Some vaccines are prepared using hens' eggs and a history of anaphylaxis to egg ingestion is a contraindication to the use of such vaccines; caution is required if such vaccines are used in persons with less severe hypersensitivity to egg.

When two live virus vaccines are required (and are not available as a combined preparation) they should be given *either* simultaneously at different sites using separate syringes or with an interval of at least 3 weeks. Live virus vaccines should normally be given either at least 2-3 weeks before or at least 3 months after the administration of immunoglobulin.

Live vaccines should not be routinely administered to preg-



nant women because of the possible harm to the fetus but where there is significant risk of exposure, the need for immunization may outweigh any possible risk to the fetus.

Live vaccines should not be given to anyone with malignant disease such as leukaemia or lymphomas or other tumours of the reticulo-endothelial system. Live vaccines should not be given to individuals with an impaired immune response caused by disease, radiotherapy or drug treatment (for example, high doses of corticosteroids).

However, the WHO recommends that immunocompromized individuals who are HIV-positive should, under certain circumstances, be given some live vaccines. *Asymptomatic* and *symptomatic* HIV-positive children and women of child-bearing age should receive diphtheria, pertussis, tetanus, hepatitis B and oral poliomyelitis vaccines (included in the Expanded Programme on Immunization (EPI)). Because of the risk of early and severe measles infection, infants should receive an extra dose of measles vaccine at 6 months of age with the EPI dose as soon after 9 months of age as possible. Individuals with *symptomatic* HIV infection must not be given either BCG or yellow fever vaccines. Measles, Mumps and Rubella Virus (MMR) vaccine should not be given to severely immunocompromized children with HIV infection. Individuals with *asymptomatic* HIV infection should only be given BCG or yellow fever vaccines where the prevalence of tuberculosis or yellow fever, respectively, is high. National policies on immunization of HIV-positive individuals may vary.

### Adverse Reactions:

Local reactions including inflammation and lymphangitis may occur. Sterile abscess may develop at the injection site; fever, headache, malaise starting a few hour after injection and lasting for 1-2 days may occur. Hypersensitivity reactions can occur including rarely, anaphylaxis.

### Vaccines for Universal Immunization:

The WHO EPI currently recommends that all countries immunize against diphtheria, hepatitis B, measles, poliomyelitis, pertussis, tetanus and that countries with a high incidence of tuberculosis infections should immunize against tuberculosis. Immunization against yellow fever is recommended in endemic countries. Routine vaccination against *Haemophilus influenzae* type b infection is also recommended in some countries. In geographical regions where the burden of disease is unclear, efforts should be made to evaluate the magnitude of the problem.

## Immunization schedule recommended by WHO:

### Scheme A

Recommended in countries where perinatal transmission of hepatitis B virus is frequent (for example, countries in South-east Asia)

Age	Vaccines
Birth	BCG; Poliomyelitis, oral (1 <sup>st</sup> ); Hepatitis B (1 <sup>st</sup> )
6 weeks	Diphtheria, pertussis, tetanus (1 <sup>st</sup> ); Haemophilus influenzae (type b) <sup>1</sup> (1 <sup>st</sup> ); Poliomyelitis, oral (2 <sup>nd</sup> ); Hepatitis B (2 <sup>nd</sup> )
10 weeks	Diphtheria, pertussis, tetanus (2 <sup>nd</sup> ); Haemophilus influenzae (type b) <sup>1</sup> (2 <sup>nd</sup> ); Poliomyelitis, oral (3 <sup>rd</sup> )
14 weeks	Diphtheria, pertussis, tetanus (3 <sup>rd</sup> ); Haemophilus influenzae (type b) <sup>1</sup> (3 <sup>rd</sup> ); Poliomyelitis, oral (4 <sup>th</sup> ); Hepatitis B (3 <sup>rd</sup> )
9 months	Yellow fever (in countries where yellow fever poses a risk); Measles

### Scheme B

Recommended in countries where perinatal transmission of hepatitis B virus is less frequent (for example, countries in sub-Saharan Africa)

Schedule as Scheme A, but hepatitis B (1<sup>st</sup>) given at 6 weeks and hepatitis B (2<sup>nd</sup>) given at 10 weeks

- <sup>1</sup> Haemophilus influenzae (type b).

### BCG Vaccine (Dried):

Where tuberculosis remains highly prevalent, routine immunization of infants within the first year of life with BCG vaccine, derived from *Bacillus Calmette-Guérin* (an attenuated strain of *Mycobacterium bovis*), is highly cost-effective. This has been estimated, in several settings, to reduce the incidence of meningial and miliary tuberculosis in early childhood by 50 to 90%. However, estimates of its effectiveness in older children have differed greatly from region to region and because efficacy against pulmonary tuberculosis is doubtful, the mainstay of the tuberculosis control programme is case-finding and treatment.

### Diphtheria, Pertussis and Tetanus (DPT) Vaccines:

#### Diphtheria

Diphtheria is a bacterial infection caused by *Corynebacte-*

*rium diphtheriae*, transmitted from person to person through close physical and respiratory contact. Diphtheria vaccine is a formaldehyde-inactivated preparation of diphtheria toxin, adsorbed onto a mineral carrier to increase its antigenicity and reduce adverse reactions. Immunized individuals can be infected by toxin-producing strains of diphtheria but systemic manifestations of the disease do not occur.

When administered for primary immunization in infants, diphtheria vaccine is almost always given together with pertussis and tetanus vaccines as part of a *three-component* preparation (DPT).

A *two-component* diphtheria vaccine with tetanus but without pertussis exists in two forms, DT and Td. Diphtheria-tetanus vaccine for children (DT) is used for primary immunization in infants who have contraindications to pertussis vaccine; it is also used in children under the age of 10 years for reinforcing immunization against diphtheria and tetanus in those countries which recommend it. Tetanus-diphtheria vaccine for adults, adolescents and children over 10 years of age (Td), which has a reduced amount of diphtheria toxoid to reduce the risk of hypersensitivity reactions, is used for primary immunization in persons over the age of 10 years; it is also used for reinforcing immunization in persons over the age of 10 years in those countries that recommend it.

## Pertussis

Pertussis (whooping cough) is a bacterial respiratory infection caused by *Bordetella pertussis*. Many of the symptoms are thought to be caused by toxins released by *B. pertussis*. Whole cell vaccine composed of whole pertussis bacteria killed by chemicals or heat is effective in preventing serious illness. It causes frequent local reactions and fever and rarely, it may be associated with neurological reactions. Neurological complications after pertussis infection are considerably more common than after the vaccine. It is combined with diphtheria-tetanus vaccine for primary immunization unless immunization against pertussis is contraindicated. Single component pertussis vaccines are available in some countries for use when the pertussis component has been omitted from all or part of the primary immunization Schedule. An acellular form of the vaccine is also available.

In some countries it is recommended that children with a personal or family history of febrile convulsions or a family history of idiopathic epilepsy should be immunized. It is also recommended that children with well-controlled epilepsy are immunized. Advice on prevention of fever should be given at the time of immunization. In children with evolving neurolog-

ical problems, immunization with pertussis should be deferred until the condition is stable; in such children diphtheria and tetanus vaccine should be offered for primary immunization, and there may be an opportunity at a later date to complete immunization with a single-component pertussis vaccine. Where there is doubt advice should be sought from a paediatrician.

## Tetanus

Tetanus is caused by the action of a neurotoxin of *Clostridium tetani* in necrosed tissues such as occur in dirty wounds. Tetanus vaccine is available as a single component vaccine for primary immunization in adults who have not received childhood immunization against tetanus and for reinforcing immunization. The vaccine is also used in the prevention of neonatal tetanus and in the management of clean wounds and tetanus-prone wounds. Some countries recommend a max. of 5 doses of tetanus vaccine in a life-time; for the fully immunized patient reinforcing doses at the time of a tetanus-prone injury should only be required if more than 10 years have elapsed since the last dose.

Neonatal tetanus due to infection of the baby's umbilical stump during unclean delivery is the cause of many deaths of newborn infants. Control of neonatal tetanus may be achieved by ensuring adequate hygiene during delivery and by ensuring protective immunity of mothers in late pregnancy. Tetanus vaccine is highly effective and the efficacy of two doses during pregnancy in preventing neonatal tetanus ranges from 80-100%. Women of child-bearing age may be immunized by a course of 5 doses (3 primary and 2 reinforcing) of tetanus vaccine.

Wounds are considered to be tetanus-prone if they are sustained either more than 6 h before surgical treatment of the wound or at any interval after injury and show one or more of the following: a puncture-type wound, a significant degree of devitalized tissue, clinical evidence of sepsis, contamination with soil/manure likely to contain tetanus organisms. All wounds should receive thorough surgical toilet. Antibacterial prophylaxis may also be required for tetanus-prone wounds.

- For **clean wounds**; fully immunized individuals (those who have received a total of 5 doses of tetanus vaccine at appropriate intervals) and those whose primary immunization is complete (with boosters up to date) do not require tetanus vaccine; individuals whose primary immunization is incomplete or whose boosters are not up to date require a reinforcing dose of tetanus vaccine (followed by further doses as

required to complete the schedule); non-immunized individuals (or whose immunization status is not known) should be given a dose of the vaccine immediately (followed by completion of the full course of the vaccine if records confirm the need).

- For **tetanus-prone wounds**; management is as for clean wounds with the addition of a dose of antitetanus immunoglobulin given at a different site; in fully immunized individuals and those whose primary immunization is complete (see above) the immunoglobulin is needed only if the risk of infection is especially high (for example, contamination with manure). Antibacterial prophylaxis (with benzylpenicillin or Amoxycillin with clavulanic acid, or metronidazole) may also be required for tetanus-prone wounds.

### Hepatitis B Vaccine:

Hepatitis B is caused by hepatitis B virus. It is transmitted in blood and blood products, by sexual contact and by contact with infectious body fluids. Persons at increased risk of infection because of their life-style, occupation or other factors include parenteral drug abusers, individuals who change sexual partners frequently, health care workers who are at risk of injury from blood-stained sharp instruments and haemophiliacs. Also at risk are babies born to mothers who are HbsAg-positive (hepatitis B virus surface antigen positive) and individuals who might acquire the infection as the result of medical or dental procedures in countries of high prevalence. The main public health consequences are chronic liver disease and liver cancer rather than acute infection. Routine immunization is recommended and has been implemented in some countries. Plasma-derived hepatitis B vaccine is highly efficacious. Over 90% of susceptible children develop a protective antibody response. A recombinant DNA vaccine is also available.

### Measles Vaccines:

Measles is an acute viral infection transmitted by close respiratory contact. In some countries routine immunization of children against measles is given as one dose of a single component vaccine; in other areas, a two-dose schedule has been found to be more applicable. In developing countries, clinical efficacy is usually greater than 85%. Convulsions and encephalitis are rare complications. Measles vaccine is administered in many countries as part of a combined preparation with mumps vaccine and rubella vaccine (MMR vaccine); a single-

dose primary immunization is followed by a reinforcing dose 2-5 years later.

Single-component vaccines or MMR may be used in the control of outbreaks of measles and should be offered to susceptible children within 3 days of exposure. It is important to note that MMR vaccine is not suitable for prophylaxis following exposure to mumps or rubella since the antibody response to the mumps and rubella components is too slow for effective prophylaxis.

### **Poliomyelitis Vaccines:**

Poliomyelitis is an acute viral infection spread by the faecal-oral route which can cause paralysis of varying degree. There are two types of vaccine against poliomyelitis: oral and injectable. Oral poliomyelitis vaccine (OPV) is composed of three types of live attenuated poliomyelitis viruses. The efficacy of OPV in preventing paralytic polio in developing countries ranges from 72% to 98% and is the vaccine of choice in eradication of the disease. Oral poliomyelitis vaccine may need to be repeated in patients with diarrhoea or vomiting. Those infected with HIV should receive poliomyelitis vaccine according to the standard schedule but the vaccine is contraindicated in those with primary immune deficiency or those who are immunosuppressed. The need for strict personal hygiene must be stressed as the vaccine virus is excreted in the faeces. The contacts of a recently vaccinated baby should be advised particularly of the need to wash their hands after changing the baby's nappies. After primary immunization reinforcing doses may be given. Inactivated polio vaccine (IPV) is injectable and composed of inactivated strains of three types of poliomyelitis virus. It should be used for individuals who are immunosuppressed or for their household contacts.

### **Vaccines for Specific Groups of Individuals:**

There are several other vaccines available which are used in different countries but are not yet recommended for routine use throughout the world.

Allergic patients require specific immunotherapy.

### **Influenza Vaccine:**

While most viruses are antigenically stable, the influenza viruses A and B (especially A) are constantly changing their antigenic structure as indicated by changes in the haemagglutinins (H) and neuraminidases (N) on the surface of the viruses. It is essential that influenza vaccines in use contain the H and N components of the prevalent strain or strains. The changes are monitored and recommendations are made each year

regarding the strains to be included in influenza vaccines for the following season. The recommended vaccine strains are grown on chick embryos and the vaccine is therefore contraindicated in individuals hypersensitive to egg. There are three forms of influenza vaccine; whole virion vaccine (not recommended for use in children because of the increased risk of severe febrile reactions), split-virion vaccine and surface-antigen vaccine.

The vaccines will not control epidemics and they are recommended only for those at high risk. Annual immunization is recommended in the elderly and those of any age with diabetes mellitus, chronic heart disease, chronic renal failure, chronic respiratory disease including asthma, or immunosuppression due to disease or drug treatment.

### **Meningococcal Polysaccharide Vaccine:**

Meningococcal polysaccharide vaccine is effective against serogroups A and C of *Neisseria meningitidis* but infants respond less well than adults. Immunity to some meningococcal vaccines may be insufficient to confer adequate protection against infection in infants under about 2 years of age and the minimum age recommended by manufacturers varies from 2 months to 2 years. It is indicated for persons at risk of serogroups A and C meningococcal disease in epidemics (where it must be administered early in the course of the epidemic) or endemic areas and as an adjunct to chemoprophylaxis in close contacts of persons with the disease. It is indicated for visits of longer than 1 month to areas of the world where risk of infection is high.

### **Mumps Vaccine:**

Mumps vaccine is used for active immunization against mumps. In some countries the single antigen vaccine is no longer available and a combined measles, mumps and rubella vaccine (MMR vaccine) is used for primary immunization.

### **Rabies Vaccine (Inactivated):**

Rabies vaccine is used as part of the *post-exposure treatment* to prevent rabies in patients who have been bitten by rabid animals or animals suspected of being rabid. Treatment is dependent upon the individual's immune status and upon the level of risk of rabies in the country concerned in certain circumstances such as patients with incomplete prophylaxis or unimmunized individuals *passive immunization* with rabies immunoglobulin may be indicated (see Rabies Immunoglobulin). Treatment should also include thorough wound cleansing.

The vaccine is also used for *pre-exposure prophylaxis* against rabies in those at high risk such as laboratory workers,

veterinary surgeons, animal handlers and health workers who are likely to come into close contact with infected animals or patients with rabies. Pre-exposure prophylaxis is also recommended for those living or travelling in enzootic areas who may be exposed to unusual risk.

### Rubella Vaccine:

Rubella vaccine should be given to women of child-bearing age if they are seronegative to protect them from the risks of rubella in pregnancy. It should not be given in pregnancy and patients should be advised not to become pregnant within one month of vaccination. However, congenital rubella syndrome has not been reported following inadvertent immunization shortly before or during pregnancy. There is no evidence that the vaccine is teratogenic and routine termination of pregnancy following inadvertent immunization should not be recommended. There is no risk to a pregnant woman from contact with recently vaccinated persons as the vaccine virus is not transmitted.

The vaccine may contain traces of antibiotics and if so should not be used in individuals with hypersensitivity to them.

In some countries the policy of protecting women of child-bearing age has been replaced by a policy of eliminating rubella in children. Rubella vaccine is a component of the MMR vaccine. Countries seeking to eliminate rubella should ensure that women of child-bearing age are immune and that over 80% of children are immunized.

### Typhoid Vaccine:

Typhoid vaccine is used for active immunization against typhoid fever and immunization is advised for those travelling to endemic areas. The efficacy of the vaccine is not complete and the importance of maintaining scrupulous attention to food and water hygiene as well as personal hygiene must also be emphasized.

Typhoid vaccine is available as a capsular polysaccharide injection.

In children under 2 years the injection may show sub-optimal response. Immunization is also recommended for laboratory workers handling specimens from suspected cases.

A live oral typhoid vaccine containing an attenuated strain of *Salmonella typhi* (Ty21a) may also be available.

### Yellow Fever Vaccine:

Yellow fever is a viral haemorrhagic fever endemic in some countries of South America and Africa. The disease is trans-



mitted by *Haemagogus* and *Aedes* mosquito bites. The vaccine is highly immunogenic and offers about 10 years protection. Over 92% of children develop protective antibodies. It is recommended that all countries in which yellow fever is endemic should incorporate this vaccine into their immunization Schedule. It is also used for travellers to endemic areas.

## BCG Vaccine\*

### Pregnancy Category-C

<b>Indications</b>	<i>Active immunisation against tuberculosis.</i>
<b>Availability</b>	Between $1 \times 10^6$ and $33 \times 10^6$ CFU/ml <b>INJECTION</b> (1 million units of BCG Strain/dose).
<b>Dose</b>	<b><i>Intradermal injection</i></b> <b>Adult-</b> 0.1 ml. <b>Child-</b> Over 3 months: 0.1 ml; Infant, up to 3 months: 0.05 ml.
<b>Contraindications</b>	See introductory notes; generalized oedema; antimycobacterial treatment; HIV infection, febrile illness, burn patients; hypersensitivity.
<b>Precautions</b>	Eczema, scabies-vaccine site must be lesion-free; severely immunocompromised patients; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	See introductory notes; lymphadenitis and keloid formation; osteitis and localized necrotic ulceration; rarely, disseminated BCG infection in immunodeficient patients; rarely, anaphylaxis; bladder irritation, anorexia, weight loss.
<b>Storage</b>	Store as stated in the label.

## Diphtheria, Pertussis and Tetanus (DPT) Vaccine\*

<b>Indications</b>	<i>Active immunisation against diphtheria, tetanus and pertussis.</i>
<b>Availability</b>	<b>INJECTIONS</b> 0.5 ml/ampoule and 5 ml/vial.
<b>Dose</b>	<b><i>Intramuscular injection</i></b> <b>Child-</b> Infant; 0.5 ml at 6, 10 and 14 weeks.
<b>Contraindications</b>	See introductory notes and notes above; hypersensitivity, do not administer i.v., seizures, hypotension, hyporeactivity syndrome.
<b>Precautions</b>	See introductory notes and notes above; in cases of severe reaction, the pertussis component should be omitted and the primary course of immunization completed with diphtheria and tetanus vaccine; postpone vaccination if fever, acute disease.

**Adverse Effects** See introductory notes; tetanus component rarely, associated with peripheral neuropathy; pertussis component rarely, associated with convulsions and encephalopathy; induction, oedema.

## Haemophilus Influenza Type B Vaccine

### Pregnancy Category-C

**Indications** *Active immunisation against influenza in individuals at risk.*

**Availability** **INJECTION** 10 µg/vial.

**Dose** ***Intramuscular or deep subcutaneous injection***

**Adult-** 0.5 ml as a single dose.

**Child-** Over 13 years: 0.5 ml as a single dose. 3 to 12 years: 0.5 ml with a second dose after at least 4 weeks if child was not previously infected or vaccinated. 6 to 35 months; 0.25 ml repeated after at least 4 weeks if child was not previously infected or vaccinated.

**Precautions** Allergy to ranitidine; pregnancy (Appendix 7c).

**Adverse Effects** Soreness or redness at injection site; breathing problem; numbness in hand.

**Storage** Store as stated in the label.

## Hepatitis A Vaccine

### Pregnancy Category-C

**Indications** *Active immunization against hepatitis A.*

**Availability** **INJECTIONS** vials 0.5 ml (80, 160, 360 and 720 units), 1 ml (1440 units).

**Dose** ***Intramuscular injection***

**Adult-** 1440 Elisa units.

**Child-** 360 or 720 Elisa units in accordance with age. 6 months to 1 year: 360 Elisa units, up to 18 years: 720 Elisa units.

**Contraindications** Thrombocytopenia; hypersensitivity.

**Precautions** Haemodialysis, febrile illness; pregnancy (Appendix 7c).

**Adverse Effects** Usually mild, include transient soreness, erythema, and induration at the injection site, fever, malaise, fatigue, headache, nausea, diarrhoea, and loss of appetite; arthralgia, myalgia and convulsions; anorexia.

**Storage** Store as stated in the label.

## Hepatitis B Vaccine\*

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Active immunisation against hepatitis B.</i>
<b>Availability</b>	<b>INJECTIONS</b> 2 ml/vial (10 µg/0.5 ml) 10 µg/ml, 10 µg/2 ml, 10 µg/5 ml, 10 µg/10 ml, 100 µg/10 ml, and multidose vial 10 ml/vial (20 µg/ml).
<b>Dose</b>	<p><b>Intramuscular injection</b></p> <p><b>Adult-</b> Immunisation of unimmunised and high risk persons: 3 doses of 1 ml with an interval of 1 month between the first and second dose and 5 months between the second and third doses.</p> <p><b>Child-</b> Immunisation of children, Infant: 0.5 ml either (Scheme A) at birth and at 6 and 14 weeks of age or (Scheme B) at 6, 10 and 14 weeks of age.</p> <p>Immunisation of unimmunised and high risk children, over 15 years: 3 doses of 1 ml with an interval of 1 month between the first and second dose and 5 months between the second and third doses. Under 15 years; 0.5 ml.</p>

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*Note: The vaccine should be given in the deltoid region in Adult and older children; anterolateral thigh is the preferred site in infants and young children; subcutaneous route is used for patients with thrombocytopenia or bleeding disorders.*

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<b>Contraindications</b>	See introductory notes; acute febrile illness.
<b>Precautions</b>	See introductory notes; severely compromised cardiopulmonary status; pregnancy (Appendix 7C).
<b>Adverse Effects</b>	See introductory notes; abdominal pain and gastrointestinal disturbances; muscle and joint pain, dizziness and sleep disturbance; occasionally cardiovascular effects; convulsions, neuropathy, meningitis, paralysis, syncope.
<b>Storage</b>	Store as stated in the label.

## Influenza Vaccine

Pregnancy Category-C

<b>Indications</b>	<i>Active immunisation against influenza in individuals at risk.</i>
<b>Availability</b>	<b>INJECTION</b> 0.5 ml Pre filled syringes ampoule.

<b>Dose</b>	<b><i>Intramuscular or deep subcutaneous injection</i></b>  <b>Adult-</b> 0.5 ml as a single dose.  <b>Child-</b> Over 13 years: 0.5 ml as a single dose. 3 to 12 years: 0.5 ml with a second dose after at least 4 weeks if child was not previously infected or vaccinated. 6 to 35 months: 0.25 ml repeated after at least 4 weeks if child was not previously infected or vaccinated.
<b>Contraindications</b>	See introductory notes; whole virion vaccine not recommended in children; hypersensitivity to any antibiotic present in vaccine (consult literature); hypersensitivity to egg; thrombocytopenia, febrile illness.
<b>Precautions</b>	See introductory notes; pregnancy (Appendix 7c), lactation.
<b>Adverse Effects</b>	See introductory notes; occasionally, severe febrile reactions-particularly after whole virion vaccine in children; convulsions; thrombocytopenia, angioedema, neuritis; encephalomyelitis; urticaria.
<b>Storage</b>	Store as stated in the label.

## Measles Vaccine\*

### Pregnancy Category-X

<b>Indications</b>	<i>Active immunization against measles.</i>
<b>Availability</b>	<b>INJECTION</b> 0.5 ml ampoule containing at least 1000 CCID - 50.
<b>Dose</b>	<b><i>Intramuscular or deep subcutaneous injection</i></b>  <b>Child-</b> For immunisation of children against measles; Infant, at 9 months: 0.5 ml.  Prophylaxis in susceptible children after exposure to measles; over 9 months: 0.5 ml within 72 h of contact.
<b>Contraindications</b>	See introductory notes; hypersensitivity to any antibiotic present in vaccine (consult literature); hypersensitivity to egg or gelatin; respiratory tract infection, tuberculosis, AIDS.
<b>Precautions</b>	See introductory notes; febrile seizures, cerebral injury, pregnancy (Appendix 7c),.
<b>Adverse Effects</b>	See introductory notes; rashes sometimes accompanied by convulsions; rarely, encephalitis and thrombocytopenia; headache, pruritus, purpura.
<b>Storage</b>	Store as stated in the label.

## Polio Vaccine\* (OPV/IPV)

<b>Indications</b>	<i>Active immunisation against poliomyelitis.</i>
<b>Availability</b>	<b>INJECTION</b> 0.5 ml/vial.
<b>Dose</b>	<p><b>Oral</b></p> <p>Primary immunisation of unimmunised adult: 3 doses each of 3 drops with an interval of at least 4 weeks between each dose.</p> <p>Reinforcing immunisation of unimmunised adult: 3 doses after 10 years of completion of primary course.</p> <p><b>Intramuscular injection</b></p> <p>2 booster doses of injection first before school entry and second at leaving school. Further booster doses may be required to adults at special risk of polio endemic areas.</p> <p><b>Child-</b> Primary immunisation: 3 drops at birth and at 6, 10 and 14 weeks of age.</p> <p>Reinforcing immunisation of children: 3 drops at least 3 years after completion of primary course and a further 3 drops at 15 to 19 years of age.</p>
<b>Contraindications</b>	See introductory notes; primary immunodeficiency or immunosuppression; not to be taken with food which contains a preservative; hypersensitivity to any antibiotic present in vaccine (consult literature).
<b>Precautions</b>	See introductory notes.
<b>Adverse Effects</b>	Rarely, vaccine-associated poliomyelitis in recipients of vaccine and contacts of recipients; paralytic poliomyelitis.
<b>Storage</b>	Store as stated in the label.

## Rabies Vaccine\*

### Pregnancy Category-C

<b>Indications</b>	<i>Active immunisation against rabies; pre-exposure prophylaxis, post-exposure treatment.</i>
<b>Availability</b>	<b>INJECTIONS</b> 1 ml/vial and 1 ml/ampoule containing 2.5 IU inactivated rabies antigen for reconstitution before use.
<b>Dose</b>	<p><b>Intramuscular or deep subcutaneous injection</b></p> <p><b>Adult-</b> Immunisation against rabies; pre-exposure prophylaxis: 1 ml on days 0, 7 and 28 with reinforcing doses 2 to 3 years for those at continued risk.</p>

Immunisation against rabies; post-exposure treatment (in unimmunised individuals): 5 doses of 1 ml each on days 0, 3, 7, 14 and 28 (plus rabies immunoglobulin given on day 0).

Immunisation against rabies; post-exposure treatment (in fully immunised individuals): 2 doses of 1 ml separated by 3 to 7 days.

**Child-** Immunisation against rabies; pre-exposure prophylaxis: 1 ml on days 0, 7 and 28 with reinforcing doses 2 to 3 years for those at continued risk.

Immunisation against rabies; post-exposure treatment (in unimmunised individuals): 5 doses of 1 ml on days 0, 3, 7, 14 and 28 (plus rabies immunoglobulin given on day 0).

Immunisation against rabies; post-exposure treatment (in fully immunised individuals): 2 doses of 1 ml separated by 3 to 7 days.

<b>Contraindications</b>	See introductory notes; febrile illness.
<b>Precautions</b>	See introductory notes; acute illness; pregnancy (Appendix 7c).  If schedule requires rabies vaccine and rabies immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites.
<b>Adverse Effects</b>	See introductory notes; pain, erythema and induration at injection site; nausea, myalgia; hypersensitivity-less likely with vaccines from human sources; headache, fever.
<b>Storage</b>	Store in single dose, light-resistant containers.

## Rubella Vaccine

### Pregnancy Category-X

<b>Indications</b>	<i>Active immunisation against rubella in women of child-bearing age.</i>
<b>Availability</b>	<b>INJECTION</b> 0.5 ml vial containing 1000 CCID- 50 of live virus particles.
<b>Dose</b>	<b><i>Intramuscular or deep subcutaneous injection</i></b>  <b>Adult-</b> 0.5 ml as a single dose.
<b>Contraindications</b>	See introductory notes; pregnancy (Appendix 7c) (see notes above); hypersensitivity to any antibiotic present in vaccine-consult manufacturer's literature; hypersensitivity to egg.
<b>Precautions</b>	See introductory notes; illness, infection, blood disorder.

**Adverse Effects** See introductory notes; rash, lymphadenopathy; arthralgia and arthritis; rarely, thrombocytopenia, neurological symptoms; pharyngitis.

**Storage** Store in single dose, light-resistant containers.

## Tetanus Vaccine\*

### Pregnancy Category-C

**Indications** *Active immunisation against tetanus and neonatal tetanus; wound management (tetanus-prone wounds and clean wounds).*

**Availability** **INJECTION** 0.5 ml ampoule.

**Dose** ***Intramuscular injection***

**Adult-** Primary immunisation: 3 doses each of 0.5 ml with an interval of 4 weeks between each dose.

Reinforcing immunisation: 2 doses each of 0.5 ml, the first dose; 10 years after completion of primary course and the second dose; after 10 years.

Immunisation of women of child-bearing age against tetanus: 3 primary doses each of 0.5 ml with an interval of not less than 4 weeks between the first and second doses and 6 months between the second and third dose. 2 reinforcing doses each of 0.5 ml, the first dose; 1 year after completion of the primary course and the second dose; 1 year later.

Unimmunised pregnant women: 2 doses each of 0.5 ml with an interval of 4 weeks between each dose (second dose at least 2 weeks before delivery) and 1 dose during each of subsequent 3 pregnancies (max. 5 doses).

***Intramuscular or deep subcutaneous injection***

**Adult-** Management of tetanus-prone wounds and clean wounds: 0.5 ml, the dose schedule being dependent upon the immune status of the patient and the level of contamination of the wound.

**Contraindications** See introductory notes and notes above; anaphylactic reaction, hypersensitivity.

**Precautions** See introductory notes and notes above; mild cold.

If schedule requires tetanus vaccine and antitetanus immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites, pregnancy (Appendix 7c).

**Adverse Effects** See introductory notes; tetanus component rarely, associated with peripheral neuropathy; seizures, neurological disturbance, fever, loss of appetite.

## Typhoid Vaccine

### Pregnancy Category-B

**Indications** *Active immunization against typhoid.*

**Availability** **INJECTIONS** 30 µg/vial and 150 µg/vial.

**Dose** **Oral**

**Adult-** Each dose given on days 0, 2 and 4 (total of 3 doses), with reinforcing doses every year for travellers to disease-endemic countries and every 3 years for those living in disease-endemic areas.

**Child-** Over 6 years: each dose given on days 0, 2 and 4 (total of 3 doses), with reinforcing doses every year for travellers to disease-endemic countries and every 3 years for those living in disease-endemic areas.

***Intramuscular or deep subcutaneous injection***

**Adult-** 0.5 ml, with reinforcing doses every 3 years for those at continued risk.

**Child-** 0.5 ml, with reinforcing doses every 3 years for those at continued risk.

**Contraindications** See introductory notes; hypersensitivity.

**Precautions** See introductory notes and notes above; illness, infection, allergy, radiation therapy, interactions (Appendix 6d); pregnancy (Appendix 7c).

**Adverse Effects** See introductory notes; anaphylactoid reaction; nausea; vomiting; fever; redness; itching; abdominal pain.

**Storage** Store at a temperature 2 to 8°C. When stored under these conditions may retain potency for 1 year.

## Varicella Vaccine

### Pregnancy Category-B

**Indications** *Active immunization against varicella in healthy subjects and their susceptible healthy close contacts from the age of 12 onwards.*

**Availability** **INJECTION** 0.5 mg/vial.

**Dose** ***Subcutaneous injection***



**Adult-** 2 doses of 0.5 ml at dose intervals of 6 to 10 weeks.

**Child-** Below 1 year: not recommended; 1 to 12 years: 1 dose of 0.5 ml; Above 12 years: 2 doses of 0.5 ml at dose intervals of 6 to 10 weeks.

<b>Contraindications</b>	Contraindicated in pregnancy (avoid pregnancy for 3 months after vaccination, Appendix 7c). It must not be given to individuals with primary or acquired immunodeficiency or to individuals receiving immunosuppressive therapy; leukaemia, tuberculosis, febrile illness, neoplastic diseases, respiratory depression.
<b>Precautions</b>	Blood or plasma transfused patients, leukaemia, blood dyscrasias, interactions (Appendix 6c).
<b>Adverse Effects</b>	Skin rashes; breathing difficulty; face and eye swelling.
<b>Storage</b>	Store as stated in the label.

## Yellow Fever Vaccine

<b>Indications</b>	<i>Active immunization against yellow fever.</i>
<b>Availability</b>	<b>INJECTION</b> 1000 IU/vial.
<b>Dose</b>	<b><i>Subcutaneous injection</i></b>  <b>Adult-</b> Immunisation of travellers and others at risk against yellow fever; 0.5 ml.  <b>Child-</b> Immunisation of travellers and others at risk against yellow fever; over 9 months: 0.5 ml; Infant, 6 to 9 months: 0.5 ml only if risk of yellow fever is unavoidable. At 9 months of age: 0.5 ml.
<b>Contraindications</b>	See introductory notes; not recommended for infants under 6 months of age; hypersensitivity to any antibiotic present in vaccine-consult manufacturer's literature; hypersensitivity to egg; febrile illness, impaired immune response.
<b>Precautions</b>	See introductory notes; acute illness.
<b>Adverse Effects</b>	See introductory notes; rarely, encephalitis, generally in infants under 9 months; lymphangitis, myalgia; inflammation.
<b>Storage</b>	Store as stated in the label.



## 26. Muscle Relaxants

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## 26. Muscle Relaxants

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The muscle relaxants are mainly of two types- peripherally acting and centrally acting and are used along with general anaesthetics for carrying out surgical procedures and to control painful muscle spasms and spastic neurological conditions. They should never be given until it is certain that general anaesthesia has been established and ventilation must be mechanically assisted until they have been completely inactivated. The most common adverse effects of muscle relaxants are vision changes, such as double vision or blurred vision, dizziness, light headness, drowsiness, dry mouth etc.

### Atracurium Besylate\*

Pregnancy Category-B

Schedule H

#### Indications

*Used adjunctively in anaesthesia to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.*

#### Availability

**INJECTION** 2.5 and 5 ml ampoule (10 mg/ml).

#### Dose

##### ***Intravenous injection***

**Adult and child over 1month-** Surgery or intubation: 300 to 600 µg/kg body weight, maintenance by 100 to 200 µg as required. Intensive care: 300 to 600 µg/kg body weight.

##### ***Intravenous infusion***

**Adult and child-** 5 to 10 µg/kg body weight/min (300 to 600 µg/kg/h).

#### Contraindications

Hypersensitivity.

**Precautions**

Allergic cross-reactivity between neuromuscular blocking agents has been reported; caution is advised in cases of hypersensitivity. Their activity is prolonged in patients with myasthenia gravis and in hypothermia, therefore lower doses are required. Non-depolarising muscle relaxants should be used with great care in those with other neuromuscular disorders and those with fluid and electrolyte disturbances, as response is unpredictable. Resistance may develop in patients with burns who may require increased doses; low plasma cholinesterase activity in these patients requires dose titration for mivacurium, renal or hepatic dysfunction, severe electrolyte disturbance, smoking, pregnancy (Appendix 7c), lactation, peripheral neuropathy, demyelinating lesions, denervations. Neonates, severe CVS disorder, severe electrolyte imbalance, respiratory insufficiency or pulmonary disease.

**Adverse Effects**

Skin flushing; hypotension, tachycardia; bronchospasm and very rarely; anaphylactoid reactions, acute myopathy have also been reported after prolonged use in intensive care; prolonged musculoskeletal block, wheezing or bronchial secretion, erythema, dyspnoea.

**Storage**

Store protected from light in single dose containers.

**Baclofen****Pregnancy Category-C****Schedule H****Indications**

*Severe chronic spasticity.*

**Availability**

**TABLETS** 10 and 25 mg;  
**INJECTIONS** 20 ml ampoule (50 µg/ml).

**Dose****Oral**

**Adult-** 5-10 mg thrice daily to 25 mg thrice daily Max. 100 mg daily.

**Child-** 0.75-2.0 mg/kg daily.

**Intrathecal****Adult**

**Screening dose:** 50 µg administered into intrathecal space by barbotage over not less than 1 minute, observe for 4-8 hours. Increase dose by 25 µg not more often every 24 hours until appropriate response is obtained or a maximum dose of 100 µg is achieved. Non responders to 100 µg dose are not suitable for intrathecal baclofen therapy. For responders with response lasting >8-12 hours the screening dose can be given as 24 hour infusion, if response lasted ≤ 8-12 hours then a dose equivalent to twice the screening dose is given as 24 hour infusion.

**Child-** Similar to that of adult except that the screening dose to be started initially is 25 µg.

**Contraindications** Hypersensitivity; active peptic ulcer disease.

**Precautions** Cerebrovascular disorder; epilepsy; severe psychotic disorder; respiratory depression; hepatic or renal impairment; elderly; pregnancy (Appendix 7c), avoid sudden withdrawal; interactions (Appendix 6c, 6d).

**Adverse Effects** Drowsiness; mental confusion; weakness; ataxia; rise in serum transaminases, sudden withdrawal after chronic use may cause hallucinations; tachycardia and seizures, respiratory or cardiovascular depression.

## Neostigmine\* (Refer Page No. 435)

Pregnancy Category-C

**Schedule H**

**Indications** *Myasthenia gravis; reversal of non-depolarizing neuromuscular block, postoperative urinary retention.*

**Availability** **TABLETS** 15 mg; **INJECTION** 1 and 5 ml ampoule (0.5 mg/ml).

**Dose** ***Subcutaneous or intramuscular injection***

**Adult-** Myasthenia gravis: as neostigmine metilsulfate: 0.5 to 2.5 mg as required, total daily dose 5 to 20 mg.

**Child-** 200-500 µg as required. Neonate: 50 to 250 µg 30 min before feeds (not usually required beyond 8 weeks of age).

**Contraindications** Recent intestinal or bladder surgery; mechanical intestinal or urinary tract obstruction; after suxamethonium; pneumonia; peritonitis.

<b>Precautions</b>	Asthma; urinary tract infections; cardiovascular disease including arrhythmias (especially bradycardia, vagotonia, recent myocardial infarction or atrioventricular block); hyperthyroidism; hypotension; peptic ulcer; epilepsy; parkinsonism; renal impairment; lactation (Appendix 7b); pregnancy (Appendix 7c); interactions (Appendix 6c).
<b>Adverse Effects</b>	Increased salivation, nausea and vomiting, abdominal cramps, diarrhoea; signs of overdose include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defecation and micturition, miosis, nystagmus, bradycardia, heart block, arrhythmias, hypotension, agitation, excessive dreaming, weakness eventually leading to fasciculation and paralysis; thrombophlebitis reported; rash associated with bromide salt, anaphylaxis; dizziness; rash; frequent urination.
<b>Storage</b>	Tablets: Store protected from light and moisture. Injection: Store protected from light.

## Pancuronium

### Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Adjunct to general anaesthesia to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.</i>
<b>Availability</b>	<b>INJECTION</b> 2 ml ampoule (2 mg/ml).
<b>Dose</b>	<b>Intravenous injection</b>  <b>Adult-</b> Initially 50 to 100 µg/kg body weight, 10-20 µg/kg body weight for maintenance dose.  <b>Neonates-</b> 30-40 µg/kg body weight.
<b>Contraindications</b>	Anuria, reduced airway control, lactation.
<b>Precautions</b>	Refer Atracurium; hypermagnesaemia, hypercalcaemia, hyperkalemia, hypoproteinaemia; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Skin flushing, hypotension, tachycardia, bronchospasm, anaphylactoid reactions, acute myopathy have also been reported after prolonged use in intensive care.
<b>Storage</b>	Store protected from light in single dose container.

## Pyridostigmine\* (Refer Page No. 436)

Pregnancy Category-C

Schedule H

**Indications** *Myasthenia gravis.*

**Availability** TABLETS 30, 60 and 180 mg.

**Dose** *Oral*

**Adult-** Myasthenia gravis: initially 30 to 120 mg at suitable intervals throughout the day, gradually increased until desired response obtained, total daily dose within range 0.3 to 1.2g, taken at appropriate intervals when max. strength required.

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*Note: Doses above 450 mg daily not usually advisable in order to avoid acetylcholine receptor downregulation.*

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**Child-** Up to 6 years: initially 30 mg. 6 to 12 years initially 60 mg; dose may be gradually increased by 15-30 mg on daily basis.

**Contraindications** Recent intestinal or bladder surgery; gastrointestinal or urinary tract obstruction; after suxamethonium; pneumonia; peritonitis.

**Precautions** Asthma; urinary tract infection; cardiovascular disease including arrhythmias (especially bradycardia or atrioventricular block); hyperthyroidism; hypotension; peptic ulcer; epilepsy; parkinsonism; renal impairment; pregnancy (Appendix 7c); lactation.

**Adverse Effects** Muscarinic effects generally weaker than with neostigmine: increased salivation, nausea, vomiting, abdominal cramps, diarrhoea; signs of overdose include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defecation and micturition, miosis, nystagmus, bradycardia, heart block, arrhythmias, hypotension, agitation, excessive dreaming, weakness eventually leading to fasciculation and paralysis; thrombophlebitis; rash associated with bromide salt; diaphoresis, increased peristalsis.

**Storage** Store protected from light and moisture.



## Succinyl Choline Chloride\*

Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Short-term muscle relaxation needed for surgical or diagnostic procedures; adjunct to general anesthesia, facilitate tracheal intubation.</i>
<b>Availability</b>	<b>INJECTION</b> 50, 100 and 500 mg Vial (50 mg/ml).
<b>Dose</b>	<b><i>Intravenous injection</i></b>  Initially 1 mg/kg body weight, maintenance by 0.5 to 1 mg/kg body weight every 5 to 10 min interval (max 500 mg).  <b><i>Intravenous infusion</i></b>  1 to 2 mg/ml (0.1 to 0.2%), reduce infusion rate in child.
<b>Contraindications</b>	Low serum levels of serum cholinesterase; myasthenia gravis; hypokalemia; glaucoma.
<b>Precautions</b>	Severe burns, pregnancy (Appendix 7c), should not be administered until anaesthetic is fully effective, hepatic and renal failure, reduced plasma cholinesterase activity.
<b>Adverse Effects</b>	Cardiac arrest, malignant hyperthermia, arrhythmia, increased intraocular pressure; jaw rigidity; muscle pain.
<b>Storage</b>	Store protected from light. Injection should not be allowed to freeze.



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## 27. Ophthalmological Preparations

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### Administration of Eye Preparations:

Preparations for the eye should be sterile when issued. Use of single-application containers is preferable; multiple-application preparations include antimicrobial preservatives and when used particular care should be taken to prevent contamination of the contents, including the avoidance of contact between the applicator and the eye or other surfaces.

Eye drops are generally instilled into the lower conjunctival sac which is accessed by gently pulling down the lower eyelid to form a pocket into which one drop is instilled. The eye should be kept closed for as long as possible after application, preferably 1-2 min. A small amount of eye ointment is applied similarly; the ointment melts rapidly and blinking helps to spread it.

When two different eye drops are required at the same time, dilution and overflow may occur when one immediately follows the other; an interval of 5 min should be allowed between the two applications.

Systemic absorption, which may occur after topical application of eye drops, can be minimized by using the finger to compress the lacrimal sac at the medial canthus for at least one min after instillation of the drops. This helps block the passage of the drops through the naso-lacrimal duct.

### Performance of Skilled Tasks

Application of eye preparations may cause blurring of vision which is generally transient; patients should be advised not to carry out skilled tasks such as operating machinery or driving until their vision has cleared.

## 27.1 Antiglaucoma Drugs

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Glaucoma is one of the leading causes of irreversible blindness world wide. Glaucoma is normally associated with raised intra-ocular pressure and eventual damage to the optic nerve which may result in blindness. The rise in pressure is almost always due to reduced outflow of aqueous humour, the inflow remaining constant. The most common condition is chronic open-angle glaucoma (chronic simple glaucoma) in which the intra-ocular pressure increases gradually and the condition is usually asymptomatic until well advanced. In contrast, angle-closure glaucoma (closed-angle glaucoma) usually occurs as an acute emergency resulting from a rapid rise in intra-ocular pressure; if treatment is delayed, chronic angle-closure glaucoma may develop. Ocular hypertension is a condition in which intra-ocular pressure is raised without signs of optic nerve damage.

Drugs used in the treatment of glaucoma lower the intra-ocular pressure by a variety of mechanisms including reduction in secretion of aqueous humour by the ciliary body, or increasing the outflow of the aqueous humour by opening of the trabecular network. Antiglaucoma drugs used include topical application of a beta-blocker (beta-adrenoceptor antagonist), a miotic, or a sympathomimetic such as epinephrine; systemic administration of a carbonic anhydrase inhibitor may be used as an adjunct.

Timolol is a non-selective beta-blocker that reduces the secretion of aqueous humour. A beta-blocker is usually the drug of choice for initial and maintenance treatment of chronic open-angle glaucoma. If further reduction in intra-ocular pressure is required a miotic, a sympathomimetic or a systemic carbonic anhydrase inhibitor may be used with timolol. In angle-closure glaucoma, timolol should be used with a miotic and not alone. Since systemic absorption can occur, an ophthalmic beta-blocker should be used with caution in certain individuals.

A miotic such as pilocarpine, through its parasympathomimetic action, contracts the iris sphincter muscle and the ciliary muscle, and opens the trabecular network. It is used in chronic open-angle glaucoma either alone or, if required, with a beta-blocker, epinephrine or a systemic carbonic anhydrase inhibitor. Pilocarpine is used with systemic acetazolamide in an acute attack of angle-closure glaucoma prior to surgery; however, it is not advisable to use pilocarpine after surgery because of a risk of posterior forming. Systemic absorption of topically applied pilocarpine can occur producing muscarinic adverse effects.

The sympathomimetic drug epinephrine (adrenaline) probably acts by reducing the rate of production of aqueous humour and increasing the outflow through the trabecular network. Epinephrine is usually used with a miotic, a beta-blocker or a systemic carbonic anhydrase inhibitor in the treatment of chronic open-angle glaucoma; however, because epinephrine is also a mydriatic, it is contraindicated for angle-closure glaucoma unless an iridectomy has been carried out.

Acetazolamide, by reducing carbonic anhydrase in the eye, reduces the production of aqueous humour and so reduces intra-ocular pressure. It is used systemically as an adjunct in chronic open-angle glaucoma unresponsive to treatment with topically applied antiglaucoma drugs. Prolonged therapy with acetazolamide is not normally recommended, but if treatment is unavoidable blood count and plasma electrolyte concentration should be monitored. Acetazolamide is also used as part of emergency treatment for an acute attack of angle-closure glaucoma; however it should not be used in chronic angle-closure glaucoma as it may mask deterioration of the condition.

## Acetazolamide\*

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>As an adjunct in the treatment of chronic open-angle glaucoma; secondary glaucoma; as part of pre-operative treatment of acute angle-closure glaucoma.</i>
<b>Availability</b>	<b>TABLET</b> 250 mg; <b>CAPSULE</b> 250 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> 0.25 to 1g daily in divided doses.
<b>Contraindications</b>	Hypersensitivity to sulfonamides; chronic angle-closure glaucoma (may mask deterioration); hypokalaemia, hyponatraemia, hyperchloraemic acidosis; renal impairment (Appendix 7d), severe hepatic impairment; renal hyperchloremic acidosis, Addison's disease.
<b>Precautions</b>	Elderly; lactation; diabetes mellitus; pulmonary obstruction; monitor blood count and electrolytes if used for long periods; interactions (Appendix 6b, 6c); pregnancy (Appendix 7c); severe respiratory acidosis.  May impair ability to perform skilled tasks, for example operating machinery, driving.

**Adverse Effects** Nausea, vomiting, diarrhoea, taste disturbance; loss of appetite, paraesthesia, flushing, headache, dizziness, fatigue, irritability, depression; thirst, polyuria; reduced *libido*; metabolic acidosis and electrolyte disturbances on long-term therapy; occasionally drowsiness, confusion, hearing disturbances, urticaria, melaena, glycosuria, haematuria; abnormal liver function; renal calculi, blood disorders including agranulocytosis and thrombocytopenia; rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis; transient myopia reported; blood dyscrasias; crystalluria.

**Storage** Store protected from light.

## Betaxolol\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *Glaucoma.*

**Availability** **EYE DROPS** 5 ml (0.5% w/v).

**Dose** ***Instillation into the eye***

**Adult-** 1 to 2 drops, twice daily.

**Child-** Not recommended.

**Contraindications** Systemic absorption may follow topical application to the eyes, therefore they are contraindicated in patients with bradycardia, heart block, or uncontrolled heart failure; hypersensitivity.

**Precautions** Avoid in asthma, poor cardiac reserve, hepatic impairment; not for injection; pregnancy (Appendix 7c).

**Adverse Effects** Ocular stinging, burning, pain, itching, erythema, dry eyes and allergic reactions including anaphylaxis and blepharoconjunctivitis; occasionally corneal disorders have been reported; crusty taste, photophobia, corneal punctuate staining, decreased corneal sensitivity, keratitis, anisocoria; headache; sleep disturbances.

## Clonidine (Refer Page No. 314)

**Pregnancy Category-C**

**Schedule H**

**Indications** *Long term treatment of glaucoma and ocular hypertension.*

<b>Availability</b>	<b>EYE DROPS</b> 0.125%, 0.2%, 0.25% and 0.5%w/v.
<b>Precautions</b>	Patients with coronary insufficiency; interactions (Appendix 6a, 6c), pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Systemic hypotension; sedation; syncope.

## Latanoprost

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>To lower intraocular pressure in open angle glaucoma or ocular hypertension.</i>
<b>Availability</b>	<b>EYE DROPS</b> 0.005% w/v.
<b>Dose</b>	One drop once daily in the evening.
<b>Contraindications</b>	Hypersensitivity.
<b>Precautions</b>	Patients with a history of intraocular inflammation (iritis/uveitis) or active intraocular inflammation, with torn posterior lens capsule, brittle or severe asthma, inflammatory, angle closure or congenital glaucoma, pregnancy (Appendix 7c), lactation, interactions (Appendix 6c).
<b>Adverse Effects</b>	Conjunctival hyperaemia, iris pigmentation; upper respiratory tract infection; cold, flu; darkening and thickening of eyelashes, eyelid skin darkening; intraocular inflammation, ocular irritation and pain; exacerbation of asthma; blepharitis.

## Physostigmine

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>Glaucoma in conjunction with other drugs and not alone (as it is very potent).</i>
<b>Availability</b>	<b>EYE DROPS</b> 5 ml (0.25%w/v).
<b>Dose</b>	<b><i>Instillation into the eye</i></b> <b>Adult</b> -1 to 2 drops, 4 to 5 times daily.
<b>Precautions</b>	Care to be taken when administered into eye, pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Twitching lids, myopia, ocular and periorbital pain, ciliary and conjunctival congestion.



## Pilocarpine\*

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Chronic open-angle glaucoma, ocular hypertension; emergency treatment of acute angle-closure glaucoma; to antagonize effects of mydriasis and cycloplegia following surgery or ophthalmoscopic examination; Accommodative esotropia.</i>
<b>Availability</b>	<b>EYE DROPS</b> 5 ml (2% w/v, 4%w/v).
<b>Dose</b>	<p><b>Instillation into the eye</b></p> <p><b>Adult-</b> Chronic open-angle glaucoma before surgery: 1 drop (2% or 4 %) up to 4 times daily.</p> <p>Acute angle closure glaucoma before surgery: 1 drop (2%) every 10 min for 30 to 60 min, then 1 drop every 1 to 3 h until intra-ocular pressure subsides.</p>
<b>Contraindications</b>	Acute iritis, acute uveitis, anterior uveitis, some forms of secondary glaucoma; acute inflammation of anterior segment; not advisable after angle-closure surgery (risk of posterior synechiae).
<b>Precautions</b>	<p>Retinal disease, conjunctival or corneal damage; monitor intra-ocular pressure in chronic open-angle glaucoma and in long-term treatment; cardiac disease, hypertension; asthma; peptic ulceration; urinary-tractobstruction; Parkinson's disease; stop treatment if symptoms of systemic toxicity develop; ulcer; hyperthyroidism; seizures.</p> <p>Causes difficulty with dark adaptation; may cause accommodation spasm. Do not carry out skilled tasks, for example operating machinery or driving until vision is clear, pregnancy (Appendix 7c).</p>
<b>Adverse Effects</b>	Eye pain, blurred vision, ciliary spasm, lacrimation, myopia, browache; conjunctival vascular congestion, superficial keratitis, vitreous haemorrhage and increased pupillary block; lens opacities have occurred following prolonged use; rarely, systemic effects including hypertension, tachycardia; bronchial spasm, pulmonary oedema; salivation; sweating; nausea, vomiting, diarrhoea; flushing, rhinitis, chills, middle ear disturbances.
<b>Storage</b>	Store protected from light.

## Timolol\*

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Ocular hypertension; chronic open-angle glaucoma, aphakic glaucoma, some secondary glaucomas.</i>
<b>Availability</b>	<b>DROPS</b> 5 ml (0.2% w/v, 0.25% and 0.5%w/v); <b>GEL</b> (0.5%/5 ml).
<b>Dose</b>	<b><i>Instillation into the eye</i></b>  <b>Adult-</b> 1 drop (0.25% or 0.5%) twice daily.
<b>Contraindications</b>	Uncontrolled heart failure, bradycardia, heart block; asthma, obstructive airways disease; hypersensitivity.
<b>Precautions</b>	Older people (risk of keratitis); if used in angle-closure glaucoma, use with a miotic, and not alone; interactions (Appendix 6c); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Stinging, burning, pain, itching, erythema, transient dryness, allergic blepharitis, transient conjunctivitis, keratitis, decreased corneal sensitivity, diplopia, ptosis; systemic effects; particularly on the pulmonary, cardiovascular and central nervous systems, may follow absorption; blurred vision; headache.
<b>Storage</b>	Store protected from light and moisture.

## 27.2 Anti-Infective Drugs

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Blepharitis, conjunctivitis and keratitis are common acute infections of the eye and can be treated topically. However, in some cases, for example, in gonococcal conjunctivitis, both topical and systemic anti-infective treatment may be necessary. Blepharitis and conjunctivitis are often caused by staphylococcus, while keratitis and endophthalmitis may be bacterial, viral or fungal. Bacterial blepharitis is treated with an anti-bacterial eye ointment or drops. Although most cases of acute bacterial conjunctivitis may resolve spontaneously, anti-infective treatment shortens the infectious process and prevents complications. Acute infective conjunctivitis is treated with antibacterial eye drops by day and eye ointment applied at night. A poor response may indicate viral or allergic conjunctivitis. Keratitis requires immediate specialist treatment.

Gentamicin is a broad-spectrum bactericidal aminoglycoside antibiotic with particular activity against *Pseudomonas aeruginosa*, *Neisseria gonorrhoea* and other bacteria that may be implicated in blepharitis or conjunctivitis. Topical application may lead to systemic absorption and possible adverse effects.

Silver nitrate is a topical anti-infective. Its antibacterial activity is attributed to precipitation of bacterial proteins by silver ions. It is available in 1% ophthalmic solutions and is used for prophylaxis of gonococcal ophthalmia neonatorum.

Tetracycline is a broad spectrum antibiotic with activity against many Gram-positive and Gram-negative bacteria including *N. gonorrhoea*, and most chlamydia, rickettsia, mycoplasma and spirochetes. Ophthalmic tetracycline is used in blepharitis, conjunctivitis, and keratitis produced by susceptible bacteria. Tetracycline is also used in the treatment of trachoma caused by *Chlamydia trachomatis* and in the prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) caused by *N. gonorrhoea* and *C. trachomatis*.

### Acyclovir\* (Refer Page No. 230)

Pregnancy Category-B

Schedule H

#### Indications

*Treatment of Herpes simplex keratitis; long term suppression of skin infections in Herpes simplex as well as mucous membrane, prophylaxis in immunocompromised patients; Herpes zoster treatment.*

#### Availability

**OINTMENT** 5g (3% w/w); **DROPS** 5 ml (3% w/w).

<b>Dose</b>	<b>Adult-</b> Herpes simplex keratitis: apply 3% w/w ointment 5 times daily for 3 days.
<b>Contraindications</b>	Hypersensitivity.
<b>Precautions</b>	Maintain adequate hydration (especially with infusion or high doses); monitor neutrophil count at least twice weekly in neonates; renal impairment (Appendix 7d); lactation (Appendix 7b); pregnancy (Appendix 7c); not to be applied on mucous membrane.
<b>Adverse Effects</b>	Nausea, vomiting, abdominal pain, diarrhoea, headache, fatigue, rash, urticaria, pruritus, photosensitivity; very rarely, hepatitis, jaundice; dyspnoea; neurological reactions (including dizziness, confusion, hallucinations, convulsions and drowsiness); acute renal failure; anaemia, thrombocytopenia and leucopenia; on intravenous infusion; severe local inflammation (sometimes leading to ulceration), and very rarely, agitation, tremors; psychosis and fever; increase in blood urea and creatinine, encephalopathy; seizures; anorexia, tremors.

## Chloramphenicol\* (Refer Page No. 127)

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>Susceptible bacterial infection; corneal ulcers, intraocular infection, keratoconjunctivitis sicca.</i>
<b>Availability</b>	<b>OINTMENT</b> (1%w/w); <b>DROPS</b> (1%w/v, 0.5% w/v); <b>SUSPENSION</b> 125 mg/5 ml.
<b>Dose</b>	Doses instilled into affected eye 3 to 4 times daily. Ointment at night, preferably at bed time.
<b>Contraindications</b>	Pregnancy (Appendix 7c), lactation (Appendix 7b), porphyria; hypersensitivity.
<b>Precautions</b>	Avoid repeated courses and prolonged treatment; reduce doses in hepatic impairment (Appendix 7a); renal impairment; blood counts required before and periodically during treatment; monitor plasma-chloramphenicol concentration in neonates; interactions: (Appendix 6c).
<b>Adverse Effects</b>	Blood disorders including reversible and irreversible aplastic anaemia (with reports of resulting leukaemia); peripheral neuritis, optic neuritis; headache; depression; urticaria, erythema multiforme; nausea, vomiting, diarrhoea; stomatitis, glossitis, dry mouth; nocturnal haemoglobinuria; grey syndrome (abdominal distension, pallid cyanosis, circulatory collapse) may follow excessive doses in neonates with immature hepatic metabolism.

**Storage** Store protected from moisture at a temperature not exceeding 30°C.

## Ciprofloxacin\* (Refer Page No. 128)

**Pregnancy Category-C**

**Schedule H**

**Indications** *Bacterial infections of eye.*

**Availability** **TABLETS** 250, 500 and 750 mg; **INJECTION** 100 ml infusion (20 mg/10 ml); **OINTMENT** 5g (0.3% w/w); **DROPS** 5 and 10 ml (0.3% w/v).

**Dose** **Adult and child above 12 years-** Instill 2 to 3 drops in affected eye 3 to 4 times daily to start with thereafter reduce slowly as infection subsides. Apply about 0.5 cm ribbon of ointment in lower conjunctival sac for 3 to 4 times daily. Reduce as infection subsides.

**Contraindications** Epilepsy and hypersensitivity to quinolones.

**Precautions** It should be used with caution in patients with a history of epilepsy or conditions that predispose to seizures; in G-6-PD deficiency; myasthenia gravis (risk of exacerbation); in renal impairment (Appendix 7d); pregnancy (Appendix 7c), during lactation (Appendix 7b), and in children or adolescents. Exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs). Avoid excessive alkalinity of urine and ensure adequate fluid intake (risk of crystalluria); interactions (Appendix 6c); paediatric use.

**Adverse Effects** Nausea, vomiting, dyspepsia, abdominal pain, diarrhoea (rarely, antibiotic-associated colitis); headache; dizziness; sleep disorders; rash (rarely, Stevens-Johnson syndrome and toxic epidermal necrolysis) and pruritus. Less frequent side-effects include anorexia, increase in blood urea and creatinine; drowsiness, restlessness, asthenia, depression, confusion, hallucinations, convulsions, tremor, paraesthesia, hypoaesthesia; photosensitivity, hypersensitivity reactions including fever, urticaria, angioedema, arthralgia, myalgia, and anaphylaxis; blood disorders (including eosinophilia, leucopenia, thrombocytopenia); disturbances in vision, taste, hearing and smell. Other side-effects that have been reported include haemolytic anaemia, renal failure, interstitial nephritis, and hepatic dysfunction (including hepatitis and cholestatic jaundice). The drug should be discontinued if psychiatric, neurological or hypersensitivity reactions (including severe rash) occur. Ophthalmic solution: local burning, discomfort, corneal ulcers, lid oedema, corneal infiltration. Ointment: discomfort, keratopathy, blurred vision, corneal staining, epitheliopathy, photophobia.

**Storage** Ointment: Store protected from light at a temperature not exceeding 30°C. Drops: Store protected from light.

## Gentamicin\* (Refer Page No. 137)

**Pregnancy Category-C**

**Schedule H**

**Indications** *Blepharitis; bacterial conjunctivitis; keratitis, corneal ulcers.*

**Availability** **OINTMENT** (1% w/w); **DROPS** 5 ml (0.3% w/v).

**Dose** ***Instillation into the eye***

**Adult-** Mild to moderate infections: 1 drop every 2 h, reducing frequency as infection is controlled, then continue for 48 h after healing is complete.

**Contraindications** Hypersensitivity to aminoglycoside group of antibiotics.

**Precautions** Prolonged use may lead to skin sensitization and emergence of resistant organisms including fungi; discontinue if purulent discharge, inflammation or exacerbation of pain; ophthalmic ointment may retard corneal healing, renal impairment (Appendix 7d), interactions (Appendix 6c), pregnancy (Appendix 7c).

**Adverse Effects** Burning; stinging; itching; dermatitis; conjunctival epithelial defects; conjunctival hyperemia; thrombocytopenic purpura; hallucination.

## Miconazole\* (Refer Page No. 352)

**Pregnancy Category-C**

**Schedule H**

**Indications** *Fungal infections of eye.*

**Availability** **DROPS** 5 and 10 ml (1%w/v).

**Dose** **Adult and child-** Fungal infection of eye: instill 2 to 3 drops 3 to 4 times a day in infected eye or as required.

**Contraindications** Hypersensitivity.

**Precautions** Contact with eyes and mucous membranes should be avoided, pregnancy (Appendix 7c).

**Adverse Effects** Occasional local irritation and hypersensitivity reactions include mild burning sensation, erythema; pruritus and itching. Treatment should be discontinued if these are severe.

**Storage** Drops: Store protected from light.

## Oxytetracycline

**Pregnancy Category-D**

**Schedule H**

**Indications** *Infections caused by susceptible pathogens, uncomplicated gonorrhoea, external bacterial infections of the eye, acne vulgaris.*

**Availability** **CAPSULES** 250 and 500 mg. **INJECTION** 50 mg/ml and 125 mg/ml. **OPHTHALMIC OINTMENT** 1% w/w.

**Dose** **Oral**

**Infections caused by susceptible pathogens:**

**Adult**-250-500 mg 4 times daily. Max. dose-4g daily.

**Child (above 8 yrs)**- 25-50 mg/kg daily in 4 divided doses.

Therapy should be continued for at least 24–48 hours after symptoms and fever have subsided.

**Uncomplicated gonorrhoea: Adult**- Initially 1.5 g, followed by 0.5 g 4 times daily upto a total of 9 g per treatment course.

**Acne vulgaris: Adult**- 250-500 mg twice daily.

**Intramuscular**

**Infections caused by susceptible pathogens:**

**Adult**- 250 mg once daily.

**Child (above 8 yrs)**- 15-25 mg/kg daily in 2-3 divided doses (Max. 250 mg).

**Ophthalmic**

**External bacterial infections of the eye:**

**Adult**- Apply the ointment 2-3 times daily.

**Contraindications** Hypersensitivity to tetracyclines, children below 8 years, renal impairment, pregnancy (Appendix 7c), lactation.

**Precautions** Hepatic impairment, myasthenia gravis, porphyria, elderly, interactions (Appendix 6b, 6c).

**Adverse Effects** GI disturbances, abdominal pain, headache, anorexia, tooth discolouration, allergic reactions, photosensitivity, blurred vision, nephrotoxicity, stinging of the eye, intracranial hypertension, blood dyscrasias.

**Storage** Store protected from light and moisture.

**Povidone\*** (Refer Page No. 273)**Sulphacetamide\*****Pregnancy Category-C****Schedule H**

<b>Indications</b>	<i>Sulphonamide sensitive infections of eye; blepharitis, conjunctivitis, vaginosis.</i>
<b>Availability</b>	<b>DROPS</b> 10 ml (10, 20 and 30%w/v).
<b>Dose</b>	Instill 2 to 3 drops in infected eye 4 to 5 times a day or as required.
<b>Contraindications</b>	Renal failure; corneal infection.
<b>Precautions</b>	Pregnancy (Appendix 7c), lactation.
<b>Adverse Effects</b>	Corneal plaques, erythema multiforme, blurred vision, stinging on application.
<b>Storage</b>	Store protected from light.

**Tetracycline** (Refer Page No. 149)**Pregnancy Category-D****Schedule H**

<b>Indications</b>	<i>Superficial bacterial infection of the eye; mass treatment of trachoma in endemic areas; prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) due to Neisseria gonorrhoea or Chlamydia trachomatis.</i>
<b>Availability</b>	<b>OINTMENT</b> (1% w/w); <b>CAPSULE</b> 250 and 500 mg.
<b>Dose</b>	<p><b>Application to the eye</b></p> <p><b>Adult-</b> Superficial bacterial infection: 1 application of ointment, 3 to 4 times daily.</p> <p>Trachoma, intermittent treatment: 1 application of ointment into each eye either twice daily for 5 days or once daily for 10 days, every month for 6 consecutive months each year, repeated as necessary.</p> <p>Trachoma, continuous intensive treatment: 1 application of ointment into each eye twice daily for at least 6 weeks.</p> <p><b>Child</b> (over 8 years)- Superficial bacterial infection: 1 application of ointment 3 to 4 times daily.</p>



Prophylaxis of neonatal conjunctivitis; newborn at birth after cleansing eyes with sterile gauze: 1 application of ointment into each eye; close eyelids and massage gently to aid spread of ointment.

Trachoma, intermittent treatment: 1 application of ointment into each eye either twice daily for 5 days or once daily for 10 days, every month for 6 consecutive months each year, repeated as necessary.

Trachoma, continuous intensive treatment: 1 application of ointment into each eye twice daily for at least 6 weeks.

<b>Contraindications</b>	Hypersensitivity to tetracycline group of antibiotics.
<b>Precautions</b>	Prolonged use may lead to overgrowth of non-susceptible organisms; lactation (Appendix 7b); interactions (Appendix 6d); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Rash; stinging; burning.
<b>Storage</b>	Store protected from moisture at a temperature not exceeding 30°C.

## 27.3 Anti-Inflammatory Drugs

Ophthalmic corticosteroids should only be used under supervision of an ophthalmologist as inappropriate use may lead to blindness. Dangers include the development of open-angle glaucoma (chronic simple glaucoma) and cataracts, and the aggravation of a simple herpes simplex epithelial lesion into an extensive corneal ulcer and subsequent permanent corneal scarring, with possible damage to vision and even loss of the eye.

Corticosteroids such as prednisolone are useful in the treatment of inflammatory conditions including uveitis and scleritis. They are also used for reducing postoperative ocular inflammation. Before administration of an ophthalmic corticosteroid, the possibility of bacterial, viral or fungal infection should be excluded. Treatment should be the lowest effective dose for the shortest possible time; if long-term therapy (more than 6 weeks) is unavoidable, withdrawal of an ophthalmic corticosteroid should be gradual to avoid relapse.

### Prednisolone\* (Refer Page No. 35, 436 and 481)

#### Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Short-term local treatment of inflammation of the eye; malignant disease; inflammatory and allergic reactions.</i>
<b>Availability</b>	<b>TABLETS</b> 5, 10, 20 and 40 mg; <b>DROPS</b> 5 ml (1% w/v).
<b>Dose</b>	Doses to be instilled into affected eye 3 to 4 times daily. Ointment at night, preferably at bed time.
<b>Contraindications</b>	Undiagnosed 'red eye' caused by herpetic keratitis; glaucoma; viral diseases of cornea and conjunctiva.
<b>Precautions</b>	Cataract, corneal thinning, corneal or conjunctival infection; discontinue treatment if no improvement within 7 days; risk of adrenal suppression after prolonged use in infants; hepatic impairment (Appendix 7a); lactation (Appendix 7b); interactions (Appendix 6c, 6d); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Secondary ocular infection; impaired corneal healing (due to corneal thinning), optic nerve damage, cataract; glaucoma, mydriasis, ptosis, epithelial punctate keratitis, delayed hypersensitivity reactions including burning, stinging.

**Storage** Tablets: Store protected from light. Injection: Store protected from light, in a single dose or in multi dose containers.

## Xylometazoline

**Pregnancy Category-C**

**Schedule H**

**Indications** *Nasal congestion, conjunctival decongestant.*

**Availability** **DROPS** 10 and 15 ml (0.05 to 0.1 %w/v).

**Dose** Instill 3 to 4 drops every 3 to 4 h or as required.

**Contraindications** Narrow angle glaucoma, atrophic rhinitis, vasomotor rhinitis.

**Precautions** Avoid excessive or prolonged use; caution in infants under 3 months (no good evidence of value-if irritation occurs, might narrow nasal passage); infants and cardiac patients; pregnancy (Appendix 7c).

**Adverse Effects** Local irritation, nausea, headache; after excessive use tolerance with diminished effect, rebound congestion; cardiovascular effects also reported; dryness of eye and nose, rhinitis medicamentose.

**Storage** Store protected from light.

## 27.4 Local Anaesthetics

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Topical local anaesthetics are employed for simple ophthalmological procedures and for short operative procedures involving the cornea and conjunctiva. Tetracaine, available in 0.5% ophthalmic solution, provides a rapid local anaesthesia which lasts for 15 min or more. Prolonged or unsupervised use of tetracaine is not recommended.

### Tetracaine\*

#### Pregnancy Category-C

<b>Indications</b>	<i>Short-acting local anaesthesia of cornea and conjunctiva.</i>
<b>Availability</b>	<b>DROPS</b> (0.5 and 1% w/v).
<b>Dose</b>	<b><i>Instillation into the eye</i></b>  Instill 2 to 3 drops every 15 to 20 min till the desired effect is achieved.  <b>Adult &amp; Child-</b> 1 drop.
<b>Contraindications</b>	Hypersensitivity to ester-type local anaesthetics; eye inflammation or infection.
<b>Precautions</b>	Avoid prolonged use (cause of severe keratitis, permanent corneal opacification, scarring, delayed corneal healing); protect eye from dust and bacterial contamination until sensation fully restored; not to be applied on highly vascular surface; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Burning, stinging, redness; rarely, allergic reactions may occur; twitching; nystagmus; numbness of tongue; convulsions.
<b>Storage</b>	Store protected from light.

## 27.5 Mydriatics

Antimuscarinics, by blocking the cholinergic effects of acetylcholine, paralyse the pupillary constrictor muscles causing dilation of the pupil (mydriasis) and paralyse the ciliary muscles resulting in paralysis of accommodation (cycloplegia). Mydriasis may precipitate acute angle-closure glaucoma particularly in elderly or far-sighted patients. In patients with dark iridic pigmentation, higher concentrations of mydriatic drugs are usually required and care should be taken to avoid overdosing.

Atropine is a long-acting antimuscarinic used for cycloplegic refraction procedures, particularly in children. It is also used to immobilize the ciliary muscle and iris and to prevent formation of posterior synechiae in the treatment of inflammatory eye disorders such as iritis and uveitis.

### Atropine\* (Refer Page No. 88 and 419)

**Pregnancy Category-C**

**Schedule H**

**Indications** *Iritis, uveitis; cycloplegic refraction procedures; iridocyclitis.*

**Availability** **DROPS** 5 ml (1% w/v).

**Dose** ***Instillation into the eye***

**Adult-** Cycloplegic refraction: 1 drop (1%) twice daily for 1 to 2 days before procedure or a single application of 1 drop (1%), 1 h before procedure.

Iritis and uveitis: 1 drop (0.5 to 1%) up to 4 times daily.

**Child-** Cycloplegic refraction: 3 months to 1 year: 0.1%; 1 to 5 years: 0.1 to 0.5%; Over 5 years: 0.5 to 1.0%. 1 drop twice daily for 1 to 3 days before procedure with a further dose given 1 h before procedure.

Iritis and uveitis: 1 drop (0.5 to 1% w/v) up to 3 times daily.

**Contraindications** Angle-closure glaucoma; pregnancy (Appendix 7c).

**Precautions** May precipitate acute attack of angle-closure glaucoma, particularly in the elderly or far-sighted; risk of systemic effects with eye drops in infants under 3 months-eye ointment preferred.

May cause sensitivity to light and blurred vision. Do not carry out skilled tasks, for example operating machinery or driving, until vision is clear, lactation (Appendix 7b); interactions (Appendix 6a).

**Adverse Effects** Transient stinging and raised intra-ocular pressure; on prolonged administration, local irritation, hyperaemia, oedema and conjunctivitis may occur; contact dermatitis; systemic toxicity may occur in the very young and the elderly; blurred vision, dry mouth, photophobia.

**Storage** Store at a temperature not exceeding 30°C.

## Epinephrine\* (Refer Page No. 28)

**Pregnancy Category-C**

**Schedule H**

**Indications** *Chronic open-angle glaucoma, ocular hypertension.*

**Availability** **DROPS** 0.25 ml (2%w/v), 5 ml (5%w/v); **OINTMENT** 3g.

**Dose** 1 to 2 drops in affected eye, every 4 to 6 h.

**Contraindications** Angle closure glaucoma, unless an iridectomy has been carried out; occlusive vascular disease.

**Precautions** Hypertension, heart disease, aneurysm, arrhythmias, tachycardia; hyperthyroidism; cerebral arteriosclerosis; diabetes mellitus; elderly, interactions (Appendix 6c); pregnancy (Appendix 7c); lactation (Appendix 7b).

**Adverse Effects** Stinging, blurred vision, photophobia, eye pain, conjunctival hyperaemia, headache or browache; occasionally, conjunctival sensitization and local skin reactions; after prolonged use conjunctival pigmentation and macular oedema in aphakia; systemic adverse reactions are rare following topical use at normal dosage but tachycardia, hypertension, arrhythmia, dizziness, sweating may occur; dyspnoea, weakness.

**Storage** Store protected from light.

## Homatropine\*

**Pregnancy Category-C**

**Indications** *To dilate pupil and paralyze ciliary muscle for fundus examination.*

<b>Availability</b>	<b>DROPS</b> 5 ml (2%w/v).
<b>Dose</b>	<b>Adult-</b> 1 to 2 drops in each eye till the desired effect is achieved.  <b>Child-</b> 1 to 2 drops in each eye till the desired effect is achieved.
<b>Contraindications</b>	Narrow angle glaucoma, tendency for glaucoma.
<b>Precautions</b>	Darkly pigmented iris is more resistant to pupillary dilatation and caution should be exercised to avoid overdosage. Mydriasis can precipitate acute angle-closure glaucoma in a few patients, usually aged over 60 years and hypermetropic (long-sighted), who are predisposed to the condition because of a shallow anterior chamber; glaucoma, check intraocular pressure before use; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Ocular side-effects of mydriatics and cycloplegics include transient stinging and raised intra-ocular pressure; on prolonged administration, local irritation, hyperaemia, oedema and conjunctivitis can occur. Contact dermatitis can occur with the antimuscarinic mydriatic drugs, especially atropine. Systemic side-effects of atropine and cyclopentolate can occur in the young and the old; posterior synechia, headache, drowsiness, loss of taste, photophobia, brow ache, lacrimation.
<b>Storage</b>	Store protected from light.

## Phenylephrine\*

**Pregnancy Category-C**

**Schedule H**

<b>Indications</b>	<i>Used in cough syrups, hypotension; mydriatic for eye conditions; uveitis, wide angle glaucoma, refraction, ophthalmoscopic examinations.</i>
<b>Availability</b>	<b>DROPS</b> 5 ml (5% w/v).
<b>Dose</b>	1 to 2 drops in affected eye, every 4 to 6 h.
<b>Contraindications</b>	Hypertension (monitor blood pressure and rate of flow frequently); pregnancy (Appendix 7c); narrow angle glaucoma.

<b>Precautions</b>	Coronary, mesenteric, or peripheral vascular thrombosis; following myocardial infarction, Prinzmetal's variant angina; hyperthyroidism, diabetes mellitus; hypoxia or hypercapnia; uncorrected hypovolaemia; elderly; extravasation at injection site may cause necrosis; infants.
<b>Adverse Effects</b>	Headache, hypertension, bradycardia, arrhythmias, peripheral ischaemia.
<b>Storage</b>	Store protected from light.



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## 28. Psychotherapeutic Drugs

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### 28.1 Antianxiety Agents and Drugs Used In Sleep Disorders

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A sedative drug decreases activity, moderates excitement and calms the recipient, whereas, a hypnotic drug produces drowsiness and facilitates the onset and maintenance of a sleep state that resembles natural sleep. The most widely used anxiolytics and hypnotics are the benzodiazepines. Treatment of anxiety should be limited to the lowest effective dose for the shortest possible time. The cause of insomnia should be established and appropriate treatment for underlying factors instituted before hypnotics are considered. Hypnotics may be of value for a few days but rarely, longer than a week.

Tolerance and dependence (both physical and psychological) and subsequent difficulty in withdrawing the drug may occur after regular use for more than a few weeks. Patients with chronic anxiety, alcohol or drug dependence or those with personality disorders are more likely to become dependent. Anxiolytics and hypnotics should be prescribed in carefully individualized dosage and use should be limited to control of acute conditions such as panic attacks and acute anxiety and severe, incapacitating insomnia. There is usually no justification for prolonging treatment with anxiolytics and hypnotics for more than one to two weeks.

If used for longer periods, withdrawal should be gradual by reduction of the dose over a period of weeks or months, as abrupt discontinuation may produce confusion, toxic psychosis, convulsions or a condition resembling delirium tremens. The benzodiazepine withdrawal syndrome may develop at any time up to 3 weeks after stopping a long-acting benzodiazepine but may occur within a few hour in the case of a short-acting one. The syndrome is characterized by insomnia, anxiety, loss of appetite and body-weight, tremor, perspiration, tinnitus and perceptual disturbances. These symptoms may be similar to the original complaint and encourage further prescribing. Some symptoms may continue for weeks or months after stopping benzodiazepines.

Patients should be warned that their ability to drive or operate machinery may be impaired and that the effects of alcohol may be enhanced.

## Alprazolam\*

Pregnancy Category-D

Schedule H

<b>Indications</b>	<i>Anxiety disorders; panic attacks.</i>
<b>Availability</b>	<b>TABLETS</b> 0.25, 0.5 and 1 mg.
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> 0.25 to 0.5 mg daily 2 to 3 times a day.  <b>Child-</b> Not recommended.
<b>Contraindications</b>	Respiratory depression; marked neuromuscular respiratory weakness including unstable myasthenia gravis; acute pulmonary insufficiency; sleep apnoea syndrome; severe hepatic impairment; not for chronic psychosis; should not be used alone in depression or in anxiety with depression; avoid injections containing benzyl alcohol in neonates; narrow angle glaucoma, hypersensitivity.
<b>Precautions</b>	Respiratory disease; muscle weakness and myasthenia gravis; history of drug or alcohol abuse; marked personality disorder; pregnancy (Appendix 7c), lactation; reduce dose in elderly and debilitated and in hepatic impairment, renal impairment; avoid prolonged use (and abrupt withdrawal thereafter); interactions (Appendix 6a); periodic blood count; liver function test.  Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.
<b>Adverse Effects</b>	Drowsiness and lightheadedness on the next day; confusion and ataxia (especially in the elderly); amnesia; dependence; paradoxical increase in aggression; muscle weakness; occasionally: headache, vertigo, hypotension, salivation changes, gastro-intestinal disturbances, visual disturbances, dysarthria, tremor, changes in <i>libido</i> , incontinence, urinary retention; blood disorders and jaundice reported; skin reactions; rarely, apnoea and insomnia.
<b>Storage</b>	Store protected from light.

## Diazepam\* (Refer Page No. 57 and 420)

Pregnancy Category-D

**Schedule H**

**Indications** *Short-term treatment of anxiety and insomnia; status epilepticus, recurrent seizures; febrile convulsions, adjunct in acute alcohol withdrawal; premedication; agitation.*

**Availability** **TABLETS** 2.5, 5 and 10 mg; **INJECTION** 10 mg/2 ml; **CAPSULES** 10 and 15 mg.

**Dose** **Oral**

**Adult-** Anxiety: 2 mg 3 times daily, increased if necessary to 15 to 30 mg daily in divided doses. Insomnia: 5 to 15 mg at bedtime.

**Child-** Oral 1-2.5 mg, 3 or 4 times daily (Not for use under 6 months).

**Elderly or debilitated-** Anxiety: half adult dose.

**Contraindications** Respiratory depression; acute pulmonary insufficiency; sleep apnoea; severe hepatic impairment; myasthenia gravis; hypersensitivity.

**Precautions** Respiratory disease; muscle weakness; history of alcohol or drug abuse; marked personality disorder; lactation (Appendix 7b); reduce dose in elderly or debilitated and in hepatic impairment (avoid if severe, Appendix 7a); renal impairment; avoid prolonged use and abrupt withdrawal; porphyria; interactions (Appendix 6a, 6c); pregnancy (Appendix 7c); liver function test to be done, least amount of drug should be given in patients in whom depression accompanies anxiety and suicidal tendencies.

May impair ability to perform skilled tasks, for example operating machinery, driving.

**Adverse Effects** Drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia; dependence; paradoxical increase in aggression; muscle weakness; occasionally headache, vertigo, salivation changes, gastrointestinal disturbances, visual disturbances, dysarthria, tremor, changes in *libido*, incontinence, urinary retention; blood disorders and jaundice; skin reactions; raised liver enzymes; reduces reflexes; jaundice; psychological dependence; physiological dependence, respiratory arrest.

**Storage** Tablet: Store protected from light. Injection: Store in single dose or multi dose container protected from light.

## Lorazepam\*

**Pregnancy Category-D**

**Schedule H**

**Indications** *Anxiety disorders.*

**Availability** **TABLETS** 0.5, 1, 2, 2.5 and 3 mg  
**INJECTIONS** 2 ml ampoule (2 mg/ml).

**Dose** 2 to 6 mg/day given in divided doses, initial dose of 2 to 3 mg/day given twice or thrice a day.

**Elderly or debilitated patients:** Initial dosage of 1 to 2 mg/day in divided doses.

**Contraindications** Severe hepatic impairment; respiratory depression; acute narrow angle glaucoma; pregnancy (Appendix 7c), lactation.

**Precautions** Hepatic dysfunction; impaired ability to drive or operate machinery; interactions (Appendix 6a).

**Adverse Effects** Nausea and vomiting, dizziness; weakness; blurred vision; vertigo.

## Nitrazepam

**Pregnancy Category-D**

**Schedule H**

**Indications** *Insomnia; epilepsy, vertigo, infantile spasm.*

**Availability** **CAPSULES/TABLETS** 2.5, 5 and 10 mg.

**Dose** **Oral**

**Insomnia-** 5 to 10 mg at bed time.

**Child**

**Infantile spasm-** 125 µg/kg twice daily, gradually increase to 250-500 µg/kg twice daily.

**Contraindications** Respiratory depression; marked neuromuscular respiratory weakness including unstable myasthenia gravis; acute pulmonary insufficiency; severe hepatic impairment; sleep apnoea syndrome; not for use alone to treat depression (or anxiety associated with depression) or chronic psychosis.

**Precautions** Muscle weakness and myasthenia gravis; history of drug or alcohol abuse; marked personality disorder; pregnancy (Appendix 7c), lactation; reduce dose in elderly and debilitated, and in hepatic impairment and renal impairment; avoid prolonged use (and abrupt withdrawal thereafter); porphyria; interactions (Appendix 6a); blood count, increased salivation.

Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

**Adverse Effects** Drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia may occur; dependence; aggression, anaphylaxis, dysarthria, blurred vision, slurred speech.

**Storage** Store protected from light and moisture.

## Zolpidem

**Pregnancy Category-C**

**Schedule H**

**Indications** *Short term management of insomnia.*

**Availability** **TABLETS** 5 and 10 mg, 6.25 and 12.5 mg **CR**, **CAPSULES** 5 and 10 mg.

**Dose** **Adult-** 10 mg immediately before bed time, maximum 10 mg/day, controlled release tablets 12.5 mg immediately before bed time.

**Elderly-** 5 mg before bed time.

**Contraindications** Severe hepatic insufficiency.

**Precautions** Myasthenia gravis; depressed patients; hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle; obstructive sleep apnoea, compromised respiratory function; pregnancy (Appendix 7c), lactation, interactions (Appendix 6a,6c).

**Adverse Effects** Abnormal thinking, behaviour changes, and complex behaviours, withdrawal effects, CNS-depressant effects, ataxia, confusion, diplopia, euphoria; hepatitis; anaphylactic reactions.

## 28.2 Antidepressants

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Tricyclic and related antidepressants and the more recently introduced selective serotonin reuptake inhibitors (SSRIs) are the most widely used drugs in the treatment of depressive disorders. The response to antidepressant therapy is usually delayed with a lag-period of up to two weeks and at least six weeks before max. improvement occurs. It is important to use doses that are sufficiently high for effective treatment, but not so high as to cause toxic effects. Low doses should be used for initial treatment in the elderly. The use of more than one antidepressant at a time is not recommended since this does not enhance effectiveness and it may result in enhanced adverse effects or interactions.

Patients should be reviewed every 1-2 weeks at the start of treatment. Treatment should be continued for at least 4 weeks (6 weeks in the elderly) before considering whether to change to another antidepressant due to lack of efficacy. In the case of a partial response, treatment may be continued for a further 2 weeks (elderly patients may take longer to respond). Remission usually occurs after 3-12 months. Treatment at full therapeutic dose should be continued for at least 4-6 months after resolution of symptoms (about 12 months in the elderly). Treatment should not be withdrawn prematurely otherwise symptoms are likely to recur. Patients with a history of recurrent depression should continue to receive maintenance treatment (for at least 5 years and possibly indefinitely). Lithium may be used as an alternative for maintenance treatment. Reduction in dose should be gradually carried out over a period of about 4 weeks or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

Tricyclic and related antidepressants can be divided into those with more or less sedative effect. Those with sedative properties include amitriptyline and those with less sedative effects include imipramine. These drugs are most effective in the treatment of depression associated with psychomotor and physiological disturbances. Adverse effects include anticholinergic (more correctly antimuscarinic) symptoms of dry mouth, blurred vision, constipation and urinary retention. Arrhythmias and heart block can occur. Minimal quantities of tricyclic antidepressants should be prescribed at any one time because they are dangerous in overdose.

The SSRIs characteristically cause gastrointestinal disturbances, sleep disturbances and hypersensitivity reactions including rash (may be a sign of an impending serious systemic reaction and discontinuation should be considered) but they are less sedating and have fewer anticholinergic (antimuscarinic) and cardiotoxic effects than tricyclic antidepressants. The SSRIs are less toxic in overdose than the older tricyclic

compounds. They may be preferred in patients in whom the risk of suicide is strong, but there is some concern that SSRIs may increase suicidal ideation.

## Amitriptyline\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *Moderate to severe depression, migraine prophylaxis; tension, headache, enuresis.*

**Availability** **TABLETS** 10, 25, 50 and 75 mg; **INJECTION** 10 ml ampoule (10 mg/ml).

**Dose** **Oral**

**Adult-** Initially 75 mg (adolescents 30 to 75 mg) daily in divided doses or as a single dose at bed time increased gradually as necessary to 150 to 200 mg daily. Prophylaxis of migraine: 10-75 mg at night.

**Child-** Under 16 years; not recommended.

**Contraindications** Recent myocardial infarction, arrhythmias (especially heart block); manic phase in bipolar disorders; severe liver disease; children; porphyria; glaucoma, prostatic hypertrophy.

**Precautions** Cardiac disease (see Contraindications above); history of epilepsy; lactation (Appendix 7b); elderly; hepatic impairment (Appendix 7a); thyroid disease; pheochromocytoma; history of mania, psychoses (may aggravate psychotic symptoms); angle-closure glaucoma; history of urinary retention; concurrent electroconvulsive therapy; avoid abrupt withdrawal; anaesthesia (increased risk of arrhythmias and hypotension); interactions (Appendix 6a, 6b, 6c); pregnancy (Appendix 7c); pre-existing haematological disorder, abrupt disorientation.

May impair ability to perform skilled tasks, for example operating machinery, driving.



### Adverse Effects

Sedation; dry mouth; blurred vision (disturbance of accommodation, increased intraocular pressure); constipation; nausea; difficulty in micturition; cardiovascular adverse effects particularly with high dosage including ECG changes, arrhythmias, postural hypotension, tachycardia, syncope; sweating, tremor, rash and hypersensitivity reactions (urticaria, photosensitivity); behavioural disturbances; hypomania or mania, confusion (particularly in elderly), interference with sexual function, blood sugar changes; increased appetite and weight gain (occasional weight loss); endocrine adverse effects such as testicular enlargement, gynaecomastia and galactorrhoea; convulsions, movement disorders and dyskinesias, fever, agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia, hyponatraemia (may be due to inappropriate antidiuretic hormone secretion); abnormal liver function test.

## Escitalopram

### Pregnancy Category-C

#### Indications

*Depression, obsessive compulsive disorder, anxiety disorder, panic disorder.*

#### Availability

**TABLETS** 5, 10 and 20 mg.

#### Dose

Initially 10 mg once daily. Maximum- 20 mg daily.

#### Contraindications

Concomitant use with MAO Inhibitors, thioridazine.

#### Precautions

History of panic disorder or seizure disorders, renal impairment, hepatic impairment, work requiring mental alertness, concomitant use of escitalopram with other SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs) or tryptophan, interactions (Appendix 6c), pregnancy (Appendix 7c).

#### Adverse Effects

Insomnia, nausea, ejaculation disorder.

## Fluoxetine\*

### Pregnancy Category-C

**Schedule H**

#### Indications

*Major depression (including pediatric depression); obsessive-compulsive disorder (in both adult and pediatric populations); bulimia nervosa; anorexia nervosa; panic disorder and premenstrual dysphoric disorder; depression illness, Parkinson's disease.*

#### Availability

**TABLETS** 10, 20, 40 and 60 mg; **CAPSULES** 10, 20 and 60 mg.

<b>Dose</b>	<b>Oral</b>  20 mg/day initially (max 60 mg).
<b>Contraindications</b>	Should not be used if the patient enters a manic phase; renal failure, hypersensitivity.
<b>Precautions</b>	Should be used with caution in patients with epilepsy (avoid if poorly controlled, discontinue if convulsions develop), cardiac disease, diabetes mellitus, susceptibility to angle-closure glaucoma, a history of mania or bleeding disorders (especially gastrointestinal bleeding), and if used with other drugs that increase the risk of bleeding, hepatic impairment (Appendix 7a), renal impairment, pregnancy (Appendix 7c), and lactation. They should also be used with caution in those receiving concurrent electroconvulsive therapy (prolonged seizures reported with fluoxetine). The risk of suicidal behaviour is possibly higher in young adults, calling for close monitoring of those receiving SSRIs. SSRIs may also impair performance of skilled tasks (e.g. driving), interactions (Appendix 6a, 6c).
<b>Adverse Effects</b>	Gastro-intestinal effects (dose-related and fairly common-include nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, constipation), anorexia with weight loss (increased appetite and weight gain also reported) and hypersensitivity reactions including rash (consider discontinuation-may be sign of impending serious systemic reaction, possibly associated with vasculitis), urticaria, angioedema, anaphylaxis, arthralgia, myalgia and photosensitivity; other side-effects include dry mouth, nervousness, anxiety, headache, insomnia, tremor, asthenia, hallucinations, drowsiness, convulsions, galactorrhoea, sexual dysfunction, urinary retention, sweating, hypomania or mania, movement disorders and dyskinesias, visual disturbances, hyponatraemia; serum sickness, elevation of liver enzymes.
<b>Storage</b>	Store protected from moisture.

## Imipramine\*

**Pregnancy Category-D**

**Schedule H**

<b>Indications</b>	<i>Panic attacks; chronic pain; nocturnal enuresis; Kleine-Levin syndrome; depression, hyperactivity, attention deficit disorder.</i>
<b>Availability</b>	<b>TABLETS</b> 5, 25 and 75 mg; <b>CAPSULES</b> 25 and 75 mg.
<b>Dose</b>	<b>Oral</b>

75 mg/day initially, usual dose 100 to 200 mg daily.

**Child-** <6 years: not recommended, 6-12 years: 25 mg at bed time, >12 years: 50 mg at bed time.

### Contraindications

Recent myocardial infarction, arrhythmias (particularly heart block), not indicated in manic phase, severe liver disease; epilepsy, mania, narrow angle glaucoma, hypersensitivity.

### Precautions

Cardiac disease (particularly with arrhythmias), history of epilepsy, pregnancy (Appendix 7c), lactation, elderly, hepatic impairment, interactions (Appendix 6a), thyroid disease, pheochromocytoma, history of mania, psychoses (may aggravate psychotic symptoms), susceptibility to angle-closure glaucoma, history of urinary retention, concurrent electroconvulsive therapy; if possible avoid abrupt withdrawal; anaesthesia (increased risk of arrhythmias and hypotension), see surgery; porphyria; for additional nocturnal enuresis warnings; acetylsalicylic acid hypersensitivity.

Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

### Adverse Effects

Dry mouth, sedation, blurred vision (disturbance of accommodation, increased intraocular pressure), constipation, nausea, difficulty with micturition; cardiovascular side-effects (such as ECG changes, arrhythmias, postural hypotension, tachycardia, syncope, particularly with high doses); sweating, tremor, rashes and hypersensitivity reactions (including urticaria, photosensitivity), behavioural disturbances (particularly children), hypomania or mania, confusion or delirium (particularly elderly), headache, interference with sexual function, blood sugar changes; increased appetite and weight gain (occasionally weight loss); endocrine side-effects such as testicular enlargement, gynaecomastia, galactorrhoea; also convulsions, movement disorders and dyskinesias, dysarthria, paraesthesia, taste disturbances, tinnitus, fever, agranulocytosis, leucopenia, eosinophilia, purpura, thrombocytopenia, hyponatraemia (see Hyponatraemia and Antidepressant Therapy), abnormal liver function tests (jaundice); impairment of memory, cutaneous vasculitis.

### Storage

Store protected from light.

## 28.3 Antipsychotics

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Treatment of psychotic disorders is both pharmacological and psychosocial. Individual and community programmes for relearning old skills and developing new ones and for learning to cope with the illness should be initiated. Classes of antipsychotic drugs include phenothiazines (for example chlorpromazine), butyrophenones (for example haloperidol), thioxanthenes (for example flupentixol) and newer 'atypical' neuroleptics including clozapine and risperidone. The various antipsychotic drugs do not, in general, differ in their antipsychotic activity, but differ in range and quality of adverse effects (see below).

### Acute Phase Treatment:

The administration of chlorpromazine or haloperidol will relieve symptoms such as thought disorder, hallucinations and delusions and prevent relapse. They are usually less effective in apathetic, withdrawn patients. However, haloperidol may restore an acutely ill schizophrenic, who was previously withdrawn, or even mute and akinetic, to normal activity and social behaviour. In the acute phase chlorpromazine may be administered by intramuscular injection in a dose of 25-50 mg which can be repeated every 6-8 h while observing the patient for possible hypotension. In most cases, however, the intramuscular injection is not needed and patients can be treated with an oral dose. Haloperidol may be administered in the acute phase.

### Maintenance Therapy:

Long-term treatment in patients with a definite diagnosis of schizophrenia may be necessary after the first episode to prevent the manifest illness from becoming chronic.

The lowest possible dose of antipsychotic drug that will prevent major exacerbations of florid symptoms is used for long-term management. Too rapid a dose reduction should be avoided. Intramuscular depot preparations such as fluphenazine may be used as an alternative to oral maintenance therapy especially when compliance with oral treatment is unreliable. Exacerbations of illness in patients on maintenance drug therapy can be precipitated by stress.

Withdrawal of maintenance drug treatment requires careful surveillance since it is not possible to predict the course of the disease and the patient may suffer a relapse if treatment is withdrawn inappropriately. Further, the need for continuation of treatment may not be evident on withdrawal of treatment because relapse may be delayed for several weeks.

## Adverse Effects

They are very common with long-term administration of antipsychotic drugs. Hypotension and interference with temperature regulation, neuroleptic malignant syndrome and bone-marrow depression are the most life-threatening. Hypotension and interference with temperature regulation are dose-related. They can result in dangerous falls and hypothermia in the elderly and this must be considered before prescribing these drugs for patients over 70 years of age.

Extrapyramidal symptoms are the most troublesome and are caused most frequently by the piperazine phenothiazines such as fluphenazine, the butyrophenones such as haloperidol and the depot preparations. Although easily recognized, they are not so easy to predict because they depend in part on the dose and patient susceptibility as well as the type of drug. However, there is a general tendency for low-potency drugs to have less extrapyramidal adverse effects, while high-potency drugs such as haloperidol have more extrapyramidal effects but less sedation and anticholinergic (more correctly antimuscarinic) effects. Sedation and anticholinergic effects usually diminish with continued use. Extrapyramidal symptoms consist of parkinsonian-type symptoms including tremor which may occur gradually; dystonia (abnormal face and body movements) and dyskinesia, which may appear after only a few doses; akathisia (restlessness), which may occur after large initial doses and may resemble an exacerbation of the condition being treated; and tardive dyskinesia (an orofacial dyskinesia), which usually takes longer to develop but may develop on short-term treatment with low doses; short-lived tardive dyskinesia may occur after withdrawal of the drug. Parkinsonian symptoms are usually reversible on withdrawal of the drug and may be suppressed by anticholinergic (antimuscarinic) drugs but they may unmask or worsen tardive dyskinesia. Tardive dyskinesia is usually associated with long-term treatment and high dosage of an antipsychotic, particularly in elderly patients. There is no established treatment for tardive dyskinesias, which may be irreversible on withdrawing therapy. However, withdrawal at the earliest signs of tardive dyskinesia may halt its full development. Treatment of all patients on antipsychotics must be carefully and regularly reviewed.

Neuroleptic malignant syndrome (hypothermia, fluctuating levels of consciousness, muscular rigidity, and autonomic dysfunction with pallor, tachycardia, labile blood pressure, sweating and urinary incontinence) is a rare adverse effect of haloperidol and chlorpromazine. It is managed by discontinuing the antipsychotic, correcting fluid and electrolyte defects, and giving bromocriptine and sometimes dantrolene.

## Chlorpromazine\*

Pregnancy Category-C

Schedule H

**Indications** *Schizophrenia and other psychotic disorders, mania, psychomotor agitation and violent behaviour; adjunct in severe anxiety; psychosis, mania, hiccups.*

**Availability** **TABLETS** 25, 50 and 100 mg; **SYRUP** 60 ml (25 mg/5 ml); **INJECTION** 2 ml ampoule (25 mg/ml).

**Dose** **Oral**

**Adult-** Schizophrenia and other psychoses, mania, psychomotor agitation, violent behaviour and severe anxiety (adjunct): initially 25 mg 3 times daily (or 75 mg at night) adjusted to response to usual maintenance dose of 100-300 mg daily (but up to 1.2g daily may be required in psychosis).

**Elderly or debilitated-** Schizophrenia and other psychoses, mania, psychomotor agitation, violent behaviour and severe anxiety (adjunct): one-third to one-half adult dose.

**Child-** Schizophrenia and other psychoses, mania, psychomotor agitation, violent behaviour and severe anxiety (adjunct); (for childhood schizophrenia and autism) 1 to 5 years: 500 µg/kg every 4-6 h (max. 40 mg daily). 6 to 12 years: one-third to one-half adult dose (max. 75 mg daily).

### **Deep intramuscular injection**

**Adult-** Relief of acute symptoms: 25 to 50 mg every 6 to 8 h.

**Child-** Relief of acute symptoms: 500 µg/kg every 6 to 8 h (1 to 5 years: max. 40 mg daily. 6 to 12 years: max. 75 mg daily).

**Contraindications** Impaired consciousness due to CNS depression; bone-marrow depression; pheochromocytoma; epilepsy, narrow angle glaucoma, Parkinson's disease; depressed level of consciousness.

### Precautions

Cardiovascular and cerebrovascular disorders, respiratory disease, parkinsonism, epilepsy, acute infections, pregnancy (Appendix 7c), lactation (Appendix 7b), renal and hepatic impairment (avoid if severe; Appendices 7a), history of jaundice, leukopenia (blood counts if unexplained fever or infection); hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma; elderly (particularly in very hot or very cold weather); avoid abrupt withdrawal; patients should remain supine and the blood pressure monitored for 30 min after intramuscular injection; interactions (Appendix 6a, 6c); extreme heat, alcohol withdrawal, peptic ulcer.

May impair ability to perform skilled tasks, for example operating machinery, driving.

### Adverse Effects

Extrapyramidal symptoms and on prolonged administration, occasionally potentially irreversible tardive dyskinesias (see notes above); hypothermia (occasionally pyrexia), drowsiness, apathy, pallor, nightmares, dizziness, excitement, insomnia, headache, confusion, depression; more rarely, agitation; EEG changes; convulsions; nasal congestion; anticholinergic symptoms including dry mouth, constipation; blurred vision, difficulty in micturition; hypotension, tachycardia and arrhythmias; ECG changes; respiratory depression; menstrual disturbances, galactorrhoea, gynaecomastia, impotence, weight gain; sensitivity reactions such as agranulocytosis, leukopenia, leukocytosis, haemolytic anaemia, photosensitization, contact sensitization and rashes, jaundice and alterations in liver function; neuroleptic malignant syndrome; lupus erythematosus-like syndrome; with prolonged high dosage, corneal and lens opacities, and purplish pigmentation of the skin, cornea and retina; intramuscular injection may be painful and cause hypotension and tachycardia (see Precautions) and nodule formation; seizures, temperature disorder, hyperprolactinemia, ocular complication.

### Storage

Store protected from light.

## Fluphenazine

Pregnancy Category-C

**Schedule H**

### Indications

*Maintenance treatment of schizophrenia and other psychoses; mania, postoperative nausea.*

### Availability

**TABLET** 1 mg; **INJECTION** 1 ml ampoule (25 mg/ml).

## Dose

**Deep intramuscular injection into gluteal muscle.**

**Adult-** Maintenance in schizophrenia and other psychoses: test dose of 12.5 mg, then after 4 to 7 days, 12.5 to 100 mg repeated at intervals of 2 to 5 weeks, adjusted according to the response.

**Elderly-** Maintenance in schizophrenia and other psychoses: test dose of 6.25 mg, then after 4 to 7 days, 12.5 to 100 mg repeated at intervals of 2 to 5 weeks, adjusted according to the response.

**Child-** Maintenance in schizophrenia and other psychoses: not recommended.

## Contraindications

Children; confusional states; impaired consciousness due to CNS depression; parkinsonism; intolerance to antipsychotics; depression; bone-marrow depression; pheochromocytoma; blood dyscrasias, coma, brain damage.

## Precautions

Treatment requires careful monitoring for optimum effect; initial small test dose as adverse effects are prolonged; extrapyramidal symptoms occur frequently; when transferring from oral to depot therapy, dosage by mouth should be reduced gradually; cardiovascular and cerebrovascular disorders; respiratory disease, epilepsy; acute infections; pregnancy (Appendix 7c), lactation (Appendix 7b); renal and hepatic impairment (avoid if severe; Appendices 7a), history of jaundice; leukopenia (blood counts if unexplained fever or infection); hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma; elderly (particularly in very hot or very cold weather); interactions (Appendix 6a, 6c); alcohol withdrawal, extreme heat.

May impair ability to perform skilled tasks, for example operating machinery, driving.

## Adverse Effects

As for Chlorpromazine (see above), but less sedating and fewer hypotensive and anticholinergic symptoms; higher incidence of extrapyramidal symptoms (most likely to occur a few hours after injection and continue for about 2 days but may be delayed); systemic lupus erythematosus; pain at injection site, occasionally erythema, swelling, nodules; tardive dyskinesia, neurological disturbances, blood dyscrasias.

## Storage

Store protected from light.



## Haloperidol\*

Pregnancy Category-C

Schedule H

### Indications

*Schizophrenia and other psychotic disorders, mania, psychomotor agitation and violent behaviour; adjunct in severe anxiety; agitation, psychosis, neuroleptanalgesia.*

### Availability

**TABLETS** 1.5, 5, 10 and 20 mg; **LIQUID** 30 ml (25 mg/ml); **INJECTION** 5 ml ampoule (5 mg/ml).

### Dose

#### **Oral**

**Adult**-Schizophrenia and other psychoses, mania, psychomotor agitation and violent behaviour and severe anxiety (adjuvant): initially 1.5 to 3 mg 2 to 3 times daily or 3 to 5 mg 2 to 3 times daily in severely affected or resistant patients (up to 30 mg daily in resistant schizophrenia).

**Elderly or debilitated**-Schizophrenia and other psychoses, mania, psychomotor agitation and violent behaviour and severe anxiety (adjuvant): initially half adult dose.

**Child**-Schizophrenia and other psychoses, mania, psychomotor agitation and violent behaviour and severe anxiety (adjuvant): initially 25 to 50 µg/kg daily in 2 divided doses (max. 10 mg daily).

#### **Intramuscular injection**

**Adult**- Acute psychotic conditions: initially 2 to 10 mg, subsequent doses every 4 to 8 h according to response (up to every h if necessary) to max. of 18 mg; severely disturbed patients may require initial dose of up to 18 mg.

**Elderly or debilitated**- Acute psychotic conditions: initially half adult dose.

**Child**- Acute psychotic conditions: not recommended.

### Contraindications

Impaired consciousness due to CNS depression; bone-marrow depression; pheochromocytoma; porphyria; basal ganglia disease; parkinsonism, thyrotoxicosis, cardiac arrhythmia, depression, close angle glaucoma.

### Precautions

Cardiovascular and cerebrovascular disorders; respiratory disease; parkinsonism; epilepsy; acute infections; pregnancy (Appendix 7c), lactation (Appendix 7b); renal and hepatic impairment (avoid if severe; Appendices 7a), history of jaundice; leukopenia (blood count required if unexplained fever or infection); hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma; also subarachnoid haemorrhage and metabolic disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia; elderly (particularly in very hot or very cold weather); children and adolescents; avoid abrupt withdrawal; patients should remain supine and the blood pressure monitored for 30 min after intramuscular injection; interactions (Appendix 6a, 6c); photosensitisation, peptic ulcers.

May impair ability to perform skilled tasks, for example operating machinery, driving.

### Adverse Effects

As for Chlorpromazine (see above), but less sedating and fewer hypotensive and anticholinergic symptoms; pigmentation and photosensitivity reactions rare; extrapyramidal symptoms are common, particularly acute dystonia and akathisia (especially in thyrotoxic patients); rarely, weight loss, hypoglycaemia, inappropriate antidiuretic hormone secretion.

### Storage

Store protected from light.

## Olanzapine\*

### Pregnancy Category-C

**Schedule H**

### Indications

*Schizophrenia, acute mania episodes in bipolar disorder.*

### Availability

**TABLETS** 2.5, 5, 7.5, 10, 15 and 20 mg.

### Dose

Schizophrenia: initial 5-10 mg, usual dose is 10-20 mg. Acute maniac episodes in bipolar illness: 10-15 mg/day.

### Precautions

Impaired renal, hepatic and cardiovascular function; prostatic hypertrophy; paralytic ileus; parkinsonism; blood dyscrasias; myelosuppression; seizures; dementia; pregnancy (Appendix 7c).

### Adverse effects

Postural hypotension, dizziness, constipation, weight gain, agitation, insomnia, akathisia, tremors, personality disorder, oedema, increases appetite, antimuscarinic effects, hallucination, bradycardia.

## Trifluoperazine

Pregnancy Category-C

Schedule H

**Indications** *Schizophrenia, non-psychotic anxiety, acute psychosis.*

**Availability** **TABLETS** 1, 2, 5 and 10 mg;  
**INJECTION** 10 ml ampoule (10 mg/10 ml), 5 ml ampoule (2 mg/ml).

**Dose** **Oral**

**Schizophrenia and Psychosis:**

**Adult and child over 12 years-** Initially 5 mg twice daily, increase by 5 mg daily to 15-20 mg daily after 1 week and then at intervals of 3 days, according to response.

**Elderly-** reduce initial dose by at least half.

**Anxiety management:**

**Adult-** 1-2 mg twice daily. Max.- 6 mg daily.

**Child-** 3 to 5 years, Max.- 1 mg daily in divided dose.

**Child-** 6 to 12 years, Max.- 4 mg daily.

**Elderly-** reduce initial dose by at least half.

**Antiemetic:** 2–4 mg daily in divided doses or as a single dose of a modified-release preparation; max. 6 mg daily.

**Child-** 3–5 years up to 1 mg daily, 6–12 years up to 4 mg daily.

**Parenteral**

**Psychosis:**

**Adult-** 1-2 mg by deep i.m injection, repeat every 4-6 h, if necessary.

**Child-** 1 mg by deep i.m injection, once or twice daily.

**Contraindications** Hypersensitivity to phenothiazines; bone marrow depression; blood dyscrasias; pre-existing CNS depression and coma; pheochromocytoma.

**Precautions** Myasthenia gravis; renal and hepatic impairment; benign prostatic hyperplasia; glaucoma; epilepsy; exposure to extreme heat or phosphorous insecticides; peptic ulcer, Parkinson's disease, interactions (Appendix 6a), pregnancy (Appendix 7c).

**Adverse effects**

Extrapyramidal symptoms particularly in children, elderly and debilitated patients more frequently at doses exceeding 6 mg daily; pancytopenia, thrombocytopenia; hyperpyrexia; dizziness, anorexia; insomnia; dry mouth; blurred vision; postural hypotension.

**Storage**

Injection: Store protected from light. Tablets: Store protected from light and moisture.

## 28.4 Drugs for Bipolar Disorders

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Treatment of bipolar disorders has to take account of three stages: treatment of the acute episode, continuation phase and prophylaxis to prevent further episodes. Lithium is effective in acute mania but symptomatic control of the florid symptoms with an antipsychotic or benzodiazepine is often necessary whilst waiting for the antimania drug to exert its effect. Benzodiazepines may be given during the initial stages until lithium becomes effective but they should not be used for long periods because of the risk of dependence. Lithium may be given concurrently with antipsychotics and treatment with the antipsychotic should be tailed off as lithium becomes effective. Alternatively, lithium therapy may be delayed until the patient's mood is stabilized with the antipsychotic. However, there is a risk of neurotoxicity and increased extrapyramidal disorders when lithium and antipsychotics are used concurrently (Appendix 6c). Lithium is the mainstay of treatment but its narrow therapeutic range is a disadvantage. Sodium valproate is effective and carbamazepine may also be used.

Treatment of depressive episodes in bipolar disorders will mostly involve combination treatment using either lithium or Sodium valproate together with a tricyclic antidepressant. Increased adverse effects are a problem which may compromise treatment.

Lithium prophylaxis should usually only be undertaken with specialist advice and the likelihood of recurrence considered. Long-term lithium therapy has been associated with thyroid disorders and mild cognitive and memory impairment. Patients should continue the treatment for longer than 3 to 5 years only if benefit persists.

Withdrawal appears to produce high levels of relapse. If lithium is to be discontinued, the dose should be reduced gradually over a few weeks and patients should be warned of possible relapses if discontinued abruptly.

Lithium salts have a narrow therapeutic/toxic ratio and should only be prescribed if there are facilities for monitoring serum lithium concentrations. Doses are adjusted to achieve serum-lithium concentrations of 0.4-1 mmol/litre (lower end of range for maintenance therapy and the elderly) on samples taken 12 h after the preceding dose. The optimum range for each patient should be determined.

Overdosage, usually with serum-lithium concentration of over 1.5 mmol/litre may be fatal and toxic effects include coarse tremor, ataxia, dysarthria, nystagmus, renal impairment and convulsions. If any of these effects occur, treatment should be stopped, serum-lithium concentration determined and in mild overdosage large amounts of sodium and fluid should be given to reverse the toxicity; in severe toxicity, haemodialysis may be required.

For patients who are unresponsive to or intolerant of lithium, carbamazepine may be used in the prophylaxis of bipolar illness particularly in those with rapid cycling affective disorders (more than four affective episodes per year).

## Carbamazepine\* (Refer Page No. 55)

### Pregnancy Category-D

**Schedule H**

**Indications** *Prophylaxis of bipolar disorder unresponsive to or intolerant of lithium; epilepsy, trigeminal neuralgia.*

**Availability** **TABLETS** 100, 200 and 400 mg Plain; 100 mg (DT) **SYRUP** 100 mg/5 ml.

**Dose** **Oral**

**Adult-** Initially 400 mg daily in divided doses increased until symptoms are controlled to a max. of 1.6g daily: usual maintenance range 400 to 600 mg daily.

Trigeminal neuralgia: initially 100 mg twice daily, maintenance dose is 400-800 mg/day.

**Contraindications** Atrioventricular conduction abnormalities; history of bone-marrow depression; porphyria.

**Precautions** Hepatic impairment (Appendix 7a); renal impairment; cardiac disease (see also Contraindications); skin reactions (see Adverse effects); history of blood disorders (blood counts before and during treatment); glaucoma; (neural tube screening); lactation (Appendix 7b); avoid sudden withdrawal; interactions (Appendix 6b, 6c, 6d); pregnancy (Appendix 7c); patients on anticoagulants.

Patients or their caretakers should be told how to recognize signs of blood, liver or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising or bleeding develop. Leukopenia which is severe, progressive and associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative).

May impair ability to perform skilled tasks, for example operating machinery, driving.

### Adverse Effects

Dizziness; drowsiness; headache; ataxia; blurred vision; diplopia (may be associated with high plasma concentrations); gastrointestinal intolerance including nausea and vomiting, anorexia, abdominal pain, dry mouth, diarrhoea or constipation; commonly, mild transient generalized erythematous rash (withdraw if worsens or is accompanied by other symptoms); leukopenia and other blood disorders (including thrombocytopenia, agranulocytosis and aplastic anaemia); cholestatic jaundice, hepatitis, acute renal failure, Stevens-Johnson syndrome (erythema multiforme), toxic epidermal necrolysis, alopecia, thromboembolism, arthralgia, fever, proteinuria, lymph node enlargement, arrhythmias, heart block and heart failure, dyskinesias, paraesthesia, depression, impotence, male infertility, gynaecomastia, galactorrhoea, aggression, activation of psychosis, photosensitivity, pulmonary hypersensitivity, hyponatraemia, oedema, disturbances of bone metabolism with osteomalacia also reported; confusion and agitation in elderly; exfoliative dermatitis, ankle swelling.

## Lithium Carbonate\*

Pregnancy Category-D

**Schedule H**

### Indications

*Treatment and prophylaxis of mania, prophylaxis of bipolar disorder and recurrent depression; ADH secretion syndrome, psychosis.*

### Availability

**TABLETS** 150, 200, 300 and 400 mg;  
**CAPSULES** 150 and 300 mg.

### Dose

#### **Oral**

**Adult**-Treatment of mania: initially 0.6 to 1.8g daily.

Prophylaxis of mania, bipolar disorder and recurrent depression: initially 0.6 to 1.2g daily.

**Elderly**-Treatment of mania: initially 300 to 900 mg daily.

Prophylaxis of mania, bipolar disorder and recurrent depression: initially 300 to 900 mg daily.

### Contraindications

Renal impairment; cardiac insufficiency; conditions with sodium imbalance such as Addison's disease; fetal goiter; heart failure; psoriasis; kidney infection; hypothyroidism.

## Precautions

Measure serum-lithium concentration about 4 days after starting treatment, then weekly until stabilized, then at least every 3 months; monitor thyroid function every 6-12 months on stabilized regimens-risk of hypothyroidism (see below); monitor renal function; maintain adequate fluid and sodium intake; reduce dose or discontinue in diarrhoea, vomiting and intercurrent infection (especially if associated with profuse sweating); lactation (Appendix 7b); pregnancy (Appendix 7c); elderly (reduce dose); diuretic treatment, myasthenia gravis; surgery; if possible, avoid abrupt withdrawal (see notes above); interactions (Appendix 6c, 6d); kidney, thyroid and heart function test, children and adolescents.

Patients should maintain adequate fluid intake and should avoid dietary changes which may reduce or increase sodium intake. Patients should be advised to seek medical attention if symptoms of hypothyroidism (for example, feeling cold, lethargy) develop (women are at greater risk).

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*Note: Different preparations vary widely in bioavailability; a change in the preparation used requires the same precautions as initiation of treatment.*

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## Adverse Effects

Gastrointestinal disturbances; fine tremor, renal impairment (particularly impaired urinary concentration and polyuria); polydipsia, weight gain and oedema (may respond to dose reduction); hyperparathyroidism and hypercalcaemia reported; signs of intoxication include blurred vision; muscle weakness, increasing gastrointestinal disturbances (anorexia, vomiting, diarrhoea); increased CNS disturbances (mild drowsiness and sluggishness, increasing to giddiness with ataxia, coarse tremor, lack of co-ordination, dysarthria) and require withdrawal of treatment; with severe overdosage (serum concentrations above 2 mmol/litre), hyperreflexia and hyperextension of the limbs; convulsions; toxic psychoses; syncope; renal failure; circulatory failure; coma; occasionally death; goitre, raised antidiuretic hormone concentration, hypothyroidism, hypokalaemia, ECG changes, exacerbation of psoriasis and kidney changes may occur; sinus bradycardia, leukocytosis, glycosuria, weight gain.

## Storage

Store protected from moisture.



## 28.5 Drugs Used for Obsessive Compulsive Disorders and Panic Attacks

Obsessive-compulsive disorders can be treated with a combination of pharmacological, behavioural and psychological treatments. Antidepressants such as clomipramine which inhibit reuptake of serotonin have been found to be effective. Panic attacks may be treated with behavioural or cognitive therapy. If this management fails, drug therapy may be tried. Some tricyclic antidepressants including clomipramine or SSRIs can reduce frequency of attacks or prevent them completely. Benzodiazepines may be used in panic attacks resistant to antidepressants.

### Clomipramine

Pregnancy Category-C

Schedule H

<b>Indications</b>	<i>Phobic and obsessional states; panic attacks; blocking replacement, cataplexy, chronic diarrhoea.</i>
<b>Availability</b>	<b>TABLETS</b> 10, 25, 50 and 75 mg; <b>CAPSULES</b> 10 and 25 mg.
<b>Dose</b>	<p><b>Oral</b></p> <p><b>Adult</b>-Initially 25 mg daily, usually at bedtime increased over 2 weeks to 100 to 150 mg daily.</p> <p><b>Elderly</b>- Initially 10 mg daily, usually at bedtime increased over 2 weeks to 100 to 150 mg daily.</p> <p><b>Child</b>- Not usually recommended.</p>
<b>Contraindications</b>	Recent myocardial infarction, arrhythmias (especially heart block); manic phase in bipolar disorders; severe liver disease; children; porphyria; narrow angle glaucoma, urinary retention.
<b>Precautions</b>	Cardiac disease (see Contraindications above), history of epilepsy; lactation (Appendix 7b); pregnancy (Appendix 7c); elderly; hepatic impairment (Appendix 7a); thyroid disease; pheochromocytoma; history of mania, psychoses (may aggravate psychotic symptoms); angle-closure glaucoma, history of urinary retention; concurrent electroconvulsive therapy; avoid abrupt withdrawal; anaesthesia (increased risk of arrhythmias and hypotension); interactions (Appendix 6a, 6b); decreased urine output, breathing problem.

May impair ability to perform skilled tasks, for example operating machinery, driving.

#### Adverse Effects

Sedation; dry mouth; blurred vision (disturbance of accommodation, increased intra-ocular pressure); constipation; nausea; difficulty in micturition; cardiovascular adverse effects particularly with high dosage including ECG changes, arrhythmias, postural hypotension, tachycardia, syncope; sweating, tremor, rash and hypersensitivity reactions (urticaria, photosensitivity); behavioural disturbances; hypomania or mania, confusion (particularly in elderly), interference with sexual function, blood sugar changes; increased appetite and weight gain (occasional weight loss); endocrine adverse effects such as testicular enlargement, gynaecomastia and galactorrhoea; convulsions, movement disorders and dyskinesias, fever, agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia, hyponatraemia (may be due to inappropriate antidiuretic hormone secretion); abnormal liver function test; extrapyramidal syndrome, bone marrow depression, hypertension, stroke.

#### Storage

Store protected from light and moisture.

#### Fluoxetine\* (Refer Page No. 572)

## 28.6 Drugs Used in Substance Dependence Programme

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### Methadone

Pregnancy Category-C

**Schedule H**

<b>Indications</b>	<i>Adjunct in treatment of opioid dependence.</i>
<b>Availability</b>	<b>TABLETS</b> 5, 10, 20 and 40 mg; <b>SYRUP</b> 5 mg/ml.
<b>Dose</b>	<b>Oral</b>  20-30 mg initially followed by increase of 5 to 10 mg until a dose of 60 to 100 mg/day is achieved.
<b>Contraindications</b>	Avoid in acute respiratory depression, acute alcoholism and where risk of paralytic ileus; also avoid in raised intracranial pressure or head injury (affects pupillary responses vital for neurological assessment); avoid injection in pheochromocytoma (risk of pressor response to histamine release).
<b>Precautions</b>	Hypotension, hypothyroidism, asthma (avoid during attack) and decreased respiratory reserve, prostatic hypertrophy; pregnancy (Appendix 7c), lactation; may precipitate coma in hepatic impairment (Appendix 7a) (reduce dose or avoid but many such patients tolerate morphine well); reduce dose or avoid in renal impairment, elderly and debilitated (reduce dose); convulsive disorders, dependence (severe withdrawal symptoms if withdrawn abruptly); use of cough suppressants containing opioid analgesics not generally recommended in children and should be avoided altogether in those under at least 1 year; interactions (Appendix 6a, 6c, 6d); CNS depression, ulcerative colitis, gastrointestinal surgery, bradyarrhythmia, pulmonary diseases.

### Adverse Effects

Nausea and vomiting (particularly in initial stages), constipation and drowsiness; larger doses produce respiratory depression; hypotension, and muscle rigidity; other side-effects include difficulty with micturition, ureteric or biliary spasm, dry mouth, sweating, headache, facial flushing, vertigo, bradycardia, tachycardia, palpitation, postural hypotension, hypothermia, hallucinations, dysphoria, mood changes, dependence, miosis, decreased *libido* or potency, rashes, urticaria and pruritus; seizures, exacerbation of asthma, itching, pulmonary oedema.

### Storage

Store protected from light and moisture.

## **29. Solutions Correcting Water, Electrolyte and Acid Base Disturbances 593**

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# 29. Solutions Correcting Water, Electrolyte and Acid Base Disturbances

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## 29.1 Oral

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### Oral Rehydration Salts\*

(Refer Page No. 78)

## 29.2 Parenteral

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Solutions of electrolytes are given intravenously, to meet normal fluid and electrolyte requirements or to replenish substantial deficits or continuing losses, when the patient is nauseating or vomiting and is unable to take adequate amounts by mouth.

The nature and severity of the electrolyte imbalance must be assessed from the history and clinical and biochemical examination of each individual. Sodium, potassium, chloride, magnesium, phosphate, and water depletion can occur singly and in combination with or without disturbances of acid-base balance.

Isotonic solutions may be infused safely into a peripheral vein. More concentrated solutions, for example 20% glucose, are best given through an indwelling catheter positioned in a large vein.

Sodium chloride in isotonic solution provides the most important extracellular ions in near physiological concentrations and is indicated in sodium depletion which may arise from conditions such as gastroenteritis, diabetic ketoacidosis, ileus and ascites. In a severe deficit of from 4 to 8 litres, 2 to 3 litres of isotonic sodium chloride may be given over 2 to 3 h; thereafter infusion can usually be at a slower rate.

Excessive administration should be avoided; the jugular venous pressure should be assessed; the bases of the lungs should be examined for crepitations, and in elderly or seriously ill patients it is often helpful to monitor the right atrial (central) venous pressure.

Chronic hyponatraemia should ideally be managed by fluid restriction. However, if sodium chloride is required, the deficit should be corrected slowly to avoid risk of osmotic demyeli-

nation syndrome; the rise in plasma-sodium concentration should be limited to no more than 10 mmol/litre in 24 h.

The more physiologically appropriate compound solution of sodium lactate can be used instead of isotonic sodium chloride solution during surgery or in the initial management of the injured or wounded.

Sodium chloride and glucose solutions are indicated when there is combined water and sodium depletion. A 1:1 mixture of isotonic sodium chloride and 5% glucose allows some of the water (free of sodium) to enter body cells which suffer most from dehydration while the sodium salt with a volume of water determined by the normal plasma  $\text{Na}^+$  remains extracellular. Combined sodium, potassium, chloride, and water depletion may occur, for example, with severe diarrhoea or persistent vomiting; replacement is carried out with sodium chloride intravenous infusion 0.9% and glucose intravenous infusion 5% with potassium as appropriate.

Glucose solutions (5%) are mainly used to replace water deficits and should be given alone when there is no significant loss of electrolytes. Average water requirement in a healthy adult are 1.5 to 2.5 litres daily and this is needed to balance unavoidable losses of water through the skin and lungs and to provide sufficient for urinary excretion. Water depletion (dehydration) tends to occur when these losses are not matched by a comparable intake, as for example may occur in coma or dysphagia or in the aged or apathetic who may not drink water in sufficient amount on their own initiative.

Excessive loss of water without loss of electrolytes 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 replace deficits varies with the severity of the disorder, but usually lies within the range of 2 to 6 litres.

Glucose solutions are also given in regimens with calcium, bicarbonate, and insulin for the emergency treatment of hyperkalaemia. They are also given, after correction of hyperglycaemia, during treatment of diabetic ketoacidosis, when they must be accompanied by continuing insulin infusion.

If glucose or sugar cannot be given orally to treat hypoglycaemia, glucose 50% may be given intravenously into a large vein through a large-gauge needle; this concentration is very irritant on extravasation and it is also viscous and difficult to administer. Larger volumes of less concentrated glucose solutions (10% or 20%) can be used as alternatives and are less irritant.

Sodium hydrogen carbonate (sodium bicarbonate) is used to control severe metabolic acidosis (as in renal failure). Since this condition is usually attended by sodium depletion, it is reasonable to correct this first by the administration of isotonic sodium chloride intravenous infusion, provided the kidneys are not primarily affected and the degree of acidosis is not so severe as to impair renal function. In these circumstances, isotonic sodium chloride alone is usually effective as it restores the ability of the kidneys to generate bicarbonate. In renal acidosis or in severe metabolic acidosis of any origin, for example blood pH < 7.1, sodium hydrogen carbonate (1.4%) may be infused with isotonic sodium chloride when the acidosis remains unresponsive to correction of anoxia or fluid depletion; a total volume of up to 6 litres (4 litres of sodium chloride and 2 litres of sodium hydrogen carbonate) may be necessary in the adult. In severe shock due for example to cardiac arrest, metabolic acidosis may develop without sodium depletion; in these circumstances sodium hydrogen carbonate is best given in a small volume of hypertonic solution (for example 50 ml of 8.4% solution intravenously); plasma pH should be monitored. Sodium hydrogen carbonate is also used in the emergency management of hyperkalaemia.

Intravenous potassium chloride in sodium chloride infusion is the initial treatment for the correction of severe hypokalaemia when sufficient potassium cannot be taken by mouth. Potassium chloride concentrate may be added to sodium chloride 0.9% infusion, thoroughly mixed and given slowly over 2 to 3 h with specialist advice and ECG monitoring in difficult cases. Repeated measurements of plasma potassium are necessary to determine whether further infusions are required and to avoid the development of hyperkalaemia which is especially likely to occur in renal impairment.

Initial potassium replacement therapy should not involve glucose infusions because glucose may cause a further decrease in the plasma-potassium concentration.

## Glucose\*

### Indications

*Fluid replacement without significant electrolyte deficit; treatment of hypoglycaemia; varicose veins.*

### Availability

**INJECTION** Infusion 250 ml, 500 ml and 1L (5% w/v); i.v.solution 10 and 20 ml (5% w/v).

### Dose

***Intravenous infusion***

Fluid replacement



**Adult and Child-** Determined on the basis of clinical and wherever possible, electrolyte monitoring.

Treatment of hypoglycaemia

Infusion of 50% glucose solution into a large vein.

**Adult-**25 ml.

<b>Contraindications</b>	Anuria; thiamine deficiency; trauma; intracranial haemorrhage; haemodilution; acute ischaemic shock; hypophosphatemia; sepsis.
<b>Precautions</b>	Diabetes mellitus (may require additional insulin); mannitol fluid balance.
<b>Adverse Effects</b>	Glucose injections, especially if hypertonic, may have a low pH and cause venous irritation and thrombophlebitis; fluid and electrolyte disturbances; oedema or water intoxication (on prolonged administration or rapid infusion of large volumes of isotonic solutions); hyperglycaemia (on prolonged administration of hypertonic solutions); anaphylactoid reaction.
<b>Storage</b>	Store in a single dose container at a temperature not exceeding 30°C.

## Glucose + Sodium Chloride\*

<b>Indications</b>	<i>Fluid and extracellular volume depletion with excess diuresis; gastroenteritis.</i>
<b>Availability</b>	<b>INJECTION</b> 250, 450, 500 ml and 1 L. (Dextrose 5% and sodium chloride 0.9%).
<b>Dose</b>	<b>Intravenous infusion</b>  <b>Adult and Child-</b> Fluid replacement: determined on the basis of clinical and wherever possible, electrolyte monitoring.
<b>Precautions</b>	Restrict intake in impaired renal function; cardiac failure, hypertension, peripheral and pulmonary oedema; toxemia of pregnancy.
<b>Adverse Effects</b>	Administration of large doses may give rise to oedema.
<b>Storage</b>	Store in a single dose container at a temperature not exceeding 30°C.

## Hypertonic Saline

<b>Indications</b>	<i>Used in increased intracranial pressure (ICP) with hypovolemia/shock and renal failure.</i>
<b>Availability</b>	3% w/v solution

**Dose** Initial dose- 4 ml/kg at a rate of 15 min can be given in case of impending herniation.

Continuous infusion of 3% NaCl ranging between 0.1 and 1.0 ml/kg/hour (Administered on a sliding scale if ICP monitoring available to maintain ICP <20).

**Precautions** If serum osmolarity >320 -mannitol of little use may be harmful, given along with mannitol if no response in 3-6 hours, monitor serum sodium levels.

**Adverse Effects** Hyperchloremic metabolic acidosis; acute renal failure; subarachnoid hemorrhage; central pontine myelinosis; coagulopathies disorder; pulmonary edema; congestive heart failure due to overload; hypokalemia; hemolysis; phlebitis; rebound cerebral edema.

## Potassium Chloride\*

**Pregnancy Category-C**

**Indications** *Electrolyte imbalance; hypokalaemia.*

**Availability** **INJECTION** 10 ml ampoule (11.2%w/v).

**Dose** ***Slow Intravenous infusion***

**Adult and Child-** Electrolyte imbalance; depending on the deficit or the daily maintenance requirements.

**Contraindications** Plasma-potassium concentrations above 5mmol/litre; chronic renal failure; systemic acidosis; acute dehydration; adrenal insufficiency.

**Precautions** For intravenous infusion the concentration of solution should not usually exceed 3.2g (43 mmol)/litre; specialist advice and ECG monitoring (see notes above); renal impairment; interactions (Appendix 6d); pregnancy (Appendix 7c); acute alkalosis, paediatric use.

**Adverse Effects** Cardiac toxicity on rapid infusion; nausea, vomiting, flatulence, diarrhoea.

**Storage** Store in a single dose container at a temperature not exceeding 30°C.

## Sodium Bicarbonate\*

**Pregnancy Category-C**

**Indications** *Metabolic acidosis; cardiopulmonary resuscitation; hyperkalaemia; muscle spasm.*

<b>Availability</b>	<b>INJECTION</b> 10 ml ampoule (1.4%w/v), (8.4%w/v).
<b>Dose</b>	<b><i>Slow intravenous infusion</i></b>  <b>Adult and Child-</b> Metabolic acidosis: a strong solution (up to 8.4%), an amount appropriate to the body base deficit.  <b><i>Continuous intravenous infusion</i></b>  <b>Adult and Child-</b> a weaker solution (up to 1.4%), an amount appropriate to the body base deficit.
<b>Contraindications</b>	Metabolic or respiratory alkalosis, hypocalcaemia, hypochlorhydria; hypoventilation; hypoosmolarity.
<b>Precautions</b>	Restrict intake in impaired renal function, cardiac failure, hypertension, peripheral and pulmonary oedema, toxemia of pregnancy (Appendix 7c); monitor electrolytes and acid-base status; stomach disorder; allergies.
<b>Adverse Effects</b>	Excessive administration may cause hypokalaemia and metabolic alkalosis, especially in renal impairment; large doses may give rise to sodium accumulation and oedema seizures; lactic acidosis; pulmonary oedema; hyperventilation.
<b>Storage</b>	Store in a single dose container at a temperature not exceeding 30°C.

## Sodium Chloride

<b>Indications</b>	<i>Electrolyte and fluid replacement; hyponatremia; diabetic ketoacidosis; leg cramps; poisoning.</i>
<b>Availability</b>	<b>INJECTION</b> 250 and 500 ml (0.9% Solution); <b>NASAL DROPS</b> 5 ml (0.9% w/v).
<b>Dose</b>	<b><i>Intravenous infusion</i></b>  <b>Adult and Child-</b> Fluid and electrolyte replacement: determined on the basis of clinical and wherever possible, electrolyte monitoring.
<b>Contraindications</b>	Hypertension; liver cirrhosis; ischaemic heart disease; nephrotic syndrome; congestive heart failure.

<b>Precautions</b>	Restrict intake in impaired renal function; cardiac failure, hypertension; peripheral and pulmonary oedema; toxæmia of pregnancy; interactions (Appendix 6d).
<b>Adverse Effects</b>	Administration of large doses may give rise to sodium accumulation and oedema; vomiting; intraocular coagulopathy.
<b>Storage</b>	Store in a single dose container at a temperature not exceeding 30°C.

## Sodium Lactate

<b>Indications</b>	<i>Perioperative fluid and electrolyte replacement; hypovolaemic shock; metabolic acidosis; peritoneal dialysis.</i>
<b>Availability</b>	<b>INJECTIONS</b> 250, 500 ml and 1L (1.87% w/v).
<b>Dose</b>	<b><i>Intravenous infusion</i></b>  <b>Adult and Child-</b> Fluid and electrolyte replacement or hypovolaemic shock: determined on the basis of clinical and wherever possible, electrolyte monitoring. Common adult dose is 1 to 3 litre/day.
<b>Contraindications</b>	Metabolic or respiratory alkalosis; hypocalcaemia or hypochlorhydria; hypernatremia.
<b>Precautions</b>	Restrict intake in impaired renal function; cardiac failure, hypertension; peripheral and pulmonary oedema; toxæmia of pregnancy; corticosteroid therapy; shock; hypoxemia.
<b>Adverse Effects</b>	Excessive administration may cause metabolic alkalosis; administration of large doses may give rise to oedema; tissue necrosis; hypernatremia; hypervolemia; reaction at injection site.
<b>Storage</b>	Store in a single dose container at a temperature not exceeding 30°C.

## Water for Injection\*

<b>Indications</b>	<i>In preparations intended for parenteral administration and in other sterile preparations.</i>
<b>Availability</b>	Ampoule 1, 5 and 10 ml.
<b>Storage</b>	Store in a single dose container at a temperature not exceeding 30°C.

## 29.3 Miscellaneous

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### Glycerol\*

<b>Indications</b>	<i>Used in increased intracranial pressure and hydrocephalus.</i>
<b>Availability</b>	10% w/v solution
<b>Dose</b>	<b>Oral</b> 0.5-1.5 g/kg every 6-8 hourly. <b>Parenteral</b> Intravenous- 0.5 to 1.0 g/kg every 4-6 hours; do not exceed 0.2-1.0 g/kg/hour. Administer as a 10% solution every 4 hours.
<b>Contraindications</b>	Renal failure.
<b>Precautions</b>	Preparation should not be greater than 10%, intravenous preparations should be administered slowly to prevent haemolysis.
<b>Adverse Effects</b>	Haemolysis, haemoglobinuria; renal failure; hyperosmolar coma; much frequent and severe rebound effect; hyperglycemia.



**30. Vitamins, Minerals and Antianaemic  
Drugs 603**

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## 30. Vitamins, Minerals and Antianaemic Drugs

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### Vitamins:

Vitamins are used for the prevention and treatment of specific deficiency states or when the diet is known to be inadequate. It has often been suggested but never convincingly proved, that subclinical vitamin deficiencies cause much chronic ill-health and liability to infections. This has led to enormous consumption of vitamin preparations, which have no more than placebo value. Most vitamins are comparatively non-toxic but prolonged administration of high doses of retinol (vitamin A), ergocalciferol (vitamin D<sub>2</sub>) and pyridoxine (vitamin B<sub>6</sub>) may have severe adverse effects.

**Retinol** (vitamin A) is a fat-soluble substance stored in body organs, principally the liver. Periodic high-dose supplementation is intended to protect against vitamin A deficiency which is associated with ocular defects particularly xerophthalmia (including night blindness which may progress to severe eye lesions and blindness), and an increased susceptibility to infections, particularly measles and diarrhoea. Universal vitamin A distribution involves the periodic administration of supplemental doses to all preschool-age children with priority given to age groups, 6 months to 3 years, or regions at greatest risk. All mothers in high-risk regions should also receive a high dose of vitamin A within 8 weeks of delivery. Since vitamin A is associated with a teratogenic effect it should be given in smaller doses (no more than 10,000 units/day) to women of child-bearing age. It is also used in the treatment of active xerophthalmia. Doses of vitamin A should be administered orally immediately upon diagnosis of xerophthalmia and thereafter patients with acute corneal lesions should be referred to a hospital on an emergency basis. In women of child-bearing age there is a need to balance the possible teratogenic effects of vitamin A should they be pregnant with the serious consequences of xerophthalmia. Where there are severe signs of xerophthalmia high dose treatment as for patients over 1 year should be given. When less severe symptoms are present (for example night blindness) a much lower dose is recommended. Vitamin A therapy should also be given during epidemics of measles to reduce complications.

**Vitamin B** is composed of widely differing substances which are, for convenience, classed as 'vitamin B complex'. Thiamine



(vitamin B<sub>1</sub>) is used orally for deficiency due to inadequate dietary intake. Severe deficiency may result in 'beri-beri'. Chronic dry 'beri-beri' is characterized by peripheral neuropathy, muscle wasting and weakness, and paralysis; wet 'beri-beri' is characterized by cardiac failure and oedema. Wernicke-Korsakoff syndrome (demyelination of the CNS) may develop in severe deficiency. Thiamine is given by intravenous injection in doses of up to 300 mg daily (parenteral preparations may contain several B group vitamins) as initial treatment in severe deficiency states. Potentially severe allergic reactions may occur after parenteral administration. Facilities for resuscitation should be immediately available. **Riboflavin** (vitamin B<sub>2</sub>) deficiency may result from reduced dietary intake or reduced absorption due to liver disease, alcoholism, chronic infection or probenecid therapy. It may also occur in association with other deficiency states such as pellagra. **Pyridoxine** (vitamin B<sub>6</sub>) deficiency is rare as the vitamin is widely distributed in foods, but deficiency may occur during isoniazid therapy and is characterized by peripheral neuritis. High doses are given in some metabolic disorders, such as hyperoxaluria and it is also used in sideroblastic anaemia. **Nicotinic acid** inhibits the synthesis of cholesterol and triglyceride and is used in some hyperlipidaemias. Nicotinic acid and **nicotinamide** are used to prevent and treat nicotinic acid deficiency (pellagra). Nicotinamide is generally preferred as it does not cause vasodilation. **Hydroxocobalamin** is the form of vitamin B<sub>12</sub> used to treat vitamin B<sub>12</sub> deficiency due to dietary deficiency or malabsorption (see chapter 13.1).

**Folic acid** is essential for the synthesis of DNA and certain proteins. Deficiency of folic acid or vitamin B<sub>12</sub> is associated with megaloblastic anaemia. Folic acid should not be used in undiagnosed megaloblastic anaemia unless vitamin B<sub>12</sub> is administered concurrently, otherwise neuropathy may be precipitated (see chapter 13.1). Supplementation with folic acid 500 µg daily is recommended for women of child-bearing potential in order to reduce the risk of serious neural tube defects in their offspring.

**Ascorbic acid** (vitamin C) is used for the prevention and treatment of scurvy. Claims that ascorbic acid is of value in the treatment of common colds are unsubstantiated.

The term **vitamin D** covers a range of compounds including ergocalciferol (vitamin D<sub>2</sub>) and **cholecalciferol** (vitamin D<sub>3</sub>). These two compounds are equipotent and either can be used to prevent and treat rickets.

Simple deficiency of vitamin D occurs in those who have an inadequate dietary intake or who fail to produce enough

cholecalciferol (vitamin D<sub>3</sub>) in their skin from the precursor 7-dehydrocholesterol in response to ultraviolet light.

**Vitamin K** is necessary for the production of blood clotting factors.

## Minerals:

**Calcium gluconate:** Calcium supplements are usually only required where dietary calcium intake is deficient. This dietary requirement varies with age and is relatively greater in childhood, pregnancy and lactation due to an increased demand, and in old age, due to impaired absorption. In osteoporosis, a calcium intake which is double the recommended daily amount reduces the rate of bone loss. In hypocalcaemic tetany calcium gluconate must be given parenterally but plasma calcium must be monitored. Calcium gluconate is also used in cardiac resuscitation.

**Iodine** is among the body's essential trace elements. The recommended intake of iodine is 150 µg daily (200 µg daily in pregnant and lactation women); in children the recommended intake of iodine is 50 µg daily for infants under 1 year, 90 µg daily for children aged 2-6 years, and 120 µg daily for children aged 7-12 years. Deficiency causes endemic goitre and results in endemic cretinism (characterized by deaf-mutism, intellectual deficit, spasticity and sometimes hypothyroidism), impaired mental function in children and adults and an increased incidence of still-births and perinatal and infant mortality. Iodine and iodides may suppress neonatal thyroid function and in general iodine compounds should be avoided in pregnancy. Where it is essential to prevent neonatal goitre and cretinism, iodine should not be withheld from pregnant women. Control of iodine deficiency largely depends upon salt iodization with potassium iodide or potassium iodate and through dietary diversification. In areas where iodine deficiency disorders are moderate to severe, iodized oil given either before or at any stage of pregnancy is found to be beneficial.

**Sodium fluoride:** Availability of adequate fluoride confers significant resistance to dental caries. It is now considered that the topical action of fluoride on enamel and plaque is more important than the systemic effect. Where the natural fluoride content of the drinking water is significantly less than 1 mg per litre, artificial fluoridation is the most economical method of supplementing fluoride intake. Daily administration of fluoride tablets or drops is a suitable alternative, but systemic fluoride supplements should not be prescribed without reference to the fluoride content of the local water supply; they are not advisable when the water contains more than 700 µg per litre. In addition, infants need not receive

fluoride supplements until the age of 6 months. Dentifrices which incorporate Sodium fluoride are a convenient source of fluoride. Individuals who are either particularly caries prone or medically compromised may be given additional protection by the use of fluoride rinses or by application of fluoride gels. Rinses may be used daily or weekly; daily use of a less concentrated rinse is more effective than weekly use of a more concentrated one. High-strength gels must be applied on a regular basis under professional supervision; extreme caution is necessary to prevent the child from swallowing any excess.

## Ascorbic Acid (Vitamin C)\*

**Pregnancy Category-A, C**

<b>Indications</b>	<i>Prevention and treatment of scurvy.</i>
<b>Availability</b>	<b>TABLETS</b> 100 and 500 mg; <b>DROP</b> 100 mg/ml; <b>INJECTION</b> 5 ml ampoule (100 mg/ml)
<b>Dose</b>	<b>Oral</b>  <b>Adult and child-</b> Prophylaxis of scurvy: 25 to 75 mg daily. Treatment of scurvy: 0.5 to 1.5g/day.
<b>Contraindications</b>	Hyperoxaluria.
<b>Precautions</b>	Acetylsalicylic acid hypersensitivity; G-6-PD deficiency; large doses may cause renal calcium oxalate calculi; pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Gastrointestinal disturbances reported with large doses; failure of conception; kidney oxalate stones.
<b>Storage</b>	Store protected from light and moisture. Avoid contact with metals.

## Calcium Carbonate + Vitamin D<sub>3</sub>

**Pregnancy Category-A**

<b>Indications</b>	<i>Prevention and treatment of osteoporosis and osteomalacia, nutritional supplement.</i>
<b>Availability</b>	<b>TABLET</b> Vitamin D <sub>3</sub> 250 IU + Calcium 500 mg <b>SUSPENSION</b> 200 ml (Calcium 100 mg+Vitamin D <sub>3</sub> 200 IU/5 ml).
<b>Dose</b>	<b>Oral</b>

**Adult**

**Calcium** 1000 -1300 mg daily

**Vitamin D<sub>3</sub>** 200 - 800 IU daily.

**Contraindications** Hypersensitivity to any of the components, hypercalcaemia and/or hypercalciuria, nephrolithiasis, hypervitaminosis.

**Precautions** Renal impairment, impaired calcium absorption in achlorhydria, risk of hypercalcaemia and hypercalciuria in hypoparathyroid patients receiving high doses of vitamin D; interactions (Appendix 6c); pregnancy (Appendix 7c).

**Adverse Effects** Constipation, flatulence, nausea, abdominal pain and diarrhoea; pruritus, rash and urticaria.

## Calcium Gluconate\*

**Indications** *Hypocalcaemic tetany; cardiopulmonary bypass.*

**Availability** **TABLETS** 250 and 500 mg; **INJECTION** 10 ml (1g/10 ml).

**Dose** ***Slow intravenous injection and continuous intravenous infusion***

**Adult-** Hypocalcaemic tetany: 1g (2.2 mmol) by slow intravenous injection, followed by continuous intravenous infusion of about 4g (8.8 mmol) daily.

**Contraindications** Conditions associated with hypercalcaemia and hypercalciuria (for example some forms of malignant disease).

**Precautions** Monitor plasma calcium concentration; renal impairment; interactions (Appendix 6c); diarrhoea, parathyroid disease; stomach trouble.

**Adverse Effects** Mild gastrointestinal disturbances; bradycardia, arrhythmias, hypotension; irritation at injection site; soft tissue calcification; nephrocalcinosis, renal calculi.

## Ergocalciferol (Vitamin D<sub>2</sub>)\*

**Pregnancy Category-C**

**Indications** *Prevention of vitamin D deficiency; vitamin D deficiency caused by malabsorption or chronic liver disease; hypocalcaemia of hypoparathyroidism; osteomalacia; osteoporosis.*

<b>Availability</b>	<b>CAPSULES</b> 0.25 and 1 mg (50,000 IU).
<b>Dose</b>	<b>Oral</b>  <b>Adult and child-</b> Prevention of vitamin D deficiency: 10 µg (400 units) daily.
<b>Contraindications</b>	Hypercalcaemia; metastatic calcification.
<b>Precautions</b>	Ensure correct dose in infants; monitor plasma calcium at weekly intervals in patients receiving high doses or those with renal impairment; nausea and vomiting may indicate overdose and hypercalcaemia; lactation (Appendix 7b); interactions (Appendix 6a); pregnancy (Appendix 7c).
<b>Adverse Effects</b>	Symptoms of overdosage include anorexia; lassitude; nausea and vomiting, diarrhoea, weight loss; polyuria; sweating; headache; thirst, vertigo and raised concentrations of calcium and phosphate in plasma and urine; tissue calcification may occur if dose of 1.25 mg continued for several months; cardiac arrhythmia; hypervitaminosis D; over psychosis; paralytic ileus.
<b>Storage</b>	Store protected from light in a hermetically sealed container.

## **Iodine\*** (Refer Page No. 505)

### **Pregnancy Category-D**

<b>Indications</b>	<i>Prevention and treatment of iodine deficiency; thyrotoxicosis; hyperthyroidism.</i>
<b>Availability</b>	<b>CRYSTALS BULK.</b>
<b>Dose</b>	<b>Oral</b>  <b>Adult-</b> Endemic moderate to severe iodine deficiency: during pregnancy and one year postpartum, 300 to 480 mg once a year or 100 to 300 mg every 6 months; women of child-bearing age, 400 to 960 mg once a year or 200 to 480 mg every 6 months. Iodine deficiency; 400 mg, during pregnancy, single dose of 200 mg.  <b>Child-</b> Iodine deficiency: infant under 1 year, single dose 100 mg; 1 to 5 years, 200 mg once a year; above 6 years 400 mg once a year.  <b><i>Intramuscular injection</i></b>

Endemic moderate to severe iodine deficiency: women of child-bearing age, including any stage of pregnancy, 480 mg once each year; iodine deficiency: 380 mg (if aged over 45 or with nodular goiter then 76 mg).

**Child-** Iodine deficiency; 380 mg but for infant up to 1 year, 190 mg.

**Contraindications** Lactation (Appendix 7b); bronchitis; goitre; hyperkalaemia; asthma; acne vulgaris; tuberculosis.

**Precautions** Over 45 years old or with nodular goitre (especially susceptible to hyperthyroidism when given iodine supplements-iodized oil may not be appropriate); may interfere with thyroid-function tests; pregnancy (see notes above and Appendix 7c); acute iodide toxicity; cardiac toxicity; interactions (Appendix 6c).

**Adverse Effects** Hypersensitivity reactions; goitre and hypothyroidism; hyperthyroidism; bronchitis; eosinophilia; rashes; headache; salivation.

## Iron Salts\* (Refer Page No. 618)

### Methylcobalamin

#### Pregnancy Category-A

**Indications** *To prevent neurological disorder in patients with neuropathy due to diabetes, alcohol or other drug induced neuropathies.*

**Availability** **TABLETS** 500 µg, **INJECTION** 500 µg/ml and 0.2 mg/vial.

**Dose** Initially 1000 µg 3 times a day for 2 weeks, thereafter 1000 µg every 3 months by intramuscular injection in case of pernicious anaemia and other macrocytic anaemia. In case with neurological involvement, initially 1 µg on alternate days. Until no further improvement, thereafter 1000 µg every 2 to 3 months. Prophylaxis: 1000 µg every 2 to 3 months.

**Contraindications** Hypersensitivity.

**Precautions** Allergies; pregnancy (Appendix 7c).

**Adverse Effects** Itching; anaphylactic shock with parenterals, pulmonary oedema; CHF; polycythemia vera.

**Storage** **INJECTION** Store in single-dose or multi-dose container protected from light in a refrigerator (2° to 8°C). Do not freeze.

**Tablet:** Store protected from light and moisture.

## Nicotinamide\*

### Pregnancy Category-A

**Indications** *Treatment of pellagra; hartnup disease; inflammatory skin disease.*

**Availability** **TABLET** 50 mg.

**Dose** **Oral**

**Adult-** Treatment of pellagra: up to 500 mg daily in divided doses.

**Precautions** Avoid contact with eyes and mucous membranes (including nose and mouth); reduce frequency of application if excessive dryness, irritation or peeling; history of heart disease; insulin dependent diabetes; pregnancy (Appendix 7c).

**Adverse Effects** Dryness of skin; also pruritus, erythema, burning and irritation; hepatotoxicity, cholestasis; portal fibrosis; transient liver dysfunction; tautness of face.

**Storage** Store protected from light and moisture.

## Nicotinic acid (Refer Page No. 343)

## Pyridoxine\* (Refer Page No. 621)

### Pregnancy Category-A

**Indications** *Treatment of pyridoxine deficiency due to metabolic disorders; isoniazid neuropathy; sideroblastic anaemia.*

**Availability** **TABLETS** 10, 25, 40, 50 and 100 mg.

**Dose** **Oral**

**Adult-** Deficiency states: 25 to 50 mg up to 3 times daily. Isoniazid neuropathy, prophylaxis: 10 mg daily. Isoniazid neuropathy, treatment: 50 mg, 3 times daily. Sideroblastic anaemia: 100 to 400 mg daily in divided doses.

**Precautions** Interactions (Appendix 6c), pregnancy (Appendix 7c).

**Adverse Effects** Generally well tolerated, but chronic administration of high doses may cause peripheral neuropathies; paresthesia; neurotoxicity; muscular weakness.

## Riboflavin\*

### Pregnancy Category-A

**Indications** *Vitamin B<sub>2</sub> deficiency; arabinoflavinosis.*

**Availability** **TABLETS** 5 mg.

**Dose** **Oral**

**Adult and child-** Treatment of vitamin B<sub>2</sub> deficiency: up to 30 mg daily in divided doses. Prophylaxis of vitamin B<sub>2</sub> deficiency: 1 to 2 mg daily.

**Contraindications** Cataract; hypersensitivity.

**Precautions** Large doses result in dark yellow discolouration of urine; pregnancy (Appendix 7c).

**Adverse Effects** Swelling of lips, face and tongue and difficulty in breathing.

**Storage** Store protected from light.

## Sodium Fluoride

**Indications** *Prevention of dental caries.*

**Availability** **POWDER IN BULK.**

**Dose** **As oral rinse**

**Child-** Prevention of dental caries: over 6 years of age 10 ml 0.05% solution daily or 10 ml 0.2% solution weekly.

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*Note: Fluoridated toothpastes are also a convenient source of fluoride for prophylaxis of dental caries.*

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**Contraindications** Not for areas where drinking water is fluoridated or where fluorine content is naturally high; neonates.

**Precautions** Kidney problems.



**Adverse Effects** In recommended doses toxicity unlikely; occasionally white flecks on teeth at recommended doses; rarely, yellowish-brown discolouration if recommended doses are exceeded; gum irritation.

**Storage** Store protected from moisture.

## Thiamine\*

### Pregnancy Category-A

**Indications** *Prevention and treatment of vitamin B<sub>1</sub> deficiency, acute alcohol intoxication.*

**Availability** **TABLETS** 25, 50 and 100 mg.

**Dose** **Oral**

**Adult-** Mild chronic thiamine deficiency: 10 to 25 mg daily.  
Acute alcohol intoxication: 50-100 mg daily.  
Wernicke-Korsakoff syndrome: 50-100 mg daily.

**Precautions** Parenteral administration (see notes above); lactation (Appendix 7b); pregnancy (Appendix 7c).

**Adverse Effects** Nausea; urticaria; gastrointestinal bleeding; oedema; pruritus; dizziness; anorexia.

**Storage** Store protected from light and moisture in a non-metallic container.

## Vitamin A\*

### Pregnancy Category-X

**Indications** *Prevention and treatment of vitamin A deficiency; prevention of complications of measles.*

**Availability** **TABLETS** 5000 and 10,000 IU; **INJECTION** 50,000 IU/ml.

**Dose** **Oral**

**Adult-** Prevention of vitamin A deficiency: 2,00,000 units every 6 months; pregnant woman, max. of 10,000 units daily or max. 25,000 units weekly; mothers, 200,000 units at delivery or within 6 weeks. Treatment of xerophthalmia; (except woman of child-bearing age) 2,00,000 units on diagnosis, repeated next day and then after 2 weeks; (woman of child-bearing age), 5000 to 10,000 units daily for at least 4 weeks or up to 25000 units weekly.

**Child-** Prevention of vitamin A deficiency: infant under 6 months, 50,000 units; 6 to 12 months, 100,000 units every 4 to 6 months, preferably at measles vaccination; over 1year, 200,000 units every 4 to 6 months. Treatment of xerophthalmia; infant under 6 months, 50,000 units on diagnosis, repeated next day and then after 2 weeks; 6 to 12 months, 1,00,000 units immediately on diagnosis, repeated next day and then after 2 weeks; over 1 year, same as adults.

**Contraindications**

Hypervitaminosis.

**Precautions**

Pregnancy (teratogenic; see notes above and Appendix 7c); lactation.

**Adverse Effects**

No serious or irreversible adverse effects in recommended doses; high intake may cause birth defects; transient increased intracranial pressure in adults or a tense and bulging fontanelle in infants (with high dosage); massive overdose can cause rough skin, dry hair, enlarged liver, raised erythrocyte sedimentation rate, raised serum calcium and raised serum alkaline phosphatase concentrations; hair loss; redness of skin; anorexia; weight loss.

**Storage**

Store protected from light and moisture.

## Antianaemic Drugs

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### Iron-Deficiency Anaemia:

Anaemia has many different aetiologies. It occurs when the haemoglobin concentration falls below the normal range for the age and sex of the individual. It is essential that a correct diagnosis is made before initiating therapy.

Any serious underlying cause of iron-deficiency anaemia, including gastric erosion and colonic carcinoma, should be excluded before giving iron replacement. Prophylaxis with iron salts in pregnancy should be given to women who have additional factors for iron-deficiency; low-dose iron and folic acid preparations are used for the prophylaxis of megaloblastic anaemia in pregnancy.

Ferrous salts should be given orally wherever possible. They differ only marginally in efficiency of absorption and thus the choice of preparation is usually decided by incidence of adverse effects and cost. Ferric salts are much less well absorbed. The oral dose of elemental iron for treatment of iron-deficiency anaemia in adults should be 100-200 mg daily with meals.

The approximate elemental iron content of various ferrous salts is- ferrous fumarate 200 mg (65 mg iron), ferrous gluconate 300 mg (35 mg iron), ferrous succinate 100 mg (35 mg iron), ferrous sulphate 300 mg (60 mg iron) and dried ferrous sulphate 200 mg (65 mg iron).

The haemoglobin concentration should rise by about 100-200 mg/100 ml per day or 2 g/100 ml over 3-4 weeks. After the haemoglobin has risen to normal, treatment should be continued for a further 3 months to replenish the iron stores.

Iron intake in the evening has been reported to improve its absorption. Iron intake with meals may reduce bioavailability but improve tolerability and adherence.

If adverse effects arise with one salt, dosage can be reduced or a change made to an alternative iron salt but an improvement in tolerance may be due to lower content of elemental iron. Gastrointestinal irritation may occur with iron salts. Nausea and epigastric pain are dose-related. Iron preparations taken orally may be constipating, particularly in the elderly, occasionally leading to faecal impaction. Oral iron may exacerbate diarrhoea in patients with inflammatory bowel disease but care is also needed in patients with intestinal strictures and diverticula. Iron as iron dextran (a complex of ferric hydroxide with dextrans) should be given parenterally only if the patient cannot tolerate oral iron, or does not take it reliably or there is

continuing severe blood loss or malabsorption. Many patients with chronic renal failure who are receiving haemodialysis (and some on peritoneal dialysis) require intravenous iron on a regular basis. Parenteral iron may cause more harm than benefit. With the exception of patients on haemodialysis the haemoglobin response is not significantly faster with the parenteral route than the oral route.

### **Megaloblastic Anaemia:**

Megaloblastic anaemias result from a lack of either vitamin B<sub>12</sub> (hydroxocobalamin) or folate or both. The clinical features of folate-deficient megaloblastic anaemia are similar to those of vitamin B<sub>12</sub> deficiency except that the accompanying severe neuropathy does not occur; it is essential to establish the underlying cause in every case. Hydroxocobalamin is used to treat vitamin B<sub>12</sub> deficiency whether due to dietary deficiency or malabsorption including pernicious anaemia (due to a lack of intrinsic factor, which is essential for vitamin B<sub>12</sub> absorption).

Folate deficiency due to poor nutrition, pregnancy, antiepileptics or malabsorption is treated with folic acid but this should never be administered without vitamin B<sub>12</sub> in undiagnosed megaloblastic anaemia because of the risk of precipitating neurological changes due to vitamin B<sub>12</sub> deficiency.

Preparations containing a ferrous salt and folic acid are used for the prevention of megaloblastic anaemia in pregnancy. The low doses of folic acid in these preparations are inadequate for the treatment of megaloblastic anaemias.

### **Prevention of Neural Tube Defects:**

An adequate intake of folic acid before conception and during early pregnancy reduces the risk of neural tube defects in babies. Therefore, women planning a pregnancy should receive sufficient folic acid before conception and in the first 12 weeks of pregnancy; folic acid may be given as a food or a medicinal supplement in a dose of 400-500 µg daily. A woman who has not received supplementary folic acid and suspects that she might be pregnant should start taking folic acid at once and continue until 12<sup>th</sup> week of pregnancy.

Women at increased risk of giving birth to a baby with neural tube defects (for example history of neural tube defect in a previous child) should receive a higher dose of folic acid of approximately 5 mg daily, starting before conception and continuing for 12 weeks after conception. Women taking antiepileptic medication should be counselled by their doctor before starting folic acid.

## Cyanocobalamin (Vitamin B<sub>12</sub>)\*

### Pregnancy Category-C

**Indications** *Cyanocobalamin deficiency; peripheral neuropathy; diabetic neuropathy; medicine related or alcoholic neuropathy.*

**Availability** **TABLETS** 50, 500 and 1500 µg; **CAPSULES** 50 µg; **LIQUID** 35 µg/5 ml; **INJECTION** vial 500 µg/30 ml.

**Dose** **Oral**

**Adult-** Vitamin-B<sub>12</sub> deficiency of dietary origin: 50 to 150 µg daily between meals.

**Child-** 50 to 105 µg daily in 1 to 3 divided doses.

#### ***Intramuscular injection***

Initially 1 mg repeated 10 times at intervals of 2 to 3 days, maintenance 1 mg every month.

**Contraindications** Hypersensitivity, tobacco amblyopia.

**Precautions** Cobalt hypersensitivity, pregnancy (Appendix 7c).

**Adverse Effects** Asthenia; dyspepsia; pulmonary edema; shivering; bronchospasm.

**Storage** Store protected from light in a single dose or multi dose container.

## Erythropoietin

### Pregnancy Category-C

**Indications** *Anaemia of chronic renal failure, anaemia in patients with AIDs, anaemia associated with cancer chemotherapy, reduction of Allogeneic Blood Transfusion in Surgery Patients.*

**Availability** **INJECTIONS** 1000, 2000, 3000, 4000, 5000, 6000, 10000, 20000 and 40000 IU/Vial

**Dose** **Parenteral**

### **Anaemia of chronic renal failure**

**Adult:** As epoetin alfa: Initially, 50 U/kg subcutaneous/intravenous 3 times weekly for predialysis and haemodialysis patients and 50 U/kg twice weekly for peritoneal dialysis patients, dose may be increased according to response in steps of 25 U/kg 3 times weekly at 4 weekly intervals.

**Child:** As epoetin alfa: Initially, 50 U/kg 3 times weekly. Dose may be increased at 4 weekly intervals in increments of 25 U/kg 3 times weekly until a target haemoglobin concentration of 9.5-11 g/100 ml is reached. Usual maintenance dose: <10 kg: 225-450 U/kg/week; 10-30 kg: 180-450 U/kg/week and >30 kg: 90-300 U/kg/week.

### **Anaemia in zidovudine-treated HIV-infected patients**

**Adult:** As epoetin alfa: Initially, 100 U/kg subcutaneous/intravenous thrice weekly for 8 weeks; increase every 4-8 week by 50-100 U/kg according to response. Max: 300 U/kg thrice weekly.

### **Subcutaneous**

#### **Anaemia related to non-myeloid malignant disease chemotherapy**

**Adult:** As epoetin alfa or zeta: Initially, 150 U/kg 3 times weekly. Dose may be increased at 4-8 week intervals to 300 U/kg 3 times weekly. Stop treatment if response is still inadequate after 4 week of treatment using this higher dose.

### **Intravenous**

#### **Increase yield of autologous blood**

**Adult:** As epoetin alfa or zeta: 600 U/kg over 2 minutes twice weekly for 3 week before surgery; in conjunction with iron, folate and B<sub>12</sub> supplementation.

### **Contraindications**

Hypersensitivity to mammalian cell products and human albumin, uncontrolled hypertension.

### **Precautions**

Ischaemic heart diseases, chronic renal failure, hypertension, seizures, liver dysfunction, pregnancy (Appendix 7c) and lactation, interactions (Appendix 6c).

### **Adverse Effects**

Nausea, vomiting, increased risk of hypertension, myalgia, arthralgia, rashes and urticaria, headache, confusion, generalized seizures, thrombosis specifically during dialysis, fever, diarrhoea, tissue swelling, flu-like syndrome, paraesthesia, constipation, nasal or chest congestion, immunogenicity leading to Pure Red Cell Aplasia.

### **Storage**

Store in an air tight container at a temperature below - 20°C. Avoid repeated freezing and thawing.

## Iron Salts\*

**Ferrous Gluconate, Ferrous Sulphate: Pregnancy Category A**

**Iron Sucrose, Sodium Ferric Gluconate: Pregnancy Category B**

**Iron Dextran: Pregnancy Category C**

**Indications** *Iron-deficiency anaemia.*

**Availability** **TABLETS** (sugar coated, film coated) Ferrous sulphate 200 mg, Ferrous fumarate 200 mg, Ferrous gluconate 300 mg. (all equivalent to 65 mg elemental iron). In women, folic acid may also be given. **SYRUPS** also available. **CAPSULES** Iron sulfate 60-150 mg (20% Iron), Iron fumarate 200-300 mg (33% Iron). **INJECTIONS** Iron dextran 50 mg/ml, Iron sucrose 20, 50 and 100 mg/ml, Sodium ferric gluconate 12.5 mg/ml.

**Dose** **Oral**

**Adult-** Iron-deficiency anaemia: elemental iron 100 to 200 mg daily in divided doses. Prevention of iron deficiency anaemia (in those at particular risk): for woman- elemental iron 60 mg daily.

**Child-** under 5 years: elemental iron 2 mg/kg (max. 30 mg) daily. Over 5 years: elemental iron 30 mg daily. Over 5 years: folic acid may also be given.

### **Parenteral**

Total dose (ml) =  $0.0442 \text{ (desired haemoglobin- observed haemoglobin) } \times \text{LBW} + (0.26 \times \text{LBW})$

[Note: LBW = Lean Body Weight (Kg)]

Total dose may be given in divided doses in a daily or twice weekly basis via IM inj. (into the upper quadrant of the buttock); may also be given intravenously by total-dose infusion or as divided inj. A-Z track technique (displacement of the skin laterally prior to injection) is recommended to avoid injection or leakage into subcutaneous tissue.

**Contraindications** Haemosiderosis, haemochromatosis; any form of anaemia not caused by iron deficiency; evidence of iron overload; patients receiving repeated blood transfusions; parenteral iron therapy.

**Precautions** A test dose of 0.5 ml should be given & observe patient for at least 1 hour for signs of hypersensitivity, respiratory distress, tachycardia or back/chest pain; should not be administered for longer than 6 months; pregnancy (Appendix 7c); peptic ulcer; hypotension; regional enteritis, ulcerative colitis, intestinal strictures, diverticula; interactions (Appendix 6c, 6d).

**Adverse Effects** Nausea, vomiting, metallic taste; constipation, diarrhoea, dark stools, epigastric pain, gastrointestinal irritation; long-term or excessive administration may cause haemosiderosis; allergic reaction; back pain; staining of teeth.  
Parenteral: Pain at injection site, sterile abscess.

**Storage** Store protected from light at temperature not exceeding 30°C.

## Folic Acid\*

### Pregnancy Category-A

**Indications** *Treatment of folate-deficiency megaloblastic anaemia; prevention of neural tube defect in pregnancy.*

**Availability** TABLETS 1, 5 and 10 mg.

**Dose** *Oral*

**Adult-** Treatment of folate-deficiency, megaloblastic anaemia: 5 mg daily for 4 months (up to 15 mg daily may be necessary in malabsorption states).

Prevention of first occurrence of neural tube defect: 400 to 500 µg daily before conception and during the first twelve weeks of pregnancy.

Prevention of recurrence of neural tube defect: 5 mg daily (reduced to 4 mg daily, if suitable preparation available) from at least 4 weeks before conception until twelfth week of pregnancy.

**Contraindications** Should never be given without vitamin B<sub>12</sub> in undiagnosed megaloblastic anaemia or other vitamin B<sub>12</sub> deficiency states because risk of precipitating subacute combined degeneration of the spinal cord; folate-dependent malignant disease.

**Precautions** Women receiving antiepileptic therapy need counselling before starting folic acid; pernicious anaemia; folate dependent tumor; interactions (Appendix 6c); pregnancy (Appendix 7c).



**Adverse Effects** Neuropathy; bronchospasm; skin eruption; anorexia; skin rash; status epilepticus.

**Storage** Store protected from light.

## Hydroxocobalamin

**Pregnancy Category-C**

**Indications** *Megaloblastic anaemia due to vitamin B<sub>12</sub> deficiency, congenital intrinsic factor disease.*

**Availability** **INJECTION** 1 ml (1 mg/ml).

**Dose** ***Intramuscular injection***

**Adult and Child-** Megaloblastic anaemia without neurological involvement: initially 1 mg 3 times a week for 2 weeks, then 1 mg every 3 months.

Megaloblastic anaemia with neurological involvement: initially 1 mg on alternate days until no further improvement occurs, then 1 mg every 2 months.

Prophylaxis of macrocytic anaemias: 1 mg every 2 to 3 months.

Tobacco amblyopia and Leber optic atrophy: 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, then 1 mg every 1 to 3 months.

**Contraindications** Anaphylactic reaction.

**Precautions** Except in emergencies, should not be given before diagnosis confirmed; monitor serum potassium levels-arrhythmias secondary to hypokalaemia in early therapy; pregnancy (Appendix 7c).

**Adverse Effects** Itching, exanthema, fever, chills, hot flushes, nausea, dizziness; rarely, acneiform and bullous eruptions, anaphylaxis; hypersensitivity; headache; diarrhoea.

**Storage** Store protected from light.

## Iron Dextran\*

**Pregnancy Category-C**

**Schedule H**

**Indications** *Iron deficiency anaemia, prevention of iron deficiency before, during or after pregnancy, to make up iron deficiency after pregnancy and during lactation.*

**Availability** **INJECTION** (iron as iron dextran) 1.5 ml ampoule (50 mg/ml).

**Dose** Deep intramuscular injection into the gluteal muscle or slow intravenous injection or intravenous infusion.

**Adult-** Calculated according to body-weight and iron deficit. While deciding on parenteral therapy, oral therapy should be stopped at least 24 h before. Urine may darken on starting.

**Child-** Under 14 years: not recommended.

**Contraindications** History of allergic disorders including asthma and eczema; infection; active rheumatoid arthritis; liver disease.

**Precautions** Oral iron not to be given until 5 days after last injection; hepatic impairment; renal impairment; pregnancy (Appendix 7c); interactions (Appendix 6d).

Anaphylactic reactions can occur with parenteral iron and a test dose is recommended before each dose; the patient should be carefully observed for 60 min after the first test dose and for 15 min after subsequent test doses (subsequent test doses not necessary for intramuscular administration). Facilities for cardiopulmonary resuscitation must be at hand; risk of allergic reactions increased in immune or inflammatory conditions.

**Adverse Effects** Less commonly nausea, vomiting, abdominal pain, flushing, dyspnoea, anaphylactic reactions (see Anaphylaxis above), numbness, cramps, blurred vision, pruritus and rash; rarely, diarrhoea, chest pain, hypotension, angioedema, arrhythmias, tachycardia; dizziness, restlessness, fatigue; seizures, tremor, impaired consciousness, myalgia, arthralgia and sweating; injection-site reactions also reported, thrombophlebitis; peripheral vascular flushing; taste disturbances; syncope.

## Pyridoxine\* (Refer Page No. 610)

### Pregnancy Category-A

**Indications** *Isoniazid, hydralazine and cycloserine induced-neurological disturbances; pyridoxine responsive anaemia and haemocysteinuria; morning sickness and hyperemesis gravidarum; convulsions in infants and children; mental symptoms in women on oral contraceptives.*

**Availability** **TABLETS** 10, 25, 40 and 50 mg and 100 mg (sustained release); **INJECTION** 1 ml (50 mg/ml).

**Dose**

**Oral**

**Adult**-Deficiency states: 25 to 50 mg up to 3 times daily.

Isoniazid neuropathy (prophylaxis): 10 mg daily.

Isoniazid neuropathy (treatment): 50 mg 3 times daily.

Sideroblastic anaemia: 100 to 400 mg daily in divided doses.

**Precautions**

Interactions (Appendix 6c); pregnancy (Appendix 7c); long term administration of high dose may cause severe peripheral neuropathies.

**Adverse Effects**

Sensory neuropathy reported with high doses given for extended periods, numbness; neurotoxicity; hyperesthesia; muscle weakness.

**Storage**

Store protected from light and moisture.



## Appendices

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## Appendix 1: Antimicrobial Resistance

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Development and spread of antimicrobial resistance (AMR) is commonly due to overuse, misuse, and indiscriminate use of antimicrobials by doctors, nurses and pharmacists, non-compliance and self medication by patients and use in animal husbandry and agriculture. It is estimated that 70-80% of prescriptions for antimicrobials are probably advised unnecessarily by the health professionals. In spite of the fact that most common colds and diarrhoeal episodes are viral in origin, yet, antimicrobials are used indiscriminately. Reasons for over prescribing are often lack of confidence, peer pressure, patient pressure and pharmaceutical company pressure. Antimicrobial use is a key driver of the resistance. Poverty and inadequate access to antibiotics constitute a major factor in the development of resistance. Another common cause of developing resistance is improper diagnosis. In many instances death of an adequately equipped diagnostic laboratory in the vicinity compels the physician to prescribe antibiotics empirically, thus, increasing the likelihood of the patient receiving a wrong antibiotic. Furthermore, ready availability of antibiotics over-the-counter and sales promotion schemes by the pharmaceutical manufacturers also leads to the promotion of indiscriminate use, thus, increasing the likelihood of development of resistance. Counterfeit drugs are also a problem contributing to development of resistance. These contain either the wrong ingredient, or lesser amount of the active ingredient. In some instances, the medication poisons are capable of causing disability or even death. The impact of the media has also contributed to the development of resistance. Patients often demand antibiotics for their ailment on the basis of advertisements read or seen. Unwitting use of more active drugs at sub therapeutic doses leads directly to the development of multi drug resistance. Irrational use of antimicrobials is widespread throughout the world. This is harmful in terms of increased cost of therapy, unnecessary adverse drug reactions, therapeutic failure, reduced quality of care and worst of it is AMR.

The bacterial infections which contribute most to human mortality and morbidity are also those in which emerging antimicrobial resistance is most obvious: diarrhoeal diseases, respiratory infections, meningitis, sexually transmitted diseases, and hospital-acquired infections. Some important

examples include penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, multi-resistant *Salmonella typhi*, *Shigella dysenteriae*, *Neisseria gonorrhoea*, *Pseudomonas aeruginosa* and multi-resistant *Mycobacterium tuberculosis*. The development of resistance to drugs commonly used to treat *P. falciparum* malaria is of particular concern, as is the emerging resistance to antiretroviral drugs.

### Established mechanisms of AMR

For an antibiotic to be effective, it must reach the target site in an active form, bind to the target, and interfere with its function. Thus, bacterial resistance to an antimicrobial agent can occur due to three general mechanisms:

#### The drug does not reach its target

In Gram negative bacteria, many antibiotics enter the cell through protein channels called porins. Mutations or loss of these channels can prevent/slow the rate of antibiotic entry into a cell, effectively reducing drug concentration at the target site. If the drug target is intracellular and the drug requires active transport across the cell membrane, a mutation that interferes with the transport mechanism can confer resistance e.g. aminoglycosides. Bacteria can also transport antimicrobial drugs out of the cell through efflux pumps. Resistance to numerous drugs, including fluoroquinolones, macrolides, tetracyclines and beta lactam antibiotics, is mediated by this mechanism.

#### The drug is inactivated

Bacterial resistance to aminoglycosides can be due to a plasmid encoded aminoglycoside-modifying enzymes. Similarly,  $\beta$ -lactamase production is the most common mechanism of resistance to penicillins and other  $\beta$ -lactam drugs. Many hundreds of different  $\beta$ -lactamases have now been identified. A variation of this mechanism is failure of the bacterial cell to activate a prodrug e.g. loss of ability of *M. tuberculosis* to activate isoniazid (INH).

#### The target site is altered

This may be due to mutations in drug binding region of target enzyme e.g. fluoroquinolones, target modification e.g. ribosomal protection type of resistance to macrolides and acquisition of a resistant form of the susceptible target e.g., methicillin resistance in *Staphylococcus* Spp. due to production of a low-affinity penicillin-binding protein (PBP).

### Strategies to prevent AMR in healthcare settings

**Prudent antibiotic use:** Antibiotics should be used only when they improve patient outcome. Not all infections need antibiotic treatment e.g. in patients with sore throat, benefit from antimicrobial therapy is small and is counterbalanced by the risk of adverse events like rash. Narrow spectrum agents should be used whenever possible. Broad spectrum agents should not be used as a cover for lack of diagnostic precision. Antibiotics should be prescribed in optimal doses, regimens, and should be stopped when the infection is treated. Restrict the use of last line antibiotics for serious infections and only when simpler agents are likely to be ineffective. Whenever used for prophylaxis, antibiotics should be used for short courses and at appropriate times (e.g. during surgical prophylaxis, antibiotics should be given within an hour prior to incision).

**Prevention of infection:** Use of antimicrobials can also be reduced if infections are prevented in the first place. This can be achieved by improved use of vaccines and improved hygiene and infection control practices like compliance with hand washing protocols and aseptic techniques for catheterization. Catheters and drains should be removed when no longer needed.

Clinicians should be familiar with local antibiotic sensitivity profiles and should comply with the local antibiotic guidelines. A hospital antibiotic policy should be formulated based on local antimicrobial resistance data. Prescribers should be educated about the use of antibiotics, when not to use them and also the infection control strategies.

Hospitals should carry out surveillance of resistance patterns-how much, where, in which organisms and to what antibiotics. Similarly antibiotic use pattern can be studied and these data can be used to devise targeted interventions to minimize antimicrobial use.

The intent of giving this write up in the formulary is to encourage rational prescribing of antimicrobials and minimize the development of resistance to antimicrobials.



## Appendix 2: Calculation of Electrolytes

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### Milliequivalents

The milliequivalent is related to the total number of ionic charges in solution and it takes note of the valency of the ions. In other words, it is a unit of measurement of the amount of chemical activity of an electrolyte. The total concentration of cations always equals the total concentration of anions.

A milliequivalent (mEq) weight is 1/1000 of the equivalent weight. An equivalent weight of an element is the atomic weight expressed in grams, divided by its valency.

$$1\text{mEq} = \frac{\text{atomic weight in mg}}{\text{valency}}$$

$$\text{e.g. } 1 \text{ mEq Na}^+ = \frac{23}{1} = 23 \text{ mg}$$

$$1 \text{ mEq Cl}^- = \frac{35.5}{1} = 35.5 \text{ mg}$$

Thus, a solution containing 1 mEq of Sodium per litre contains 23 mg Sodium. A solution containing 1 mEq of Sodium Chloride contains 23 mg Na<sup>+</sup> and 35.5 mg Cl<sup>-</sup>, i.e. 58.5 mg Sodium Chloride per litre.

In a salt containing ions of different valencies,

Weight of a salt containing 1 mEq of specified ion	=	Sum of the atomic weights (valency of the specified ion) x no. of specified ions in molecule
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e.g. Weight of magnesium chloride ( mgCl<sub>2</sub>.6H<sub>2</sub>O) required to prepare a solution containing 1 mEq of magnesium per litre.

$$\frac{24.3 + (2 \times 35.5) + 6[(2 \times 1) + 16]}{2 \times 1} = 101.7 \text{ mg mgCl}_2.6\text{H}_2\text{O}$$

For the conversion of grams per 100 ml (percentage) of a solution to mEq/litre, the following formula may be used.

$$\text{mEq per litre} = \frac{\text{percentage strength} \times 10000}{\text{mg of salt containing 1 mEq of specified ions}}$$

e.g. Number of mEq of Na<sup>+</sup> per litre contained in Sodium Chloride injection 0.9% (1mEq Sodium is contained in 58.5 mg Sodium Chloride)

$$\text{mEq per litre of Na}^+ \text{ in Sodium Chloride 0.9\% solution} = \frac{0.9 \times 10,000}{58.5} = 154 \text{ approximately}$$

$$\text{mEq} = \frac{\text{Wt (g)}}{\text{mEq weight (g)}}$$

e.g. mEq in 5g of Potassium Chloride (atomic weight of Potassium Chloride = 74.6, valency = 1)

$$\text{mEq Wt} = \frac{74.6}{1000} = \frac{0.0746}{1}$$

$$\text{mEq} = \frac{5}{0.0746} = 67 \text{ approximately}$$

To convert mg per 100 ml ( mg%) to mEq per litre, the following formula is used :

$$\frac{\text{mg. per 100 ml.} \times 10 \times \text{valency}}{\text{atomic weight}} = \text{mEq. per litre}$$

In the case of gases (i.e. carbon dioxide) the volume per cent of the gas is multiplied by 10 and divided by 22.4, the later figure being the volume in litres occupied by a molecular weight of a gas. The results are expressed in millimoles per litre.

$$\frac{\text{vol. percent} \times 10}{22.4} = \text{mM. per litre}$$

To convert mg per 100 ml ( mg%) to milliosmoles:

$$\frac{\text{mg. per 100 ml} \times 10}{\text{molecular weight}} = \text{mOsm per litre}$$

**Table 1: Atomic weight, Valency, and Normal Ranges of the Common Electrolytes**

Normal Ranges, Plasma or Serum

Electrolyte	Atomic Weight	Valency	mg. per 100 ml	mEq. per litre
Na	23	1	310-34	135-147
NaCl	58.5	1	570-620	98-106
K	39	1	16-22	4.1-5.7
Ca (total)	40	1	9.1-11.5	2.1-2.6
Ca <sup>2+</sup> (ionized)	40	1	4.25-5.25	2.1-2.6
mg	24	2	1.8-3.6	1.5-3.1

$(\text{HCO}_3)^-$	Use formula for gases.		55-70	25-31
(mM. $\text{CO}_2$ ) Infants			45-60	20-2
			(vol. percent)	(mM/L)
Cl	35.5	1	350-375	98-106
$\text{NH}_4 \text{Cl}$	Contains 66.28 per-cent of Cl.			
$\text{SO}_4^{2-}$	96	2	0.5-2.5	0.3-1.5

**Table 2: mg of a salt containing 1 mEq of a specified ion**

Ion	weight of mEq in mg	Salt	mg of salt containing 1 mEq of the specified ion
$\text{Ca}^{++}$	20.0	Calcium Chloride, $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$	147
		Calcium Gluconate, $\text{C}_{12}\text{H}_{22}\text{CaO}_{14} \cdot \text{H}_2\text{O}$	224
		Calcium Lactate, $\text{C}_6\text{H}_{10}\text{CaO}_6 \cdot 5\text{H}_2\text{O}$	154
$\text{K}^+$	39.1	Potassium Chloride, KCl	74.5
		Potassium Citrate, $\text{C}_6\text{H}_5\text{K}_3\text{O}_7 \cdot \text{H}_2\text{O}$	108
$\text{mg}^{++}$	12.5	Magnesium Sulphate, $\text{mgSO}_4 \cdot 7\text{H}_2\text{O}$	123
$\text{Na}^+$	23.0	Sodium Acetate, $\text{C}_2\text{H}_3\text{NaO}_2 \cdot 3\text{H}_2\text{O}$	136
		Sodium Acid Citrate, $\text{C}_6\text{H}_6\text{Na}_2\text{O}_7 \cdot 1\frac{1}{2}\text{H}_2\text{O}$	131
		Sodium Bicarbonate, $\text{NaHCO}_3$	84
		Sodium Chloride, NaCl	58.5
		Sodium Citrate, $\text{C}_6\text{H}_5\text{Na}_3\text{O}_7 \cdot 2\text{H}_2\text{O}$ Sodium Lactate*	98
Cl	35.5	Calcium Chloride, $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$	73.5
		Potassium Chloride, KCl	74.5
		Sodium Chloride, NaCl	58.5
$\text{C}_2\text{H}_3\text{O}_2$ (Acetate)	59.0	Sodium Acetate, $\text{C}_2\text{H}_3\text{NaO}_2 \cdot 3\text{H}_2\text{O}$	136

## Appendix 2

$C_3H_5O_3^-$ (Lactate)	89.0	Calcium Lactate, $C_6H_{10}CaO_6 \cdot 5H_2O$ Sodium Lactate*	308.3
$HCO_3^-$	61.0	Sodium Bicarbonate, $NaHCO_3$	84

\*Prepared in solution by neutralising lactic acid with sodium hydroxide: 1.0 ml of 1 M sodium contains the equivalent of 112 mg.

## Appendix 3:

# Common Laboratory Parameters

S. No.	Biochemical Parameter	Reference Range
<b>1.</b>	<b>Liver Function Tests</b>	
	Aspartate Aminotransferase (AST/SGOT)	12-38 Units/L
	Alanine Aminotransferase (ALT/SGPT)	7-41 Units/L
	Bilirubin	
	Total	0.3-1.3 mg/dL
	Direct	0.1-0.4 mg/dL
	Indirect	0.2-0.9 mg/dL
	Protein Total	6.7-8.6 g/dL
	Albumin	3.5-5.5 mg/dL
	γ Glutamyl Transpeptidase (GGT)	9-58 Units/L
<b>2.</b>	<b>Kidney Function Tests</b>	
	Blood Urea Nitrogen (BUN)	7-20 mg/dL
	Creatinine (Cr)	0.6-1.2 mg/dL
	Uric Acid	
	Male	3.1-7.0 mg/dL
	Female	2.5-5.6 mg/dL
	Glomerular Filtration Rate	>60 ml/min/1.73 m <sup>2</sup>
<b>3.</b>	<b>Lipid Profile</b>	
	HDL Cholesterol	
	Male	27-67 mg/dL
	Female	34-88 mg/dL
	LDL Cholesterol	
	Desirable	<130 mg/dL
	High Risk	≥160 mg/dL
	Triglycerides	<165 mg/dL

**4. Pancreatic Function Tests**

Amylase 20-96 Units/L

Lipase 3-43 Units/L

**5. Thyroid Function Tests**

Thyroxine

Free ( $fT_4$ ) 0.8 – 1.7 ng/dLTotal ( $T_4$ ) 5.4-11.7  $\mu$ g/dLTriiodothyronine ( $T_3$ ) Total 77-135 ng/dLThyroid Stimulating Hormone (TSH) 0.34-4.25  $\mu$ IU/ml**6. Parathyroid Function Tests**

Calcium 8.5-10.5 mg/dL

Calcium (Ionized) 4.6-5.3 mg/dL

**7. Reproductive Function Tests**

Follicle Stimulating Hormone (FSH)

Male 1.0-12.0 m IU/ml

Female

Menstruating

Follicular phase 3.0-20.0 m IU/ml

Ovulatory phase 9.0-26.0 m IU/ml

Luteal phase 1.0-12.0 m IU/ml

Post menopausal 18.0-153.0 m IU/ml

Leuteinsing Hormone (LH)

Male 2.0-12.0 U/L

Female

Menstruating

Follicular phase 2.0-15.0 U/L

Ovulatory phase 22.0-105.0 U/L

Luteal phase 0.6-19.0 U/L

Postmenopausal 16.0-64.0 U/L

	Testosterone total, morning sample	
	Male	270.0-1070.0 ng/dL
	Female	6.0-86 ng/ml
<b>8.</b>	<b>Electrolytes</b>	
	Sodium (Na <sup>+</sup> )	136-146 mEq/L
	Potassium (K <sup>+</sup> )	3.5-5.0 mEq/L
	Magnesium ( mg <sup>2+</sup> )	1.5-2.3 mg/dL
	Phosphorus	2.5-4.3 mg/dL
	Chloride (Cl <sup>-</sup> )	102-109 mEq/L
	Calcium	8.7-10.2 mg/dL
	Calcium (Ionized)	4.5-5.3 mg/dL
<b>9.</b>	<b>Arterial Blood Gases</b>	
	Carbondioxide, Partial Pressure (PCO <sub>2</sub> )	32-45 mm Hg
	Oxygen, Partial Pressure (PO <sub>2</sub> )	72-104 mm Hg
	Osmolality Serum	275-295 mOsm/kg serum water
	pH blood (arterial)	7.35-7.45
	Anion Gap	7-16 mmol/L
	Bicarbonate	22-30 mEq/L
<b>10.</b>	<b>Normal Haematological Parameters</b>	
	Total Leucocyte Count (TLC)	4.8-10.8 x 10 <sup>3</sup> /mm <sup>3</sup>
	Basophil Count	0-2%
	Eosinophil Count	0-6%
	Lymphocyte Count	20-50%
	Monocyte Count	4-8%
	Platelet Count	165-415 x 10 <sup>3</sup> /mm <sup>3</sup>
	Reticulocyte Count	
	Males	0.8-2.3% red cells
	Females	0.8-2.0% red cells

Neutrophil Count	0.40-0.7 (40-70%)/ mm <sup>3</sup>
Red Blood Cell Count	
Male	4.3-5.6 x 10 <sup>6</sup> /mm <sup>3</sup>
Female	4.0-5.2 x 10 <sup>6</sup> /mm <sup>3</sup>
Hemoglobin	
Male	13.3-16.2 g/dL
Female	12.0-15.8 g/dL
Erythrocyte Sedimentation Rate (ESR)	
Male	0-15 mm/h
Female	0-20 mm/h
<b>11. Corpuscular Values of Erythrocytes</b>	
Mean Corpuscular Hemo- globin (MCH)	26.7-31.9 pg/cell
Mean Corpuscular Hemo- globin Concentration (MCHC)	32.3-35.9 g/dL
Mean Corpuscular Volume (MCV)	79-93.3 fL
<b>12. Coagulogram</b>	
Fibrinogen	233-496 mg/dL
Partial Thromboplastin Time, Activated (aPTT)	26.3-39.4 seconds
Prothrombin Time (PT)	12.7-15.4 seconds
Thrombin Time	15.3-18.5 seconds
Bleeding Time (Adult)	< 7.1 min
Coagulation factors	50- 150% of normal
<b>13. Cerebrospinal Fluid</b>	
Leukocytes - Total	less than 5 cells/cu mm (all mononu- clear)
Differential	
Lymphocytes	60-70%



Monocytes	30–50%
Neutrophils	None
Chloride	116 – 122 mEq/L
Glucose	40-70 mg/dL
Pressure	50-180 mm of water
Total protein	15-50 mg/dL (lumbar)
Albumin	6.6-44.2 mg/dL
<b>14. Miscellaneous</b>	
Glucose	75-110 mg/dL
Glycosylated Hemoglobin (HbA <sub>1c</sub> )	4.0-6.0%
Iron	41-141 µg/dL
Total Iron Binding Capacity (TIBC)	251-406 µg/dL
Methemoglobin (Met Hb)	<1% of total Hb
Ferritin	
Male	29-248 ng/ml
Female	10-150 ng/ml
Transferrin	190-375 mg/dL
Lactate Dehydrogenase (LDH)	115-221 Units/L
Folic Acid (Red Cells)	165-760 ng/ml
Glucose-6-Phosphate Dehydrogenase (G-6-PD)	5-14 Units/g Hb
Vitamin B <sub>12</sub>	140-820 pg/ml

## Appendix 4: Disposal of Unused/Expired Pharmaceutical Products

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Shelf life of a drug is defined as the time interval within which it remains physically, chemically and/or biologically stable as well as safe and effective for human consumption if stored under the label specified conditions and it is in the original container closure system. Shelf life can be determined by the accelerated stability testing method. Expiry/expiration date is the actual date placed on the label/container indicating the time during which a batch of drug product is expected to remain with the approved shelf life specifications if stored under defined conditions and after which it should not be used. Expired medicines lose their potency and are capable of producing toxins, causing serious reaction or failure of therapy.

Thus disposal of unused/expired pharmaceutical products is required for every pharmacy - retail and wholesale, clinic, dispensary, hospital, manufacturing unit and testing laboratory. Indiscriminate disposal of drugs is likely to pollute the environment resulting in contamination of vegetables, fruits, fish and other aquatic life and even drinking water. Pharmaceuticals and Personal Care Products (PPCP) have been found present as pollutant in water and environment and this poses a serious issue of ecological imbalance due to indiscriminate disposal of expired pharmaceutical products.

With increasing awareness of pollution and their effect on human beings, animals and environment, it is imperative to assure Regulatory compliance by Individuals, Retail and Wholesale Chemists, Clinics, Hospitals, Manufacturers of PPCP, Clinical Research Organizations conducting Biostudies, Analytical Testing Laboratories and other organizations involved in drug distribution (in the event of any disaster) to augment Government efforts.

### Managing Disposal of PPCP:

Mass awareness, at every level, of impact of casual approach in such disposal of unwanted and expired PPCP is very much desirable. Following steps are suggested for safe disposal of unused/not required/expired PPCP:

1. Expired or near expiry or unused/not required PPCP in large quantity should be returned by Retail Chemists and Druggists/Pharmacies/Clinics/Hospitals/NGO involved in drug distribution to Wholesalers or stockists

of manufacturer(s) who in turn will return the same to the location of the manufacturer where the products were manufactured, for proper disposal.

2. Expired/short expiry PPCP are received at the segregated area for Expired Goods/Market Returns in the Finished Goods Warehouse of the manufacturing location with proper documentation in compliance with Regulatory requirements under i) Drugs and Cosmetics Rules 1945 and amendments therein, ii) Central Excise/State Excise Laws- as applicable and iii) Local authority of Pollution Control Board of the State before undertaking disposal of PPCP. Short expiry PPCP should be analyzed and if found satisfactory, could be used for treatment ensuring that it is consumed before expiration.
3. In the event of expired goods returned from overseas customers, appropriate documentation for disposal of PPCP should be provided to the custom authority at the importing port for Bill of Entry.
4. Finished Goods Warehouse receiving the PPCP shall inform Quality System/Quality Assurance authority of the organization for verification and appropriate documentation before undertaking disposal.
5. For small quantity of expired products in Clinics, Hospitals, Health Care Centers and Dispensaries, Pharmacist at the location should be assigned responsibility for disposal of PPCP. He/she should be trained for proper documentation and disposals as indicated below.
6. Disposal of expired retention samples of API, Excipients and that of Pharmaceutical dosage forms in the manufacturing unit or Testing laboratories should be assigned to a responsible Quality control person under supervision of Quality System/Quality Assurance ensuring appropriate documentation.
7. After compliance to administrative control procedure, the expired PPCP should be transferred to a segregated area under the control of Safety, Health and Environment department in the manufacturing location for undertaking disposal.

## Disposal Methods of Pharmaceutical and Personal Care Products

### Sorting of Materials:

Materials to be disposed off should be segregated. Different methods are employed depending on

- i) **Type of dosage forms-** Tablets, Capsules, Powders, Injectables, Creams, Ointments, Liquids, Ampoules, Vials, Intravenous Infusions etc.
- ii) **Chemical nature of drugs** e.g. Antineoplastics/Anticancer,  $\beta$ -Lactams, Hormones, Steroids, Anti-infective, Narcotics, Antiseptics and Psychotropic substances etc. Tertiary (Printed/Labelled Corrugated Boxes) and Secondary (Printed Cartons/Paper box) packaging materials are removed and destroyed with the help of heavy duty paper shredder. The methods of disposal of various pharmaceutical dosage forms and that of specific category medicines are mentioned below.

## Pharmaceutical Dosage Forms

### 1. Tablets/Capsules:

Up to 50 tablets or capsules soak in about 100 ml of water and collect the same in a polyethylene bag containing used Tea/Coffee grind. Seal the bag and put in trash. Big quantity - Pulverize using heavy duty crusher. Collect in a poly bag and seal. Dispose it in high temperature incinerator (Temp. 850°C to 1200°C)/approved site for solid waste disposal by the Pollution Control Board of the State.

### 2. Injectables - ampoules/vials:

Up to 50 Ampoules/Vials (up to 10 ml)-break ampoules/open vials and collect liquid in a polyethylene bag containing used Tea/Coffee grind. Seal the bag and put in trash. For bigger quantity, use heavy duty crusher to separate liquid and dilute it with water and transfer it to Effluent Treatment Plant (ETP) of the manufacturing unit. Broken glass/vials (after removal of label), rubber stoppers and seals should be disposed off as scrap. Powder Injectables (in Vials/Ampoules) to be disposed off in an incinerator as indicated above.

### 3. Oral liquids and Intravenous fluids:

Small quantity – Dilute the liquid with water and drain it. For bigger quantity, dilute collected liquid with water and transfer it to ETP of the manufacturing unit. Liquids with high solid contents to be disposed off in an incinerator as indicated above.

### 4. Semi solids:

Small quantity, mix it with used Tea/Coffee grind in a polyethylene bag. Seal the bag and put in a trash. Deshape the containers/remove the label and discard the containers. Semisolids in bigger quantity to be disposed off in an incinerator mentioned earlier.

Containers - Tubes to be reshaped and remove the label from glass/plastic container before disposal as a scrap.

### Specific categories:

#### 1. Anti-infectives- $\beta$ -lactams:

Small quantity of all  $\beta$ -lactam antibiotics to be destroyed by soaking in 1N Sodium Hydroxide for 30 mins or 1% Hydroxylamine in Water for 10 mins and trash. Bigger quantity to be disposed off in an incinerator (Temp. 850°C to 1200°C) indicated above.

#### 2. Anti-infectives - others:

Tetracyclines- Small quantity to be soaked in 10% of Calcium Hydroxide/any other Calcium salt in Water for 30 mins and trash. Macrolides- (Erythromycin, Clarithromycin etc.)-Small quantity, soak in 1N Hydrochloric Acid and trash. Amino glycosides ( Gentamycin, Amikacin etc.) - Small quantity dilute with large volume of water and drain it. Bigger quantity of all the above anti-infective should be disposed of in an incinerator as mentioned above.

#### 3. Steroids:

Small quantity- Soak in 1N Sodium Hydroxide for 30 mins and trash. Bigger quantity- all dosage forms (taken out from the primary packing materials) to be incinerated at the temperature range indicated above.

#### 4. Hormones:

Small quantity- Aqueous solution to be exposed to UV for 20 minutes and trash. Estrogens- small quantity in aqueous solution should be exposed to ultrasound at 0.6 and 2 kw in a sonicator for 60 mins. and trash. Bigger quantity- all solid dosage forms (taken out from primary packaging materials) to be incinerated as indicated above.

#### 5. Disinfectants:

Small quantity- use it. Bigger quantity- Not more than 50L. Dilute with enough quantity of water to ensure dilution with loss of activity and drain it in ETP.

#### 6. Controlled substances:

Small quantity- Flush down the toilet to avoid misuse. Bigger quantity- All dosage forms (take out from primary packaging material) to be incinerated as mentioned above.

Disposal by incineration is preferred over chemical inactivation for all dosage forms/APIs.

### **Cost of Disposal of Pharmaceutical Products:**

In India Solid Waste Disposal of PPCP at an approved solid waste disposal site by the local Pollution Control Board works out to Rs. 15 to 25 per kg. Disposal of PPCP by incineration requires about 5% of the fuel feed to that of the total quantity to be disposed of. Total cost of such disposal works out to about 0.5 % to 2% of the total sales.

There is an urgent need to minimize this wastage on account of disposal of Unused/Expired Pharmaceutical products. This not only involves huge cost but also danger of contaminating water bodies, rivers, sea, air, land and aquatic lives, which ultimately get recycled and comes back to human beings, animals and vegetation in one or the other form.

### **Reuse of Expired Pharmaceutical Products:**

In the event of Emergency situation, Regulatory Agencies do allow Revalidation, after Analysis of Expired Pharmaceutical Drug Products, if found satisfactory, for Human/Animal consumption.

### **Reduction in Level of Disposal:**

Reduced level of disposal of PPCP can help significantly. If recovery of API (Active Pharmaceutical Ingredient) and purification there of, out of near expiry/expired PPCP be attempted and regulated, it will reduce the level of PPCP disposal. This will be a challenging task for pharmaceutical professionals, which will help industry in reducing quantum of disposal.

### **Education and Training:**

Continuing education and training at every level is desirable to generate awareness of hazards associated with indiscriminate disposal of unused/expired pharmaceutical products - an emerging environmental issue.

It is expected that awareness of the stakeholders with systematic preventive and corrective actions in time will ensure the safe disposal of unused/expired pharmaceutical products.

## Appendix 5: Drugs and Poisons Information Centres in India

S. No.	Address	Contact No.	E-mail
1.	National Poisons Information Centre, Department of Pharmacology, All India Institute of Medical Sciences (AIIMS) <b>New Delhi-110029</b>	011-26589391 011-26593677	npicaiims@hotmail.com, npicaiims2010@gmail.com
2.	Medicine and Poison-Antidote Information Centre (MAPIC) Delhi Institute of Pharmaceutical Sciences and Research (DIPSAR) Pushp Vihar, Sector-III, M.B. Road, <b>New Delhi-110017</b>	011-29553173 011-29554649	mapicdipsar@indiatimes.com, dipsarmapic@gmail.com
3.	Poison Information Centre, Toxicology and IMCU Unit, Govt. General Hospital, <b>Chennai-600003</b>	044-536 3208 044-536 3131 ext. 108 Fax: 044-538 8521	thiruma@satyam.net.in ghpictn@vsnl.net www.chennaipic.com
4.	Sri Ramachandra Hospital, Porur, Chennai No.1, Ramachandra Nagar Porur, <b>Chennai-600 116</b>	044-24768403 ext. 8927 Fax: 044-2476 7008	dicsrmc@yahoo.co.in
5.	Poisons Information Centre National Institute of Occupational Health, Meghani Nagar <b>Ahmedabad-380 016</b>	079 286 7351 079 562 1400 Fax: 079 286 6630	dewan4@satyam.net.in
6.	Poison Information and Laboratory Services (Department of Toxicology) Amrita Institute of Medical Sciences and Research <b>Cochin-682 026</b>	0484 400 8056 0484 400 1234 9895282388 Fax: 0484 280 2051	toxicology@medical.amrita.edu; poisonunit@aimshospital.org

## Appendix 6a: Drug-Alcohol Interactions

Mixing alcohol with medications can cause a variety of symptoms like nausea, vomiting, headache, drowsiness, fainting, or loss of coordination. By virtue of its effects on the CNS consumption of alcohol, even in small quantities, puts the patient at a high risk. There are medicines which should never be taken with alcohol (Table 1). However, there are many other medicines which should be used with high level of caution while the patient is on alcohol (Table 2).

**Table 1: Drugs not to be used with alcohol**

Acetylsalicylic Acid	Losartan
Alprazolam	Lovastatin
Amitriptyline	Lovastatin+ Niacin
Atorvastatin	Meperidine
Benazepril	Metronidazole
Butalbital + Codeine	Naproxen
Carisoprodol	Nicotinic acid
Cefoperazone	Nitrazepam
Chlordiazepoxide	Nitrofurantoin
Clomipramine	Nitroglycerin
Clonazepam	Paracetamol
Clonidine	Paroxetine
Cyclobenzaprine	Phenobarbital
Desipramine	Phenytoin
Diazepam	Pravastatin
Diphenhydramine	Pravastatin + Acetylsalicylic acid
Doxazosin	Prazosin
Doxylamine	Propoxyphene
Enalapril	Quinapril
Eszopiclone	Ramipril
Fluoxetine	Rosuvastatin
Griseofulvin	Simvastatin
Herbal Preparations	Simvastatin + Ezetimibe
Hydrochlorothiazide	Temazepam
Ibuprofen	Terazosin
Isoniazid	Tinidazole
Isosorbide	Vitamin D
Ketoconazole	Warfarin
Leflunomide	Zolpidem
Lorazepam	



Table 2: Drugs to be avoided with alcohol

Abacavir	Metformin
Amobarbital	Methadone
Atenolol	Methotrexate
Atropine	Metoclopramide
Bromocriptine	Midazolam
Brompheniramine	Morphine
Cetirizine	Nizatidine
Chlorpheniramine	Oxytocin
Chlorpromazine	Pentazocine
Cimetidine	Prazosin
Dextromethorphan	Procarbazine
Diclofenac	Prochlorperazine
Dimenhydrinate	Promethazine
Diphenhydramine	Propranolol
Doxycycline	Ranitidine
Fexofenadine	Sodium Valproate
Fluphenazine	Tamsulosin
Furazolidone	Thiopental
Glyburide	Tolbutamide
Guaiifenesin + Codeine	Trifluoperazine
Haloperidol	Trihexyphenidyl
Imipramine	
Insulin	
Loratadine	

## Appendix 6b:

# Drug–Contraceptive Interactions

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### CONTRACEPTIVES, ORAL

Acetazolamide	Antagonism of diuretic effect
Amiloride	Antagonism of diuretic effect
Amitriptyline	Antagonism of antidepressant effect but adverse effects increased due to increased plasma concentration of amitriptyline
Amoxicillin	Reduced contraceptive effect of estrogen-containing preparations
Ampicillin	Reduced contraceptive effect of estrogen-containing preparations
Atenolol	Antagonism of hypotensive effect
Carbamazepine	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception); reduced contraceptive effect (does not apply to injectable norethisterone enantate for contraception)
Ceftazidime	Reduced contraceptive effect of estrogen-containing preparations
Ceftriaxone	Reduced contraceptive effect of estrogen-containing preparations
Cefuroxime	Reduced effect of contraceptives
Corticosteroids	Oral contraceptives increase plasma concentration of corticosteroids
Clomipramine	Antagonism of antidepressant effect but adverse effects increased due to increased plasma concentration of clomipramine
Cyclosporine	Inhibition of cyclosporine metabolism (increased plasma–cyclosporine concentration)
Doxycycline	Reduced contraceptive effect of estrogen-containing preparations
Efavirenz	Efficacy of oral contraceptives reduced
Enalapril	Antagonism of hypotensive effect
Fluconazole	Anecdotal reports of contraceptive failure

Fosphenytoin	Reduced contraceptive effect
Furosemide	Antagonism of diuretic effect
Glibenclamide	Antagonism of hypoglycaemic effect
Glimepiride	Reduced hypoglycaemic action
Glucagon	Antagonism of hypotensive effect
Glyceryl trinitrate	Antagonism of hypotensive effect
Griseofulvin	Reduced contraceptive effect of levonorgestrel, accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception); does not apply to injectable norethisterone enantate for contraception
Hydralazine	Antagonism of hypotensive effect
Hydrochlorothiazide	Antagonism of diuretic effect
Insulins	Antagonism of hypoglycaemic effect
Isosorbide dinitrate	Antagonism of hypotensive effect
Metformin	Antagonism of hypoglycaemic effect
Methyldopa	Antagonism of hypotensive effect
Nelfinavir	Accelerated metabolism of levonorgestrel, medroxyprogesterone and norethisterone (reduced contraceptive effect); does not apply to injectable medroxyprogesterone acetate for contraception
Nevirapine	Accelerated metabolism of levonorgestrel, medroxyprogesterone and norethisterone (reduced contraceptive effect); does not apply to injectable medroxyprogesterone acetate for contraception
Nifedipine	Antagonism of hypotensive effect
Phenobarbital	Metabolism accelerated (reduced contraceptive effect); does not apply to injectable medroxyprogesterone acetate for contraception; does not apply to injectable norethisterone enantate for contraception
Phenytoin	Accelerated metabolism of levonorgestrel, norethisterone (reduced contraceptive effect); does not apply to injectable medroxyprogesterone acetate for contraception; does not apply to injectable norethisterone enantate for contraception

Propranolol	Antagonism of hypotensive effect
Rifampicin	Accelerated metabolism of levonorgestrol and medroxyprogesterone (reduced contraceptive effect); does not apply to injectable medroxyprogesterone acetate for contraception; does not apply to injectable norethisterone enantate for contraception
Ritonavir	Accelerated metabolism of levonorgestrol and norethisterone (reduced contraceptive effect); does not apply to injectable medroxyprogesterone acetate for contraception; does not apply to injectable norethisterone enantate for contraception
Sodium nitroprusside	Antagonism of hypotensive effect
Spirolactone	Antagonism of diuretic effect
Topiramate	Failure of contraceptive effect
Theophylline	Delayed excretion of theophylline; increased plasma concentration
Verapamil	Antagonism of hypotensive effect
Warfarin	Antagonism of anticoagulant effect

## Appendix 6c:

# Drug–Drug Interactions

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Two or more drugs administered at the same time may interact with each other. The interactions may be potentiation or antagonism of one drug by another or occasionally some other effect. Drug interactions may be of pharmacokinetic or pharmacodynamic type. The pharmacokinetic interactions can be because of absorption mechanism, competition of two drugs at the protein binding sites, metabolizing enzyme system or excretion. When two or more drugs are concomitantly administered there is always a possibility of pharmacokinetic or pharmacodynamic interaction. The pharmacodynamic interactions can be at the receptor level for competition at same drug target (enzyme/receptor) acting synergistically or antagonizing the effect of each other. The drugs which have narrow therapeutic window have greater potential to cause unexpected adverse effect when their pharmacokinetics or pharmacodynamics is altered. In such situation, the following precautions are advisable:

1. Concomitant administration of drugs should possibly be avoided.
2. When unavoidable, care should be taken and TDM is recommended.
3. When TDM is not possible logistically, clinical symptomatology be done.
4. Careful dose titration (upward/downward) be done to get optimum dose modification.

The following drug categories are considered as drugs of narrow therapeutic window:

Antiepileptics, anticoagulants, anticancers, xanthenes, antidepressants, antiarrhythmics etc.

Some representative clinically relevant drug–drug interactions are listed below:

### **ABCIXIMAB**

Anticoagulants	Increased risk of bleeding
Antiplatelet agents	Increased risk of bleeding

### **ACETAZOLAMIDE**

Carbamazepine	Increased risk of hyponatraemia; acetazolamide increases plasma-carbamazepine concentration
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Digoxin	Cardiac toxicity of digoxin increased if hypokalaemia occurs
Furosemide	Increased risk of hypokalaemia
Nifedipine	Enhanced hypotensive effect
Phenytoin	Increased risk of osteomalacia
<b>ACETYLSALICYLIC ACID</b>	
Corticosteroids	Increased risk of gastrointestinal bleeding and ulceration; corticosteroids reduce plasma-salicylate concentration
Heparin	Enhanced anticoagulant effect
Methotrexate	Reduced excretion of methotrexate (increased toxicity)
Warfarin	Increased risk of bleeding due to antiplatelet effect
<b>ALENDRONATE</b>	
Calcium supplements	Reduced absorption of alendronate
Antacids	Reduced absorption of alendronate
<b>ALLOPURINOL</b>	
Azathioprine	Effects of azathioprine enhanced with increased toxicity; reduce dose when given with allopurinol
Mercaptopurine	Effects of 6-mercaptopurine enhanced with increased toxicity; reduce dose when given with allopurinol
<b>ALTEPLASE</b>	
Prostacyclin, nitrates	Increased plasma-alteplase clearance
Abciximab	Additive effect
Nitroglycerin	Decreased thrombolytic effect of alteplase
Warfarin, Antiplatelet agents	Increased risk of bleeding
NSAIDs	Increased risk of GI bleeding

**AMILORIDE**

Artemether + Lumefantrine	Increased risk of ventricular arrhythmias if electrolyte disturbance occurs
Cisplatin	Increased risk of nephrotoxicity and ototoxicity
Cyclosporine	Increased risk of hyperkalaemia
Enalapril	Enhanced hypotensive effect; risk of severe hyperkalaemia

**AMINOPHYLLINE**

Febuxostat	Increased effect of aminophylline.
Rifamycin	Decreased effect of aminophylline.

**AMITRIPTYLINE**

Artemether + Lumefantrine	Increased risk of ventricular arrhythmias
Carbamazepine	Antagonism of anticonvulsant effect
Haloperidol	Increased plasma–amitriptyline concentration; increased risk of ventricular arrhythmias
Phenobarbital	Antagonism of anticonvulsant effect
Phenytoin	Antagonism of anticonvulsant effect
Valproic acid	Antagonism of anticonvulsant effect

**AMOXYCILLIN**

Methotrexate	Reduced excretion of methotrexate; increased risk of toxicity
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**AMOXYCILLIN + CLAVULANIC ACID**

Probenecid	Increased concentrations of amoxicillin in serum and bile
Allopurinol	Occurrence of allergic cutaneous reactions
Digoxin	Increased absorption
Warfarin	Increased incidence of bleeding

**AMPHOTERICIN B**

Corticosteroids	Increased risk of hypokalaemia
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Cyclosporine	Increased risk of nephrotoxicity
Digoxin	Increased digoxin toxicity if hypokalaemia occurs
Tacrolimus	Synergistic effect of amphotericin

**AMPICILLIN**

Methotrexate	Reduced excretion of methotrexate; increased risk of toxicity
Warfarin	Studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of ampicillin

**ANTACIDS (ALUMINIUM HYDROXIDE; MAGNESIUM HYDROXIDE)**

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*Note: Antacids should preferably not be taken at the same time as other drugs since they may impair absorption*

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Ciprofloxacin	Reduced absorption of ciprofloxacin
Digoxin	Reduced absorption of digoxin
Isoniazid	Reduced absorption of isoniazid
Phenytoin	Reduced absorption of phenytoin
Rifampicin	Reduced absorption of rifampicin

**ARTEMETHER + LUMEFANTRINE**

Amitriptyline	Increased risk of ventricular arrhythmias
Azithromycin	Avoid concomitant use
Chloroquine	Increased risk of ventricular arrhythmias
Ciprofloxacin	Avoid concomitant use
Fluconazole	Avoid concomitant use
Furosemide	Increased risk of ventricular arrhythmias if electrolyte disturbance occurs
Mefloquine	Increased risk of ventricular arrhythmias
Ofloxacin	Avoid concomitant use
Pyrimethamine	Avoid concomitant use



Quinine	Increased risk of ventricular arrhythmias
Sulfadoxine + Pyrimethamine	Avoid concomitant use
<b>ATENOLOL</b>	
Glibenclamide	Masking of warning signs of hypoglycaemia such as tremor
Insulins	Enhanced hypoglycaemic effect; masking of warning signs of hypoglycaemia such as tremor
Lidocaine	Increased risk of myocardial depression
Nifedipine	Severe hypotension and heart failure occasionally
Verapamil	Asystole, severe hypotension and heart failure
<b>ATORVASTATIN</b>	
Ketoconazole	Increased plasma concentration of atorvastatin and risk of myotoxicity in frequent
Itraconazole	Increased plasma concentration of atorvastatin and risk of myotoxicity in frequent
Ritonavir	Increased plasma concentration of atorvastatin and risk of myotoxicity in frequent
Erythromycin	Increased plasma concentration of atorvastatin and risk of myotoxicity in frequent
Fibrates	Increased risk of rhabdomyolysis
<b>AZATHIOPRINE</b>	
Allopurinol	Effects of azathioprine enhanced
Phenytoin	Reduced absorption of phenytoin
Rifampicin	Transplants rejected
Sulfamethoxazole + Trimethoprim	Increased risk of haematological toxicity
Vaccines, Live	Avoid use of live vaccines with azathioprine (impairment of immune response)
Warfarin	Reduced effect of anticoagulant

**AZITHROMYCIN**

Cyclosporine	Plasma concentration of cyclosporine increased
Digoxin	Effect of digoxin enhanced
Warfarin	Enhanced anticoagulant effect of warfarin

**BACLOFEN**

Tricyclic antidepressants	Risk of muscle weakness
MAO inhibitors	Depression of brain function as well as low blood pressure
Antidiabetic drugs	Increased blood sugar level

**BENZATHINE BENZYL PENICILLIN**

Aminoglycosides	Reduced effect of aminoglycosides in patient with renal impairment
Methotrexate	Reduced excretion of methotrexate

**BLEOMYCIN**

Vaccines, Live	Avoid use of live vaccines with bleomycin (impairment of immune response)
Vinblastine	Increased risk of cardiovascular toxicity

**BROMOCRIPTINE**

Ergot derivatives	Additive dopamine agonistic activity
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**BUDESONIDE**

Ketoconazole	Plasma concentration of orally administered budesonide increased
Itraconazole	Metabolism of budesonide inhibited
Clarithromycin	Metabolism of budesonide inhibited
Erythromycin	Metabolism of budesonide inhibited

**BUPIVACAINE**

Lidocaine	Increased myocardial depression
Procainamide	Increased myocardial depression
Quinidine	Increased myocardial depression

**BUSULPHAN**

Itraconazole	Increased level of busulphan
Metronidazole	Increased level of busulphan
Nalidixic acid	Risk of gastrointestinal toxicity
Thioguanine	Risk of portal hypertension and esophageal varices

**CALCIUM CARBONATE + VITAMIN D<sub>3</sub>**

Quinolones	Risk of decreased absorption into the body
Tetracycline	Risk of decreased absorption into the body
Mycophenolate mofetil	Decreased effectiveness of mycophenolate mofetil

**CALCIUM SALTS**

Digoxin	Large intravenous doses of calcium can precipitate arrhythmias
Tetracyclines	Reduced absorption of tetracyclines

**CAPREOMYCIN**

BCG vaccine	May make the vaccine ineffective
Neuromuscular blocking agents	Increase in neuromuscular blocking effects
Typhoid vaccine	May make the vaccine ineffective

**CARBAMAZEPINE**

Acetazolamide	Increased risk of hyponatraemia; acetazolamide increases plasma-carbamazepine concentration
Amitriptyline	Antagonism (convulsive threshold lowered); accelerated metabolism of amitriptyline; reduced plasma concentration; reduced effect antidepressant
Chloroquine	Convulsive threshold occasionally lowered
Chlorpromazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Corticosteroids	Accelerated metabolism of corticosteroids

Cyclosporine	Accelerated metabolism (reduced plasma–cyclosporine concentration)
Diltiazem	Increased carbamazepine level
Erythromycin	Increased plasma–carbamazepine concentration
Fluphenazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Haloperidol	Antagonism of anticonvulsant effect
Isoniazid	Increased plasma–carbamazepine concentration (also isoniazid hepatotoxicity increased)
Lopinavir	Reduced plasma–lopinavir concentration
Progestins	Accelerated metabolism of progestins
Sulfamethoxazole + Trimethoprim	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of carbamazepine often lowered
Phenytoin	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin often lowered
Ritonavir	Plasma concentration increased by ritonavir
Valproic acid	Plasma concentration of valproic acid often lowered; plasma concentration of active metabolite of carbamazepine often raised
Verapamil	Enhanced effect of carbamazepine
Warfarin	Accelerated metabolism of warfarin (reduced anticoagulant effect)
<b>CEFAZOLIN</b>	
Oral anticoagulants	Increased hypoprothrombinemic effect of anticoagulant.
<b>CEFIXIME</b>	
Carbamazepine	Elevated carbamazepine levels

Anticoagulants	Increased prothrombin time
<b>CEFTAZIDIME</b>	
Furosemide	Nephrotoxicity of ceftazidime increased
Warfarin	Enhanced anticoagulant effect
<b>CEFTRIAZONE</b>	
Warfarin	Enhanced anticoagulant effect
<b>CHLORAMPHENICOL</b>	
Cyclosporine	Plasma concentration of cyclosporine increased
Iron	Avoid as can cause bone marrow depression which appears treatment of anaemia
Phenobarbital	Metabolism of chloramphenicol accelerated (reduced chloramphenicol concentration)
Phenytoin	Plasma–phenytoin concentration increased (risk of toxicity)
Vitamin B <sub>12</sub>	Avoid concomitant use, can cause bone marrow depression
<b>CHLOROQUINE</b>	
Artemether + Lumefantrine	Increased risk of ventricular arrhythmias
Carbamazepine	Convulsive threshold occasionally lowered
Cyclosporine	Increased plasma–cyclosporine concentration (increased risk of toxicity)
Digoxin	Plasma–digoxin concentration increased
Mefloquine	Increased risk of convulsions
Phenytoin	Convulsive threshold occasionally lowered
Valproic acid	Convulsive threshold occasionally lowered
<b>CHLORPROMAZINE</b>	
Amitriptyline	Increased antimuscarinic adverse effects; increased plasma–amitriptyline concentration; increased risk of ventricular arrhythmias

Artemether + Lumefantrine	Increased risk of ventricular arrhythmias
Clomipramine	Increased antimuscarinic adverse effects; increased plasma-clomipramine concentration; increased risk of ventricular arrhythmias
Ether, Anaesthetic	Enhanced hypotensive effect
Halothane	Enhanced hypotensive effect
Ketamine	Enhanced hypotensive effect
Nitrous oxide	Enhanced hypotensive effect
Phenobarbital	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Phenytoin	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Procainamide	Increased risk of ventricular arrhythmias
Propranolol	Concomitant administration may increase plasma concentration of both drugs; enhanced hypotensive effect
Quinidine	Increased risk of ventricular arrhythmias
Ritonavir	Plasma concentration increased by ritonavir
Thiopental	Enhanced hypotensive effect
Valproic acid	Antagonism of anticonvulsant effect (convulsive threshold lowered)

**CINNARIZINE**

CNS depressants (alcohol, barbiturates, hypnotics, narcotic analgesics, tricyclic antidepressants, sedatives and tranquillizers)	Additive sedation
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Zolpidem	Additive toxicity
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**CIPROFLOXACIN**

Artemether + Lumefantrine	Avoid concomitant use
Cyclosporine	Increased risk of nephrotoxicity
Glibenclamide	Enhanced effect of glibenclamide

Ibuprofen	Increased risk of convulsions
Warfarin	Enhanced anticoagulant effect
<b>CISPLATIN</b>	
Aminoglycoside antibiotics	Increased risk of nephrotoxicity and ototoxicity
Furosemide	Increased risk of nephrotoxicity and ototoxicity
Hydrochlorothiazide	Increased risk of nephrotoxicity and ototoxicity
Vancomycin	Increased risk of nephrotoxicity and ototoxicity
<b>CLARITHROMYCIN</b>	
Oral anticoagulants	Increased anticoagulant effect.
Carbamazepine	Increased serum concentration of carbamazepine.
Digoxin	Increased concentration of digoxin.
Lovastatin	Avoid concomitant use
Sildenafil	Dose reduction of sildenafil may be required.
Simvastatin	Avoid concomitant use
Sirolimus	Elevation in serum sirolimus level
Tacrolimus	Elevation in serum sirolimus level
Tadalafil	Dose reduction of tadalafil may be required.
<b>CLINDAMYCIN</b>	
Erythromycin	Antagonist activity
Pancuronium	Neuromuscular blockade exaggerated
Kaoli-pectin	Reduced absorption rate
Gentamycin	Synergistic effect
<b>CLOBAZAM</b>	
Cimetidine	Increased effect of clobazam
Barbiturates	Decreased serum level of clobazam
<b>CLONAZEPAM</b>	

Carbamazepine	Decreased level of carbamazepine
Ketoconazole	Inhibition of metabolism of clonazepam
<b>CLOPIDOGREL</b>	
Omeprazole	Plasma concentration of active metabolite of clopidogrel is decreased
NSAIDs	Increased risk of gastrointestinal bleeding
<b>CLONIDINE</b>	
Beta blockers	Sinus bradycardia, monitor heart rate
Clomipramine	Risk of hypertensive crisis
<b>CODEINE</b>	
Diazepam	Enhanced sedative effect
Ritonavir	Ritonavir increases plasma concentration of codeine
<b>CORTICOSTEROIDS</b>	
Acetylsalicylic acid	Increased risk of gastrointestinal bleeding and ulceration; hydrocortisone reduces plasma-salicylate concentration
Amphotericin B	Increased risk of hypokalaemia
Atenolol	Antagonism of hypotensive effect
Carbamazepine	Accelerated metabolism of hydrocortisone (reduced effect)
Digoxin	Increased risk of hypokalaemia
Enalapril	Antagonism of hypotensive effect
Furosemide	Antagonism of diuretic effect; increased risk of hypokalaemia
Glibenclamide	Antagonism of hypoglycaemic effect
Hydrochlorothiazide	Antagonism of diuretic effect; increased risk of hypokalaemia
Insulins	Antagonism of hypoglycaemic effect
Levonorgestrel	Levonorgestrel increases plasma concentration of corticosteroids



Methotrexate	Increased risk of haematological toxicity
Nifedipine	Antagonism of hypotensive effect
Phenobarbital	Metabolism of hydrocortisone accelerated (reduced effect)
Phenytoin	Metabolism of hydrocortisone accelerated (reduced effect)
Rifampicin	Accelerated metabolism of corticosteroids (reduced effect)
Salbutamol	Increased risk of hypokalaemia if high doses of corticosteroids given with high doses of salbutamol
Warfarin	Anticoagulant effect altered

**CYCLOPHOSPHAMIDE**

Vaccines, Live	Avoid use of live vaccines with cyclophosphamide (impairment of immune response)
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**CYCLOSPORINE**

Amphotericin B	Increased risk of nephrotoxicity
Ciprofloxacin	Increased risk of nephrotoxicity
Digoxin	Reduced clearance of digoxin (risk of toxicity)
Enalapril	Increased risk of hyperkalaemia
Erythromycin	Increased plasma-cyclosporine concentration
Methotrexate	Increased toxicity
Metoclopramide	Plasma-cyclosporine concentration increased
Ofloxacin	Increased risk of nephrotoxicity
Phenobarbital	Metabolism of cyclosporine accelerated
Phenytoin	Accelerated metabolism
Rifampicin	Accelerated metabolism (reduced plasma-cyclosporine concentration)
Ritonavir	Plasma concentration increased by ritonavir
Rosuvastatin	Marked rise in serum rosuvastatin level

Sulfonamides and Trimethoprim	Increased toxicity
Vaccines, Live	Avoid use of live vaccines with cyclosporine
Vancomycin	Increased risk of nephrotoxicity

**DANAZOL**

Anticoagulants (warfarin )	Danazol inhibits metabolism of coumarins
Cyclosporine	Danazol inhibits metabolism of cyclosporine
Lovastatin	Increased risk of myopathy
Simvastatin	Increased risk of myopathy
Tacrolimus	Danazol increases plasma concentration of tacrolimus

**DAPSONE**

Rifampicin	Reduced plasma-dapsone concentration
Sulfamethoxazole + Trimethoprim	Plasma concentration of both dapsone and trimethoprim increased with concomitant use

**DEFERRIOXAMINE MESYLATE**

Ascorbic acid	May worsen iron toxicity
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**DEXAMETHASONE**

Acetazolamide	Increased risk of hypokalaemia; antagonism of diuretic effect
Acetylsalicylic acid	Increased risk of gastrointestinal bleeding and ulceration; dexamethasone reduces plasma-salicylate concentration
Albendazole	Plasma-albendazole concentration increased
Amiloride	Antagonism of diuretic effect
Amphotericin B	Increased risk of hypokalaemia (avoid concomitant use unless dexamethasone needed to control reactions)
Atenolol	Antagonism of hypotensive effect
Carbamazepine	Accelerated metabolism of dexamethasone (reduced effect)
Digoxin	Increased risk of hypokalaemia

Enalapril	Antagonism of hypotensive effect
Ephedrine	Metabolism of dexamethasone accelerated
Erythromycin	Erythromycin inhibits metabolism of dexamethasone
Furosemide	Antagonism of diuretic effect; increased risk of hypokalaemia
Glibenclamide	Antagonism of hypoglycaemic effect
Glyceryl trinitrate	Antagonism of hypotensive effect
Hydralazine	Antagonism of hypotensive effect
Hydrochlorothiazide	Antagonism of diuretic effect; increased risk of hypokalaemia
Ibuprofen	Increased risk of gastrointestinal bleeding and ulceration
Indinavir	Reduced plasma-indinavir concentration
Insulins	Antagonism of hypoglycaemic effect
Isosorbide dinitrate	Antagonism of hypotensive effect
Levonorgestrel	Levonorgestrel increases plasma concentration of dexamethasone
Lopinavir	Reduced plasma-lopinavir concentration
Medroxyprogesterone	Medroxyprogesterone increases plasma concentration of dexamethasone
Metformin	Antagonism of hypoglycaemic effect
Methotrexate	Increased risk of haematological toxicity
Methyldopa	Antagonism of hypotensive effect
Nifedipine	Antagonism of hypotensive effect
Norethisterone	Norethisterone increases plasma concentration of dexamethasone

Phenobarbital	Metabolism of dexamethasone accelerated (reduced effect)
Phenytoin	Metabolism of dexamethasone accelerated (reduced effect)
Praziquantel	Plasma-praziquantel concentration reduced
Propranolol	Antagonism of hypotensive effect
Rifampicin	Accelerated metabolism of dexamethasone (reduced effect)
Ritonavir	Increased plasma concentration by ritonavir
Salbutamol	Increased risk of hypokalaemia if high doses of dexamethasone given with high doses of salbutamol
Saquinavir	Reduced plasma-saquinavir concentration
Sodium nitroprusside	Antagonism of hypotensive effect
Spirolactone	Antagonism of diuretic effect
Theophylline	Increased risk of hypokalaemia
Vaccines, Live	High doses of dexamethasone impair immune response; avoid use of live vaccines
Verapamil	Antagonism of hypotensive effect
Warfarin	Anticoagulant effect altered
<b>DEXTRAN 40</b>	
Abciximab	Additive effect
<b>DEXTROMETHORPHAN</b>	
MAO Inhibitors	Risk of hypotension, hyperpyrexia, sedation etc.
Sibutramine	Risk of serotonin syndrome
<b>DIAZEPAM</b>	
Atenolol	Enhanced hypotensive effect
Enalapril	Enhanced hypotensive effect
Furosemide	Enhanced hypotensive effect

Glyceryl trinitrate	Enhanced hypotensive effect
Ritonavir	Plasma concentration increased by ritonavir
<b>DICLOFENAC</b>	
Cyclosporine	Decreased renal function
Methotrexate	Increased levels of methotrexate.
<b>DICYCLOMINE</b>	
Antidepressants	Increased risk of antimuscarinic side effects
Antipsychotics	Antimuscarinics reduce effects of haloperidol; increased risk of antimuscarinic side effects when antimuscarinics given with clozapine; antimuscarinics reduce plasma concentration of phenothiazines, but risk of antimuscarinic side effects increased
<b>DIDANOSINE</b>	
Divalproex	Risk of additive toxicity
Ganciclovir	Increased didanosine concentration
Metronidazole	Risk of additive toxicity
Pentamidine	Risk of additive toxicity
Stavudine	Risk of additive toxicity
Vinblastine	Risk of additive toxicity
<b>DIGOXIN</b>	
Acetazolamide	Cardiac toxicity of digoxin increased if hypokalaemia occurs
Amphotericin B	Increased digoxin toxicity if hypokalaemia occurs
Atenolol	Increased AV block and bradycardia
Corticosteroids	Increased risk of hypokalaemia
Cyclosporine	Reduced clearance of digoxin (risk of toxicity)
Furosemide	Cardiac toxicity of digoxin increased if hypokalaemia occurs

Hydrochlorothiazide	Cardiac toxicity of digoxin increased if hypokalaemia occurs
Nifedipine	Increased plasma concentration of digoxin
Timolol	Increased AV block and bradycardia
Verapamil	Increased plasma concentration of digoxin; increased AV block and bradycardia

**DIHYDROERGOTAMINE**

Amiodarone	Increased cardiac depressant effects
Azoles antifungal	Increased level of alkaloid
Buspirone	Increased serum level of buspirone
Macrolide antibiotics	Increased plasma level of unchanged alkaloid and peripheral vasoconstriction
Protease inhibitors	Elevated levels of ergot alkaloids
Sumatriptan	Additive effect with dihydroergotamine

**DILTIAZEM**

Carbamazepine	Increased serum level of carbamazepine
Rifampin	Decreased diltiazem plasma concentration

**DOBUTAMINE**

Beta-blockers	Risk of peripheral resistance
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**DOMPERIDONE**

Amiodarone	Additive toxicity with amiodarone.
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**DOPAMINE**

Ergometrine	Increased risk of ergotism
Haloperidol	Antagonism of pressor action

**DOXORUBICIN**

Cyclosporine	Increased risk of neurotoxicity
Cyclophosphamide	Chances of exacerbation of cyclophosphamide-induced hemorrhagic cystitis

Digoxin	Decreased digoxin levels
Paclitaxel	Increased risk of cardiotoxicity
Progesterone	Increased risk of doxorubicin-induced neutropenia
Quinidine	Increases the levels of doxorubicin
Stavudine	Decreased level and effectiveness of stavudine
Vaccines, Live	Avoid use of live vaccines with doxorubicin
Zidovudine	Decreased effect of zidovudine.

**DOXYCYCLINE**

Cyclosporine	Increased plasma-cyclosporine concentration
Ergotamine	Increased risk of ergotism
Warfarin	Anticoagulant effect enhanced

**EFAVIRENZ**

Ergot derivatives	Increased chance of ergotism
Itraconazole	Decreased plasma level of itraconazole
Lopinavir	Plasma concentration of lopinavir reduced
Ritonavir	Increased risk of toxicity

**ENALAPRIL**

Acetylsalicylic acid	Antagonism of hypotensive effect; increased risk of renal impairment
Antacids	Absorption of enalapril reduced
Cyclosporine	Increased risk of hyperkalaemia
Glibenclamide	Hypoglycaemic effect enhanced
Heparin	Increased risk of hyperkalaemia
Lithium	Increased plasma-lithium concentration
Spirolactone	Enhanced hypotensive effect, risk of severe hyperkalaemia

**EPINEPHRINE (ADRENALINE)**

Halothane	Risk of arrhythmias
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**ERYTHROMYCIN**

Artemether + Lumefantrine	Avoid concomitant use
Carbamazepine	Increased plasma-carbamazepine concentration
Corticosteroids	Inhibits metabolism of corticosteroids
Cyclosporine	Increased plasma-cyclosporine concentration
Digoxin	Enhanced effect of digoxin
Warfarin	Enhanced anticoagulant effect

**ERYTHROPOIETIN**

Haematinics	Enhanced efficiency of erythropoietin.
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**ESCITALOPRAM**

Carbamazepine	Carbamazepine toxicity may be precipitated
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**ESMOLOL**

Verapamil	Chances of cardiac arrest
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**ETHINYL ESTRADIOL**

Hydantoin	Decreased effect of estrogen
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**ETOPOSIDE**

Vaccines, Live	Avoid use of live vaccines with etoposide
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**EZETIMIBE**

Bile Acid Sequestrants	Decreased levels and clinical effectiveness of ezetimibe
Fibrates	Elevated levels of ezetimibe leading to toxicity.
Cyclosporine	Increased ezetimibe levels in patients with severe renal insufficiency.

**FACTOR IX**

Acetylsalicylic acid	Risk of bleeding
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**FAMOTIDINE**

Antacids	Reduced absorption of famotidine
Ketoconazole, itraconazole	Reduced absorption of ketoconazole and itraconazole



Ethanol	Gastric mucosal irritation may occur.
<b>FENOFIBRATE</b>	
Anticoagulants	Increased effect of anticoagulants
Statins	Increased risk of kidney and muscle problems
Cyclosporine	Increased risk of nephrotoxicity
<b>FERROUS SALTS</b>	
Ciprofloxacin	Absorption of ciprofloxacin reduced by oral ferrous salts
Doxycycline	Reduced absorption of oral ferrous salts by doxycycline; reduced absorption of doxycycline by oral ferrous salts
Methyldopa	Reduced hypotensive effect of methyldopa
<b>FEXOFENADINE</b>	
Antacids	Decreased absorption of fexofenadine
Erythromycin	Increased plasma concentration of fexofenadine
Ketoconazole	Increased plasma concentration of fexofenadine
<b>FLUCONAZOLE</b>	
Artemether + Lumefantrine	Avoid concomitant use
Cyclosporine	Metabolism of cyclosporine inhibited
Glibenclamide	Plasma concentration of glibenclamide increased
Rifampicin	Accelerated metabolism of fluconazole
Warfarin	Enhanced anticoagulant effect
Zidovudine	Increased plasma concentration of zidovudine (increased risk of toxicity)
<b>FLUCYTOSINE</b>	
Amphotericin B	Renal excretion of flucytosine decreased and cellular uptake increased (flucytosine toxicity increased)

**5-FLUOROURACIL**

Metronidazole	Metabolism of 5-fluorouracil inhibited
Phenytoin	Reduced absorption of phenytoin
Warfarin	Anticoagulant effect enhanced

**FLUOXETINE**

Benzodiazepines	Increased level of benzodiazepines
Clozapine	Increased levels of clozapine
Selected MAO inhibitors	Risk of serotonin syndrome

**FLUPHENAZINE**

Amitriptyline	Increased antimuscarinic adverse effects; increased plasma-amitriptyline concentration; increased risk of ventricular arrhythmias
Artemether + Lumefantrine	Increased risk of ventricular arrhythmias
Atenolol	Enhanced hypotensive effect
Carbamazepine	Antagonism of anticonvulsant effect
Enalapril	Enhanced hypotensive effect
Lithium	Increased risk of extrapyramidal effects and neurotoxicity
Methyldopa	Enhanced hypotensive effect; increased risk of extrapyramidal effects
Metoclopramide	Increased risk of extrapyramidal effects
Nifedipine	Enhanced hypotensive effect
Phenobarbital	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Phenytoin	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Valproic acid	Antagonism of anticonvulsant effect (convulsive threshold lowered)

**FOLIC ACID AND FOLINIC ACID**

Phenobarbital	Plasma concentration of phenobarbital reduced
Phenytoin	Plasma-phenytoin concentration reduced

**FORMOTEROL + FLUTICASONE PROPIONATE**

Ritonavir	Systemic corticosteroid effects including cushing syndrome and adrenal suppression
Ketoconazole	Increased plasma fluticasone propionate concentrations.
MAO inhibitors	Increased risk of cardiovascular adverse effects.

**FOSPHENYTOIN**

Albendazole	Efficacy is impaired by phenytoin
Antipsychotics	Efficacy is impaired by phenytoin
Furosemide	Efficacy is impaired by phenytoin
Quinidine	Efficacy is impaired by phenytoin
Theophylline	Efficacy is impaired by phenytoin
Vitamin D	Efficacy is impaired by phenytoin

**FRAMYCETIN**

Capreomycin	Additive toxicity with capreomycin
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**FURAZOLIDONE**

SSRIs	Risk of serotonin syndrome
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**FUROSEMIDE**

Amphotericin B	Increased risk of hypokalaemia
Artemether + Lumefantrine	Increased risk of ventricular arrhythmias if electrolyte disturbance occurs
Cisplatin	Increased risk of nephrotoxicity and ototoxicity
Digoxin	Cardiac toxicity of digoxin increased if hypokalaemia occurs
Enalapril	Enhanced hypotensive effect
Glibenclamide	Antagonism of hypoglycaemic effect

Corticosteroids	Antagonism of diuretic effect; increased risk of hypokalaemia
Lithium	Increased plasma-lithium concentration and risk of toxicity
Salbutamol	Increased risk of hypokalaemia with high doses of salbutamol
Streptomycin	Increased risk of ototoxicity
Vancomycin	Increased risk of ototoxicity
<b>GEMCITABINE</b>	
Live vaccines	Serum antibody response may not be obtained
Zidovudine	Additive toxicity
<b>GENTAMICIN</b>	
Cyclosporine	Increased risk of nephrotoxicity
Cisplatin	Increased risk of nephrotoxicity and ototoxicity
Suxamethonium	Enhanced muscle relaxant effect
Vancomycin	Increased risk of nephrotoxicity and ototoxicity
Vecuronium	Enhanced muscle relaxant effect
<b>GLIBENCLAMIDE</b>	
Ciprofloxacin	Enhanced effect of glibenclamide
Corticosteroids	Antagonism of hypoglycaemic effect
Enalapril	Hypoglycaemic effect enhanced
Fluconazole	Plasma concentration of glibenclamide increased
Hydrochlorothiazide	Antagonism of hypoglycaemic effect
Levonorgestrel	Antagonism of hypoglycaemic effect
Sulfadoxine + Pyrimethamine	Effect of glibenclamide may be enhanced
Sulfamethoxazole + Trimethoprim	Effect of glibenclamide may be enhanced
Warfarin	Enhanced hypoglycaemic effects and changes to anticoagulant effect

**GLICLAZIDE**

Acetylsalicylic acid	Effect of gliclazide is potentiated
Clofibrate	Effect of gliclazide is potentiated
Sulphonamides	Effect of gliclazide is potentiated
Oral anticoagulants	Effect of gliclazide is potentiated
MAO inhibitors	Effect of gliclazide is potentiated
Rifampicin	Effect of gliclazide is antagonized
Barbiturates	Effect of gliclazide is antagonized
Diuretics	Effect of gliclazide is antagonized
Diazoxide	Effect of gliclazide is antagonized
Glucocorticoids	Effect of gliclazide is antagonized
Sympathomimetics	Effect of gliclazide is antagonized

**GLIMEPIRIDE**

Corticosteroids	Reduced hypoglycaemic action
Phenytoin	Reduced hypoglycaemic action
Thiazides	Reduced hypoglycaemic action

**GLUCAGON**

Anticoagulants	Excess hypoprothrombinemia and bleeding complications
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**GLYCERYL TRINITRATE**

Atenolol	Enhanced hypotensive effect
Corticosteroids	Antagonism of hypotensive effect

**GRISEOFULVIN**

Levonorgestrel	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
Warfarin	Metabolism of warfarin accelerated (reduced anticoagulant effect)

**HALOPERIDOL**

Amitriptyline	Increased plasma-amitriptyline concentration; increased risk of ventricular arrhythmias
Carbamazepine	Antagonism of anticonvulsant effect, metabolism of haloperidol accelerated
Lithium	Increased risk of extrapyramidal effects and neurotoxicity
Metoclopramide	Increased risk of extrapyramidal effects
Phenobarbital	Antagonism of anticonvulsant effect, metabolism of haloperidol accelerated
Phenytoin	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Rifampicin	Accelerated metabolism of haloperidol (reduced plasma-haloperidol concentration)
Valproic acid	Antagonism of anticonvulsant effect (convulsive threshold lowered)

**HALOTHANE**

Amitriptyline	Increased risk of arrhythmias and hypotension
Atenolol	Enhanced hypotensive effect
Diazepam	Enhanced sedative effect
Levodopa	Risk of arrhythmias
Vancomycin	Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
Verapamil	Enhanced hypotensive effect and AV delay

**HEPARIN**

Acetylsalicylic acid	Enhanced anticoagulant effect
Enalapril	Increased risk of hyperkalaemia

**HYDRALAZINE**

Corticosteroids	Antagonism of hypotensive effect
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**HYDROCHLOROTHIAZIDE**

Amitriptyline	Increased risk of postural hypotension
Amphotericin B	Increased risk of hypokalaemia
Artemether + Lumefantrine	Increased risk of ventricular arrhythmias if electrolyte disturbance occurs
Carbamazepine	Increased risk of hyponatraemia
Cisplatin	Increased risk of nephrotoxicity and ototoxicity
Digoxin	Cardiac toxicity of digoxin increased if hypokalaemia occurs
Glibenclamide	Antagonism of hypoglycaemic effect
Ibuprofen	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
Insulins	Antagonism of hypoglycaemic effect
Lithium	Reduced lithium excretion (increased plasma-lithium concentration and risk of toxicity); furosemide safer than hydrochlorothiazide
Salbutamol	Increased risk of hypokalaemia with high doses of salbutamol

**IBUPROFEN**

Acetylsalicylic acid	Avoid concurrent administration (increased adverse effects, including gastrointestinal damage); antiplatelet effect of acetylsalicylic acid reduced
Atenolol	Antagonism of hypotensive effect
Cyclosporine	Increased risk of nephrotoxicity
Ciprofloxacin	Increased risk of convulsions
Corticosteroids	Increased risk of gastrointestinal bleeding and ulceration
Digoxin	Exacerbation of heart failure, reduced GFR, and increased plasma-digoxin concentration
Enalapril	Antagonism of hypotensive effect, increased risk of renal impairment

Glibenclamide	Enhanced effect of glibenclamide
Hydrochlorothiazide	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
Lithium	Reduced excretion of lithium
Methotrexate	Excretion of methotrexate reduced
Nifedipine	Antagonism of hypotensive effect
Warfarin	Anticoagulant effect enhanced
Zidovudine	Increased risk of haematological toxicity
<b>IMATINIB</b>	
Rifampin	Increased clearance of imatinib
Warfarin	Imatinib may inhibit metabolism of warfarin
<b>IMIPENEM + CILASTATIN</b>	
Ganciclovir	May result in generalised seizures
<b>INDINAVIR</b>	
Carbamazepine	Reduced plasma concentration of indinavir
Efavirenz	Reduced plasma concentration of indinavir
Ergotamine	Increased risk of ergotism (avoid concomitant use)
Nelfinavir	Combination may lead to increased plasma concentration of either drug (or both)
Nevirapine	Reduced plasma concentration of indinavir
Phenobarbital	Reduced plasma concentration of indinavir
Rifampicin	Metabolism enhanced by rifampicin
<b>INSULINS</b>	
Atenolol	Enhanced hypoglycaemic effect; masking of warning signs of hypoglycaemia such as tremor
Corticosteroids	Antagonism of hypoglycaemic effect



Enalapril	Hypoglycaemic effect enhanced
Furosemide	Antagonism of hypoglycaemic effect
Hydrochlorothiazide	Antagonism of hypoglycaemic effect
Levonorgestrel	Antagonism of hypoglycaemic effect
Nifedipine	Occasionally impaired glucose tolerance

**IODINE**

Lithium	Synergistic toxicity
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**IOPANOIC ACID**

Atenolol	Iopanoic acid toxicity may occur
Methotrexate	Methotrexate toxicity may occur

**ISONIAZID**

Carbamazepine	Increased plasma-carbamazepine concentration
Diazepam	Metabolism of diazepam inhibited
Phenytoin	Metabolism of phenytoin inhibited

**ISOSORBIDE DINITRATE**

Sildenafil	Serious hypotension, MI may be precipitated
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**ISOTRETINOIN**

Vitamin A	Additive toxicity
Progesterone	Decreased efficacy of microdosed progesterone
Corticosteroids, phenytoin	Increased risk of osteoporosis
Carbamazepine	Decreased plasma levels of carbamazepine
Tetracyclines	Increased risk of pseudotumor cerebri

**ISPAGHULA**

Lithium	Decreased effect of lithium
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**IVERMECTIN**

Vitamin K Antagonists (eg, warfarin)	Enhanced anticoagulant effect
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**KETOCONAZOLE**

Amphotericin B	Increased adverse effect
Cyclosporine	Increased level of cyclosporine
Tolbutamide	Reduces blood glucose level

**LAMIVUDINE**

Foscarnet	Concurrent use not recommended
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**LATANOPROST**

Thiomersal	Risk of precipitate formation
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**LEFLUNOMIDE**

Acenocoumarol	Increased anticoagulant effect
Warfarin	Increased anticoagulant effect
Methotrexate	Increased risk of hepatotoxicity
Cholestyramine	Enhanced leflunomide excretion and increased total clearance by approximately 50%

**LEVOCETIRIZINE**

Alcohol or CNS depressants	Additive sedation
Theophylline	Increases the levels of levocetirizine in blood

**LEVODOPA**

Metoclopramide	Antagonism of effects of levodopa
Ether, Anaesthetic	Risk of arrhythmias
Ferrous salts	Absorption of levodopa may be reduced
Halothane	Risk of arrhythmias
Methyldopa	Enhanced hypotensive effect; antagonism of antiparkinsonian effect
Nifedipine	Enhanced hypotensive effect
Propranolol	Enhanced hypotensive effect
Pyridoxine	Antagonism of levodopa unless carbidopa also given

**LEVOTHYROXINE**

Phenobarbital	Metabolism of levothyroxine accelerated (may increase levothyroxine requirements in hypothyroidism)
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Theophylline	Metabolism of theophylline is increased; larger doses are required
Warfarin	Enhanced anticoagulant effect
<b>LIDOCAINE</b>	
Acetazolamide	Action of lidocaine antagonised by hypokalaemia
Atenolol	Increased risk of myocardial depression
Bupivacaine	Increased myocardial depression
Furosemide	Action of lidocaine antagonised by hypokalaemia
Hydrochlorothiazide	Action of lidocaine antagonised by hypokalaemia
Procainamide	Increased myocardial depression
Propranolol	Increased risk of myocardial depression; increased risk of lidocaine toxicity
Quinidine	Increased myocardial depression
Timolol	Increased risk of myocardial depression
Verapamil	Increased risk of myocardial depression
<b>LITHIUM</b>	
Acetazolamide	Excretion of lithium increased
Amiloride	Reduced lithium excretion (increased plasma-lithium concentration and risk of toxicity)
Enalapril	Enalapril reduces excretion of lithium (increased plasma-lithium concentration)
Furosemide	Reduced lithium excretion (increased plasma-lithium concentration and risk of toxicity); furosemide safer than hydrochlorothiazide
Haloperidol	Increased risk of extrapyramidal effects and possibility of neurotoxicity
Hydrochlorothiazide	Reduced lithium excretion (increased plasma-lithium concentration and risk of toxicity); furosemide safer than hydrochlorothiazide

Ibuprofen	Reduced excretion of lithium (risk of toxicity)
Methyldopa	Neurotoxicity may occur without increased plasma-lithium concentration
Spirolactone	Reduced lithium excretion (increased plasma-lithium concentration and risk of toxicity)
Suxamethonium	Enhanced muscle relaxant effect
<b>LOPERAMIDE</b>	
Quinidine	Increased CNS level of loperamide
<b>MEBENDAZOLE</b>	
Carbamazepine	Reduced plasma-mebendazole concentration (increase mebendazole dose for tissue infection)
Phenytoin	Reduced plasma-mebendazole concentration (increase mebendazole dose for tissue infection)
<b>MEFENAMIC ACID</b>	
Warfarin	Risk of serious GI bleeding higher than users of either drug alone.
Lithium	Reduced renal clearance and increased risk of lithium toxicity.
Methotrexate	Reduced excretion of methotrexate and possible increased risk of toxicity
Phenobarbital	Reduced plasma-mebendazole concentration (increase mebendazole dose for tissue infection)
<b>6-MERCAPTOPURINE</b>	
Allopurinol	Effects of 6-mercaptopurine enhanced with increased toxicity, reduce dose when given with allopurinol
Phenytoin	Reduced absorption of phenytoin
Sulfamethoxazole + Trimethoprim	Increased risk of haematological toxicity

Sulfasalazine	Increased risk of leukopenia
Trimethoprim	Increased risk of haematological toxicity
Vaccines, Live	Avoid use of live vaccines with 6-mercaptopurine (impairment of immune response)
Warfarin	Anticoagulant effect reduced
<b>MEROPENEM</b>	
Probenecid	Renal excretion of meropenem is inhibited
Valproic acid	Serum valproic acid concentration is decreased
<b>METFORMIN</b>	
Atenolol	Masking of warning signs of hypoglycaemia such as tremor
Corticosteroids	Antagonism of hypoglycaemic effect
Enalapril	Hypoglycaemic effect enhanced
Levonorgestrel	Antagonism of hypoglycaemic effect
Lithium	May occasionally impair glucose tolerance
Medroxyprogesterone	Antagonism of hypoglycaemic effect
Norethisterone	Antagonism of hypoglycaemic effect
<b>METHADONE</b>	
Cimetidine	Effect of methadone may be increased
MAO Inhibitors	Risk of hypotension, hyperexia etc.
<b>METHOTREXATE</b>	
Acetylsalicylic acid	Reduced excretion of methotrexate (increased toxicity)
Amoxycillin	Reduced excretion of methotrexate (increased risk of toxicity)
Cyclosporine	Increased toxicity
Ibuprofen	Excretion of methotrexate reduced (increased risk of toxicity)

Nitrous oxide	Increased antifolate effect (avoid concomitant use)
Phenytoin	Reduced absorption of phenytoin; antifolate effect of methotrexate increased
Pyrimethamine	Antifolate effect of methotrexate increased
Sulfadoxine + Pyrimethamine	Antifolate effect of methotrexate increased; risk of methotrexate toxicity increased
Sulfamethoxazole + Trimethoprim	Antifolate effect of methotrexate increased (avoid concomitant use); risk of methotrexate toxicity increased
Trimethoprim	Antifolate effect of methotrexate increased (avoid concomitant use)
Vaccines, Live	Avoid use of live vaccines with methotrexate (impairment of immune response)
<b>METHYLDOPA</b>	
Ferrous salts	Reduced hypotensive effect of methyldopa
Propranolol	Enhanced hypotensive effect
<b>METHYL PREDNISOLONE</b>	
Amphotericin B	Chances of potentiation of K <sup>+</sup> concentration
Cyclosporine	Levels increased up to 2 fold
<b>METRONIDAZOLE</b>	
Phenytoin	Metabolism of phenytoin inhibited (increased plasma-phenytoin concentration)
Warfarin	Enhanced anticoagulant effect
MMR vaccine	See vaccines, live
<b>MIDAZOLAM</b>	
Ketoconazole	Increased levels of midazolam
Verapamil	Increased levels of midazolam
<b>MIFEPRISTONE</b>	
Dexamethasone	Decreased serum levels of mifepristone

**MOMETASONE**

Anticoagulants	Increased or decreased effects of anticoagulants
Bupropion	Increased risk of seizures
Quinolones	Increased risk of tendonitis and/or tendon rupture
Quetiapine	Decreased levels of quetiapine

**MORPHINE**

Ciprofloxacin	Avoid premedication with morphine (reduced plasma-ciprofloxacin concentration)
Quinidine	Decreased analgesic effect
Ritonavir	Ritonavir increases plasma concentration of morphine

**MYCOPHENOLATE**

Bile acid sequestrants	Decreased level and clinical effect of mycophenolate
Antacids	Decreased effect

**NALIDIXIC ACID**

Cyclosporine	Increased risk of nephrotoxicity
Ibuprofen	Increased risk of convulsions
Theophylline	Increased risk of convulsions
Warfarin	Enhanced anticoagulant effect

**NELFINAVIR**

Ergotamine	Increased risk of ergotism (avoid concomitant use)
Phenobarbital	Plasma concentration of nelfinavir reduced
Quinidine	Increased risk of ventricular arrhythmias (avoid concomitant use)
Rifampicin	Plasma concentration of nelfinavir significantly reduced (avoid concomitant use)

**NEOSTIGMINE**

Gentamicin	Antagonism of effect of neostigmine
Streptomycin	Antagonism of effect of neostigmine

**NEVIRAPINE**

Lopinavir	Plasma concentration of lopinavir reduced
Rifampicin	Reduced plasma concentration of nevirapine (avoid concomitant use)
Saquinavir	Plasma concentration of saquinavir reduced (avoid concomitant use)

**NICOTINIC ACID**

Ganglionic blocking agents and vasoactive drugs	Potentiates the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension
Bile acid sequestrants (for example, cholestyramine)	Bind and prevent absorption of niacin, should be separated by 4-6 hours.

**NIFEDIPINE**

Atenolol	Severe hypotension and heart failure occasionally
Cyclosporine	Increased plasma-nifedipine concentration (increased risk of adverse effects such as gingival hyperplasia)
Digoxin	Increased plasma concentration of digoxin
Magnesium (parenteral)	Profound hypotension reported with nifedipine and intravenous magnesium sulphate in pre-eclampsia
Phenobarbital	Effect of nifedipine reduced
Phenytoin	Reduced effect of nifedipine
Propranolol	Severe hypotension and heart failure occasionally
Ritonavir	Plasma concentration increased by ritonavir
Rifampicin	Accelerated metabolism of nifedipine (plasma concentration significantly reduced)
Theophylline	Enhanced theophylline effect (increased plasma-theophylline concentration)



Timolol	Severe hypotension and heart failure occasionally
<b>NITROUS OXIDE</b>	
Chlorpromazine	Enhanced hypotensive effect
Fluphenazine	Enhanced hypotensive effect
Haloperidol	Enhanced hypotensive effect
Methotrexate	Increased antifolate effect (avoid concomitant use)
Verapamil	Enhanced hypotensive effect and AV delay
<b>NORADRENALINE</b>	
Guanethidine + methyldopa + reserpine + tricyclic antidepressants	Pressor response to norepinephrine may be increased
Cocaine	Increased risk of arrhythmias
MAOIs	Hypertensive crisis occurs
Nonselective $\beta$ -blockers	Increased hypertensive effects
<b>OMEPRAZOLE</b>	
Cilostazol	Increased levels of cilostazole
Nelfinavir	Decreased level of nelfinavir
Raltegravir	Increased levels of raltigavir
<b>ONDANSETRON</b>	
Tramadol	Decreased effectiveness of tramadol.
<b>OXCARBAMAZEPINE</b>	
Lamotrigine	Decreased levels of lamotrigine
<b>OXYTETRACYCLINE</b>	
Calcium and Iron dextran	Formation of non-absorbable complexes
Penicillins	Antagonism of effect of oxytetracycline
Etritenate and isotretinoin	Associated with increased risk of intracranial hypertension
Oral contraceptives	May decrease the effect of oral contraceptives.
<b>PHENOBARBITAL</b>	

Amitriptyline	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of amitriptyline accelerated (reduced plasma concentration)
Carbamazepine	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of carbamazepine often lowered
Cyclosporine	Metabolism of cyclosporine accelerated (reduced effect)
Haloperidol	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration)
Nifedipine	Effect of nifedipine reduced
Phenytoin	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of phenobarbital often raised
Valproic acid	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; phenobarbital concentration often raised
Warfarin	Metabolism of warfarin accelerated (reduced anticoagulant effect)

**PHENOXYMETHYL PENICILLIN**

Methotrexate	Reduced excretion of methotrexate (increased risk of toxicity)
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**PHENYTOIN**

Amitriptyline	Antagonism (convulsive threshold lowered); reduced plasma-amitriptyline concentration
Carbamazepine	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of carbamazepine often lowered

Chloramphenicol	Plasma-phenytoin concentration increased (risk of toxicity)
Chloroquine	Convulsive threshold occasionally lowered
Cyclosporine	Accelerated metabolism (reduced plasma-cyclosporine concentration)
Clonazepam	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of clonazepam often lowered
Fluconazole	Effect of phenytoin enhanced; plasma concentration increased
Haloperidol	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Isoniazid	Metabolism of phenytoin inhibited (enhanced effect)
Mefloquine	Antagonism of anticonvulsant effect
Metronidazole	Metabolism of phenytoin inhibited (increased plasma-phenytoin concentration)
Nifedipine	Reduced effect of nifedipine
Pyrimethamine	Antagonism of anticonvulsant effect; increased antifolate effect
Rifampicin	Accelerated metabolism of phenytoin (reduced plasma concentration)
Sulfadoxine + Pyrimethamine	Plasma-phenytoin concentration increased; increased antifolate effect
Sulfamethoxazole + Trimethoprim	Antifolate effect and plasma-phenytoin concentration increased
Valproic acid	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; plasma concentration of phenytoin often raised (but may also be lowered)

Warfarin Accelerated metabolism of warfarin (Reduced anticoagulant effect, but enhancement also reported)

**PIOGLITAZONE**

NSAID Increased risk of fluid retention

Rifampicin Decreased plasma concentration.

Ketoconazole Increased plasma concentration.

**PIPERACILLIN + TAZOBACTAM**

Aminoglycosides Inactivation of aminoglycosides

Methotrexate Reduced clearance of methotrexate

**PREDNISOLONE**

Amphotericin B Increased risk of hypokalaemia (avoid concomitant use unless prednisolone needed to control reactions)

Carbamazepine Accelerated metabolism of prednisolone (reduced effect)

Phenobarbital Metabolism of prednisolone accelerated (reduced effect)

Phenytoin Metabolism of prednisolone accelerated (reduced effect)

Rifampicin Accelerated metabolism of prednisolone (reduced effect)

Vaccines, Live High doses of prednisolone impair immune response; avoid use of live vaccines

Warfarin Anticoagulant effect altered

**PROPOFOL**

Fentanyl Concomitant use in pediatric patients may result in serious bradycardia

CNS depressants Increased sedative, anaesthetic and cardiorespiratory effects

**PYRIDOXINE**

Levodopa Antagonism of levodopa unless carbidopa also given

**PYRIMETHAMINE**

Artemether + Lumefantrine Avoid concomitant use

Methotrexate	Antifolate effect of methotrexate increased
Phenytoin	Antagonism of anticonvulsant effect; increased antifolate effect
Sulfonamides + Trimethoprim	Increased antifolate effect
<b>RALOXIFENE</b>	
Estrogen	Increased risk of adverse effects.
<b>RAMIPRIL</b>	
Diuretics	Excessive reduction of blood pressure
Potassium supplements/ Potassium sparing diuretics	Increased risk of hyperkalemia
Lithium	Increased serum lithium levels and lithium toxicity
<b>RIFAMPICIN</b>	
Azathioprine	Transplants rejected
Cyclosporine	Accelerated metabolism (reduced plasma-cyclosporine concentration)
Dapsone	Reduced plasma-dapsone concentration
Fluconazole	Accelerated metabolism of fluconazole (reduced plasma concentration)
Glibenclamide	Accelerated metabolism (reduced effect) of glibenclamide
Haloperidol	Accelerated metabolism of haloperidol (reduced plasma-haloperidol concentration)
Nifedipine	Accelerated metabolism of nifedipine (plasma concentration significantly reduced)
Phenytoin	Accelerated metabolism of phenytoin (reduced plasma concentration)
Corticosteroids	Accelerated metabolism of corticosteroids
Verapamil	Accelerated metabolism of verapamil (plasma concentration significantly reduced)

Warfarin	Accelerated metabolism of warfarin (reduced anticoagulant effect)
<b>RITONAVIR</b>	
Carbamazepine	Plasma concentration increased by ritonavir
Cyclosporine	Plasma concentration increased by ritonavir
Diazepam	Plasma concentration increased by ritonavir (risk of extreme sedation and respiratory depression-avoid concomitant use)
Fluconazole	Plasma concentration increased by ritonavir
Verapamil	Plasma concentration increased by ritonavir
Warfarin	Plasma concentration increased by ritonavir
<b>SALBUTAMOL</b>	
Methyldopa	Acute hypotension reported with salbutamol infusion
<b>SILDENAFIL</b>	
Protease inhibitors	Sildenafil metabolism is inhibited
Alpha blockers	Avoid concomitant use (may lead to low blood pressure)
Ketoconazole	Increased action of sildenafil
Erythromycin	Increased action of sildenafil
Verapamil	Increased action of sildenafil
Nitrates	Vasoconstrictor activity of nitrates is potentiated
<b>STREPTOMYCIN</b>	
Amphotericin B	Increased risk of nephrotoxicity
Cyclosporine	Increased risk of nephrotoxicity
Cisplatin	Increased risk of nephrotoxicity and ototoxicity
Furosemide	Increased risk of ototoxicity
Neostigmine	Antagonism of effect of neostigmine
Suxamethonium	Enhanced muscle relaxant effect

**STRONTIUM RANELATE**

Calcium products	Reduced bioavailability of strontium ranelate.
Tetracycline	Reduced absorption of oral tetracycline
Quinolone antibiotics	Reduced absorption of quinolone antibiotics
Aluminium and Magnesium Hydroxides	Decreased absorption of strontium ranelate.

**SULFADOXINE + PYRIMETHAMINE**

Artemether + Lumefantrine	Avoid concomitant use
Cyclosporine	Increased risk of nephrotoxicity
Glibenclamide	Effect of glibenclamide rarely, enhanced
Methotrexate	Antifolate effect of methotrexate increased; risk of methotrexate toxicity increased
Phenytoin	Plasma-phenytoin concentration increased; increased antifolate effect
Warfarin	Enhanced anticoagulant effect

**SULFASALAZINE**

Azathioprine	Increased risk of leukopenia
Mercaptopurine	Increased risk of leukopenia

**TACROLIMUS**

Aminoglycosides	Increased risk of renal dysfunction
Carbamazepine	Decreased tacrolimus blood concentration
Cisplatin	Increased risk of renal dysfunction
Clarithromycin	Increased tacrolimus blood concentration
Chloramphenicol	Increased tacrolimus blood concentration
Clotrimazole	Increased tacrolimus blood concentration
Phenytoin	Decreased tacrolimus blood concentration
Rifampin	Decreased tacrolimus blood concentration

Diltiazem	Increased tacrolimus blood concentration
Nifedipine	Increased tacrolimus blood concentration
Verapamil	Increased tacrolimus blood concentration

**TELMISARTAN**

Lithium	Increased in serum lithium concentration and toxicity
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**THALIDOMIDE**

Barbiturates	Enhanced sedative activity
Alcohol	Enhanced sedative activity
Chlorpromazine	Enhanced sedative activity
Reserpine	Enhanced sedative activity
Vincristine	Potential to cause peripheral neuropathy
Bortezomib	Potential to cause peripheral neuropathy

**THEOPHYLLINE**

Ciprofloxacin	Increased plasma-theophylline concentration; increased risk of convulsions
Erythromycin	Inhibition of theophylline metabolism (increased plasma-theophylline concentration resulting in theophylline toxicity)
Fluconazole	Plasma-theophylline concentration increased

**TIMOLOL**

Note: Systemic absorption may follow topical application of timolol to the eye

Epinephrine	Severe hypertension
Verapamil	Asystole, severe hypotension and heart failure

**TOPIRAMATE**

Carbamazepine	Reduced plasma level of topiramate
Phenytoin	Reduced plasma level of topiramate
Rifampin	Reduced plasma level of topiramate



**TRANEXAMIC ACID**

Clotting factor complexes	Increased risk of thrombotic complications
Hormonal contraception	Exacerbate the increased thrombotic risk associated with combination hormonal contraceptives
all-trans Retinoic acid	Concomitant use in women with acute promyelocytic leukemia taking all-trans retinoic acid for remission induction may cause exacerbation of the procoagulant effect of all-trans retinoic acid

**TRIMETHOPRIM**

Mercaptopurine	Increased risk of haematological toxicity
Methotrexate	Antifolate effect of methotrexate increased (avoid concomitant use)
Phenytoin	Antifolate effect and plasma-phenytoin concentration increased
Pyrimethamine	Increased antifolate effect
Sulfadoxine + Pyrimethamine	Increased antifolate effect

**VALPROIC ACID**

Carbamazepine	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; plasma concentration of active metabolite of carbamazepine often raised
Chloroquine	Convulsive threshold occasionally lowered
Mefloquine	Antagonism of anticonvulsant effect
Phenobarbital	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; phenobarbital concentration often raised

Phenytoin	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; plasma concentration of phenytoin often raised (but may also be lowered)
<b>VANCOMYCIN</b>	
Cyclosporine	Increased risk of nephrotoxicity
Furosemide	Increased risk of ototoxicity
<b>VARICELLA VACCINE</b>	
Salicylates	Increased risk of Reye's syndrome
<b>VERAPAMIL</b>	
Atenolol	Asystole, severe hypotension and heart failure
Carbamazepine	Enhanced effect of carbamazepine
Digoxin	Increased plasma concentration of digoxin; increased AV block and bradycardia
Halothane	Enhanced hypotensive effect and AV delay
Ketamine	Enhanced hypotensive effect and AV delay
Lidocaine	Increased risk of myocardial depression
Rifampicin	Accelerated metabolism of verapamil (plasma concentration significantly reduced)
<b>VINBLASTINE</b>	
Bleomycin	Increased risk of cardiovascular toxicity
<b>WARFARIN</b>	
Acetylsalicylic acid	Increased risk of bleeding due to antiplatelet effect
Azathioprine	Anticoagulant effect reduced
Azithromycin	Enhanced anticoagulant effect of warfarin
Carbamazepine	Accelerated metabolism of warfarin (reduced anticoagulant effect)

Ceftazidime	Enhanced anticoagulant effect
Ceftriaxone	Enhanced anticoagulant effect
Chloramphenicol	Enhanced anticoagulant effect
Ciprofloxacin	Enhanced anticoagulant effect
Corticosteroids	Anticoagulant effect altered
Doxycycline	Anticoagulant effect enhanced
Erythromycin	Enhanced anticoagulant effect
Fluconazole	Enhanced anticoagulant effect
5-Fluorouracil	Anticoagulant effect enhanced
Glibenclamide	Enhanced hypoglycaemic effects and changes to anticoagulant effect
Griseofulvin	Metabolism of warfarin accelerated (reduced anticoagulant effect)
Ibuprofen	Anticoagulant effect enhanced
Levamisole	Anticoagulant effect enhanced
Levonorgestrel	Antagonism of anticoagulant effect
Levothyroxine	Enhanced anticoagulant effect
Medroxyprogesterone	Antagonism of anticoagulant effect
Mercaptopurine	Anticoagulant effect reduced
Metronidazole	Enhanced anticoagulant effect
Nalidixic acid	Enhanced anticoagulant effect
Norethisterone	Antagonism of anticoagulant effect
Ofloxacin	Enhanced anticoagulant effect
Phenobarbital	Metabolism of warfarin accelerated (reduced anticoagulant effect)
Phenytoin	Accelerated metabolism of warfarin (reduced anticoagulant effect, but enhancement also reported)
Phytomenadione	Antagonism of anticoagulant effect by phytomenadione
Proguanil	Isolated reports of enhanced anticoagulant effect

Quinidine	Anticoagulant effect may be enhanced
Rifampicin	Accelerated metabolism of warfarin (reduced anticoagulant effect)
Ritonavir	Plasma concentration increased by ritonavir
Sulfadiazine	Enhanced anticoagulant effect
Sulfadoxine + Pyrimethamine	Enhanced anticoagulant effect
Sulfamethoxazole + Trimethoprim	Enhanced anticoagulant effect
Tamoxifen	Enhanced anticoagulant effect
<b>ZIDOVUDINE</b>	
Fluconazole	Increased plasma concentration of zidovudine (increased risk of toxicity)
Stavudine	May inhibit effect of stavudine (avoid concomitant use)
<b>ZOLPIDEM</b>	
Rifampin	Pharmacodynamic effects of zolpidem are decreased
Ketoconazole	Pharmacodynamic effects of zolpidem are increased

## Appendix 6d:

# Drug – Food Interactions

Several drugs when given orally can interact with food consumed by the patients. Table 1 shows the medications which should be taken on an empty stomach.

**Table 1: Medications which should be taken on an EMPTY stomach**

Drug	Food interactions and effect
Ampicillin	Reduced absorption
Alendronate	Decreased bioavailability
Azithromycin	Reduced absorption
Bisacodyl	Dissolves enteric coating
Didanosine	Decreased absorption
Indinavir	Reduced absorption with fat, proteins
Isoniazid	Reduced absorption
Isosorbide dinitrate	Delayed absorption
Levothyroxine	Reduced absorption; anionic exchange resins reduce absorption
Melphalan	Reduced absorption
Methotrexate	Reduced absorption
Mycophenolate	Enhanced absorption
Omeprazole	Delayed absorption
Oxytetracycline	Reduced absorption when taken with dairy products.
Rifampin	Delayed absorption
Roxithromycin	Reduced absorption
Sulfadiazine	Formation of crystalluria on consumption with vitamin C or acidifying agents
Tacrolimus	Reduced absorption
Tetracycline	Reduced absorption, especially when taken with antacids or dairy products
Thyroid	Reduced absorption

## Appendix 6d

Typhoid vaccine (oral)	Reduced absorption
Zidovudine	Enhanced absorption

Food can also impact the effectiveness of a drug due to the way it is consumed. Generally, medicine is to be taken almost at the same time the food is eaten. This is because the medicine may upset the stomach if the stomach is empty. Certain medications are recommended to be taken with food (Table 2).

**Table 2: Medications which should be taken WITH FOOD**

<b>Drug</b>	<b>Food interactions and effect</b>
Acetylsalicylic Acid	Reduced side effects.
Allopurinol	Reduced side effects; reduced clearance of active metabolite with protein-poor diet
Amiodarone	Enhances both the rate and extent of absorption.
Amoxicillin/clavulanic acid	Reduced side effects
Azathioprine	Reduced side effects
Baclofen	Reduced side effects
Bromocriptine	Reduced side effects
Carbamazepine	Increased absorption
Cefuroxime	Increased absorption
Chloroquine	Reduced side effects
Clofazimine	Increased drug absorption
Conjugated estrogens	Reduced side effects
Diclofenac	Reduced peak concentration but not extent of absorption; reduced side effects
Doxycycline	Reduced side effects; reduced absorption with milk
Ethinyl estradiol	Reduced side effects
Ferrous salts	Take between meals, if gastrointestinal upset occurs take with food
Griseofulvin	Increased rate or extent of absorption with fats; reduced side effects
Hydroxychloroquine	Reduced bowel side effects; masks the bitter taste of drug
Hydrocortisone	Slows rate of absorption; reduced peak levels; reduced side effects

## Appendix 6d

Ibuprofen	Reduced side effects
Iron preparations	See ferrous salts
Levocetirizine	May be taken with or without food
Lithium	Reduced side effects
Mebendazole	Increased absorption
Methadone	Reduced side effects
Methylprednisolone	Reduced side effects
Metronidazole	Reduced side effects
Mexiletine	Reduced side effects; slows rate of absorption; reduces rate of caffeine clearance
Morphine	Increased absorption
Nelfinavir	Greatly increases absorption and AUC
Niacin	Reduced absorption; decreases side effects
Nitrofurantoin	Increased absorption
Pioglitazone	Food slightly delays absorption rate but extent of absorption is not affected.
Potassium salts	Reduced side effects
Prednisolone	Reduced side effects
Prednisone	Reduced stomach irritation
Procainamide	Reduced side effects; increased absorption with fat
Propranolol	Slows rate but increases extent of absorption
Quinine	Reduced side effects
Ritonavir	Increased absorption
Salsalate	Reduced stomach irritation.
Saquinavir	Increased absorption.



Sodium chloride	Reduced side effects
Spiroinolactone	Increased absorption; reduced side effects
Sulfasalazine	Reduced side effects
Sodium valproate	Reduced side effects

**Table 3: Selected herbal or food products resulting in adverse effects**

Herb/Food	Drug	Adverse Effects/Reported Drug Interactions/ Remark
Licorice	Digoxin Spiroinolactone	Elevates serum digoxin levels 4-fold, arrhythmias Hypokalemia and muscle weakness
Foods high in vitamin K (broccoli, sprouts, turnip greens, spinach, cauliflower, legumes, mayonnaise, soybean oils and fish)	Anticoagulants (warfarin)	Such foods may reduce the effectiveness of anticoagulants, increasing the risk of clotting. Intake of such foods should be limited, and the amount consumed daily should remain constant.
Foods high in sodium (like licorice, processed meats, canned foods)	Amlodipine	Such foods decrease the effectiveness of the drug
Calcium or foods containing calcium (milk and other dairy products)	Tetracycline	These foods can reduce the absorption of tetracycline, which should be taken 1 hr before or 2 hr after eating
Foods high in tyramine, (includes cheese, yoghurt, sour cream, cured meats, liver, dried fish, bananas, yeast extracts, raisins, soya sauce, red wine, certain beers)	MAO - inhibitors (such as phenelzine and tranlycypromine)	Severe headache and a potentially fatal increase in BP (hypertensive crisis) can occur if people taking MAO - inhibitors consume these foods. These foods must be avoided.

## Appendix 7a: Hepatic Impairment

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### Dosing considerations in hepatic impairment

Hepatobiliary system plays an important role in the interactions between drugs and the body. Liver diseases can affect pharmacokinetics and pharmacodynamics of various drugs. However there has to be moderate to severe hepatic impairment to significantly alter the response to drugs as liver has a large reserve capacity. Hepatic impairment may alter response to drugs not only because of its role in metabolism of drugs but it also affects their absorption and distribution. Looking at the importance of liver in dealing with the drug, knowledge of a patient's hepatic function is required for the safe prescribing of many drugs. Unlike renal disease, where estimation of renal function based on creatinine clearance can fairly help in knowing the drug elimination and hence dose adjustment, there is no endogenous marker for hepatic clearance that can be used as a guide for drug dosing.

Hepatic impairment can lead to altered response to drugs due to all or some of the following reasons:

- Metabolism of many drugs depend on adequate liver function. Generally, metabolism result in the loss of pharmacological activity and therefore reduced metabolism in case of impaired liver function can lead to the accumulation of drug in the body to the toxic level at the normal dose. However in some cases drugs are metabolised to the active form and in these drugs normal dose may not be able to achieve desired response.
- For drugs with low bioavailability (high hepatic extraction), bioavailability increases and hepatic clearance decreases in cirrhotic patients. If such drug is to be administered orally to cirrhotic patients, their initial dose has to be reduced according to their hepatic extraction. For drugs with low bioavailability (low hepatic extraction), hepatic clearance may be affected due to impaired metabolism. For such drugs only the maintenance dose has to be adjusted according to estimated decrease in their hepatic metabolism.
- Portal hypertensive gastropathy and ulcers of upper gastrointestinal tract, frequently seen in cirrhotic patients may alter the absorption of orally administered drugs. Absorption of drugs may be increased because of high intestinal permeability in patients

with portal hypertension. Impaired gastrointestinal motility seen in cirrhotic patients can lead to delayed drug absorption

- Volume of distribution of hydrophilic drugs is increased due to presence of oedema and/or ascitis. Hence, loading dose of these drugs may have to be increased if a rapid action is required. On the other hand increase in volume of distribution is associated with an increase in the elimination half life of such drugs.
- Impaired elimination of drugs which are excreted in the bile can lead to their accumulation in the body.
- Impaired albumin production can lead to decreased protein binding and increased toxicity of highly plasma protein bound drugs.
- High percentage of drugs may reach systemic circulation without passing through liver due to development of portosystemic shunts in cirrhotic patients.
- Cirrhotic patients can often have impaired renal function and in these cases dosage of the drugs have to be carefully adjusted.

The use of certain drugs in patients with cirrhosis may increase the risk of hepatic decompensation. In patients with impaired liver function dose related hepatotoxic reaction may occur at lower doses. Drugs that cause fluid retention (for example, prednisolone, ibuprofen, dexamethasone etc.) may exacerbate oedema and ascitis in chronic liver disease. Sensitivity of brain to depressant action of some drugs (for example, morphine and barbiturates) is markedly increased in cirrhotic patients and can precipitate hepatic encephalopathy at normal doses.

As evident from above, there is a complex interactions between the drugs and liver function. Absence of any endogenous marker for hepatic clearance makes it highly difficult to accurately adjust the dose of various drugs in hepatic impairment. Therefore, if no immediate pharmacological effect is needed, drug therapy should be started cautiously in these patients and titrated individually until desired effect is achieved or toxicity appears. Drugs with a narrow therapeutic range and low hepatic extraction for e.g. theophylline are the most dangerous drugs. If such drugs are administered orally, both loading dose and maintenance doses have to be reduced by  $\geq 50\%$  of the normal dose, depending on the severity of hepatic impairment.

The following table contains information to help prescribing

## Appendix 7a

common drugs in hepatic impairment. The table provided is not exhaustive and absence from this table does not imply safety of drug, it is therefore important to refer to the individual drug entries.

<b>Drug</b>	<b>Status</b>	<b>Comments</b>
Abacavir	Avoid in severe hepatic impairment	Avoid in moderate hepatic impairment unless essential
Acetylsalicylic acid	Avoid in severe hepatic impairment	Increased risk of Gastrointestinal bleeding
Allopurinol	Reduce the dose	
Aluminium hydroxide	Avoid in severe hepatic impairment	Can precipitate hepatic encephalopathy by causing constipation. Antacids containing high amount of sodium to be avoided in patients with fluid retention.
Amidotrizoate	Use with caution	
Amitriptyline	Avoid in severe hepatic impairment	Increased sedation
Amlodipine	Reduce dose	Half life of a mlodipine is prolonged
Amodiaquine	Avoid in hepatic impairment	
Amoxicillin + Clavulanic acid	Use with caution	Monitor liver function, cholestatic jaundice reported either during or shortly after therapy (more common in males and patients over 65 years), duration of treatment should not exceed 2 weeks.
Azathioprine	Reduce dose	
Azithromycin	Avoid	May cause jaundice
Bupivacaine	Avoid or reduce dose in severe hepatic impairment	
Carbamazepine	Avoid in severe moderate to severe hepatic impairment	Cautiously given in mild hepatic impairment
Ceftriaxone	Reduce dose and monitor plasma concentration if there is associated renal impairment	
Chlorambucil	Reduce dose and use cautiously in hepatic impairment	

Chloramphenicol	Avoid if possible, reduce dose and monitor plasma concentration	Increased risk of bone marrow depression
Chlorpheniramine	Avoid	May cause inappropriate sedation
Chlorpromazine	Use with caution	May precipitate coma
Clindamycin	Reduce dose	
Clomifene	Avoid in severe hepatic impairment	
Clomipramine	Avoid in severe hepatic impairment	Increased sedation
Cloxacillin	Use with caution	Cholestatic jaundice may occur up to several weeks after treatment has stopped. Risk increases with increasing age and if given for more than 2 weeks.
Codeine	Avoid or reduce dose	May precipitate coma. Causes constipation
Contraceptive, oral	Avoid in case of active liver disease	Avoid if history of cholestasis and pruritus during pregnancy.
Cyclophosphamide	Reduce dose	Monitor plasma level
Cyclosporine	Reduce dose and use with caution	Hepatotoxic
Cytarabine	Reduce dose	
Dacarbazine	Avoid in severe hepatic impairment	Dose reduction in mild to moderate hepatic impairment.
Daunorubicin	Reduce dose	Use with caution as toxicity increases in hepatic impairment.
Diazepam	Avoid in severe hepatic impairment.	Can precipitate coma
Didanosine	Monitor for toxicity	
Doxorubicin	Reduce dose according to bilirubin concentration	
Doxycycline	Avoid or use with caution	

## Appendix 7a

Efavirenz	Avoid in severe hepatic impairment	Dose reduction and/or use with caution in mild to moderate hepatic impairment.
Enalapril	Use with caution	Closely monitor liver function in patients with hepatic impairment
Ergometrine	Avoid in severe hepatic impairment	
Erythromycin	Avoid in severe hepatic impairment	May cause idiosyncratic hepatotoxicity
Ethinylestradiol	Avoid	See also Contraceptives, Oral
Etoposide	Avoid in severe hepatic impairment	Increased risk of toxicity in case of hepatic impairment
Fluconazole	Use with caution	Hepatotoxicity
5-Fluorouracil	Use with caution; dose reduction may be required	
Fluoxetine	Reduce dose or administer on alternate days	
Fluphenazine	Avoid in severe hepatic impairment	Hepatotoxic, can precipitate coma
Furosemide	Avoid or use with caution in severe hepatic impairment	Hypokalaemia may precipitate coma (use potassium sparing diuretic to prevent this); Increased risk of hypomagnesaemia in alcoholic cirrhosis
Glibenclamide	Avoid or reduce the dose	Increased risk of hypoglycaemia. Can produce jaundice
Griseofulvin	Avoid in severe hepatic impairment	
Haloperidol	Use with caution	Can precipitate coma
Heparin	Reduce dose in severe liver disease	
Hydralazine	Reduce dose	
Hydrochlorothiazide	Avoid in severe hepatic impairment	Hypokalaemia may precipitate coma (use potassium sparing diuretic to prevent this); Increased risk of hypomagnesaemia in alcoholic cirrhosis

## Appendix 7a

Ibuprofen	Avoid in severe hepatic impairment	Increased risk of gastrointestinal bleeding and can also cause fluid retention
Indinavir	Reduce dose to 600 mg 8th hly in mild to moderate hepatic impairment, not studied in severe hepatic impairment	
Isoniazid	Use with caution	Regularly monitor liver function and particularly frequently in first 2 months.
Levonorgestrel	Use with caution in active liver disease and recurrent cholestatic jaundice	
Lidocaine	Avoid or reduce the dose in severe hepatic impairment	
Magnesium hydroxide/sulphate	Avoid in hepatic coma if risk of renal failure	
Medroxyprogesterone	Avoid in active liver disease.	Avoid if history of pruritus and cholestasis during pregnancy
Mefloquine	Avoid for prophylaxis in severe liver disease	
6-Mercaptopurine	May need dose reduction	
Metformin	Avoid	Withdraw if tissue hypoxia likely
Methadone	Avoid or reduce the dose	May precipitate coma
Methotrexate	Avoid in severe hepatic impairment	Hepatotoxic, monitor liver functions
Methyldopa	Avoid in active liver disease	
Metoclopramide	Reduce dose	
Metronidazole	Reduce total daily dose to one third and give once daily in case of severe hepatic impairment	



## Appendix 7a

Morphine	Avoid or reduce the dose	May precipitate coma
Nevirapine	Avoid in severe hepatic impairment	Use with caution in moderate hepatic impairment.
Nitrofurantoin	Use with caution	Cholestatic jaundice and chronic active hepatitis reported
Norethisterone	Avoid in active liver disease.	Avoid if history of pruritus and cholestasis during pregnancy
Ofloxacin	Reduce dose in severe hepatic impairment	Hepatic dysfunction reported
Paracetamol	Avoid large doses-dose related toxicity	
Phenobarbital	Avoid in severe hepatic impairment	May precipitate coma
Phenytoin	Reduce dose to avoid toxicity	
Prednisolone	Use with caution	Adverse effects more common
Procainamide	Avoid or reduce the dose	
Procarbazine	Avoid in severe hepatic impairment	
Promethazine	Avoid in severe hepatic impairment	May precipitate coma, Hepatotoxic
Propylthiouracil	Reduce dose	
Pyrazinamide	Avoid in severe hepatic impairment	Monitor hepatic function- idiosyncratic hepatotoxicity more common
Pyrimethamine	Use with caution	
Ranitidine	Reduce dose	Increased risk of confusion
Ribavirin	Avoid in severe hepatic impairment	
Rifampicin	Avoid or do not exceed 8 mg/kg daily	Monitor liver function

Saquinavir	Avoid in severe hepatic impairment. Caution in moderate hepatic impairment	
Simvastatin	Avoid in active liver disease or unexplained persistent elevation in serum transaminases	
Sodium nitroprusside	Avoid in severe hepatic impairment	
Sulfadiazine	Avoid in severe hepatic impairment	
Sulfamethoxazole + trimethoprim	Avoid in severe hepatic impairment	
Suxamethonium		Prolonged apnoea may occur in severe liver disease due to reduced hepatic synthesis of plasma cholinesterase
Testosterone	Preferably avoid	Possibility of dose related toxicity and fluid retention.
Thiopental	Reduce dose in severe liver disease	
Valproic acid	Avoid if possible	Hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months)
Verapamil	Reduce oral dose	
Vinblastine	Reduction of dose may require	
Vincristine	Reduction of dose may require	
Warfarin	Avoid in severe liver disease	Reduced production of clotting factors in hepatic impairment, may increase risk of bleeding
Zidovudine	Reduction of dose as accumulation may occur	

## Appendix 7b: Lactation

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Administration of some drugs (for example, ergotamine) to nursing mothers may harm the infant, whereas administration of others (for example, digoxin) has little effect. Some drugs inhibit lactation (for example, estrogens).

Toxicity to the infant can occur if the drug enters the milk in pharmacologically significant quantities. The concentration in milk of some drugs (for example, iodides) may exceed that in the maternal plasma so that therapeutic doses in the mother may cause toxicity to the infant. Some drugs inhibit the infant's sucking reflex (for example, phenobarbital). Drugs in breast milk may, at least theoretically, cause hypersensitivity in the infant even when the concentration is too low for a pharmacological effect.

The following table lists drugs:

- which should be used with caution or which are contraindicated in lactation for the reasons given above;
- which are not known to be harmful to the infant although they are present in milk in significant amounts.

For many drugs insufficient evidence is available to provide guidance and it is advisable to administer only drugs essential to a mother during lactation. Because of the inadequacy of information on drugs in breast milk the following table should be used only as a guide; absence from the table does not imply safety.

Drug	Comment
Abacavir	Lactation recommended during first 6 months if no safe alternative to breast milk
Acetylsalicylic acid	Short course safe in usual dosage; monitor infant; regular use of high doses could impair platelet function and produce hypoprothrombinaemia in infant if neonatal vitamin K stores low; possible risk of Reye syndrome
Acyclovir	Significant amount in milk after systemic administration, but considered safe to use
Alcohol	Large amounts may affect infant and reduce milk consumption
Aminophylline	Present in milk-irritability in infant reported
Amitriptyline	Detectable in breast milk; continue lactation; adverse effects possible, monitor infant for drowsiness
Amoxicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Amoxicillin + Clavulanic acid	Trace amounts in milk
Ampicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Artemether + Lumefantrine	Discontinue lactation during and for 1 week after stopping treatment; present in milk in <i>animal</i> studies
Asparaginase	Lactation contraindicated
Atenolol	Significant amounts in milk; safe in usual dosage; monitor infant
Atropine	Small amount present in milk; monitor infant
Azathioprine	Lactation contraindicated
Beclomethasone	Systemic effects in infant unlikely with maternal dose of <i>less than equivalent</i> of prednisolone 40 mg daily; monitor infant's adrenal function with higher doses

Benzathine benzylpenicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Benzylpenicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Betamethasone	Systemic effects in infant unlikely with maternal dose of <i>less than equivalent</i> of prednisolone 40 mg daily; monitor infant's adrenal function with higher doses
Bleomycin	Lactation contraindicated
Carbamazepine	Continue lactation; adverse effects possible (severe skin reaction reported in 1 infant); monitor infant for drowsiness;
Ceftazidime	Excreted in low concentrations; safe in usual dosage; monitor infant
Ceftriaxone	Excreted in low concentrations; safe in usual dosage; monitor infant
Chlorambucil	Lactation contraindicated
Chloramphenicol	Continue lactation; use alternative drug if possible; may cause bone-marrow toxicity in infant; concentration in milk usually insufficient to cause 'grey syndrome'
Chlormethine	Lactation contraindicated
Chloroquine	For malaria prophylaxis, amount probably too small to be harmful; inadequate for reliable protection against malaria, ; avoid lactation when used for rheumatic disease
Chlorpheniramine	Safe in usual dosage; monitor infant for drowsiness
Chlorpromazine	Continue lactation; adverse effects possible; monitor infant for drowsiness
Ciprofloxacin	Continue lactation; use alternative drug if possible; high concentrations in breast milk
Cisplatin	Lactation contraindicated
Clindamycin	Amount probably too small to be harmful but bloody diarrhoea reported in 1 infant
Clomifene	May inhibit lactation

Clomipramine	Small amount present in milk; continue lactation; adverse effects possible; monitor infant for drowsiness
Clonazepam	Continue lactation; adverse effects possible; monitor infant for drowsiness;
Cloxacillin	Trace amounts in milk; safe in usual dosage; monitor infant
Colchicine	Present in milk but no adverse effects reported; caution because of risk of cytotoxicity
Contraceptives, oral	Combined oral contraceptives may inhibit lactation-use alternative method of contraception until weaning or for 6 months after birth; progestogen-only contraceptives do not affect lactation (start 3 weeks after birth or later)
Cyclophosphamide	Lactation contraindicated during and for 36 h after stopping treatment
Cyclosporine	Present in milk-avoid
Cytarabine	Lactation contraindicated
Dacarbazine	Lactation contraindicated
Dactinomycin	Lactation contraindicated
Dapsone	Although significant amount in milk risk to infant very small; continue lactation; monitor infant for jaundice
Daunorubicin	Lactation contraindicated
Dexamethasone	Systemic effects in infant unlikely with maternal dose of <i>less than equivalent</i> of prednisolone 40 mg daily; monitor infant's adrenal function with higher doses
Diazepam	Continue lactation; adverse effects possible; monitor infant for drowsiness;
Didanosine	Lactation recommended during first 6 months if no safe alternative to breast milk
Diloxanide	Avoid
Doxorubicin	Lactation contraindicated

Doxycycline	Continue lactation; use alternative drug if possible (absorption and therefore discolouration of teeth in infant probably usually prevented by chelation with calcium in milk)
Efavirenz	Lactation recommended during first 6 months if no safe alternative to breast milk
Eflornithine	Avoid
Ephedrine	Irritability and disturbed sleep reported
Ergocalciferol	Caution with high doses; may cause hypercalcaemia in infant
Ergotamine	Use alternative drug; ergotism may occur in infant; repeated doses may inhibit lactation
Erythromycin	Only small amounts in milk; safe in usual dosage; monitor infant
Ethinylestradiol	Use alternative method of contraception; may inhibit lactation; <i>see also</i> Contraceptives, Oral
Etoposide	Lactation contraindicated
Fluconazole	Present in milk; safe in usual dosage; monitor infant
Flucytosine	Avoid
5-Fluorouracil	Discontinue lactation
Fluphenazine	Amount excreted in milk probably too small to be harmful; continue lactation; adverse effects possible; monitor infant for drowsiness
Glibenclamide	Hypoglycaemia in infant
Haloperidol	Amount excreted in milk probably too small to be harmful; continue lactation; adverse effects possible; monitor infant for drowsiness
Halothane	Excreted in milk
Hydralazine	Present in milk but not known to be harmful; monitor infant
Hydrochlorothiazide	Use alternative drug; may inhibit lactation

Hydrocortisone	Systemic effects in infant unlikely with maternal dose of <i>less than equivalent</i> of prednisolone 40 mg daily; monitor infant's adrenal function with higher doses
Ibuprofen	Amount too small to be harmful; short courses safe in usual doses
Imipenem + Cilastatin	Present in milk-avoid
Indinavir	Lactation recommended during first 6 months if no safe alternative to breast milk
Iodine	Stop lactation; danger of neonatal hypothyroidism or goitre; appears to be concentrated in milk
Isoniazid	Monitor infant for possible toxicity; theoretical risk of convulsions and neuropathy; prophylactic pyridoxine advisable in mother and infant
Ivermectin	Avoid treating mother until infant is 1week old
Lamivudine	Present in milk; lactation recommended during first 6 months if no safe alternative to breast milk
Levamisole	Lactation contraindicated
Levonorgestrel	Combined oral contraceptives may inhibit lactation-use alternative method of contraception until weaning or for 6 months after birth; progestogen-only contraceptives do not affect lactation (preferably start 6 weeks after birth or later)
Lithium	Present in milk and risk of toxicity in infant; continue lactation; monitor infant carefully, particularly if risk of dehydration
Lopinavir + Ritonavir	Lactation recommended during first 6 months if no safe alternative to breast milk
Lumefantrine	See Artemether + Lumefantrine
Medroxyprogesterone	Present in milk-no adverse effects reported (preferably start injectable contraceptive 6 weeks after birth or later)



Mefloquine	Present in milk but risk to infant minimal
6-Mercaptopurine	Lactation contraindicated
Metformin	Present in milk but safe in usual doses; monitor infant
Methotrexate	Lactation contraindicated
Metoclopramide	Present in milk; adverse effects possible; monitor infant for adverse effects
Metronidazole	Significant amount in milk; continue lactation; avoid large doses; use alternative drug if possible
Morphine	Short courses safe in usual doses; monitor infant
Nalidixic acid	Continue lactation; use alternative drug if possible; one case of haemolytic anaemia reported
Nelfinavir	Lactation recommended during first 6 months if no safe alternative to breast milk
Neostigmine	Amount probably too small to be harmful; monitor infant
Nevirapine	Present in milk; lactation recommended during first 6 months if no safe alternative to breast milk
Nifedipine	Small amount in milk; continue lactation; monitor infant
Nitrofurantoin	Only small amounts in milk but could be enough to produce haemolysis in G-6-PD-deficient infants
Norethisterone	Combined oral contraceptives may inhibit lactation-use alternative method of contraception until weaning or for 6 months after birth; progestogen-only contraceptives do not affect lactation (preferably start injectable contraceptive 6 weeks after birth or later)
Oxfloxacin	Continue lactation; use alternative drug if possible
Paracetamol	Small amount present in milk: short courses safe in usual dosage; monitor infant
Pentamidine	Avoid unless essential

Pentavalent antimony compounds	Avoid
Phenobarbital	Continue lactation; adverse effects possible; monitor infant for drowsiness;
Phenoxyethylpenicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Phenytoin	Small amount present in milk; continue lactation; adverse effects possible; monitor infant for drowsiness;
Potassium iodide	Stop lactation; danger of neonatal hypothyroidism or goitre; appears to be concentrated in milk
Povidone–iodine	Avoid; iodine absorbed from vaginal preparations is concentrated in milk
Praziquantel	Avoid lactation during and for 72 h after treatment; considered safe to continue lactation in treatment of schistosomiasis
Prednisolone	Systemic effects in infant unlikely with maternal dose of less than prednisolone 40 mg daily; monitor infant's adrenal function with higher doses
Primaquine	Avoid; risk of haemolysis in G-6-PD-deficient infants
Procainamide	Present in milk; continue lactation; monitor infant
Procarbazine	Lactation contraindicated
Promethazine	Safe in usual dosage; monitor infant for drowsiness
Propranolol	Present in milk; safe in usual dosage; monitor infant
Propylthiouracil	Monitor infant's thyroid status but amounts in milk probably too small to affect infant; high doses might affect neonatal thyroid function
Pyrimethamine	Significant amount-avoid administration of other folate antagonists to infant
Quinidine	Significant amount but not known to be harmful
Ranitidine	Significant amount present in milk, but not known to be harmful

Ritonavir	See Lopinavir with Ritonavir
Salbutamol	Safe in usual dosage; monitor infant
Saquinavir	Lactation recommended during first 6 months if no safe alternative to breast milk
Senna	Avoid; large doses may cause increased gastric motility and diarrhoea
Silver sulfadiazine	Continue lactation; monitor infant for jaundice-small risk of kernicterus in jaundiced infants particularly with long-acting sulphonamides, and of haemolysis in G-6-PD-deficient infants
Sodium valproate	see Valproic acid
Stavudine	Lactation recommended during first 6 months if no safe alternative to breast milk
Sulfadiazine	Continue lactation; monitor infant for jaundice-small risk of kernicterus in jaundiced infants particularly with long-acting sulphonamides, and of haemolysis in G-6-PD-deficient infants
Sulfadoxine + Pyrimethamine	Continue lactation; monitor infant for jaundice-small risk of kernicterus in jaundiced infants and of haemolysis in G-6-PD-deficient infants (due to sulfadoxine)
Sulfamethoxazole + Trimethoprim	Continue lactation; monitor infant for jaundice-small risk of kernicterus in jaundiced infants and of haemolysis in G-6-PD-deficient infants (due to sulfamethoxazole)
Sulfasalazine	Continue lactation; monitor infant for jaundice-small amounts in milk (1 report of bloody diarrhoea and rashes); theoretical risk of neonatal haemolysis especially in G-6-PD-deficient infants
Tamoxifen	Suppresses lactation; avoid unless potential benefit outweighs risk
Testosterone	Avoid; may cause masculinization in the female infant or precocious development in the male infant; high doses suppress lactation

Tetracycline	Continue lactation; use alternative drug if possible (absorption and therefore discolouration of teeth in infant probably usually prevented by chelation with calcium in milk)
Theophylline	Present in milk-irritability in infant reported; modified-release preparations preferable
Thiamine	Severely thiamine-deficient mothers should avoid lactation as toxic methylglyoxal excreted in milk
Trimethoprim	Present in milk; safe in usual dosage; monitor infant
Valproic acid	Small amount present in milk; continue lactation; adverse effects possible; monitor infant for drowsiness; (Sodium valproate)
Vancomycin	Present in milk-significant absorption following oral administration unlikely
Vinblastine	Lactation contraindicated
Vincristine	Lactation contraindicated
Warfarin	Risk of haemorrhage; increased by vitamin-K deficiency; warfarin appears safe
Zidovudine	Lactation recommended during first 6 months if no safe alternative to breast milk

## Appendix 7c: Pregnancy

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Drugs can have harmful effects on the fetus at any time during pregnancy. It is important to remember this when prescribing for a woman of childbearing age. However, irrational fear of using drugs during pregnancy can also result in harm. This includes untreated illness, impaired maternal compliance, suboptimal treatment and treatment failures. Major congenital malformations occur in 2–4% of all live births, 15% of all diagnosed pregnancies will result in fetal loss. During the first trimester drugs may produce congenital malformations (teratogenesis), and the greater risk is from third to the eleventh week of pregnancy. During the second and third trimester, drugs may affect the growth and functional development of the fetus or have toxic effects on fetal tissues. Drugs given shortly before term or during labor may have adverse effects on labor or on the neonate after delivery. Few drugs have been shown conclusively to be teratogenic in man but no drug is safe beyond all doubt in early pregnancy. Screening procedures are available where there is a known risk of certain defects.

### Prescribing in Pregnancy

Since, approximately 50% of pregnancies are unplanned and rest 50% are planned, if possible, counseling of women before a planned pregnancy should be carried out including discussion of risks associated with specific therapeutic agents, traditional drugs (alternative medicines), over the counter drugs and substances of abuse such as opioids, smoking, alcohol etc. Drugs should be prescribed in pregnancy only if the expected benefits to the mother are thought to be greater than the risk to the fetus. All drugs should be avoided if possible during the first trimester. Drugs which have been used extensively in pregnancy and appear to be usually safe should be prescribed in preference to new or untried drugs and the smallest effective dose should be used. Keeping in view the prevalence of irrational polypharmacy, emphasis should be laid on promoting the use of well known single component drugs to multicomponent drugs. Since, there does appear to be an association of very potent topical corticosteroids with low birth weight, even the dermatological drug products being used should be cautiously selected and used.

The pronounced and progressive change in drug disposition that occurs during pregnancy is another major reason which calls for attention. Major physiological changes which influence drug disposition in mother and fetus are:

S. No	Physiologic changes	Effects
1.	Plasma albumin concentration of mother is reduced	Drug protein binding alteration
2.	Increased body fat in mother	Distribution of drug is effected
3.	Increased hepatic metabolism in mother	Faster hepatic clearance

4.	Increased cardiac output in mother	Increased renal blood flow and glomerular filtration and hence, increased elimination of drug
5.	Presence of placental barrier	Selectivity of drug permeation based on its hydrophobicity or molecular weight of drug
6.	Drug metabolizing enzymes activity in fetal liver is very low	Slow elimination of drugs by fetus

Though maternal medication carry the risk of increase in the incidence of abortion, stillbirths, fetal death, premature or delayed labor or create perinatal problems; but certain medications like folic acid are recommended for all pregnant women to reduce the rate of congenital anomalies specifically, the neural tube defect.

The Food and Drug Administration has categorized the drug risks to the fetus that runs from: "Category A" (safest) to "Category X" (known danger--do not use!)

### Category A

Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

### Category B

Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

### Category C

Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

### Category D

There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

### Category X

Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

## Appendix 7d: Renal Impairment

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### Dosing considerations in renal impairment

The number of patients with chronic kidney disease (CKD) and reduced renal function have been inexorably increasing. Reduced renal function may need adjustment in drug therapy as kidney plays a major role in the pharmacokinetics of a large number of drugs.

- Renal insufficiency frequently alters drug distribution volume. Edema and ascites increase the apparent volume of distribution of highly water-soluble or protein-bound drugs. Usual doses of such drugs given to edematous patients result in inadequate, low plasma levels.
- The alteration of plasma protein binding in patients with renal insufficiency is an important factor affecting both efficacy and toxicity. In patients with uremia the unbound fraction of several acidic drugs is substantially increased which may lead to serious toxicity.
- Although renal insufficiency is thought to affect primarily the renal elimination of drugs or metabolites, renal failure substantially affects drug biotransformation. Uremia slows the rate of reduction and hydrolysis reactions.
- Many active or toxic metabolites are produced during drug metabolism. Many of these metabolites depend on the kidneys for their removal from the body. The accumulation of active metabolites can explain in part the high incidence of ADRs seen in renal failure.

### A few points should be kept in mind while prescribing;

- Renal function declines with age so that by the age of 80 it is half that in healthy young subjects.
- It is advisable to determine renal function not only before but also during the period of treatment and adjust the maintenance dose as necessary.
- One should try to keep drug prescription to minimum.
- Nephrotoxic drugs should, if possible, be avoided in all patients with renal disease because the nephrotoxicity is more likely to be serious.

- One should stay alert for unexpected ADRs.

The recommendations in the table below are meant only as a guide and do not imply efficacy or safety of a recommended dose in an individual patient.

A loading dose equivalent to the usual dose in patients with normal renal function should be considered for drugs with a particularly long half-life.

The table below gives the common drugs where in renal impairment dose adjustment is required.

When the dose method (D) is suggested, the percentage of the dose for normal renal function is given and when the interval method (I) is suggested, the actual dose interval is provided.

Drug	Dose Method	GFR >50 (ml/min)	GFR 10-50 (ml/min)	GFR <10 (ml/min)	CAPD	HD
Acetaminophen	I	q4h	q6h	q8h	Dose as GFR < 10	Dose as GFR < 10
Acetazolamide	I	q6h	q12h	Avoid	No data	No data
Acetylsalicylic Acid	I	Q4h	Q4-6h	Avoid	As normal GFR	As normal GFR dose post HD
Acyclovir	D, I	5 mg/kg q8h	5 mg/kg q12-24h	2.5 mg/kg q24h	Dose as GFR < 10	Dose as GFR < 10 dose post HD
Allopurinol	D	75%	50%	33%	Dose as GFR < 10	Dose as GFR < 10
Amikacin	D, I	60–90% q12h	30–70% q12–18h	20–30% q24–48h	15–20 mg /L/day	5 mg/kg post HD
Amiloride	D	100%	50%	Avoid	NA	NA
Aminophylline	D	100%	200–400 mg q12h	200–300 mg q12h	Dose as GFR < 10	Dose as GFR < 10
Amphotericin B	I	q24h	q24h	q24-36h	Dose as GFR < 10	Dose as GFR < 10
Ampicillin	I	q6h	q6–12h	q12-24h	Dose as GFR < 10	Dose as GFR < 10
Cefazolin	I	q8h	q12h	q24–48h	0.5 g q12h	0.5–1.0 g post HD



## Appendix 7d

Cefixime	D	100%	75%	50%	200 mg q24h	200 mg q24h dose post HD
Cefotaxime	I	100% q8h	100% q8h	50% q8–12h	1 g q24h	Dose as GFR < 10 dose post HD
Chloroquine	D	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10
Ciprofloxacin	D	100%	50-75%	50%	250 mg q8h	250 mg q12h
Cisplatin	D	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10
Cyclophosphamide	D	100%	75-100%	50-75%	Dose as GFR < 10	Dose as GFR < 10
Dapsone		100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10
Didanosine	I	100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10
Digoxin	D, I	100% q24h	25–75% q36h	10–25% q48h	Dose as GFR < 10	Dose as GFR < 10
Enalapril	D	100%	75-100%	50-75%	Dose as GFR < 10	Dose as GFR < 10
Erythromycin	D	100%	100%	50-75%	Dose as GFR < 10	Dose as GFR < 10
Ethambutol	I	q24h	q24-36h	q48h	Dose as GFR < 10	Dose as GFR < 10 dose post HD
Etoposide	D	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10
Fentanyl	D	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10
Fluconazole	D	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10 dose post HD

## Appendix 7d

Gentamicin	D, I	60–90% q8–12h	30–70% q12h	20–30% q24–72h	3–4 mg/L/ day	Dose as GFR < 10 dose post HD
Isoniazid	D	100%	100%	75%	Dose as GFR < 10	Dose as GFR < 10 dose post HD
Lamivudine	D, I	100%	50–150 mg qd	25 mg qd	Dose as GFR < 10	Dose as GFR < 10 dose post HD
Metformin	D	50%	Avoid	Avoid	Avoid	Avoid
Metoclopramide	D	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10
Penicillin G	D	100%	75%	20–50%	Dose as GFR < 10	Dose as GFR < 10
Pyrazinamide	D	100%	As normal GFR	As normal GFR	As normal GFR	As normal GFR
Quinine	I	q8h	q8–12h	q24h	Dose as GFR < 10	Dose as GFR < 10 dose post HD
Streptomycin	I	q24h	q24–72h	q72h	20–40 mg /L/day	750 mg 2–3/ week
Triamterene	I	q12h	q12h	Avoid	Avoid	Avoid
Tubocurarine	D	75%	50%	Avoid	Unknown	Unknown
Vancomycin	D, I	500 mg q6–12h	500 mg q12–48h	500 mg q48–96h	Dose as GFR < 10	Dose as GFR < 10
Zidovudine (AZT)	D, I	100% q8h	100% q8h	50% q12h	Dose as GFR < 10	Dose as GFR < 10

HD: Hemodialysis; CAPD: Chronic Ambulatory Peritoneal Dialysis.

## Appendix 8: National Health Programmes (NHPs)

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The area of government healthcare professionals covers Rural Medical Dispensary (RMD); Primary Health Centre (PHC); Community Health Centre (CHC); Urban Health Centre (UHC); district, Sub-divisional and Rural hospitals; large tertiary care and teaching hospitals and other public hospitals including Railways, ESIS, Coal India, CGHS, MPT, Airlines, Armed Forces, Jail hospitals, etc.

The government has been bringing health care to the public in special areas of concern through a top down approach through its various NHPs.

A list of NHPs is mentioned below:

1. National Vector Borne Disease Control Programme
2. National Filariasis Control Programme
3. National Leprosy Eradication Programme
4. Revised National TB Control Programme
5. National Programme for Control of Blindness
6. National Iodine Deficiency Disorders Control Programme
7. National Mental Health Programme
8. National AIDS Control Programme
9. National Programme on Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke
10. Universal Immunization Programme
11. National Programme for Prevention and Control of Deafness
12. Pilot Programme on Prevention and Control of Diabetes, Cardiovascular Disease and Stroke
13. National Tobacco Control Programme
14. School Health Programme
15. Prevention and Control of Non-Communicable Diseases
16. National Programme for Healthcare of the Elderly

## Appendix 9: National Immunization Schedule

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<b>Beneficiary</b>	<b>Age</b>	<b>Vaccine</b>
Neonates	Birth	BCG* and OPV**
Infants	6 weeks	DPT, OPV and Hepatitis B
	10 weeks	DPT, OPV and Hepatitis B
	14 Weeks	DPT, OPV and Hepatitis B
	9 months	Measles
	9, 18, 24, 30, 36, 42, 48, 54 and 60 months	Vitamin A
	18 months	DPT & OPV (Booster dose)
Children	5 years	DT
	10 years	Tetanus toxoid
Adolescents	16 years	Tetanus toxoid
Pregnant women		Tetanus toxoid is given during pregnancy (0.5 ml intramuscularly). If there is no prior history of vaccination, 2 doses are administered, the first in 2 <sup>nd</sup> trimester and the second dose one month later. If there is confirmed documentary evidence of proper and complete immunization during childhood, then a single booster dose is administered in the 2 <sup>nd</sup> trimester

\* At birth or at the time of DPT/OPV;

\*\* Dose called as Zero dose and can be given till 14 days of age, if missed early.

## Appendix 10: Pharmacogenetics

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Pharmacogenetics refers to the genetic variation in drug response. This could be due to:

- (a) Single mutant gene or genetic polymorphism.
- (b) Polygenic influence.

However the later is not of much significance in Clinical Practice. Variations in drug responses amongst fraternal twins (dizygotic) may be relatively wide when compared to identical (monozygotic) twins. Importance of Pharmacogenetics lies in the development of new drugs from information available from human genome project. It aims at individualizing and improving precision of pharmacotherapy.

When polymorphic DNA sequence variation occurs in the coding region or regulatory regions of genes, it causes variation in gene product through alteration of activity, function or level of expression. The variation to drug response can also be brought about by:

- Metabolic variation
- Idiosyncratic reaction

As an example metabolic variation can be best explained by the varied metabolic response exhibited to the antitubercular drug Isoniazid due to the presence of two different phenotypes in a population. These varied phenotypes are expressed as larger or smaller amount of enzyme N- acetylase in liver, and the population being termed as rapid acetylators and slow acetylators respectively. Some of the pharmacogenetic conditions and the drugs involved are summarized below.

S. No.	Pharmacogenetic variation	Frequency of occurrence	Drugs involved	Outcome
1.	Acetylator status	Varies with race	Isoniazid -slow acetylator -rapid acetylator Procainamide Hydralazine Sulphas, Sulphones Phenelzine	Neuropathy Hepatotoxicity SLE SLE  ADR ADR
2.	Butyrylcholinesterase enzymes	1: 3000 caucasian	Suxamethonium	Slower recovery from surgical paralysis

3.	Aromatic hydroxylase	1.5-9.0%	Debrisoquine	Postural hypotension,
	N-oxidation enzyme (aminoxidase)	5%	Sparteine	Diplopia, blurred vision,
4.	G-6-PD deficiency	Varies with race	<b>Antimalarials</b> Primaquine Mepacrine Pamaquine Pentaquine Chloroquine Quinine Proguanil Pyrimethamine <b>Cardiovascular drugs</b> Procainamide Quinidine Hydralazine Thiazide diuretics <b>Central Nervous System Drugs</b> Methyldopa Benzhexol Phenytoin <b>Anti-infectives</b> Dapsone Sulfacetamide Sulfamethoxypyrimidine Sulfanilamide Sulfapyridine Sulfasalazine Sulfisoxazole Sulfadiazine Cotrimoxazole Trimethoprim Chloramphenicol Ciprofloxacin Moxifloxacin Nalidixic acid Ofloxacin Norfloxacin Nitrofurantoin Nitrofurazone Isoniazid Furazolidone Streptomycin <b>Antineoplastics</b> Doxorubicin Rasburicase <b>Anthelmintics</b> Niridazole Stibophen <b>Analgesics</b> Acetylsalicylic acid Antipyrine	Haemolysis

			<p><b>Antigout drugs</b>                  Probenecid                  Colchicine</p> <p><b>Antidote</b>                  Dimercaprol                  Phenylhydrazine</p> <p><b>Antimethemoglobinemic Agent</b>                  Methylene Blue</p> <p><b>Antidiabetics</b>                  Glibenclamide</p> <p><b>Antihistamines</b>                  Diphenhydramine                  Tripeleennamine                  Antazoline</p> <p><b>Hormonal contraceptives</b>                  Mestranol</p> <p><b>Vitamins</b>                  Ascorbic acid                  Menadione</p> <p><b>Diagnostic agent for cancer</b>                  Toluidine blue</p>	
5.	Calcium release channel (ryanodine receptor)	1:20,000	Halothane	Malignant hyperthermia,
6.	Narrow iridocorneal angle	5% US population	Corticosteroids	Attack of angle closure glaucoma
7.	Hb variants	Rare	Oxidizing agents like quinolones	Haemolysis
8.	Hepatic porphyrias	Rare	Haem-containing hepatic oxidizing enzyme inducers like barbiturates, Sulphonamides Sulphonylureas etc.	Acute porphyria (GIT, CNS, CVS symptoms)
9.	Altered receptor or enzyme in liver with increased affinity for vitamin K	2 large pedigrees	Warfarin	Warfarin resistance
10.	Mixed function oxidase in liver microsomes hydroxylation d-ethylation	Only 1 small pedigree	Dicoumarol Phenacetin	Dicoumarol sensitivity Methemoglobinemia
11.	N-oxidation enzyme (aminoxidase)	5%	Sparteine	Sparteine -induced diplopia, blurred vision, overstimulated uterus

## Appendix 10

12.	Mixed function oxidase	25%	Tolbutamide	Tolbutamide induced cardiovascular death
13.	Cytochrome P450 2D6		Ondansetron	Ondansetron - lesser efficacy in ultrarapid metabolisers
			Tramadol	Lesser efficacy of tramadol
			Codeine	Codeine - poor analgesia
			Tamoxifen	Therapeutic failure of Tamoxifen in poor metabolisers
		~ 7% caucasians	Debrisoquine	Poor metabolism of Debrisoquine
14.	Cytochrome P450 2C9	–	Phenytoin*	Decreased hydroxylation of Phenytoin
15.	Cytochrome P450 2C9 and Vitamin K epoxide reductase complex subunit 1		Warfarin	Longer times to dose stabilisation and higher risk of serious and life threatening bleeding
16.	Increased expression of p-glycoprotein	–	Chloroquine, anticancer drugs	Development of resistance
17.	An enzyme or receptor site with altered affinity for vitamin K	Rare	Simultaneous administration of inducing agents with warfarin	Warfarin resistance
18.	Thiopurine methyl transferase enzyme	3%	Azathioprine 6-mercaptopurine	Risk of bone marrow suppression
19.	Uridine-5-diphosphoglucosyl transferase 1A1	61% Caucasians 84% Asians 47% African americans	Irinotecan	Risk of induction of neutropenia and diarrhoea
20.	Dihydropyrimidine dehydrogenase		5-fluorouracil	Risk of severe toxicity
21.	α-Thalassaemia		Artesunate	Rise in plasma drug concentration
22.	β-Thalassaemia		Somatomedin	May depress somatomedin activity

\* Study carried out in healthy individuals from South India by Rosemary *et al* (Indian J Med Res 2006, 123: 665-670).



# Appendix 11:

## Pharmacovigilance Programme of India

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To provide safe and effective health care system in India and promote rational use of medicines, the Pharmacovigilance Programme of India (PvPI) has been established by the Ministry of Health and Family Welfare, Government of India. The programme is being coordinated by the Indian Pharmacopoeia Commission, Ghaziabad as a National Coordination Centre (NCC). The mission of the programme is to ensure that the benefits of use of medicine outweigh the risk and thus safeguard the health of the Indian population.

The PvPI has the following objectives :

- Monitoring Adverse Drug Reactions (ADRs) in Indian population
- Creating awareness amongst health care professionals about the importance of ADR reporting in India
- Monitoring benefit-risk profile of medicines
- To generate independent, evidence-based recommendations on the safety of medicines
- Support the Central Drugs Standard Control Organization (CDSCO) for formulating safety related regulatory decisions for medicines.

The PvPI is being supported by ADRs Monitoring Centres from across the country. This programme is on expansion mode by enabling more centres to join the reporting of ADRs to NCC and in turn to be linked up to Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. All stakeholders using this formulary are encouraged to report ADRs by downloading the Form (Suspected Adverse Drug Reaction Reporting Form) either from the website of the Central Drugs Standard Control Organization ([www.cdsco.nic.in](http://www.cdsco.nic.in)) or the Indian Pharmacopoeia Commission ([www.ipc.gov.in](http://www.ipc.gov.in)). Integrated efforts from the regulatory authorities, pharmaceutical industry and healthcare workers are necessary for the success and effectiveness of this programme. Therefore the active participation of the all concerned in this programme will not only be useful for Indian health care system but also facilitate rational prescribing globally.

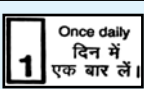
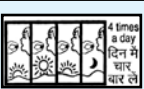

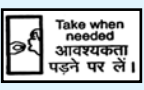


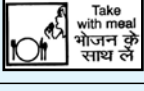
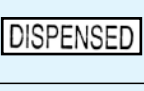
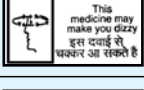
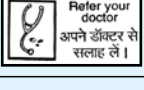
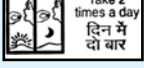
A specimen form is attached at the end of the book.

## Appendix 12: Pictograms

### Pictorial Labeling

In spite of the best efforts there are many patients who are not so literate and may forget the instructions given and are not able to read the prescriptions even if given. They may need to repeatedly refer to the instructions and they may still need help. For taking care of such patients, use of pictorial labeling is recommended. While there has not been any national standard of pictorial label adopted so far, based on a project by Delhi Pharmaceutical Trust, in collaboration with Apothecaries Foundation the following pictorial labels that were developed and used and found appropriate, are recommended for use. Such labels can be pre-printed using self-adhesive sticker label and made available in Pharmacies. Pharmacists should paste relevant pictorial label either on the bottle/pack of the drugs dispensed or on the prescription sheet against each drug prescribed. Based on the most commonly needed instructions, 11 types of messages were identified and pictorial labels have been developed. More instructions if required can be added to this list and additional labels need to be developed.

### Pictorial Labels

1.	Once Daily		7.	4 times a day	
2.	3 Times daily		8.	Take when needed	
3.	Take at bed time		9.	Take on empty stomach	
4.	Take with meals		10.	Dispensed	
5.	This medicine may make you dizzy		11.	Refer to your Doctor.	
6.	Take 2 times a day				

## Appendix 13:

# Principles of Dose Calculation in Special Conditions

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### A. Dosing considerations for the pediatric patient

Determination of a safe and effective drug dose for the pediatric patient is essential for the treating physician. Doses and dosing intervals in children differ from that of an adult because of age-related variations in drug absorption, distribution, metabolism, and elimination. Oral drug absorption matures by four to five months of age. Drugs like phenytoin and chloramphenicol are absorbed slowly and erratically whereas penicillin and ampicillin are absorbed more efficiently than in the adults because of a higher gastric pH in the neonates. Most drug metabolizing enzymes are expressed at low levels at birth followed by postnatal induction of specific isoenzymes. For most drugs including phenytoin, barbiturates, digoxin and analgesics the plasma half lives are 2-3 times longer in neonates as compared to adults. Renal elimination of drugs is also reduced in the neonates. As a result, neonatal dosing regimens for a number of drugs must be reduced to avoid toxicity. Drug pharmacodynamics may also be different in children, for e.g. antihistamines and barbiturates that are generally sedative in adults may be excitatory in pediatric age group. Similarly, specific drug toxicities may be unique to this age group as evident in case of tetracyclines affecting teeth and glucocorticoids reducing linear growth of bones.

Because of these maturational differences in infants and children, simple proportionate reduction in the adult dose may not be adequate to determine an optimal pediatric dose. The most reliable dose information is usually the one provided by the drug manufacturer in the package insert or pediatric doses listed in the formulary. However, such information is not available for the majority of drugs since proper dose optimization studies are often not performed in the pediatric age range. Consequently, initial doses are derived by scaling down the dosages used in adults and then titrating according to clinical response.

In the absence of specific pediatric dose recommendations, an estimate can be made by any of several methods based on age, weight, or surface area.

**Age- based rules:**

Various rules of dosage in which the pediatric dose is a fraction of adult dose based on relative age have been used. Two of these are mentioned below.

Young's rule (for children 2 years and older)

$$\text{Child's dose (approx.)} = \frac{\text{Age (years)}}{\text{Age (years)} + 12} \times \text{Adult dose}$$

Fried's rule (for children up to 2 years old)

$$\text{Child's dose (approx.)} = \frac{\text{Age (months)}}{150} \times \text{Adult dose}$$

**Weight based rule:**

Because of large variability in weight among children of same age group, estimation of drug dosage for children on the basis of body weight is considered more reliable than that based solely on age. A rule proposed by Professor A. J. Clark ( known as the Clark's rule) introduced weight proportional regimen for drug therapy.

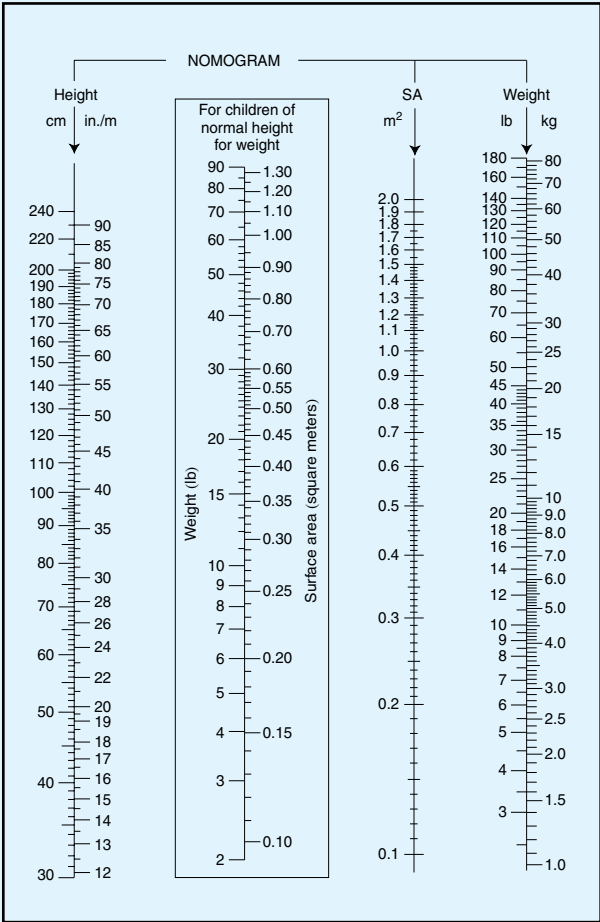
$$\text{Child's dose (approx.)} = \frac{\text{Weight ( kg)}}{70} \times \text{Adult dose}$$

**Body surface area based rule:**

The most dependable methods for calculation of pediatric drug doses are those based on body surface area (BSA). Rate of metabolism and redistribution of drug, organ size, blood volume, extracellular fluid volume, renal blood flow and assays of blood concentration of drugs correlate closely with the BSA.

$$\text{Child's dose (approx.)} = \frac{\text{Weight ( kg)}}{1.73 \text{ m}^2} \times \text{Adult dose}$$

For calculation of doses based on BSA, standard nomogram which includes both body weight and height as factors determining BSA should be used. To calculate a child's BSA, draw a straight line from the height column to the weight column. The point at which the line intersects the surface area (SA) column is the BSA (m<sup>2</sup>). If the child is of roughly normal proportion, BSA can be calculated from the weight alone (in the enclosed area).



*Note: This nomogram was published in Nelson Textbook of Pediatrics, 18th Edition, Richard E. Behrman, Robert M. Kliegman, MD, Hal B. Jenson, MD and Bonita F. Stanton, MD, Nomogram for the estimation of surface area, page no. 2951, fig no. 715-1, W. B. Saunders Company, 2007 and has been reproduced with permission.*

The above mentioned rules are helpful in situations requiring the use of a drug that is unlicensed in children and for which no pediatric prescribing information is available. However, these rules are not precise and doses should not be calculated if it is possible to obtain the actual pediatric dose. Whatever be the method chosen to calculate the child's dose, it should never exceed that of the adult.

## B. Dosing considerations for the geriatric patient

Aging is a natural process of human development and is characterized by a progressive loss of physiologic and reproductive functions. Altered response to drugs with aging occurs at both pharmacokinetic and pharmacodynamic levels.

Pharmacokinetic changes occur with the age as a result of the inevitable anatomical and physiological changes which occur with time, such as loss of an organ's functional units (nephrons, neurons) and disruption of some regulatory processes between cells and organs, resulting in decrease in function of body systems. For example, first pass metabolism decreases due to decrease in liver mass and blood flow, resulting in an increase in bioavailability of drugs which undergo extensive first pass metabolism, for example, propranolol. Another example of a pharmacokinetic change is the reduced clearance of renally-cleared drugs due to reduced renal plasma flow and glomerular filtration. This increases the potential for toxic effects particularly with those drugs where even marginal accumulation can have toxic effects, for example digoxin and lithium. Changes in body composition such as increase in body fat proportion and decrease in total body water result in a decreased volume of distribution for water soluble drugs such as digoxin, which increases their serum concentrations and potential for adverse effects.

Geriatric patients are much more "sensitive" to the action of many drugs, implying a change in the pharmacodynamic interactions of the drugs with their receptors. Elderly are more sensitive to some sedative-hypnotics and analgesics. Certain homeostatic control mechanisms appear to be blunted in elderly. Since homeostatic responses are often important components of the total response to a drug, these physiological alterations may change the pattern or intensity of drug response.

The age-related changes in the functions and composition of the human body require adjustments of drug selection and dosage for old individuals. Drug excretion via the kidneys declines with age, the elderly should therefore be treated as renally insufficient patients. A rough estimate of creatinine clearance can be obtained from the Cockcroft-Gault formula:

$$\text{Creatinine clearance} = \frac{(140 - \text{Age}) \times (\text{Weight in kg})}{72 \times \text{serum creatinine in mg/dL}} \quad (\text{for males})$$

( ml/min)

For females, the result is multiplied by 0.85. The formula is applicable to patients between the age of 40 and 80.

The metabolic clearance is primarily reduced with drugs that display high hepatic extraction ('blood flow-limited metabolism'), whereas the metabolism of drugs with low hepatic extraction ('capacity-limited metabolism') usually is not diminished. Reduction of metabolic drug elimination is more pronounced in malnourished or frail subjects. The water content of the aging body decreases, the fat content rises, hence the distribution volume of hydrophilic compounds is reduced in the elderly, whereas that of lipophilic drugs is increased. Intestinal absorption of most drugs is not altered in the elderly. Aside of these pharmacokinetic changes, one of the characteristics of old age is a progressive decline in counterregulatory (homeostatic) mechanisms. Therefore drug effects are mitigated less, the reactions are usually stronger than in younger subjects, the rate and intensity of adverse effects are higher. Examples of drug effects augmented in this manner are, postural hypotension with agents that lower blood pressure, dehydration, hypovolemia, and electrolyte disturbances in response to diuretics, bleeding complications with oral anticoagulants, hypoglycemia with antidiabetics, and gastrointestinal irritation with non-steroidal anti-inflammatory drugs. The brain is an especially sensitive drug target in old age. Psychotropic drugs but also anticonvulsants and centrally acting antihypertensives may impede intellectual functions and motor coordination. The antimuscarinic effects of some antidepressants and neuroleptic drugs may be responsible for agitation, confusion, and delirium in elderly. Hence drugs should be used very restrictively in geriatric patients. If drug therapy is absolutely necessary, the dosage should be titrated to a clearly defined clinical or biochemical therapeutic goal starting from a low initial dose.

# Appendix 14: Storage of Drugs

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## 1. Definition and Concept

### 1.1. Storage

The term used to describe the safe keeping of all finished drugs and pharmaceuticals awaiting dispatch. The term is also applied for safe stores in hospitals and dispensaries under the specified conditions, so as to maintain their quality and potency.

### 1.2. Storage Conditions

The condition specified for storing the product e.g. temperature, humidity, container etc.

### 1.3. Quality

The ability of drug product to satisfy the users need.

### 1.4. Dosage Form

Refers to the gross physical form in which a drug is administered to or used by a patient.

### 1.5. Drug Product

A dosage form containing one or more active therapeutic ingredients along with other substance included during manufacturing process.

### 1.6. Finished Product

A medicinal product which has completed all stages of manufacture including packaging.

### 1.7. Strength

The concentration of the drug substance (for example weight/weight, weight/volume or unit dose/volume basis) and the potency i.e. the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example in terms of units by reference to a standard).

### 1.8. Stability

Degree of resistance to chemical and physical changes, the efficacy of the preparation must remain constant or change only within the limit specified by official compendia.

### 1.9. Expiration Date

The date placed on the immediate container label of a drug product that designates the date through which the product is expected to remain within specifications. Kinetically it is the



time required for 10 % of the material to disappear.

### 2. Storage Procedure and Instructions

Drugs must be stored under conditions which minimize deterioration, contamination or damage. They must be stored under conditions compatible with their recommended storage requirements of temperature and humidity and where necessary to comply with legal requirements, under secured or segregated conditions.

#### **Appropriate storage conditions are:**

Temperature or humidity controlled environment must be equipped with suitable indicators, recorders and/or failure warning devices which must be checked at appropriate intervals and the results are coded. Recording thermometers should be used. Temperature in uncontrolled storage products should also be monitored.

Temperature should be measured at different levels in the warehouse and if necessary storage of sensitive drugs should be restricted to locations in the warehouse where they will be protected from extreme conditions. Temperatures of the refrigerators, deep freezers, and Relative Humidity in humidity control area as well as general areas of storage at room temperature should be recorded on a daily basis.

#### **Storage conditions not related to temperature are indicated in following terms:**

Drug storage should be regularly checked for cleanliness and good order and for misplaced/deteriorated/out dated stock. All stocks should be checked regularly for obsolescence and degradation. Drugs with expired shelf life should be destroyed unless an extension of shelf life is granted following the satisfactory results or re-analysis. All due precautions should be observed to preclude issues of outdated Drugs.

Some categories of supplies require special storage conditions which include vaccines, narcotics, and combustibles e.g. vaccines require both refrigerator and freezers.

Narcotics and other controlled substances should be kept in secure locking rooms with only one entrance. The keys should be kept in a secure place, preferably a safe. Only the warehouse director and one another person should have access to them.

### 3. Inspection for Deterioration

Pharmacists should be aware that deterioration of drug product may happen even before their expiration. This may occur perhaps due to improper storage or the fact that the product may require critical storage conditions not stated on

the label. Hence inspection should include frequent product examination to detect signs of product deterioration which differ according to dosage form. Some examples, where deterioration may be physically detected are given here. The Pharmacists in the Stores should prepare an exhaustive list of following deterioration/spoilage indicators and keep them.

### 3.1. Liquid Dosage Forms

Slight gradual discolouration, Swirly precipitation, Whickering: pin hole at ampoule tip that leaks solution which precipitate or crystalline solid matter, clouding, fading of colour, Cake sedimentation (suspension), Creaming and cracking (emulsion), Discolouration.

### 3.2. Semisolid Dosage Forms

Ointments creams, gels and suppositories -Change in consistency and feel to touch, Phase separation, Discolouration, Surface crystal growth

### 3.3. Solid Dosage Forms

Surface chipping or pitting (plain tablets), Deformation (capsules), Increased hardness, Discolouration, Colour fading (coloured tablets), Chipping of coat (coated tablets).

Most vitamins, hormones enzymes are highly sensitive to oxidation and photo decomposition.

The integrity of packaging of dosage form is one of the important tasks of inspection for pharmacist as these protect the drug in a tailored fashion.

After each inspection, products showing any signs of instability should be subjected to sample analysis to ensure quality.

## **4. Drug Products Requiring Special Storage Conditions**

### **4.1. Aerosols**

Aerosols should be stored in a clean separate area away from heat and sunlight because the container contents are under pressure, filled containers must be checked for weight loss over the expiration dating period, for contents under pressure. The label should display "Do not expose to heat or store at a temperature above 40°C, keep out of reach of children".

### **4.2. Creams**

Creams can be destroyed under extreme temperature fluctuations hence they should be stored at temperature above 10°C and not exceeding 30°C. If the creams are opened and diluted they should not be kept for more than 14 days to avoid microbial contamination.

### **4.3. Ophthalmic Solutions and Drops**

They should be stored according to the conditions specified on the label. After opening they should not be used for more than one month at home and not more than 15 days in hospitals.

### **4.4. Capsules**

Extremes of humidity and temperature should be avoided. High humidity (> 60% RH) at 21°C to 24°C produce more lasting effects. Capsules become softer, tackier and blotted. If temperature is increased the capsule shells may melt and fuse together. High temperature (>40°C) in dry place may cause cracking of capsule shell therefore capsules should be stored in air-conditioned area in which the humidity does not exceed 45% RH at 21 to 24°C.

### **4.5. Suppositories**

Suppositories should be protected from heat and preferably stored in the refrigerator. Polyethylene glycol suppositories and suppositories enclosed in solid shell are less prone to distortion at temperature slightly above body temperature. Glycerinated gelatin suppositories should be protected from heat, moisture and dry air by packaging in well sealed containers and storing in a cold place.

### **4.6. Vaccines**

Liquid vaccines are to be stored between 2° - 8°C and should not be frozen. All lyophilized vaccines should be stored between 2° - 8°C and for long term storage can be kept at or below -20°C or otherwise as specified in the individual monographs. Oral polio should be stored in a freezer -2° to -18°C.

## 5. Communicating the Prescription to the Patient

It is important that the drugs reach the patient in good and potent conditions and the patient should know and understand fully how to keep them till they are consumed. It is equally important that the patient should know the way each medicine is used. This will improve compliance and health outcome desired by the physician.

### Communicating how and where to store the drugs to the Patient:

The following table may be used to guide and provide information on the way to store the drugs when they are dispensed to the patients. This is based on the recommended storage conditions as given on the labels of the drug products and Indian Pharmacopoeial notes in the General Chapters.

<b>On the label</b>	<b>Meaning</b>	<b>Tell the Patient/ Representative of the Patient</b>
Do not store over 8°C	To be stored in refrigerator (from +2°C to +8°C)	Keep in the General Compartment of the refrigerator and do not keep in the place where you make Ice.
Do not store over 30 °C	To be stored at room temperature (from +2°C to +30°C)	Keep in any part of the house, except in Bath room/ Kitchen. Do not keep near or in the window area.
Do not freeze	To be kept in refrigerator (from +2°C to +8°C but not in the freezer chamber)	Keep in the General Compartment of the refrigerator and do not keep in the place where you make Ice.
Protect from moisture	To be stored in normal humidity at room temperature (RH less than 60%); to be provided by the manufacturer in a moisture-resistant container	The manufacturer would have provided such products in a moisture-resistant container/or packages. Keep in any part of the house, except in Bath room/Kitchen. Do not keep near or in the window area.

Protect from light

To be stored in a light-resistant cupboard/drawer; to be provided by the manufacturer in a light-resistant container.

The manufacturer would have provided such drug products in a light-resistant container/package. Keep in a cupboard/drawer or in a box with lid closed, in any part of the house, except in Bath room/Kitchen or near or in the window area.

### Transit period care and Use of Cool Packs:

It is equally important to ensure that patients who carry drugs requiring special storage conditions like anti-cancer drugs, several types of insulins, vaccines, sera, toxoids, would need to carry them in cold conditions till they reach the place where they will keep for some time before usage or to another hospital/nursing home till it is administered. In such cases during transit they need to be packed in **“Thermo cool boxes with lid”**, (#) with the drug product packs kept surrounded by adequate number of **“Cool Packs”**. (#) “Cool Packs are available which come ready filled with such special liquid in sealed bags or plastic packs, which on keeping overnight in freezer compartment of a refrigerator becomes solid ice. Such packs help in keeping the drug products in the box retain temperatures below 8°C for as much as 8 to 10 hours, which is generally adequate for transit protection. In case such cool packs are not available, it is recommended to use normal **“Hot cases”** (#) that people use to carry food, but stuffing the inside of the hot case boxes with sufficient ice cubes surrounding the drug packs kept inside, and the hot case suitably closed and sealed with sealing tapes. Cool packs can also be made by packing sufficient ice cubes into suitable sized self sealing polybags. (#) Several Pharmacists are known to innovate this way and they do serve for short transit times of up to one to two hours.

## Appendix 15:

# Therapeutic Drug Monitoring

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Therapeutic drug monitoring (TDM) is defined as measurement of drug levels in the biological fluids usually blood (serum or plasma). It has been carried out in saliva, urine, sweat, tear fluids etc also. It is carried out for specific drugs at various time intervals in order to maintain a relatively constant concentration of the particular drug in the bloodstream and to optimize drug therapy. The main focus of TDM is on drugs with narrow therapeutic range. Apart from this, it also plays a significant role for drugs having large inter-individual variations; relatively toxic drugs used in concomitant disease conditions, for escalation of dose, drugs showing wide variation in their metabolism, major organ failure, poisoning cases, failure of therapeutic response, to enhance patient compliance, etc. It is very important in such situations in which the drugs are to be taken on chronic or life long basis (chronic disease conditions such as bipolar disorder, organ transplant rejection, neurological disorders etc.). The timing and frequency of blood collection after the medication and correct interpretation of results of analysis and their correlation with clinical features ensures the best therapeutic outcome.

### Indications for drug monitoring:

- Drugs whose efficacy is difficult to establish clinically, like Phenytoin.
- Drugs with a narrow therapeutic index. Examples: Lithium, phenytoin, digoxin.
- Patients who have impaired clearance of a drug with a narrow therapeutic index. Example: Patients with renal failure have decreased clearance of digoxin and therefore are at a higher risk of toxicity.
- Drugs whose toxicity is difficult to distinguish from a patient's underlying disease. Example: Patients with chronic obstructive pulmonary disease treated with theophylline.

### When not to do TDM

1. Drugs whose pharmacological effects can easily be used to dose titration, like oral hypoglycemic agents, anti-hypertensive drugs.
2. When easier and/or cheaper methods/alternatives to TDM are available to titrate the drug like International normalized ratio(INR) for warfarin.

## Time of sample collection

1. Sample should be collected after steady state has been reached (5 half lives), unless TDM is intended to predict toxicity after single dose.
2. Usually “trough” concentrations are measured by taking the sample just before the subsequent dose.
3. Drugs whose half-lives are much shorter than the dosing interval, the peak and trough levels may be indicated to evaluate the dosage of drugs. Example: Gentamicin

TDM could be affected because of one or more of the factors relating to pharmacokinetics of the drug, or drug administration, or sample collection. Renal and hepatic alterations to half-life must also be considered. Laboratory variations also affect the TDM.

The following table summarizes the therapeutic concentration range of various drugs

**Table: Important drugs requiring therapeutic monitoring**

S. No	Pharmacological category	Drugs	Therapeutic drug conc. range
1.	Drugs acting on cardiovascular system	Amiodarone Digoxin Procainamide	1.0 - 2.5 µg/ml 0.8-2.0 ng/ml 4.0-10.0 µg/ml
2.	Antibiotics	Gentamycin Amikacin Vancomycin Tobramycin	5.0-10.0 µg/ml 15.0-25.0 µg/ml 15.0- 25.0 µg/ml 5.0-10.0 µg/ml
3.	Antiepileptics	Phenobarbital Phenytoin Valproic acid Carbamazepine Ethosuximide Gabapentin Lamotrigine	15.0-40.0 µg/ml 10.0-20.0 µg/ml 50.0-100.0 µg/ml 5.0-12.0 µg/ml 40.0-100.0 µg/ml 2.0-20.0 µg/ml 4.0-18.0 µg/ml
4.	Immunosuppressants	Cyclosporine Tacrolimus Sirolimus Mycophenolate mofetil	50.0-300.0 µg/ml 5.0-20.0 µg/l 5.0 – 15.0 µg/l 1.0- 60.0 mg/l
5.	Psychopharmacological agents	Lithium Imipramine Amitriptyline Nortriptyline Desipramine Clozapine	0.8-1.2 mEq/l 0.15- 0.3 µg/ml 0.12- 0.15 µg/ml 0.05-0.15 µg/ml 0.15- 0.3 µg/ml 0.35 to 0.6 mg/l
6.	Anti-infective	Cycloserine Ethambutol Pyrazinamide Streptomycin	20-35 µg/ml 2.0-6.0 µg/ml 20.0-50.0 µg/ml 35.0-45.0 µg/ml

## Appendix 15

TDM gives useful information regarding individual variations in drug utilization patterns as a consequence of altered physiological state or disease process and thus provides the clinician a better insight into the factors determining the patient's response to drug therapy.



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## NFI Feedback Form

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Suggested Change with Justification

Name: Contact No.: .....

Address: .....

e-mail ID: ..... Signature .....



# SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by healthcare professionals

<b>CDSCO</b> <b>Central Drugs Standard Control Organization</b> Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India, FDA Bhavan, ITO, Kotla Road, New Delhi www.cdsco.nic.in					<b>(AMC/ NCC Use only)</b> AMC Report No. _____ Worldwide Unique no. _____					
<b>A. Patient Information</b>					12. Relevant tests / laboratory data with dates _____					
1. Patient Initials _____		2. Age at time of Event or date of birth _____		3. Sex <input type="checkbox"/> M <input type="checkbox"/> F						
				4. Weight ____ Kgs						
<b>B. Suspected Adverse Reaction</b>					13. Other relevant history including pre-existing medical conditions (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction etc)					
5. Date of reaction stated (dd/mm/yyyy)					14. Seriousness of the reaction <input type="checkbox"/> Death (dd/mm/yyyy) _____ <input type="checkbox"/> Congenital anomaly <input type="checkbox"/> Life threatening <input type="checkbox"/> Required intervention to prevent permanent impairment / damage <input type="checkbox"/> Hospitalization-initial or prolonged <input type="checkbox"/> Other (specify) _____ <input type="checkbox"/> Disability <input type="checkbox"/> Other (specify) _____					
6. Date of recovery (dd/mm/yyyy)										
7. Describe reaction or problem										
					15. Outcomes <input type="checkbox"/> Fatal <input type="checkbox"/> Recovering <input type="checkbox"/> Unknown <input type="checkbox"/> Continuing <input type="checkbox"/> Recovered <input type="checkbox"/> Other (specify) _____					
<b>C. Suspected medication(s)</b>										
S.No	8. Name (brand and /or generic name)	Manufacturer (if known)	Batch No./ Lot No. (if known)	Exp. Date (if known)	Dose used	Route used	Frequency	Therapy dates (if known give duration)		Reason for use of prescribed for
								Date started	Date stopped	
i.										
ii.										
iii.										
iv.										
Sl.No As per C	9. Reaction abated after drug stopped or dose reduced					10. Reaction reappeared after reintroduction				
	Yes	No	Unknown	NA	Reduced dose	Yes	No	Unknown	NA	If reintroduced dose
i.										
ii.										
iii.										
iv.										
11. Concomitant medical product including self medication and herbal remedies with therapy dates (exclude those used to treat reaction)						<b>D. Reporter (see confidentiality section in first page)</b>				
						16. Name and Professional Address : _____				
						Pin code : _____ E-mail _____				
						Tel. No. (with STD code): _____				
						Occupation _____ Signature _____				
17. Causality Assessment						18. Date of this report (dd/mm/yyyy)				

## ADVICE ABOUT REPORTING

- Report adverse experiences with medications
- Report serious adverse reactions. A reaction is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

### ● Report even if:

- You're not certain the product caused adverse reaction
- you don't have all the details, however, point nos. 1, 5, 7, 8, 11, 15, 16 & 18 (see reverse) are essentially required.

### ● Who can report:

- Any health care professional (Doctors including Dentists, Nurses and Pharmacists)

### ● Where to report:

- Please return the completed form to the nearest **Adverse drug reaction Monitoring Centre (AMC)** or to **National Coordinating Centre**
- A list of nationwide AMCs is available at: <http://cdsco.nic.in/pharmacovigilance.htm>

### ● What happens to the submitted information:

- Information provided in this form is handled in strict confidence. The causality assessment is carried out at Adverse Drug Reaction Monitoring Centres (AMCs) by using WHO-UMC scale. The analyzed forms are forwarded to the National Coordinating Centre through the ADR database. Finally the data is analyzed and forwarded to the Global Pharmacovigilance Database managed by WHO Uppsala Monitoring Center in Sweden.
- The reports are periodically reviewed by the National Coordinating Centre (PvPI). The information generated on the basis of these reports helps in continuous assessment of the benefit-risk ratio of medicines.
- The information is submitted to the Steering Committee of PvPI constituted by the Ministry of Health and Family Welfare. The Committee is entrusted with the responsibility to review the data and suggest any interventions that may be required.

## Suspected Adverse Drug Reaction Reporting Form

For VOLUNTARY reporting of suspected adverse drug reactions by health care professionals



Central Drugs Standard Control Organization  
Directorate General of Health Services,  
Ministry of Health & Family Welfare, Government of India  
FDA Bhawan, ITO Kolla Road, New Delhi – 110002  
[www.cdsco.nic.in](http://www.cdsco.nic.in)

### Pharmacovigilance Programme of India for Assuring Drug Safety

#### Pharmacovigilance Programme of India (PvPI)

**National Coordination Centre,**  
Indian Pharmacopoeia Commission  
Ministry of Health & Family Welfare,  
Govt. of India

Sector-23, Raj Nagar, Ghaziabad-201 002. Tel.: 0120-2783400, 2783401, 2783392, FAX: 0120-2783311  
E.mail: [ipclub@vsnl.net](mailto:ipclub@vsnl.net)

**Confidentiality:** The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. **Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.**

## Objectives

- To revise and publish Indian Pharmacopoeia and the National Formulary of India on a regular basis.
- To develop comprehensive monographs for drugs to be included in the Indian Pharmacopoeia, including active pharmaceutical ingredients, excipients and dosage forms as well as medical devices, and to keep them updated.
- To accord priority to monographs of drugs included in the National List of Essential Medicines (NLEM) and their dosage forms.
- To prepare monographs for products that have normally been in the market for not less than 2 years except for certain special categories of new drugs like antiretrovirals, antituberculosis and anticancer drugs and their formulations introduced more recently, which may be accorded priority attention.
- To give special attention to the methods of manufacture used by the indigenous industry in selecting the pharmacopoeial tests for monitoring the toxic impurities of the concerned drug.
- To take note of the different levels of sophistication in analytical testing/instrumentation available while framing the monographs.
- To accelerate the process of preparation, certification and distribution of IP Reference Substances, including the related substances, impurities and degradation products.
- To collaborate with pharmacopoeias like the Ph Eur, BP, USP, JP, ChP and International Pharmacopoeia with a view to harmonizing with global standards.
- To organize educational programs and research activities for spreading and establishing awareness on the need and scope of quality standards for drugs and related articles/ materials.

**INDIAN PHARMACOPOEIA COMMISSION**  
**Ministry of Health & Family Welfare**  
Government of India

National Formulary of India provides  
information for the rational use of  
medicines for Indian healthcare  
professionals.

**INDIAN PHARMACOPOEIA COMMISSION**

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