Central Administration of Pharmaceutical Care
General Administration of Drug Utilization and Pharmacy Practice

Egyptian National Drug Formulary

Nervous system disorders

2025

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Contents

Preface

The Egyptian National Drug Formulary is published by the Egyptian Drug Authority, the Central Administration of Pharmaceutical Care, by the General Administration of Drug Utilization and Pharmacy Practice. It has been discussed within the Committee for Pharmacy Practice Guidelines and National Drug Lists.

This formulary aims to provide pharmacists and other healthcare professionals with accessible and reliable information about the available medications in the Egyptian drug database for making the right clinical decisions.

The Egyptian Drug Formulary is a guide that should be interpreted in light of professional clinical knowledge. The developers work to ensure that the information is as accurate and up-to-date as possible at the date of publication but knowledge and best practice change regularly. No responsibility for the work team for errors or omissions.

Egyptian National Drug Formulary Manual

(Nervous system disorders)

The Egyptian Drug Formulary (Nervous system medications) contains a list of medicines registered in the Egyptian drug database included in the essential medicines list or widely used in the Egyptian pharmaceutical market. It is designed as drug monographs classified pharmacologically and arranged alphabetically. There is a pharmacologically classified drug index at the beginning of the document and another alphabetically classified index at the end.

The Egyptian National Drug Formulary (Nervous system medications) presents detailed practical information for healthcare providers about each medicine.

Each monograph includes:

1. Generic name.
2. Dosage form/strengths available in Egypt from the EDA database.
3. Route of administration.
4. Pharmacological category and ATC code.
5. Indications: labeled indications.
6. Dosage regimens for adults and children.
7. Dosage adjustments if needed.
8. Contraindications.
9. Adverse drug reaction.
10. Monitoring parameters.
11. Drug Interactions: that imply avoidance or considering modifications.
12. Pregnancy and lactation.

13. Administration: detailed administration information for all routes [parenteral (preparation concentrations, compatibility with diluents, infusion rate, precautions during administration), Oral (food correlation)].
14. Warnings/Precautions.
15. Storage conditions

- For reconstituted vials, apply mentioned storage conditions only if prepared in aseptic techniques and ISO-controlled conditions according to USP 797 standards, otherwise discard immediately if not used.
- USP develops standards for compounding medications to help ensure patient benefit and reduce risks such as contamination, infection, or incorrect dosing.

N.B. Referral to the product Leaflet is needed for other specific formulation considerations.

Nervous system disorders Formulary

This document includes medications that contribute in management of nervous system disorders. Therapeutic classes include Anticonvulsants, Antiparkinsonism, Choline esterase inhibitors, and medications for Multiple Sclerosis.

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The development of the Egyptian National Drug Formulary is fostered by the exceptional expertise and insightful contributions of the **Members of the Pharmacy Practice Guides and National Drug Lists Committee - EDA.** Their rigorous scientific review, advice, and recommendations have been pivotal in ensuring that this work adhere to the highest standards of quality and effectiveness. We extend our sincere gratitude for their remarkable contributions to this important endeavor.

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Abbreviations

ADH	Antidiuretic hormone
UCD	Urea cycle disorders
AGEP	Acute generalized exanthematous pustulosis
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
AV	Atrioventricular
b.i.d	Two times a day
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CNS	Central nervous system
CPS	Refractory Complex Partial Seizures
CVS	Cardiovascular
DITP	Drug-induced immune thrombocytopenia.
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
ECG	Electrocardiogram
ER	Extended release
GGT	Gamma-glutamyl transferase
IM	Intramuscular
IR	Immediate release
IS	Infantile Spasms
IUDs	Intrauterine devices
IV	Intravenous
IVPB	IV piggyback
JCV	John Cunningham virus
MAOIs	Monoamine oxidase inhibitors

mcg	Microgram
NS	Normal saline
PD	Parkinson's disease
PML	Progressive multifocal leukoencephalopathy
PRES	Posterior Reversible Encephalopathy Syndrome (PRES)
RLS	Restless legs syndrome
SC	Subcutaneous
SCARs	Severe cutaneous adverse reactions
SJS	Stevens-Johnson syndrome
SR	Sustained release
t.i.d	Three times a day
T4	Thyroxine
TEN	Toxic epidermal necrolysis

Anticonvulsants

Barbiturates and derivatives

Phenobarbital (Phenobarbitone)

Generic Name	Phenobarbital
Dosage Form/Strengths	**Elixir**: 15mg/5ml. **Tablets**: 15mg, 30mg, 60mg, 100mg. **Solution for injection**: 40mg/ml.
Route of Administration	Oral, IV, IM
Pharmacologic Category	Antiseizure Agent, Barbiturate. **ATC**: N03AA02
Indications	Management of all forms of epilepsy, except absence seizures.
Dosage Regimen	**Adults** **Oral**: 60–200 mg daily. **IM, IV**: 50-200mg single dose (If necessary, may be repeated, after 6 hours). **Elderly** Dose should be lower due to reduced clearance. **Children** Oral: 3 - 8 mg/kg daily. IM: 3 - 5mg/kg single dose. Then adjust dose based on plasma concentration.
Dosage Adjustment	**Renal Impairment** Use with caution. **Hepatic Impairment** • Mild to moderate impairment: Use with caution; Initiate dose cautiously and adjust based on clinical response and serum concentrations. • Severe impairment: Avoid.
Contra-Indications	• Known hypersensitivity to phenobarbital, other barbiturates or other ingredients. • Acute intermittent porphyria. • Severe respiratory depression. • Severe impairment of renal and hepatic function.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Hypotension (neonates: 16%). **Gastrointestinal**: Change in appetite (feeding disorder; neonates: 16%). **Nervous system:** Sedated state (neonates: 16%). **Respiratory**: Changes in respiration (neonates: 25% [including respiratory depression and respiratory insufficiency]). **1% to 10%** **Cardiovascular**: Bradycardia (neonates: 3%). **Endocrine & metabolic**: Hyponatremia (neonates: 3%).
Monitoring Parameters	• Plasma concentration of phenobarbital. Target is 15 to 40 micrograms/ml (65 to 170 micromoles/liter). • Liver and renal functions (periodic).

Phenobarbital (Phenobarbitone)

	• Monitor for adverse effects: CNS status, respiratory depression, signs and symptoms of suicidality (e.g., anxiety, depression, behavior changes); dermatological reactions.
Drug Interactions	***Risk X: Avoid combination*** Abemaciclib, Adagrasib, Alpelisib, Antihepaciviral Combination Products, Apremilast, Aprepitant, Artemether and Lumefantrine, Asunaprevir, Avacopan, Avanafil, Avapritinib, Axitinib, Azelastine (Nasal), Bedaquiline, Bortezomib, Bosutinib, Brigatinib, Bromperidol, Bromperidol, Cabotegravir, Capmatinib, Cariprazine, Ceritinib, Copanlisib, Crizotinib, Cobicistat, Cobimetinib, Daclatasvir, Daridorexant, Dasabuvir, Deflazacort, Delamanid, Delavirdine, Disulfiram, Dolutegravir, Doravirine, Doxorubicin (Conventional), Dronedarone, Duvelisib, Elacestrant, Elbasvir and Grazoprevir, Elexacaftor, Tezacaftor, and Ivacaftor, Eliglustat, Elvitegravir, Encorafenib, Entrectinib, Erdafitinib, Etravirine, Fedratinib, Fexinidazole, Finerenone, Flibanserin, Flunarizine, Fosaprepitant, Fosnetupitant, Fostamatinib, Fostemsavir, Gemigliptin, Glasdegib, Hemin, Ibrexafungerp, Ibrutinib, Idelalisib, Infigratinib, Isavuconazonium Sulfate, Istradefylline, Itraconazole, Ivabradine, Ivacaftor, Ivosidenib, Ixazomib, Kratom, Ledipasvir, Lemborexant, Lenacapavir, Letermovir, Levoketoconazole, Lonafarnib, Lorlatinib, Lumacaftor and Ivacaftor, Lumateperone, Lurasidone, Lurbinectedin, Macimorelin, Macitentan, Mavacamten, Methotrimeprazine, Methoxyflurane, Mianserin, Midostaurin, Mifepristone, Mitapivat, Mobocertinib, Naldemedine, Naloxegol, Neratinib, Netupitant, Nilotinib, Nimodipine, Nirmatrelvir and Ritonavir, Nisoldipine, Olaparib, Olopatadine (Nasal), Olutasidenib, Orphenadrine, Oxomemazine, Pacritinib, Palbociclib, Palovarotene, Panobinostat, Paraldehyde, Pazopanib, Pemigatinib, Pexidartinib, Pimavanserin, Piperaquine, Pirtobrutinib, Ponesimod, Praziquantel, Pretomanid, Ranolazine, Regorafenib, Ribociclib, Rilpivirine, Rimegepant, Ripretinib, Roflumilast (Systemic), Rolapitant, Romidepsin, Sacituzumab Govitecan, Samidorphan, Saquinavir, Secnidazole, Selpercatinib, Selumetinib, Simeprevir, Sirolimus (Protein Bound), Sofosbuvir, Sonidegib, Sorafenib, Sotorasib, Sparsentan, Tamoxifen, Tasimelteon, Tazemetostat, Telithromycin, Tenofovir Alafenamide, Tepotinib, ezacaftor and Ivacaftor, Thalidomide, Ticagrelor, Tivozanib, Tofacitinib, Tolvaptan, Toremifene, Trabectedin, Tucatinib, Ubrogepant, Ulipristal, Upadacitinib, Valbenazine, Vandetanib, Velpatasvir, Venetoclax, Vincristine (Liposomal), Vinflunine, Voclosporin, Vonoprazan, Vorapaxar, Voriconazole, Voxilaprevir, Zanubrutinib. ***Risk D: Consider therapy modification*** Abiraterone Acetate, Acalabrutinib, Afatinib, ALfentanil, Apixaban, Aripiprazole , Aripiprazole Lauroxil, Atazanavir, Atogepant, Belumosudil, Benzhydrocodone, Bictegravir, Blonanserin, Brexpiprazole, Buprenorphine, Buspirone, Cabozantinib, Cabozantinib, Cholestyramine Resin, Clarithromycin, Clozapine, Codeine, Dasatinib, Deferasirox, Dexamethasone (Systemic), Dexmedetomidine, Diltiazem, Droperidol, Etoposide, Etoposide Phosphate, Everolimus, Exemestane, Felodipine, Fenfluramine, Fentanyl, Flunitrazepam,

Phenobarbital (Phenobarbitone)

	Ganaxolone, Gefitinib, Guanfacine, Hormonal Contraceptives, Hydrocodone, Hydroxyzine, Imatinib, Indinavir, Irinotecan Products, Ixabepilone, Ketoconazole (Systemic), Lamotrigine, Lapatinib, Larotrectinib, Lefamulin, Lefamulin (Intravenous), Levomethadone, Linagliptin, Lopinavir, Manidipine, Maraviroc, Maribavir, Mefloquine, Meperidine, Methadone, Methylprednisolone, Metyrapone, Mirodenafil, Nevirapine, Nifedipine, Opioid Agonists, Osimertinib, Oxybate Salt Products, Oxycodone, Perampanel, Pitolisant, Ponatinib, Pralsetinib, Quetiapine, Quinine, Radotinib, Risperidone, Ritonavir, Rivaroxaban, Ropeginterferon Alfa-2b, Sirolimus (Conventional), Stiripentol, Sufentanil, Sunitinib, Suvorexant, Tacrolimus (Systemic), Tadalafil, Temsirolimus, Tetrahydrocannabinol and Cannabidiol, Thiotepa, Tramadol, Trazodone, Triazolam, Tricyclic Antidepressants, Vemurafenib, Verapamil, Vilazodone, Vitamin K Antagonists, Vortioxetine, Voxelotor, Zaleplon, Zolpidem.
Pregnancy and Lactation	**Pregnancy** Avoid use during pregnancy unless potential benefit is judged to outweigh the risks. Phenobarbital is associated with risk to the fetus in terms of major and minor congenital defects. A highly effective contraception must be used during use. **Lactation** Not recommended due to possible risk of sedation to neonates.
Administration	**Administeration:** Oral, IM. **Administration: IV** Dilute 1 in 10 with Water for Injection. N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Suicidal tendency** Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. **Serious dermatologic reactions** Serious and sometimes fatal hypersensitivity reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of phenobarbital. Patients should be advised of the signs and symptoms (e.g. progressive skin rash often with blisters or mucosal lesions). Early diagnosis and immediate discontinuation are associated with a better prognosis. Do not restart phenobarbital. **Sudden withdrawal** It should be avoided as severe withdrawal syndrome (rebound insomnia, anxiety, tremor, dizziness, nausea and delirium) may be precipitated. **Dependence** Care should be used in prolonged treatment for patients with a history of drug abuse or alcoholism due to resulted dependance. Avoid sudden withdrawal to prevent rebound seizures. **Care should be taken in the following situations** Respiratory depression (avoid if severe), young, debilitated or senile patients, thyroid patients, renal impairment or existing liver disease.

Phenobarbital (Phenobarbitone)

	Bone effects Phenobarbital possibly increases the requirements for Vitamin D. As a precautionary measure, it is recommended that Vitamin D supplementation is considered. **Contraceptives** Increased clearance of estrogens and progestogens, possibly leading to oral contraceptive failure and breakthrough bleeding. Additional method of contraception may be required. **Folic acid** Folic acid supplements may be associated with fall in serum phenobarbital levels, leading to decreased seizure control in some patients. Caution as phenobarbital may cause folate insufficiency.
Storage	Store below 25°C. Protect from light. N.B. Refer to manufacturer PIL if there are specific considerations.

Benzodiazepine derivatives

Clonazepam

Generic Name	Clonazepam
Dosage Form/Strengths	**Tablet**: 0.5 mg, 2 mg. **Orally disintegrating tablets**: 0.5mg, 1 mg, 2mg. **Oral drops**: 2.5 mg/ml.
Route of Administration	Oral
Pharmacologic Category	Anti-seizure agent, Benzodiazepine. **ATC:** N03AE01
Indications	• All clinical forms of epileptic disease and seizures in infants, children and adults. • Treatment of panic disorder with or without agoraphobia.
Dosage Regimen	**Adult dosing** **Seizures** **Initial:** 0.5 mg 2-3 times daily. **Maintenance:** 4- 8 mg/day. **Maximum dose**: 20 mg/day. **Titration increments**: 0.5 – 1 mg every 3 days. **Panic disorder** **Initial**: 0.25 mg twice daily then titrate to target dose after 3 days. **Recommended Maintenance**: 1 mg/day. Higher doses are associated with adverse reactions; however, some patients may need higher doses. **Maximum dose:** 4 mg/day. **Elderly dosing**: Start with smaller doses and titrate carefully as geriatric patients are more sensitive to CNS-depressants. **Pediatric dosing** **Seizures** **Initial** **Infants and small children** (0 to 5 years): 0.25 mg/day. **Older children** (5 to 12 years): 0.5 mg/day. **Maintenance** **Infants** (0 to 1 year): 0.5 to 1 mg/day. **Small children** (1 to 5 years): 1 to 3 mg/day. **Older children** (5 to 12 years): 3 to 6 mg/day. **Titration increments**: 0.5 – 1 mg every 3 days. **General dosing considerations** • Treatment with Clonazepam should be started at low doses then titrated gradually till symptoms are controlled or side effects prevent further dose increments.

Clonazepam

	• If doses are not equally divided, larger doses of Clonazepam should be given at bedtime if the daily dose is not equally divided. • Patients treated with clonazepam may develop dependence. Abrupt discontinuation or interruption of treatment with Clonazepam may cause severe withdrawal symptoms or relapses.
Dosage Adjustment	**Renal impairment** No dose adjustment is required. Caution. **Hepatic impairment** • Mild-to-moderate hepatic impairment: Adjust individually. May need lower doses. • Severe hepatic impairment: Contraindicated.
Contra-Indications	• Hypersensitivity to clonazepam or any of the excipients. • Severe liver disease. • Acute narrow angle glaucoma. • Acute pulmonary insufficiency. • Severe respiratory insufficiency. • Sleep apnea. • Myasthenia gravis.
Adverse Drug Reactions	**>10%** **Nervous system**: Ataxia (seizure disorder: 30%; panic disorder: 1% to 9%), behavioral problems (seizure disorder: 25%), dizziness (5% to 12%), drowsiness (seizure disorder: 50%; panic disorder: 26% to 50%). **1% to 10%** **Endocrine & metabolic**: Decreased libido (1% to 3%). **Gastrointestinal**: Abdominal pain (2%), constipation (3% to 5%), decreased appetite (3%). **Genitourinary**: Dysmenorrhea (3% to 6%), impotence (≤3%), urinary frequency (1% to 2%), urinary tract infection (2%), vaginitis (2% to 4%). **Hypersensitivity**: Hypersensitivity reaction (2% to 4%). **Infection**: Influenza (4% to 5%). **Nervous system**: Confusion (1% to 2%), decreased mental acuity (2% to 4%), delayed ejaculation (1% to 2%), depression (6% to 8%), dysarthria (2% to 4%), emotional lability (2%), fatigue (6% to 9%) (See Table 3), memory impairment (4% to 5%), nervousness (3% to 4%). **Neuromuscular & skeletal**: Myalgia (2% to 4%). **Ophthalmic**: Blurred vision (2% to 3%). **Respiratory**: Bronchitis (2%), cough (2% to 4%), pharyngitis (2% to 3%), rhinitis (2% to 4%), sinusitis (4% to 8%), upper respiratory tract infection (6% to 10%).
Monitoring Parameters	• Liver and renal function prior to use. • Monitor patients for emergence of suicidal behavior or ideas, signs and symptoms of respiratory depression and sedation.

Clonazepam

Drug Interactions	***Risk X: Avoid combination*** Azelastine (nasal), Bromperidol, Flunarizine, Kratom, Nabilone, Olopatadine (nasal), Orphenadrine, Oxomemazine, Oxybate Salt Products, Paraldehyde, Thalidomide. ***Risk D: Consider therapy modification*** Blonanserin, Buprenorphine, Chlormethiazole, Clozapine, Daridorexant, Dexmedetomidine, Droperidol, Flunitrazepam, Hydroxyzine, Lemborexant, Loxapine, Methadone, Methotrimeprazine, Opioid Agonists, Oxycodone, Ropeginterferon Alfa-2b, Suvorexant, Zolpidem, Zuranolone.
Pregnancy and Lactation	**Pregnancy** Clonazepam has harmful pharmacological effects on pregnancy and the fetus and possible congenital malformations. During pregnancy, clonazepam may be administered only if the benefits outweigh the risks. **Lactation** • Lactation during treatment with clonazepam is not recommended. • Infants exposed to clonazepam from breast milk are reported to suffer from sedation, poor feeding, and poor weight gain.
Administration	**Administration: Oral** • Tablets should be swallowed whole with water. • Orally-disintegrating tablets: Remove the tablet immediately upon opening the blister, using dry hands and place it in the mouth. Tablet disintegrates rapidly in saliva so it can be easily swallowed with or without water. • To reduce the inconvenience of somnolence, administration of one dose at bedtime may be desirable. N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Risk from concurrent use with CNS depressants and opioids** • The concurrent use of benzodiazepines with opioids may result in profound sedation, respiratory depression, coma, and death. • Benzodiazepines and opioids should be combined only if no other alternatives are available. • If benzodiazepines and opioids are prescribed concurrently, they should be used at the lowest effective doses and for the shortest duration. • Patients should be evaluated for CNS and respiratory depression. **Risk of decreased alertness while performing hazardous activities** Clonazepam causes CNS depression and sedation which predisposes patients to injuries when they drive, operate machinery, or perform other activities that require alertness. **Suicidal tendency** • Antiepileptic drugs are associated with a risk of emergence of suicidal thoughts and behavior. • Patients should be monitored closely for the emergence of suicidal

Clonazepam

	tendencies and new onset or worsening of depression. **Dependence, tolerance and withdrawal reactions** • Continuous treatment with benzodiazepines may cause physical and psychological dependence. To avoid withdrawal reactions, clonazepam should never be abruptly stopped and should always be gradually tapered to discontinuation. • Abrupt withdrawal after higher doses and longer treatment durations leads to precipitating status epilepticus. • Acute withdrawal symptoms include anxiety, insomnia, irritability, tremors, panic, restlessness, memory impairment, tachycardia, nausea, and vomiting. Other life-threatening symptoms include: seizures, depression, catatonia, mania, psychosis, and suicidal tendency. **Neonatal withdrawal symptoms** Neonates may develop withdrawal symptoms (e.g., irritability, poor feeding, tremors) from exposure to clonazepam late in pregnancy. **Loss of effect and worsening of seizures** • Clonazepam may lose its anticonvulsant effect after a period of treatment (3 months). • The effect may be restored by increasing the dose or interrupting treatment for a short duration (2 – 3 weeks). **Risk in patients with respiratory conditions** Given the risk of respiratory depression, Clonazepam should be avoided in patients with severe or acute respiratory conditions. Carefully adjust dose in patient with chronic pulmonary conditions. **Porphyria** Clonazepam might be porphyrogenic and should be used with caution in patients with porphyria.
Storage	Store between 15 – 30 °C. Protect from light. N.B. Refer to manufacturer PIL if there are specific considerations.

Diazepam

Generic Name	Diazepam
Dosage Form/Strengths	**Solution for I.M Injection, I.V Injection/Infusion**: 10 mg/2ml. **Tablets**: 2mg, 5mg, 10mg **Oral Syrup**: 2mg/5ml **Rectal Suppositories**: 10 mg
Route of Administration	IM, IV, Oral, Rectal
Pharmacologic Category	Anticonvulsant, Antiseizure Agent, Benzodiazepine. **ATC**: N05BA01
Indications	• Short-term relief of the severe or disabling symptoms of anxiety (2-4 weeks). • As an anti-convulsant in the management of status epilepticus, febrile convulsions and poisoning. • Alcohol withdrawal syndrome. • Relief of muscle spasm as in tetanus or cerebral spasticity. • Insomnia (severe, disabling or subjecting the individual to extreme distress). • Premedication for procedural anxiety.
Dosage Regimen	**Dosing: Adults** **N.B.** Dosage regimes with benzodiazepines should always be gradually withdrawn. **N.B.** For all indications, doses for geriatrics and debilitated patients should not exceed half of those recommended for adults. **N.B**. It is not known if diazepam is safe and effective for use longer than 4 months. • **Management of Anxiety Disorders and Relief of Symptoms of Anxiety** **Oral:** 2 mg to 10 mg, 2 to 4 times daily, according to severity, up to 30 mg daily in divided doses. The lowest effective dose should be used; duration of use should not exceed 4 weeks. **IM, IV:** 2 mg to 5 mg **(for moderate cases)** or 5 mg to 10 mg **(for severe cases)**. Dose may be repeated in 3 to 4 hours, if necessary. • **Adjunct to the management of some types of epilepsy** **Oral:** 2-10 mg daily 2 to 4 times daily. • **Status Epilepticus** **IV (preferred) or IM (if IV is inaccessible):** 5 mg to 10 mg initially (slow injection). This injection may be repeated if necessary at 10 to 15-minute intervals up to a maximum dose of 30 mg. If necessary, repeat therapy in 2 to 4 hours; caution with patients with chronic lung disease or unstable cardiovascular status. • **Symptomatic relief in acute alcohol withdrawal** **Oral:** 10 mg, 3 or 4 times during the first 24 hours, reducing to 5 mg, 3 or 4 times daily as needed. **IM, IV:** 10 mg initially, then 5 mg to 10 mg in 3 to 4 hours, if necessary.

Diazepam

- **Adjunctively for relief of muscle spasm**
  Oral: 2 mg to 15 mg daily in divided doses up to 60 mg in severe spastic disorders such as cerebral spasticity, epilepsy and muscle spasms associated with upper-motor neuron disease.
  IM/IV: 5 mg to 10 mg initially, then repeat in 3 to 4 hours, if necessary.
  For tetanus, Initially, an IV dose of 0.1 - 0.3 mg/kg body weight, repeated at intervals of 1 - 4 hours. Continuous IV infusion of 3 – 10 mg / kg body weight per 24 hours can also be used.
- **Insomnia associated with anxiety**
  Oral: 5-15 mg at bedtime. Dosage regimes should not exceed beyond 4 weeks.
- **Premedication in dental patients**
  Oral: 5 mg the night before, 5 mg on waking and 5 mg two hours before the appointment.
- **Premedication before surgery**
  Oral: 5 mg - 20 mg.
  IM (preferred), or IV: 10-20 mg before surgery.
- **Adjunct in endoscopic Procedures**
  IV: 10 mg slowly prior to the procedure. Titrate IV dosage to desired sedative response up to 20 mg particularly if narcotics are omitted.
  IM: 5 mg to 10 mg IM approximately 30 minutes prior to the procedure. (If IV cannot be used).

Dosing: Pediatric

N.B. Initiate therapy with lowest dose and increase as required. Not recommended for use in pediatric patients under 6 months.
General dosing: Oral: 1 mg to 2.5 mg, 3 or 4 times daily initially; increase gradually as needed and tolerated.

- **Night terrors and somnambulism**
  Oral: 1 mg to 5 mg daily at bedtime.
- **Status epilepticus, convulsions due to poisoning, febrile convulsions**
  Children 1 month – 11 years: IV: 0.2-0.4 mg/kg, second dose may be given after 10 minutes if required. Maximum per dose 10 mg.
  Each injection to be given over 1 – 5 minutes.
  Children 12 – 17 years: IV: 10 mg then a further 10 mg after 10 minutes, if required.
  Each injection to be given over 1– 5 minutes.
- **Management of cerebral spasticity**
  Oral: 2 mg to 40 mg daily in divided doses.
- **In the control of muscle spasms as in tetanus**
  Oral: 3 mg to 10mg/kg body weight daily.
  IV: 0.1– 0.3 mg/ kg every 1–4 hours.
  IV infusion: 3–10 mg/ kg, to be given over 24 hours.
  Respiratory assistance should be available.
- **Premedication before surgery**
  Oral: 2 mg to 10 mg.
  IM, IV: 0.2 mg/kg (slow injection).

Diazepam

Dosage Adjustment	**Renal Impairment** Dosage reduction may be required in patients with kidney dysfunction. **Hepatic Impairment** There are no dosage adjustments available; use with caution because clearance may decrease significantly. Diazepam is contraindicated in severe hepatic impairment.
Contra-Indications	• Hypersensitivity to Diazepam or any component of the formulation. • phobic or obsessional states, primary treatment of psychotic illness (inadequate evidence of safety and efficacy), hyperkinesis (paradoxical reactions may occur). • Acute pulmonary insufficiency; acute or chronic severe respiratory insufficiency, respiratory depression, including sleep apnea syndrome. • Severe hepatic disease. • Myasthenia gravis • Acute Porphyria • Acute narrow-angle glaucoma, Untreated open-angle glaucoma • Avoid injections containing benzyl alcohol in neonates or pregnant women. • Pregnancy or Planning a pregnancy unless there are compelling reasons.
Adverse Drug Reactions	**>10%** **Nervous system**: Drowsiness (23%). **1% to 10%** **Cardiovascular**: Hypotension (≥1%), vasodilation (2%). **Dermatologic**: Skin rash (3%). **Gastrointestinal**: Abdominal pain (≥1%), diarrhea (4%), dysgeusia (3%), hiccups (≥1%). **Nervous system**: Abnormality in thinking (≥1%), agitation (≥1%), ataxia (3%), confusion (≥1%), dizziness (3%), dysarthria (≥1%), emotional lability (≥1%), euphoria (3%), headache (5%), nervousness (≥1%), pain (≥1%), speech disturbance (≥1%), vertigo (≥1%). **Neuromuscular & skeletal**: Asthenia (1%). **Respiratory**: Asthma (2%), epistaxis (2%), nasal discomfort (6%), rhinitis (≥1%).
Monitoring Parameters	• Periodically evaluate need for continued use; long-term use can result in dependence, abuse, or tolerance. • Blood pressure. • Signs and symptoms of respiratory depression and sedation. • Liver enzymes (prior to use).
Drug Interactions	***Risk X: Avoid combination*** Azelastine (Nasal), Bromperidol, Disulfiram, Fexinidazole, Flunarizine, Kratom, Methotrimeprazine, Nabilone, Olopatadine (Nasal), Ornidazole, Orphenadrine, Oxomemazine, Oxybate Salt Products, Paraldehyde, Secnidazole, Thalidomide. ***Risk D: Consider therapy modification*** Blonanserin, Buprenorphine, Chlormethiazole, Clozapine, Daridorexant, Dexmedetomidine, Droperidol, Flunitrazepam, Fusidic Acid (Systemic),

Diazepam

	Hydroxyzine, Lemborexant, Loxapine, Methadone, Opioid Agonists, Oxycodone, Ropeginterferon Alfa-2b, Suvorexant, Zolpidem, Zuranolone.
Pregnancy and Lactation	**Pregnancy** • It should not be used, especially in the first and third trimesters, unless the benefit is considered to outweigh the risk. An increased risk of congenital malformations associated with the use of diazepam during the first trimester of pregnancy. • Use during the later stages of pregnancy may develop physical dependence and withdrawal symptoms in infants. **Lactation** Diazepam is excreted in the breast milk and therefore its use during lactation should be avoided.
Administration	**Administration: Oral** Administer with water with or without food. **Administration: IM** Administer undiluted deep into muscle mass. **Administration: IV** Administer undiluted by slow IV push; do not mix with other solutions or medications. Intravenous injections of diazepam should be given into a large vein of the antecubital fossa to minimize local reactions, thrombophlebitis and venous thrombosis. **Rate of infusion:** Injection should be given slowly (5mg per minute) in order to reduce the likelihood of respiratory depression or hypotension. It is advisable to keep the patient supine and under medical supervision for at least an hour after administration. **Continuous infusion:** Mix 2 ml with at least 200ml of infusion fluid (sodium chloride injection or dextrose injection) and use immediately. It is recommended that glass bottles should be used for the administration of diazepam by infusion because diazepam is adsorbed onto plastic infusion bags and giving sets. **Vesicant**: Ensure proper needle or catheter placement prior to and during administration; avoid extravasation. Extreme care should be taken to avoid intra-arterial administration or extravasation. **N.B.** Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Elderly and debilitated patients** Lower doses are needed to reduce CNS effects. Caution as long-term use is associated with an increased risk of developing dementia. **Dependence and withdrawal symptoms** • Use of diazepam may lead to the development of physical and psychic dependence. The dependence potential increases with high doses and when given over long periods. • Diazepam should be withdrawn gradually. Withdrawal symptoms may consist of headache, muscle pain, tension, extreme anxiety, confusion, restlessness and irritability. More severe acute reactions may include life-threatening reactions of convulsions, delirium tremens, depression,

Diazepam

hallucinations, mania, psychosis, seizures, and suicidality.

Abuse, Misuse, and Addiction

Patients with a history of alcoholism or drug abuse are most susceptible. Before prescribing, assess each patient's risk for abuse, misuse, and addiction.

Rebound phenomena

Rebound insomnia and anxiety may occur. This is a transient syndrome where the symptoms that led to the use of diazepam recur in an enhanced form after sudden discontinuation.

Concomitant alcohol use or CNS depressants

Should be avoided during treatment with diazepam (additive CNS depression).

Concomitant use of opioids

Concomitant use of diazepam and opioids may result in sedation, respiratory depression, coma and death. The lowest effective dose should be used, and the duration of treatment should be as short as possible if concomitant use of diazepam and opioids is required.

Amnesia

Benzodiazepines may induce anterograde amnesia. Amnestic effects may be associated with inappropriate behaviour. Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages.

Duration of use

Should be as short as possible. Evaluation for need of continued use should be made in no more than 4 weeks. Patient should be informed that use will be of limited duration and how the dosage will be progressively decreased.

Hypo-albuminemia

May predispose patient to higher incidence of sedative side effects.

Hepatic dysfunction

Benzodiazepines should not be used in patients with severe hepatic insufficiency as they may precipitate encephalopathy.

Paradoxical reactions

Inappropriate adverse behavioural effects can occur. Reactions include restlessness, agitation, aggressiveness, confusion, delusions, rage, nightmares, hallucinations, psychoses. These reactions are more likely in children and the elderly, and patients with personality disorders. If they occur, treatment should be discontinued.

Patients with depression

Diazepam should not be used alone to treat depression or anxiety associated with depression as suicide may be precipitated in such patients.

Respiratory disease

Benzodiazepines may cause significant respiratory depression. Reduce dose or avoid use in patients with respiratory disease.

Benzyl alcohol

Benzyl alcohol, that may be as excipient in the injection form, has been

Diazepam

	reported to be associated with a fatal gasping syndrome in premature infants. Caution. **Propylene glycol** Some dosage forms of injections may contain propylene glycol; large amounts are potentially toxic and have been associated with hyperosmolality, lactic acidosis, seizures, and respiratory depression; use caution.
Storage	**Injection:** Store between (15°C to 30°C). Protect from light. Do not refrigerate. **Oral solution:** Store between (15°C to 30°C). Protect from light. **Tablet**: Store between (15°C to 30°C). Protect from moisture. N.B. Refer to manufacturer PIL if there are specific considerations.

Carboxamide derivatives

Carbamazepine

Generic Name	Carbamazepine
Dosage Form/Strengths	**Oral suspension:** 100 mg/5ml. **Tablet:** 200 mg, 400 mg. **Chewable Tablets:** 100mg. **Modified Release Tablet:** 200mg, 300mg, 400mg, 600mg.
Route of Administration	*Oral*
Pharmacologic Category	Anticonvulsant, miscellaneous **ATC:** N03AF01
Indications	• **Epilepsy** - Partial seizures with complex symptomatology (psychomotor, temporal lobe). - Generalized tonic-clonic seizures (grand mal). - Not for absence seizures (petit mal) and myoclonic seizures. • **Trigeminal Neuralgia** - Treatment of the paroxysmal pain associated with true trigeminal neuralgia and glossopharyngeal neuralgia. This medicine is not a basic analgesic and should not be used to treat minor aches or pains. • **For the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy.**
Dosage Regimen	**General instructions** • A low initial daily dosage with a gradual increase is advised to suit the needs of each patient. • ***Conversion from oral conventional tablets to extended-release tablets:*** The same total daily mg dose of extended-release tablet should be given but usually in two divided doses. • ***Conversion from oral tablets to suspension:*** Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., b.i.d. tablets to t.i.d. suspension) as suspension produces higher peak levels than the tablet at the same dose. **Dosing: Adults** • **Epilepsy: Monotherapy or adjunctive therapy** **N.B.** Because of the possibility of drug interactions, carbamazepine should be used with caution in older patients. **Initial** 100- 200mg once or twice daily. This may be followed by a gradual increase at weekly intervals until the optimal response is achieved. - The daily dose of the extended release form is usually administered in 1 to 2 doses. While regular release tablets may be given up to three times daily. Oral solution daily dose is given usually in two or three up to four divided doses daily.

Carbamazepine

	Maintenance: The minimum effective level, usually 400-1200mg daily. In some cases, 1600mg or even 2000mg daily may be required. • **Trigeminal neuralgia** ***Elderly: Oral:*** The initial dose of 100mg twice daily. ***Adult: Oral:*** **Initial**: 200-400mg daily. Dose is slowly raised until free of pain usually 200mg 3-4 times daily. In some conditions, doses of 1200mg daily may be needed. Then, the dosage should be gradually reduced to the lowest possible maintenance level. • **Prophylaxis of manic-depressive psychosis in patients unresponsive to lithium** Initial: 400mg daily, in divided doses, increased gradually, if needed, until symptoms are controlled or a total of 1600mg given in divided doses is reached. The usual dosage range is 400- 600mg daily, given in divided doses. **Dosing: Pediatric (children and adolescents)** **Epilepsy: Monotherapy or adjunctive therapy** Dose should be gradually increased to suit the needs of the patient. The usual dosage is 10-20mg/kg body weight daily taken in several divided doses. ▪ **Age up to 1 year:** 100 to 200 mg daily (oral suspension). ▪ **1-5 years:** 200 to 400 mg daily. ▪ **5-10 years:** 400 to 600 mg daily. ▪ **10-15 years:** 600 to 1000 mg daily. ▪ **>15 years of age:** 800 to 1200 mg daily (same as adult dose) - ***Maximum recommended dose (conventional tablet, extended release tablet, and suspension)*** ▪ **Up to 6 years of age:** 35 mg/kg/day. ▪ **6-15 years of age:** 1000 mg/day. ▪ **>15 years of age:** 1200 mg/day.
Dosage Adjustment	**Renal Impairment** No dosage adjustment is available. No data. Lower doses may be needed. **Hepatic Impairment** No dosage adjustment is available. No data. **Elderly and patients with severe cardiovascular disease** A lower dosage may be needed.
Contra-Indications	• Hypersensitivity to carbamazepine, Tricyclic antidepressants, or any component of the formulation. • History of previous bone marrow depression. • Use with or within 14 days of Monoamine oxidase inhibitors (MAOIs) use. • Atrioventricular (AV) heart block. • History of hepatic porphyria.
Adverse Drug Reactions	**>10%** **Central nervous system (CNS):** Dizziness (44%), drowsiness (32%), ataxia (15%).

Carbamazepine

	Gastrointestinal: Nausea (29%), vomiting (18%). **1% to 10%** **Cardiovascular:** Hypertension (3%). **Central nervous system:** Speech disturbance (6%), abnormality in thinking (2%), paresthesia (2%), twitching (2%), vertigo (2%). **Dermatologic:** Pruritus (8%), skin rash (7%). **Gastrointestinal:** Constipation (10%), xerostomia (8%), and rectal irritation may occur with a suppository. **Ophthalmic:** Blurred vision.
Monitoring Parameters	**Baseline and periodic** • Complete blood count (CBC) with platelet count and differential, reticulocyte count. • Liver function test. • Kidney function test. • Serum iron. • Ophthalmic examinations. **As appropriate** • Total serum carbamazepine levels: Usual adult therapeutic levels for epilepsy: 4 to 12 micrograms/ml (17 to 50 micromoles/liter) measured after 1–2 weeks. **The conditions where monitoring the plasma levels is useful** ▪ Dramatic increase in seizure frequency or verification of patient compliance. ▪ During pregnancy. ▪ Treatment of children or adolescents. ▪ Absorption disorders. ▪ Suspected toxicity when more than one drug is being used. • Thyroid function monitoring is suggested in pediatrics and to adjust the dosage of thyroid replacement therapy due to induced hypothyroidism. • Serum sodium prior to therapy in patients with preexisting renal disease or in patients taking concomitant sodium-lowering medicinal products. Thereafter, measured after two weeks and then at monthly intervals for the first three months of treatment or as clinically necessary. • Monitor patients during treatment for Suicidal ideation or other potential hypersensitivity, hematological, dermatological or hepatic reactions. If developed, patient should consult physician immediately. • Pregnancy test: This is recommended for women of reproductive potential before starting carbamazepine medication.
Drug Interactions	***Risk X: Avoid combination*** Abemaciclib, Adagrasib, Alpelisib, Antihepaciviral Combination Products, Apixaban, Apremilast, Aprepitant, Artemether and Lumefantrine, Asunaprevir, Atazanavir, Avacopan, Avanafil, Avapritinib, Axitinib, BCG (Intravesical), Bedaquiline, Berotralstat, Bortezomib, Bosutinib, Brigatinib, Cabotegravir, Capivasertib, Capmatinib, Cariprazine, Ceritinib,

Carbamazepine

Chloramphenicol (Systemic), Cladribine, Cobicistat, Cobimetinib, Copanlisib, Crizotinib, Dabigatran Etexilate, Daclatasvir, Daridorexant, Darolutamide, Dasabuvir, Deflazacort, Delamanid, Delavirdine, Dipyrone, Doravirine, Doxorubicin (Conventional), Dronedarone, Duvelisib, Efavirenz, Elacestrant, Elbasvir/ Grazoprevir, Elexacaftor/ Tezacaftor/ Ivacaftor, Eliglustat, Elvitegravir, Encorafenib, Entrectinib, Erdafitinib, Etravirine, Fedratinib, Fexinidazole, Finerenone, Flibanserin, Fosaprepitant, Fosnetupitant, Fostamatinib, Fostemsavir, Fruquintinib, Fusidic Acid (Systemic), Futibatinib, Gemigliptin, Gepirone, Gilteritinib, Glasdegib, Glecaprevir/ Pibrentasvir, Ibrexafungerp, Ibrutinib, Idelalisib, Infigratinib, Isavuconazonium Sulfate, Istradefylline, Itraconazole, Ivabradine, Ivacaftor, Ivosidenib, Ixazomib, Ledipasvir, Lemborexant, Lenacapavir, Leniolisib, Letermovir, Levoketoconazole, Lonafarnib, Lorlatinib, Lumacaftor/ Ivacaftor, Lumateperone, Lurasidone, Lurbinectedin, Macimorelin, Macitentan, Mavacamten, Midostaurin, Mitapivat, Mobocertinib, Monoamine Oxidase Inhibitors, Naldemedine, Naloxegol, Nefazodone, Neratinib, Netupitant, Nevirapine, Nilotinib, Nimodipine, Nintedanib, Nirmatrelvir/ Ritonavir, Nirogacestat, Nisoldipine, Olaparib, Olutasidenib, Omaveloxolone, Orelabrutinib, Pacritinib, Palbociclib, Palovarotene, Panobinostat, Pazopanib, Pemigatinib, Pexidartinib, Pimavanserin, Piperaquine, Pirtobrutinib, Ponesimod, Praziquantel, Pretomanid, Quizartinib, Ranolazine, Regorafenib, Relugolix/ Estradiol/ Norethindrone, Repotrectinib, Ribociclib, Rilpivirine, Rimegepant, Ripretinib, Ritlecitinib, Rivaroxaban, Roflumilast (Systemic), Rolapitant, RomiDEPsin, Sacituzumab Govitecan, Samidorphan, Saquinavir, Selpercatinib, Selumetinib, Simeprevir, Siponimod, Sirolimus (Protein Bound), Sofosbuvir, Sonidegib, Sorafenib, Sotorasib, Sparsentan, Tamoxifen, Tasimelteon, Tazemetostat, Tenofovir Alafenamide, Tezacaftor/ Ivacaftor, Ticagrelor, Tivozanib, Tofacitinib, Tolvaptan, Toremifene, Trabectedin, Tramadol, Treosulfan, Tucatinib, Ubrogepant, Ulipristal, Upadacitinib, Valbenazine, Vandetanib, Velpatasvir, Venetoclax, Vincristine (Liposomal), Vinflunine, Voclosporin, Vonoprazan, Vorapaxar, Voriconazole, Voxilaprevir, Zanubrutinib, Zavegepant, Zuranolone.

Risk D: Consider therapy modification

Abiraterone Acetate, Acalabrutinib, Afatinib, ALfentanil, Aripiprazole, Aripiprazole Lauroxil, Atogepant, Belumosudil, Bictegravir, Brexpiprazole, Buspirone, Cabozantinib, Calcium Channel Blockers (Nondihydropyridine), Caspofungin, Clarithromycin, Clozapine, Cyclosporine (Systemic), Dasatinib, Deferasirox, Deferiprone, Dexamethasone (Systemic), Dolutegravir, Edoxaban, Enzalutamide, Eravacycline, Erlotinib, Etoposide, Etoposide Phosphate, Everolimus, Exemestane, Felbamate, Felodipine, Fenfluramine, Ganaxolone, Gefitinib, Guanfacine, Hormonal Contraceptives, Imatinib, Indinavir, Irinotecan Products, Ixabepilone, Ketoconazole (Systemic), Lamotrigine, Lapatinib, Larotrectinib, Lefamulin, Linagliptin, Lopinavir, Manidipine, Maraviroc, Maribavir, Mefloquine, Methylprednisolone, Metyrapone, Mifepristone, Mirodenafil, Nifedipine, Osimertinib, Perampanel, Pitolisant, Ponatinib, Pralsetinib, Quetiapine, Quinine,

Carbamazepine

	Radotinib, Relugolix, Risperidone, Ritonavir, Ropeginterferon Alfa-2b, Sirolimus (Conventional), Stiripentol, Sufentanil, Sunitinib, Tacrolimus (Systemic), Tadalafil, Temsirolimus, Tetrahydrocannabinol and Cannabidiol, Theophylline Derivatives, Thiotepa, Trazodone, Triazolam, Vemurafenib, Vilazodone, Vitamin K Antagonists (e.g., warfarin), Vortioxetine, Voxelotor, Zaleplon.
Pregnancy and Lactation	**Pregnancy** • Carbamazepine may cause major congenital malformations and other adverse development outcomes. At a dose < 400 mg per day, the rates of malformation were lower than that with higher doses of carbamazepine. Women of childbearing potential should use highly effective contraception during treatment and for at least two weeks after stopping treatment. • Carbamazepine may result in a failure of the therapeutic effect of hormonal contraceptives. • Carbamazepine should not be used during pregnancy unless the benefit/risk considerations and no alternative suitable treatment options. Maintain plasma levels at the lowest effective therapeutic range of 4 to 12 micrograms/mL. **Lactation** • Use is not recommended during lactation due to potential for serious adverse reactions. • Breast-fed infants of mothers treated with carbamazepine should be closely monitored for hepatobiliary side effects.
Administration	• **Tablets:** Administer with food (during or after meals) with a glass of water. Swallow extended-release tablet whole and do not crush or chew. • **Suspension:** Shake well before administration. It should be administered with meals (during or after meals). N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Serious Dermatological Reactions** • During treatment, severe and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), may occur. Serious dermatological reactions may need hospitalization and rarely fatal. • Carbamazepine should be discontinued at the first sign of a rash, unless it is not drug-related and alternative therapy should be considered. • The risk is increased in patients with the variant HLA-B*1502 allele. HLA-B1502 is more prevalent among patients from an Asian origin. Genetic testing cannot replace careful medical care. **Severe immediate hypersensitivity reactions** • Rare cases of anaphylaxis and fatal angioedema have been reported. If occurred, carbamazepine should be discontinued and patients should not

Carbamazepine

be re-challenged.

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity: Monitor signs including fever, rash, lymphadenopathy and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities or myocarditis. Therapy should be discontinued if another cause cannot be established.

Hypersensitivity reactions and HLA-A*3101 Allele

- The risk of developing a hypersensitivity reaction (cutaneous adverse drug reactions) may be increased in patients with the variant HLA-A*3101 allele. Application of HLA genotyping as a screening tool must not substitute appropriate clinical vigilance and patient management.
- **Hepatic effects:** Slight elevations in liver enzymes to rare cases of hepatic failure may occur. Monitor at baseline and periodically. Carbamazepine should be discontinued, based on clinical judgment If hepatic dysfunction worsens or florid liver disease occurs.

Hyponatremia

- Dose related hyponatremia may occur in patients treated with carbamazepine due to Inappropriate ADH secretion like syndrome. Symptoms include nausea, malaise, headache, lethargy, confusion, difficulty concentrating, memory impairment, or increase in seizure frequency or severity.
- Consider dose reductions, restricting fluid intake, or switching to alternative antiepileptic drugs if hyponatremia occurs.
- In the following patients, monitor sodium before starting treatment, 2 weeks after initiation, and monthly thereafter for 3 months:
    - Elderly patients.
    - Patients with renal conditions associated with low sodium.
    - Patients concurrently treated with drugs that cause sodium depletion e.g., diuretics or desmopressin.

CNS adverse effects

- Carbamazepine may cause disturbance in attention, somnolence, fatigue, and coordination abnormalities. It may activate a latent psychosis.
- Use caution in elderly and when driving or operating machinery.

Suicidal tendency

- Antiepileptic drugs have been found to be associated with the emergence of suicidal behavior or ideas.
- Patients treated with carbamazepine should undergo regular psychiatric evaluation to identify new onset or worsening of depression, mood changes, or suicidal thoughts.

Hematologic disorders

Monitor for signs of anemia, infection, or bleeding**.** Therapy should be stopped if considerable bone marrow suppression occurs

Carbamazepine

	Folic acid deficiency • Antiepileptic drugs have been reported to decrease serum folate levels which increase the incidence of birth defects in case of pregnancy. Caution. • Folic acid supplementation is recommended before and during pregnancy. **Anticholinergic effects** Carbamazepine has weak anticholinergic activity. Therefore, patients with glaucoma and urinary retention should be carefully monitored during treatment. **Hypothyroidism** • Carbamazepine may reduce serum concentrations of thyroid hormones. • Thyroid function monitoring is recommended in pediatrics while on therapy and in patients taking thyroid replacement therapy. **Hormonal contraceptives** Carbamazepine may make the contraceptives less effective due to decreased plasma concentrations of the hormones. Alternative contraception methods should be considered. **Absence seizures** • Carbamazepine can cause absences or exacerbate existing absence seizures. Caution. • In case of exacerbation of seizures, carbamazepine should be discontinued. **Photosensitization** May occur. Patients should protect themselves from strong sunlight exposure during treatment. **Discontinuation of therapy** Abrupt discontinuation of carbamazepine can precipitate seizures. Therefore, carbamazepine should be discontinued gradually or alternated with another antiepileptic therapy. **Sorbitol** Suspension may contain Sorbitol, so, it should not be administered to patients with rare hereditary problems of fructose intolerance. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.
Storage	Store between 15-30^{0}C. Protect from moisture. N.B. Refer to manufacturer PIL if there are specific considerations.

Oxcarbazepine

Generic Name	Oxcarbazepine
Dosage Form/Strengths	**Tablet**: 150 mg, 300 mg, 600 mg. **Extended-release tablet**: 150 mg, 300 mg, 600 mg. **Oral suspension**: 300 mg/5ml (100ml).
Route of Administration	Oral
Pharmacologic Category	Anti-seizure agent ATC: N03AF02
Indications	**Immediate-Release Formulations:** treatment of **p**artial-onset seizures (monotherapy in patients 4 years of age and older or as adjunctive therapy in patients 2 years and older). **Extended-release tablet:** treatment of partial-onset seizures in patients 6 years of age and older.
Dosage Regimen	**Adult dosing** **Immediate-Release Tablets for adults** **Adjunctive or monotherapy** **Initial:** 600 mg/day given in 2 divided doses. **Maintenance:** 600 - 2400 mg/day (mostly 1200mg/day) increased from the starting dose by 600 mg weekly or 300 mg every third day if needed to achieve desired response. In adjunctive therapy: If 2400 mg/day dose is used, reduction of dose of concomitant antiepileptic products will be needed because of CNS-related adverse events. **Maximum dose:** 2400 mg daily. **Extended-Release Tablets for adults** **Initial:** 600mg once daily (300mg for elderly). **Maintenance:** 1200 mg to 2400 mg/day once, daily increased from the starting dose by 600mg (300 – 450 mg for elderly) at weekly intervals. **Pediatric dosing** **Immediate-Release Tablets for pediatrics** **Initial:** 8-10 mg/kg/day divided in 2 doses. **Initial dose for adjunctive treatment in children 2 to < 4 years old** < 20 kg: 16 – 20 mg/kg/day in 2 divided doses. **Maintenance in adjunctive or monotherapy in children 6 to 16 Years old** **Oral**: 30-46 mg/kg/day increased from the starting dose by 5-10 mg/kg increments at weekly intervals if needed to achieve desired response. **Alternative method of maintenance dosing** **Monotherapy in children 4 – 16 years old** Daily dose given in 2 divided doses: 20 kg: 600 – 900 mg/day. 25-30 kg: 900 – 1200 mg/day. 35-40 kg: 900 – 1500 mg/day. 45 kg: 1200 – 1500 mg/day.

Oxcarbazepine

	50 -55 kg: 1200 – 1800 mg/day. 60 -65 kg: 1200 – 2100 mg/day. 70 kg: 1500 – 2100 mg/day. **Adjunctive treatment in children 2 – 16 years old** Daily dose given in 2 divided doses: 20 – 29 kg: 900 mg/day. >29 to 39 kg: 1200 mg/day. > 39 kg: 1800 mg/day. **Conversion to monotherapy for Patients (Aged 4–16 Years)** Maximum increment of 10 mg/kg/day at weekly intervals, concomitant antiepileptic drugs can be completely withdrawn over 3 to 6 weeks. **Extended-Release Tablets for pediatrics** **Initial:** 8 -10 mg/kg once daily. **Maintenance dosing** 20 – 29 kg: 900 mg/day. >29 to 39 kg: 1200 mg/day. > 39 kg: 1800 mg/day. **General dosing considerations** • Immediate-release Oxcarbazepine is administered twice daily while extended-release tablets are administered once daily. • Extended-release tablets should be administered without food (1 hour before or 2 hours after food). Administration with food may increase peak plasma concentrations and cause adverse reactions.
Dosage Adjustment	**Renal impairment** • CrCl ≥ 30 ml/min: No dose adjustments. • Creatinine clearance < 30 ml/min: Start at half the regular dose (300 mg/day) and increase by 300 – 450 mg every week till optimum response. **Hepatic impairment** • Mild to moderate impairment: No dose adjustment is needed. • Severe impairment: Not studies. Use is not recommended. **Concurrent use with CYP3A4 inducers** including other antiepileptic drugs: Dose adjustments for Oxcarbazepine might be necessary. A starting dose of 900 mg/day for adults and 12 – 15 mg/kg/day for pediatrics should be considered.
Contra-Indications	Hypersensitivity to oxcarbazepine or any of the components of the product.
Adverse Drug Reactions	**>10%** **Endocrine & metabolic**: Hyponatremia (ER, IR: 1% to 46%). **Gastrointestinal**: Abdominal pain (5% to 13%), nausea (15% to 25%), vomiting (ER: 15%; IR: 7% to 33%).

Oxcarbazepine

	Nervous system: Ataxia (ER: 1% to 3%; IR: 2% to 17%), dizziness (ER, IR: 20% to 41%), drowsiness (ER: 12% to 14%; IR: 19% to 31%), fatigue (ER: 3% to 6%; IR: 12% to 21%), headache (ER: 8% to 15%; IR 13% to 32%), vertigo (2% to 12%). **Ophthalmic**: Diplopia (ER: 10% to 13%; IR: 12% to 30%), nystagmus disorder (ER: 3%; IR: 2% to 20%), visual disturbance (ER: 1% to 3%; IR: 4% to 14%). **1% to 10%** **Cardiovascular**: Chest pain (2%), edema (2%), hypotension (1%), lower extremity edema (2%). **Dermatologic**: Acne vulgaris (1% to 2%), diaphoresis (3%), skin rash (4%). **Endocrine & metabolic**: Hot flash (2%), increased thirst (2%), weight gain (2%). **Gastrointestinal**: Anorexia (5%), constipation (4% to 5%), diarrhea (7%), dysgeusia (5%), dyspepsia (2% to 6%), gastritis (2% to 3%), toothache (2%), upper abdominal pain (ER: 3%), xerostomia (3%) **Genitourinary**: Urinary frequency (2%), urinary tract infection (5%), vaginitis (2%). **Hematologic & oncologic**: Bruise (4%), lymphadenopathy (2%), purpuric rash (2%), rectal hemorrhage (2%). **Hypersensitivity**: Hypersensitivity reaction (2%). **Infection**: Infection (2%), viral infection (7%). **Nervous system**: Abnormal gait (ER: ≤3%; IR: 5% to 10%), abnormality in thinking (2%), amnesia (4% to 5%), anxiety (7%), balance impairment (ER: 7%), confusion (7%), dysmetria (1% to 2%), emotional lability (3% to 8%), falling (4%), feeling abnormal (1%), hypoesthesia (3%), insomnia (2% to 6%), lack of concentration (2%), myasthenia (1% to 2%), nervousness (2% to 7%), seizure (2%; decreased seizure threshold [exacerbation of seizures]: 5%), speech disturbance (1% to 3%). **Neuromuscular & skeletal**: Asthenia (2% to 7%), back pain (4%), muscle spasm (2%), sprain (2%), tremor (4% to 8%). **Ophthalmic**: Blurred vision (ER: 4%). **Otic**: Otalgia (2%), otic infection (2%). **Respiratory**: Bronchitis (3%), cough (5%), epistaxis (4%), nasopharyngitis (ER: 3%), pharyngitis (3%), pneumonia (2%), pulmonary infection (4%), rhinitis (10%), sinusitis (3% to 4%), upper respiratory tract infection (7% to 10%). **Miscellaneous**: Fever (3%).
Monitoring Parameters	• Complete blood count (CBC). • Liver and kidney function test. • Thyroid function monitoring is suggested in pediatrics and to adjust the dosage of thyroid replacement therapy due to induced hypothyroidism. • Serum sodium prior to therapy in patients with preexisting renal disease

Oxcarbazepine

	or in patients taking concomitant sodium-lowering medicinal products. Thereafter, measured after two weeks and then at monthly intervals for the first three months of treatment or as clinically necessary. • Monitor patients for hypersensitivity, dermatologic, hematologic reactions and emergence of suicidal tendencies. **The conditions where monitoring the plasma levels is useful** • Changes in renal function. • Pregnancy. • Concomitant use of liver enzyme-inducing drugs.
Drug Interactions	***Risk X: Avoid combination*** Cabotegravir, Daclatasvir, Dolutegravir, Doravirine, Elvitegravir, Eslicarbazepine, Ledipasvir, Lenacapavir, Rilpivirine, Simeprevir, Sofosbuvir, Tenofovir Alafenamide, Ulipristal. ***Risk D: Consider therapy modification*** Atogepant, Bictegravir, Cobicistat, Hormonal Contraceptives, Lamotrigine, Mefloquine, Metyrapone, Perampanel, Ubrogepant.
Pregnancy and Lactation	**Pregnancy** • Oxcarbazepine may cause fetal harm e.g., oral clefts and cardiac malformations. Limited data. • If oxcarbazepine is used during pregnancy, the lowest effective dose should be used. Monotherapy is associated with less risk of congenital abnormalities than combination therapy. • Risk of seizures in the pregnant women due to reduced plasma levels of the active metabolite during pregnancy. Optimum seizure control during pregnancy is essential for the safety of both the mother and the fetus. • Use of oxcarbazepine with hormonal contraceptives may induce ineffectiveness of the contraceptive. Additional non-hormonal forms of contraception are recommended when using oxcarbazepine. **Lactation** Limited data. The benefits of breastfeeding should be evaluated against the risk of adverse events in infants. Infant should be monitored for adverse reactions e.g. drowsiness, and poor weight gain.
Administration	**Administration: Oral** • **Immediate-release tablet and suspension** can be taken with or without food. • Before using oxcarbazepine suspension, the bottle should be shaken well. • It is recommended to use an oral dosing syringe to accurately prepare a dose of oxcarbazepine suspension. • **Extended-release tablet** should be taken on empty stomach, (taken 1 hour before or 2 hours after meals). N.B**.** Refer to manufacturer PIL if there are specific considerations**.**
Warnings/ Precautions	**Serious Dermatological Reactions** • During treatment, severe and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), may occur. Serious dermatological reactions may need

Oxcarbazepine

hospitalization and rarely fatal. The median time of onset was 19 days after starting treatment.

- Oxcarbazepine should be discontinued at the first sign of a rash, unless it is not drug-related and alternative therapy should be considered. In some reports, symptoms recurred when patients were re-challenged with oxcarbazepine.
- The risk is increased in patients with the variant HLA-B*1502 allele. HLA-B1502 is more prevalent among patients from an Asian origin. Genetic testing cannot replace careful medical care.

Hematologic disorders

- During treatment, aplastic anemia, agranulocytosis; or other hematological problems may occur.
- Monitor for signs of anemia, unexpected infection, or bleeding**.** Therapy should be stopped if considerable bone marrow suppression occurs

Severe immediate hypersensitivity reactions

- Rare cases of anaphylaxis and fatal angioedema have been reported.
- If anaphylaxis or angioedema occur, oxcarbazepine should be discontinued and patients should not be re-challenged.
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity: Monitor signs including fever, rash, lymphadenopathy and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities or myocarditis. Therapy should be discontinued if another cause cannot be established.

Hypersensitivity reactions and HLA-A*3101 Allele

- The risk of developing a hypersensitivity reaction (cutaneous adverse drug reactions) may be increased in patients with the variant HLA-A*3101 allele. Application of HLA genotyping as a screening tool must not substitute for appropriate clinical vigilance and patient management.

Cross hypersensitivity to carbamazepine

- It is estimated that 25– 30% of patients who experienced hypersensitivity with carbamazepine will experience a reaction with oxcarbazepine as well.
- Patients with a history of hypersensitivity to carbamazepine should be treated with oxcarbazepine only if the benefits outweigh the potential risk.

Hyponatremia

- Clinically significant hyponatremia (< 125 mmol/L) occurred in 2.5% of patients during treatment with oxcarbazepine.
- Symptoms include nausea, malaise, headache, lethargy, confusion, difficulty concentrating, memory impairment, or increase in seizure frequency or severity.
- Consider dose reductions, restricting fluid intake, or switching to alternative antiepileptic drugs if hyponatremia occurs.

Oxcarbazepine

	• In the following patients, monitor sodium before starting treatment, 2 weeks after initiation, and monthly thereafter for 3 months:
	  ○ Elderly patients.
	  ○ Patients with renal conditions associated with low sodium.
	  ○ Patients concurrently treated with drugs that cause sodium depletion e.g., diuretics or desmopressin.
	
	CNS adverse effects
	• Oxcarbazepine may cause disturbance in attention, somnolence, fatigue, and coordination abnormalities. Use caution when driving or operating machinery.
	• These CNS adverse reactions are more likely to occur with high doses (2400 mg/day), or when oxcarbazepine is combined with other antiepileptic drugs.
	
	Suicidal tendency
	• Antiepileptic drugs have been found to be associated with the emergence of suicidal behavior or ideas.
	• Patients treated with oxcarbazepine should undergo regular psychiatric evaluation to identify new onset or worsening of depression, mood changes, or suicidal thoughts.
	
	Hypothyroidism
	Oxcarbazepine may reduce serum concentrations of thyroid hormones. Thyroid function monitoring is recommended in pediatrics while on therapy and in patients taking thyroid replacement therapy.
	
	Hormonal contraceptives
	Oxcarbazepine may make the contraceptives less effective due to decreased plasma concentrations of the hormones. Alternative contraception methods should be considered.
	
	Seizure aggravation
	• Oxcarbazepine has been reported to worsen or cause new onset primary generalized seizures.
	• Oxcarbazepine should be discontinued if it exacerbates seizures.
	
	Discontinuation of therapy with Oxcarbazepine
	• Oxcarbazepine should be withdrawn gradually to avoid increases in seizure frequency and status epilepticus.
	• Abrupt discontinuation of Oxcarbazepine should only be considered in case of serious and severe adverse reactions.

Storage	**Tablets** Store between 15°C and 30°C. Protect from moisture and light. **Suspension** Store between 15°C and 30°C. Oxcarbazepine suspension should be discarded 7 weeks after the bottle had been first opened. N.B. Refer to manufacturer PIL if there are specific considerations.

Hydantoin derivatives

Lamotrigine

Generic Name	Lamotrigine
Dosage Form/ Strengths	**Tablet:** 25 mg; 50 mg; 100 mg; 200 mg. **Tablet (chewable; dispersible):** 2 mg; 5mg, 25 mg, 50mg, 100mg.
Route of Administration	Oral
Pharmacologic Category	Antiseizure Agent, Miscellaneous **ATC**: N03AX09
Indications	**Epilepsy** • Treatment of partial and generalized seizures, including tonic-clonic seizures, adjunctive (in patients 2 years and above) or monotherapy (in patients 13 years and above). • Seizures associated with Lennox-Gastaut syndrome, adjunctive (in patients 2 years and above). • Monotherapy of typical absence seizures (2 to 12 years). **Bipolar disorder** • Prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes (in adults). • Maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (in adults).
Dosage Regimen	**Epilepsy** N.B. inducers of Lamotrigine glucuronidation include: phenytoin, carbamazepine, phenobarbitone, primidone, rifampicin, lopinavir/ritonavir. **Adults and adolescents aged 13 years and above**

Treatment regimen	Weeks 1 + 2	Weeks 3 + 4	Usual maintenance dose
Monotherapy	25 mg/day (once a day)	50 mg/day (once a day)	•100–200 mg/day (once a day or two divided doses). •Increments: 50-100 mg/day every 1-2 week. •Maximum: 500 mg/day.
Adjunctive therapy with valproate	12.5 mg/day (given as 25 mg on alternate days)	25 mg/day (once a day)	•100 – 200 mg/day (once a day or two divided doses). •Increments: 25-50mg/day every 1-2 week.
Adjunctive therapy without valproate and with inducers of lamotrigine glucuronidation	50 mg/day (once a day)	100 mg/day (two divided doses)	•200 – 400 mg/day (two divided doses). •Increments: 50-100 mg/day every 1-2 week. •Maximum: 700 mg/day.

Lamotrigine

Adjunctive therapy without valproate and without inducers of lamotrigine glucuronidation	25 mg/day (once a day)	50 mg/day (once a day)	•100 – 200 mg/day (once a day or two divided doses). •Increments: 50-100 mg/day every 1-2 week.

Children and adolescents aged 2 to 12 years

Treatment regimen	Weeks 1 + 2	Weeks 3 + 4	Usual maintenance dose
Monotherapy of typical absence seizures	0.3 mg/kg/day (once a day or two divided doses)	0.6 mg/kg/day (once a day or two divided doses)	•1–10 mg/kg/day. •Increments: 0.6 mg/kg/day every 1-2 week. •Maximum 200 mg/day.
Adjunctive therapy with valproate	0.15 mg/kg/day (once a day)	0.3 mg/kg/day (once a day)	•1 – 5 mg/kg/day (once a day or two divided doses) •Increments: 0.3 mg/kg/day every 1-2 week. •Maximum 200 mg/day.
Adjunctive therapy without Valproate and with inducers of Lamotrigine glucuronidation	0.6 mg/kg/day (two divided doses).	1.2 mg/kg/day (two divided doses).	•5 – 15 mg/kg/day (once a day or two divided doses). •Increments: 1.2 mg/kg/day every 1-2 week. •Maximum 400 mg/day.
Adjunctive therapy without Valproate and without inducers of Lamotrigine glucuronidation	0.3 mg/kg/day (once a day or two divided doses).	0.6 mg/kg/day (once a day or two divided doses).	•1 – 10 mg/kg/day (once a day or two divided doses). •Increments: 0.6 mg/kg/day every 1-2 week. •Maximum 300 mg/day.

Lamotrigine

Bipolar disorder
Adults aged 18 years and above

Treatment regimen	Weeks 1 + 2	Weeks 3 + 4	Week 5	Target Stabilization Dose
Monotherapy with lamotrigine OR adjunctive therapy without valproate and without inducers of lamotrigine glucuronidation	25 mg/day (once a day)	50 mg/day (once a day)	100 mg/day (once a day or two divided doses)	200 mg/day (once a day or two divided doses)
Adjunctive therapy with Valproate	12.5 mg/day (given as 25 mg on alternate days)	25 mg/day (once a day)	50 mg/day (once a day or two divided doses)	100 mg/day. (once a day or two divided doses) Maximum 200 mg/day
Adjunctive therapy without Valproate and with inducers of Lamotrigine glucuronidation	50 mg/day (once a day)	100 mg/day (two divided doses)	200 mg/day (two divided doses)	300 mg/day in week 6. 400 mg/day in week 7 if needed. (two divided doses)

Adults aged 18 years and above – maintenance stabilization total daily dose following withdrawal of concomitant medicinal products in treatment of bipolar disorder.

Treatment regimen	Current lamotrigine stabilization dose (prior to withdrawal)	Week 1	Week 2	Week 3
Withdrawal of valproate	100 mg/day	200 mg/day	200 mg/day (two divided doses)	
	200 mg/day	300 mg/day	400 mg/day	400 mg/day

Lamotrigine

Withdrawal of inducers of lamotrigine glucuronidation	400 mg/day	400 mg/day	300 mg/day	200 mg/day
	300mg/day	300mg/day	225 mg/day	150 mg/day
	200mg/day	200mg/day	150 mg/day	100 mg/day
Withdrawal of medicinal products that do NOT significantly inhibit or induce lamotrigine glucuronidation		Maintain current dose of Lamotrigine	Maintain current dose of Lamotrigine	Maintain current dose of Lamotrigine

Adults aged 18 years and above - adjustment of lamotrigine daily dosing following the addition of other medicinal products in treatment of bipolar disorder.

Treatment regimen	Current lamotrigine stabilization dose (prior to withdrawal)	Week 1	Week 2	Week 3
Addition of valproate	200 mg/day	100 mg/day	Maintain (100 mg/day).	
	300 mg/day	150 mg/day	Maintain (150 mg/day).	
	400 mg/day	200 mg/day	Maintain (200 mg/day).	
Addition of inducers of lamotrigine glucuronidation And NOT taking valproate	200mg/day	200mg/day	300 mg/day	400 mg/day
	150mg/day	150mg/day	225 mg/day	300 mg/day
	100mg/day	100mg/day	150 mg/day	200 mg/day
Addition of medicinal products that do NOT significantly inhibit or induce lamotrigine glucuronidation	Maintain target dose achieved in dose escalation (200 mg/day; dose range 100-400 mg/day).			

Dosage Adjustment

Renal Impairment

Caution. For significant renal function impairment: Reduced maintenance doses may be effective.

Hepatic Impairment

- Moderate impairment: Reduce initial dose by 50%. Then adjust according to clinical response.

Lamotrigine

	• Severe Impairment: Reduce initial dose by 75%. Then adjust according to clinical response.
Contra-Indications	Hypersensitivity to lamotrigine or to any of the excipients.
Adverse Drug Reactions	**>10%** **Gastrointestinal**: Nausea (7% to 14%). **1% to 10%** **Cardiovascular**: Chest pain, edema, peripheral edema. **Dermatologic**: Contact dermatitis, diaphoresis, skin rash, xeroderma. **Endocrine & metabolic**: Increased libido, weight gain, weight loss. **Gastrointestinal**: Abdominal pain, anorexia, constipation, dyspepsia, flatulence, peptic ulcer, vomiting, xerostomia. **Genitourinary**: Dysmenorrhea, urinary frequency. **Hematologic & oncologic**: Rectal hemorrhage. **Infection**: Infection. **Nervous system**: Abnormal dreams, abnormality in thinking, agitation, amnesia, anxiety, ataxia, confusion, depression, dizziness, drowsiness, emotional lability, fatigue, hyperreflexia, hypoesthesia, hyporeflexia, insomnia, irritability, migraine, neurologic abnormality (dyspraxia), pain, paresthesia, suicidal ideation. **Neuromuscular & skeletal**: Arthralgia, asthenia, back pain, myalgia, neck pain. **Ophthalmic**: Amblyopia, nystagmus disorder, visual disturbance **Respiratory**: Bronchitis, cough, dyspnea, epistaxis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection. **Miscellaneous**: Alcohol intolerance, fever.
Monitoring Parameters	• CBC • ECG • Monitor for side effects, rash, hypersensitivity reactions, suicidal behaviors, meningitis, worsening of symptoms of depression. • Measurement of serum levels of lamotrigine before and after starting hormonal contraceptives may be considered
Drug Interactions	***Risk X: Avoid combination*** Azelastine (Nasal), Bromperidol, Dofetilide, Flunarizine, Kratom, Nabilone, Olopatadine (Nasal), Orphenadrine, Oxomemazine, Paraldehyde, Thalidomide. ***Risk D: Consider therapy modification*** Antiseizure Agents (Sodium Channel Blockers), Blonanserin, Buprenorphine, Carbamazepine, Cenobamate, Contraceptives (Estrogens), Daridorexant Chlormethiazole, Droperidol, Dexmedetomidine, Ethinyl Estradiol-Containing Products, Flunitrazepam, Fosphenytoin, Hydroxyzine, Lemborexant, Lopinavir, Loxapine, Mefloquine, Methotrimeprazine, Metyrapone, Opioid Agonists, Oxybate Salt Products, Oxycodone, Phenobarbital, Phenytoin, Primidone, Rifampin, Ropeginterferon Alfa-2b, Rufinamide, Suvorexant, Topiramate, Valproate Products, Zolpidem, Zonisamide, Zuranolone.
Pregnancy and Lactation	**Pregnancy** • If necessary, the lowest possible therapeutic dose is recommended.

Lamotrigine

	• Animal studies have shown developmental toxicity. • During the first trimester, maintenance doses are not associated with an increased risk of major congenital malformations. • A dose of ≥325 mg lamotrigine per day is associated with increase in the rate of major congenital malformations. • Lamotrigine plasma levels may be decreased during pregnancy. Potential risk of loss of seizure control. Lamotrigine serum concentrations should be monitored before, during and after pregnancy, as well as shortly after birth. **Lactation** Lamotrigine plasma levels in nursing infants have been reported to be as high as 50% of maternal plasma concentrations. Consider benefit/risk ratio. If administered during breastfeeding, the infant should be monitored for adverse effects, such as sedation, rash and poor weight gain.
Administration	N.B. Doses should be rounded down to the nearest whole tablet**.** **Chewable/dispersible tablets**: may be chewed, dispersed in a small volume of water (at least enough to cover the whole tablet) or swallowed whole with a little water. Administration partial quantities of the chewable/dispersible tablets is not recommended. **Regular tablets**: Administer whole. If the tablet is scored and require halving, the half should be swallowed whole. Do not chew or crush. **N.B**. Refer to manufacturer PIL if there are specific considerations**.**
Warnings/ Precautions	**Serious Dermatological Reactions** • During treatment, severe and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), may occur. Serious dermatological reactions may need hospitalization and rarely fatal. • Lamotrigine should be discontinued at the first sign of a rash, unless it is not drug-related and alternative therapy should be considered. • The rate of serious rash is greater in pediatric patients than in adults. Additional risk factors include: coadministration with valproate, exceeding recommended initial dose and exceeding recommended dose escalation. **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Multiorgan Hypersensitivity:** Potentially serious, sometimes fatal reactions. If DRESS is suspected, drug should be discontinued. Monitor signs including fever, rash, lymphadenopathy, facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities. **Hematologic disorders** Hematopoietic complications, sometimes fatal, have been reported. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia. Monitor for signs of anemia, infection, or bleeding.

Lamotrigine

	Aseptic meningitis Monitor for signs of meningitis. Reversible on withdrawal of the drug in most cases. Do not rechallenge. **Cardiac rhythm and conduction abnormalities** Arrhythmogenic ST-T abnormality and typical Brugada ECG pattern have been reported in patients treated with lamotrigine. **Photosensitivity reactions** May occur, mostly with high doses (400 mg or more). Patients should protect themselves from strong sunlight. **Suicidal Behavior and Ideation** Monitor patients for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior. Appropriate treatment should be considered. **Hormonal contraceptives** Decreased contraceptive efficacy in some patients taking hormonal preparations with lamotrigine. A decrease in lamotrigine levels has been associated with loss of seizure control is associated with the use of an ethinylestradiol/levonorgestrel (30 µg/150 µg) combination increases. Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) will be needed in most cases to attain a maximal therapeutic response.
Storage	Store between 15°C to 30°C. Protect from light and moisture. **N.B**. Refer to manufacturer PIL if there are specific considerations**.**

Phenytoin

Generic Name	Phenytoin
Dosage Form/Strengths	**Capsule**: 50mg, 100mg. **Suspension**: 30 mg/5ml. **Topical cream**: 2 gm/100g. **Topical Spray**: 40 mg/150ml. **Injection**: 50 mg/ml; 250 mg/5ml.
Route of Administration	Oral, IM, IV, Topical
Pharmacologic Category	Antiseizure Agent, Hydantoin. **ATC**: N03AB02
Indications	**Oral** • Control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these, • Treatment and prevention of seizures occurring during or following neurosurgery and/or severe head injury. • Treatment of trigeminal neuralgia (only as second line therapy if carbamazepine is ineffective or patients are intolerant to carbamazepine). **Parenteral** • Control of status epilepticus of the tonic-clonic (grand mal) type • Treatment and prevention of seizures occurring during or following neurosurgery and/or severe head injury. Parenteral form should be used only when oral administration is not possible and for short term use. • Treatment of life-threatening ventricular arrhythmias or arrhythmias secondary to digitalis intoxication, when these have not responded to other available antiarrhythmic treatments or when other antiarrhythmic agents cannot be used. **N.B**. Phenytoin is not effective for absence (petit mal) seizures.
Dosage Regimen	**Oral** **Adults dosing** • **Seizures** **Initial**: 3 to 4mg/kg/day then adjust dose at weekly intervals as required. **Maintenance dose (in most cases)**: 200 to 500 mg daily in single or divided doses. • **Trigeminal Neuralgia** **Oral**: 300-500mg. Adjust dose if required. **Children and Infants dosing** • **Initial**: 5mg/kg/day in 2 or 3 divided doses. • **Maximum dosage for pediatrics:** 300mg daily.

Phenytoin

	N.B. There is a relatively small margin between full therapeutic effect and minimally toxic doses of this drug. **Parenteral** **Adult dosing** • Status Epilepticus **Loading dose**: **IV**: 10-15 mg/kg slowly (a rate not exceeding 50 mg/minute in adults to avoid hypotension) **Maintenance dose: Oral or IV:** 100 mg every 6-8 hours. In geriatric patients with heart disease, it has been recommended that the drug be given at a rate of 50 mg over 2-3 minutes. **N.B.** When converting from oral to IM administration, dose should be increased by 50% to maintain same serum levels**.** And When returned to oral administration, dose should be decreased by 50% of the original oral dose, for the same period of time the patient received phenytoin intramuscularly. **N.B.** Intramuscular administration should not be ordinarily used for status epilepticus due to slow, erratic absorption and local toxicity. • Cardiac Arrhythmias **Initial: IV:** 3.5 – 5 mg/kg slowly (a rate not exceeding 50 mg/minute), repeated once if necessary. • Neurosurgery **Initial: IM:** 100 - 200 mg at 4-hour intervals prophylactically during neurosurgery and continued for 48-72 hrs. **Maintenance dose:** Then dosage should be reduced to 300 mg and adjusted according to serum level estimations. **Infants and children and neonates dosing** **Loading dose**: **IV**: 15-20 mg/kg slowly at a rate of 1 to 3 mg/kg/minute or 50 mg/minute, whichever is slower. Continuous monitoring of the electrocardiogram, blood pressure, and respiratory function is essential. Caution from propylene glycol in less than 1-year patients.
Dosage Adjustment	**Renal Impairment** Early signs of toxicity may appear. Monitor free phenytoin levels closely. Dosage adjustments may be necessary. **Hepatic Impairment** Early signs of toxicity may appear. Monitor free phenytoin levels closely. Dosage adjustments may be necessary.
Contra-Indications	• Hypersensitivity to phenytoin, other hydantoins, or any component of the formulation. • A history of acute hepatotoxicity due to phenytoin. • Coadministration with delavirdine. **Injection only**

Phenytoin

	• Sinus bradycardia, sinoatrial block, second- and third-degree heart block and Adams-Stokes syndrome.
Adverse Drug Reactions	**Frequency not defined** **Cardiovascular**: Cardiac conduction disorder (depression), circulatory shock, Hypotension. **Dermatologic**: Bullous dermatitis, exfoliative dermatitis, morbilliform rash, scarlatiniform rash, skin or other tissue necrosis. **Endocrine** & **metabolic**: Decreased T4, increased gamma-glutamyl transferase, vitamin D deficiency (associated with chronic treatment). **Gastrointestinal**: Constipation, dysgeusia, nausea, swelling of lips, vomiting. **Genitourinary**: Peyronie's disease. **Hematologic** & **oncologic**: Thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, pancytopenia, macrocytosis, megaloblastic anemia, purpuric dermatitis. **Hepatobiliary disorders:** Acute hepatic failure, hepatitis toxic, liver injury. **Local**: Injection site reaction ("purple glove syndrome"; edema, discoloration, and pain distal to injection site), local inflammation, local irritation, local tissue necrosis, localized tenderness. **Nervous system**: Ataxia, cerebral atrophy or dysfunction (elevated serum levels and/or long-term use), confusion, dizziness, headache, insomnia, nervousness, nystagmus, paresthesia, peripheral neuropathy (associated with chronic treatment), twitching, vertigo. Advise patients not to drive, operate complex machinery, or engage in hazardous activities until they have become adopted to any CNS effects. **Miscellaneous**: Fever, tissue sloughing, anaphylactic reaction, tubulointerstitial nephritis.
Monitoring Parameters	• CBC • ECG • Blood pressure • Monitor for signs of respiratory depression, skin reactions, suicidal ideation and behaviours. • Serum phenytoin concentrations: The clinically effective level is usually 10-20mg/l (may be lower for tonic-clonic seizures).
Drug Interactions	**Drugs which may increase phenytoin serum levels include** • **Antiepileptic drugs:** ethosuximide, felbamate, oxcarbazepine, methsuximide, topiramate, sodium valproate. • **Azoles:** fluconazole, ketoconazole, itraconazole, miconazole, voriconazole. • **Anesthetics:** Halothane**.** • **Antineoplastic agents:** capecitabine, fluorouracil. • **Antidepressants:** fluoxetine, fluvoxamine, sertraline. • **Cardiovascular agents**: amiodarone, dicoumarol, diltiazem, nifedipine, ticlopidine. • **Gastric acid reducing agents:** H2 antagonists (cimetidine), omeprazole • **Sulfonamides:** sulfamethizole, sulfaphenazole, sulfadiazine,

Phenytoin

sulfamethoxazole / trimethoprim.

- **Other:** Acute alcohol intake, chloramphenicol, chlordiazepoxide, disulfiram, erythromycin, estrogen, fluvastatin, isoniazid, estrogens, methylphenidate, salicylates, tacrolimus, tolbutamide, Trazodone, Warfarin.

Drugs which may decrease phenytoin levels include:

- **Antineoplastic agents:** bleomycin, carboplatin, cisplatin, doxorubicin, methotrexate
- **Antiviral agents:** fosamprenavir, nelfinavir, ritonavir
- **Antiepileptic drugs:** carbamazepine, vigabatrin
- **Other:** Chronic alcohol abuse, rifampicin, diazepam, diazoxide, folic acid, reserpine, St. John's wortb, sucralfate, theophylline

Drugs which may either increase or decrease phenytoin serum levels include: Phenobarbital, sodium valproate, valproic acid, ciprofloxacin, carbamazepine, phenothiazines.

Drugs whose efficacy is impaired by phenytoin include:
Azoles, antilipidemic statins, antiretrovirals, calcium channel blockers, coumarin anticoagulants, digitoxin, doxycycline, estrogens, furosemide, methadone, oral contraceptives, antidepressants, quinidine, rifampicin, ticagrelor, theophylline, vitamin D, warfarin.

Risk X: Avoid combination

Abemaciclib, Adagrasib, Alpelisib, Antihepaciviral Combination Products, Apixaban, Apremilast, Aprepitant, Artemether And Lumefantrine, Atazanavir, Avacopan, Avanafil, Avapritinib, Axitinib, Bedaquiline, Berotralstat, Bortezomib, Bosutinib, Brigatinib, Cabotegravir, Capivasertib, Capmatinib, Cariprazine, Ceritinib, Cobicistat, Cobimetinib, Copanlisib, Crizotinib, Dabigatran, Etexilate, Daclatasvir, Daridorexant, Darolutamide, Dasabuvir, Deflazacort, Delamanid, Dolutegravir, Doravirine, Doxorubicin, Dronedarone, Duvelisib, Elacestrant, Elbasvir and Grazoprevir, Elexacaftor, Tezacaftor, and Ivacaftor, Eliglustat, Elvitegravir, Encorafenib, Entrectinib, Etravirine, Fedratinib, Fexinidazole, Finerenone, Flibanserin, Fosaprepitant, Fosnetupitant, Fostamatinib, Fostemsavir, Fotemustine, Fruquintinib, Futibatinib, Gemigliptin, Gepirone, Gilteritinib, Glasdegib, Glecaprevir and Pibrentasvir, Ibrexafungerp, Ibrutinib, Idelalisib, Infigratinib, Isavuconazonium Sulfate, Istradefylline, Itraconazole, Ivabradine, Ivacaftor, Ivosidenib, Ixazomib, Ledipasvir, Lemborexant, Lenacapavir, Leniolisib, Letermovir, Levoketoconazole, Lonafarnib, Lorlatinib, Lumacaftor and Ivacaftor, Lumateperone, Lurasidone, Lurbinectedin, Macimorelin, Macitentan, Mavacamten, Mavorixafor, Midostaurin, Mitapivat, Mobocertinib, Naldemedine, Naloxegol, Neratinib, Netupitant, Nilotinib, Nimodipine, Nintedanib, Nirmatrelvir and Ritonavir, Nirogacestat, Nisoldipine, Olaparib, Olutasidenib, Omaveloxolone, Orelabrutinib Ornidazole, Pacritinib, Palbociclib, Palovarotene, Panobinostat Pazopanib, Pemigatinib, Pexidartinib, Pimavanserin, Piperaquine, Pirtobrutinib, Praziquantel, Pretomanid,

Phenytoin

	Quizartinib, Ranolazine, Regorafenib, Relugolix, Estradiol, and Norethindrone, Repotrectinib, Ribociclib, Rilpivirine, Rimegepant, Ripretinib, Ritlecitinib, Rivaroxaban, Roflumilast (Systemic), Rolapitant, Romidepsin, Sacituzumab, Govitecan, Samidorphan, Saquinavir, Secnidazole, Selpercatinib, Selumetinib, Simeprevir, Sirolimus, Sofosbuvir, Sonidegib, Sorafenib, Sotorasib, Sparsentan, Tamoxifen, Tasimelteon, Tazemetostat, Tenofovir, Alafenamide, Tezacaftor And Ivacaftor, Ticagrelor, Tivozanib, Tofacitinib, Tolvaptan, Toremifene, Trabectedin, Treosulfan, Tucatinib, Ubrogepant, Ulipristal, Upadacitinib, Valbenazine, Vandetanib, Velpatasvir, Venetoclax, Vincristine (Liposomal), Vinflunine, Voclosporin, Vonoprazan, Vorapaxar, Voxilaprevir, Zanubrutinib, Zuranolone. ***Risk D: Consider therapy modification*** Abiraterone Acetate, Acalabrutinib, Afatinib, Alfentanil, Aripiprazole, Aripiprazole Lauroxil, Atogepant, Belumosudil, Bictegravir, Brexpiprazole, Buspirone, Cabozantinib, Calcium Channel Blockers (Nondihydropyridine), Canagliflozin, Carmustine, Caspofungin, Cenobamate, Cimetidine, Clarithromycin, Clozapine, Colesevelam, Cyclosporine (Systemic), Dasatinib, Deferasirox, Dexamethasone (Systemic), Edoxaban, Enzalutamide, Eravacycline, Erlotinib, Etoposide, Etoposide Phosphate, Everolimus, Exemestane, Felbamate, Felodipine, Fenfluramine, Ganaxolone, Gefitinib, Guanfacine, Hormonal Contraceptives, Imatinib, Indinavir, Irinotecan, Ixabepilone, Ketoconazole (Systemic), Lamotrigine, Lapatinib, Larotrectinib, Lefamulin, Lefamulin (Intravenous), Linagliptin, Lopinavir, Manidipine, Maraviroc, Maribavir, Mefloquine, Methylprednisolone, Metyrapone, Mifepristone, Mirodenafil, Nevirapine, Nifedipine, Osimertinib, Perampanel, Pitolisant, Ponatinib, Posaconazole, Pralsetinib, Quetiapine, Quinine, Radotinib, Relugolix, Risperidone, Ritonavir, Sirolimus (Conventional), Stiripentol, Sulfamethoxazole, Sufentanil, Sunitinib, Tacrolimus (Systemic), Tadalafil, Temsirolimus, Tetrahydrocannabinol and Cannabidiol, Thiotepa, Topotecan, Trazodone, Tretinoin (Systemic), Triazolam, Vemurafenib, Vilazodone, Voriconazole, Vortioxetine, Voxelotor, Zaleplon.
Pregnancy and Lactation	**Pregnancy** • Phenytoin may induce an increased risk of congenital malformations and adverse outcomes. Use during pregnancy and for women of childbearing potential is not recommended except where there is a clinical need and the woman is made aware of the risks of potential harm to the fetus. • Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. • Phenytoin may result in a failure of hormonal contraceptives. • Vitamin K administration to the mother prior to delivery and the newborn after birth is recommended to avoid bleeding disorder. **Lactation** Phenytoin is excreted in breast milk in low amount. Consider Benefit and potential risks.

Phenytoin

Administration	**Administration: IV** It can be given either as a loading dose or an infusion. **Preparation for administration** Phenytoin may be diluted with normal saline 50-100ml. Avoid mixing with dextrose. Solution is suitable as long it is free of haziness and precipitate. **Infusion (preferred):** Final concentration of the solution should be 5-10 mg/mL. Infusion must be completed within 4 hours after dilution • Infusion mixture should not be refrigerated to avoid precipitation. If happened, the precipitate will dissolve again after the solution is allowed to stand at room temperature. • An in-line 0.22- to 0.55-micron filter is recommended due to the potential for precipitation. • Vesicant; ensure proper needle or catheter placement prior to and during IV infusion. Monitor closely for extravasation during infusion. • Because of the risk of local toxicity, IV phenytoin should be injected slowly directly into a large vein through a large-gauge needle or intravenous catheter. • Following IV administration, NS should be injected through the same needle or IV catheter to prevent irritation. **Rate of infusion** Not exceeding 50 mg/min in adults and 1 to 3 mg/kg/min (or 50 mg/min, whichever is slower) in pediatric patients. **Administration: IM** Peak serum levels may require up to 24 hours and may cause pain, necrosis, and abscess formation at the injection site. **Administration: Oral** • Capsule: Divide daily dose into 2 to 3 doses per day; if the daily dosage cannot be divided equally, take the larger dose before retiring. • Suspension: Shake well prior to use; measure and administer dose using a calibrated oral dosing syringe (or another accurate dose-measuring device). **N.B.** Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Serious Dermatological Reactions** • During treatment, severe and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), may occur. Serious dermatological reactions may need hospitalization and rarely fatal. • Phenytoin should be discontinued at the first sign of a rash, unless it is not drug-related and alternative therapy should be considered. **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) /Multiorgan Hypersensitivity** Potentially serious, sometimes fatal reactions. If DRESS is suspected, drug

Phenytoin

should be discontinued. Monitor signs including fever, rash, lymphadenopathy, facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities or myocarditis.

Withdrawal Precipitated Seizure

Abrupt withdrawal may precipitate status epilepticus. Dose reductions or discontinuation should be done gradually.

Suicidal Behavior and Ideation

Monitor patients for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior. Appropriate treatment should be considered.

Cardiac Effects

Bradycardia and cardiac arrest have been reported.

Angioedema

Angioedema has been reported. Phenytoin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

Hepatic Injury

Cases of acute hepatotoxicity have been reported. If this occurs, phenytoin should be immediately discontinued and not re-administered. These incidents usually occur within the first 2 months of treatment and may be associated with DRESS.

Hematologic disorders

Hematopoietic complications, sometimes fatal, have been reported. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia. Follow-up is indicated and an alternative antiepileptic treatment should be used. Monitor for signs of anemia, infection, or bleeding.

CNS effects

Delirium, psychosis, encephalopathy, or cerebellar dysfunction or atrophy are associated with high serum levels of phenytoin. Dose reduction of phenytoin may be needed. If symptoms persist, discontinuation of therapy is recommended. Patients should be cautioned before performing tasks which need mental alertness.

Hyperglycemia

Phenytoin may inhibit insulin release and increase serum glucose with toxic levels of phenytoin.

Hypoalbuminemia

Use with caution in patients with any condition associated with low serum albumin levels, which will increase the free fraction of phenytoin

Phenytoin

	in the serum and, therefore, the pharmacologic response. Use free (unbound) serum concentrations to monitor. **Hepatic and renal impairment** Use with caution; use free (unbound) serum concentrations to monitor. **Extravasation** Avoid IV administration in small veins. The "purple glove syndrome" (i.e., discoloration with edema and pain of distal limb) may occur following peripheral IV administration of phenytoin. Inject phenytoin slowly and directly into a large vein through a large gauge needle or IV catheter; follow with NS flushes through the same needle or IV catheter. **Porphyria** May cause exacerbation of porphyria; use with caution in patients with porphyria. **Propylene glycol** Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, renal dysfunction, cardiotoxicity; central nervous system disorders, seizures, liver dysfunction or respiratory depression; use caution.
Storage	Store between (15°C to 30°C). Do not freeze. **N.B**. Refer to manufacturer PIL if there are specific considerations.

Miscellaneous

Ethosuximide

Generic Name	Ethosuximide
Dosage Form/Strengths	**Capsule:** 250 mg. **Syrup:** 250 mg/5 ml.
Route of Administration	*Oral*
Pharmacologic Category	Antiseizure Agent, Succinimide. **ATC:** N03AD01
Indications	• Management of absence seizures (petit mal). • Myoclonic seizures.
Dosage Regimen	**N.B.** The daily dose can be taken in a single dose if the medication is well tolerated. Higher daily doses should be divided into 2 or 3 single doses. **Dosing: Adults/Geriatric/Children >6 years** • **Initial**: 500 mg daily then adjust with increments of 250 mg every 5-7 days until control is achieved. • **Maintenance**: Usually 1000 - 1500 mg daily in 2-3 doses. Dose of 2000mg under strict supervision maybe needed. • **Withdrawal**: Therapy must be discontinued by reducing the dose gradually. **Dosing: Pediatric <6 years** • ***Children < 2 years:*** **Initial**: 125 mg and adjust with small increments every few days until control is achieved. • ***Children between 2 and 6 years*** **Initial**: 250 mg and adjust with small increments every few days until control is achieved. **The optimum daily dose** for most children is 20 mg/kg. **The maximum daily dose** is 1000 mg.
Dosage Adjustment	**Renal Impairment** Use with extreme caution. Regular monitoring of ethosuximide concentrations and blood count as bone marrow depression and thrombocytopenia may occur. **Hepatic Impairment** Use with extreme caution. Regular monitoring of ethosuximide concentrations and blood count as bone marrow depression and thrombocytopenia may occur.
Contra-Indications	Hypersensitivity to ethosuximide, succinimides, or any component of the formulation.
Adverse Drug Reactions	**Frequency not defined** • **Dermatologic:** Pruritic erythematous rash, urticaria. • **Endocrine & metabolic:** Hirsutism, increased libido, weight loss.

Ethosuximide

	• **Gastrointestinal:** Abdominal cramps, abdominal pain, anorexia, diarrhea, epigastric pain, gastric distress, gingival hyperplasia, hiccups, nausea, vomiting. • **Genitourinary:** Microscopic hematuria, vaginal hemorrhage. • **Hematologic & oncologic:** Eosinophilia, leukopenia, pancytopenia. • **Hypersensitivity:** Drug rash with eosinophilia and systemic symptoms, hypersensitivity reaction, swollen tongue. • **Nervous system:** Aggressive behavior, ataxia, delusional paranoid disorder, depression, dizziness, drowsiness, euphoria, fatigue, headache, hyperactive behavior, irritability, lack of concentration, lethargy, night terrors, sleep disturbance. • **Ophthalmic:** Myopia.
Monitoring Parameters	• Monitor CBC regularly (initially monthly, then every six months after one year). • Liver enzymes (periodic). • Urinalysis (periodic). • Signs of rash; and suicidality (e.g., suicidal thoughts, depression, behavioral changes). • Serum concentrations when needed (Therapeutic: 40 to 100 mcg/mL; levels up to 150 mcg/mL have been reported without toxicity)
Drug Interactions	***Risk X: Avoid combination*** Azelastine (Nasal), Bromperidol, Flunarizine, Kratom, Nabilone, Olopatadine (Nasal), Orphenadrine, Oxomemazine, Paraldehyde, Thalidomide. ***Risk D: Consider therapy modification*** Blonanserin, Buprenorphine, Chlormethiazole, Daridorexant, Dexmedetomidine, Droperidol, Flunitrazepam, Hydroxyzine, Lemborexant, Loxapine, Mefloquine, Methotrimeprazine, Metyrapone, Opioid Agonists, Oxybate Salt Products, Oxycodone, Ropeginterferon Alfa-2b, Suvorexant, Zolpidem, Zuranolone.
Pregnancy and Lactation	**Pregnancy** • Insufficient data. Cases of birth defects have been reported with ethosuximide, so, the risk/benefit ratio should be considered. • Ethosuximide serum levels must be checked on a regular basis (before pregnancy and up to once a month during pregnancy in patients with stable seizure control). • For the newborn infant, parenteral administration of vitamin K is advised immediately postpartum. **Lactation** • Use Ethosuximide in breastfeeding mothers only if the benefits outweigh the hazards. • Sedation, poor suckling, and irritability have been observed in individual breastfed infants, so, use with caution and breastfeeding is best avoided during therapy.
Administration	• **Capsule:** Administer with food (during or after meal). • **Syrup:** The solution can be taken during or after meals. A single dose of

Ethosuximide

	the oral solution can be blended with milk pudding or added to a glass of water. Alternatively, the oral solution can be applied directly to the mouth and followed by half a glass of water. **N.B.** Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) /Multiorgan Hypersensitivity** Potentially serious, sometimes fatal reactions. If DRESS is suspected, discontinue the drug. Monitor signs including fever, rash, lymphadenopathy, facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities or myocarditis. **Hematologic disorders** Monitor CBC regularly, especially if signs/symptoms of infection develop. At a leucocyte count of < 3500/mm³ or a granulocyte ratio of < 25%, lower the dose or terminate the medication. Monitor for signs of anemia, infection, or bleeding. **Drug-Induced Immune Thrombocytopenia** Drug-induced immune thrombocytopenia (DITP) has been reported with ethosuximide at onset of 1 to 3 weeks after initiation of ethosuximide. When DITP is suspected, discontinue, monitor platelet counts, and treat as appropriate. Avoid rechallenge **Psychiatric disorders** Paranoid and hallucination symptoms, anxiety, agitation may occur. **Suicidal ideation** Monitor all patients for any changes in behavior that could indicate suicide ideation or depression; appropriate treatment should be considered. **CNS depression** Patients should be cautioned before performing tasks which need mental alertness. **Serious Dermatologic Reactions** During treatment, severe and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), may occur early during course of therapy. Ethosuximide should be discontinued at the first sign of a rash, unless it is not drug-related and alternative therapy should be considered. **Effects on Liver and Kidneys** Abnormal liver and renal function have been reported. Extreme caution to patients with known liver or renal disease. Periodic urinalysis and liver function studies are advised for all patients receiving the drug.

Ethosuximide

	Autoimmune Disorders Such as Systemic lupus erythematous have been reported with the medication use. **Discontinuation of therapy** Anti-seizure drugs should not be discontinued abruptly due to the risk of increasing seizure frequency; therapy should be tapered gradually unless safety considerations necessitate a faster withdrawal. The medication must be withdrawn by gradually reducing the dose over a period of one or two years to avoid risk of increasing seizure frequency.
Storage	**Capsules:** Store at 15˙ C to 30˙ C. Protect from moisture. **Syrup:** Store at 15°C to 30°C. **N.B.** Refer to manufacturer PIL if there are specific considerations.

Lacosamide

Generic Name	Lacosamide
Dosage Form /Strengths	Tablet: 50 mg, 100 mg, 200 mg. Oral Solution: 10 mg/ml. Solution for I.V. Infusion: 10 mg/ml.
Route of Administration	Oral, IV
Pharmacologic Category	Antiseizure Agent, Miscellaneous ATC: N03AX18
Indications	• Treatment of partial-onset seizures with or without secondary generalization in adults, adolescents and children from 1 month of age (Monotherapy or Adjunct therapy). • Treatment of primary generalized tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalized epilepsy (Adjunct therapy).
Dosage Regimen	**Adult and adolescent dosing (weighing more than 50 kg)**

	Initial	Titration	Maximum dose
Monotherapy	50 mg twice daily or 100 mg twice daily.	50 mg twice a day at weekly intervals	up to 300 mg twice a day (600 mg/day)
Adjunct therapy	50 mg twice daily		Up to 200 mg twice a day (400 mg/day)

Adolescent and children dosing (weighing less than 50 kg)

	Initial	Titration	Maximum dose
Monotherapy	1 mg/kg twice a day.	1 mg/kg twice a day at weekly intervals.	• Patients ≥ 6 kg to < 40 kg: up to 6 mg/kg twice a day • Patients ≥ 40 kg to < 50 kg: up to 5 mg/kg twice a day.
Adjunct therapy			• Patients ≥ 30 kg to < 50 kg: up to 4 mg/kg twice a day. • Patients ≥ 20 kg to < 30 kg: up to 5 mg/kg twice a day • Patients ≥ 6 kg to < 20 kg: up to 6 mg/kg twice a day

Lacosamide

Children dosing (weighing less than 6 kg) for partial-onset seizures

	Initial	Titration	Maximum dose
Intravenous	0.66 mg/kg three times daily.	Intravenous: Increase by 0.66 mg/kg three times daily every week.	2.5 mg/kg to 5 mg/kg three times daily
Oral	1 mg/kg twice daily.	Increase by 1 mg/kg twice daily every week.	3.75 mg/kg to 7.5 mg/kg twice daily

N.B. Injection: for IV use only when oral administration is temporarily not feasible; the recommended dosage is based on body weight and is administered two or three times daily over 15 to 60 minutes.
N.B. When discontinuing, a gradual withdrawal over at least 1 week is recommended.

Dosage Adjustment

Renal impairment

- Mild and moderate impairment (CrCl > 30 ml/min): No dose adjustment is necessary.
- Severe renal impairment (CrCl ≤30 ml/min): Caution while dose titration.
  - Adult and pediatric weighing more than 50 kg: a maximum dose of 250 mg/day is recommended.
  - Pediatric patients weighing less than 50 kg: a reduction of 25 % of the maximum dose is recommended.
- Hemodialysis: removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, dosage supplementation of up to 50% should be considered.

Hepatic impairment

- Mild or moderate hepatic impairment: a reduction of 25% of the maximum dosage is recommended. Caution while dose titration.
- Severe hepatic impairment: use is not recommended.

Contra-Indications

- Hypersensitivity to the active substance or to any of the excipients.
- Known second- or third-degree atrioventricular (AV) block.

Adverse Drug Reactions

>10%

Gastrointestinal: Nausea (7% to 11%).
Nervous system: Dizziness (16% to 30%), drowsiness (5% to 17%), headache (11% to 14%).

1% to 10%

Dermatologic: Pruritus (2% to 3%).
Gastrointestinal: Diarrhea (5%), vomiting (6% to 9%).

Lacosamide

	Hematologic & oncologic: Bruise (4%). **Local**: Irritation at injection site (IV: 1%), pain at injection site (IV: 3%). **Nervous system**: Abnormal gait (2%), asthenia (2%), ataxia (4% to 7%), balance impairment (1% to 5%), depression (2%), fatigue (7%), myoclonic seizure (3%), tremor (6%), vertigo (3% to 5%). **Ophthalmic**: Blurred vision (9%), diplopia (6% to 10%), nystagmus disorder (5%). **Miscellaneous**: Laceration (3%).
Monitoring Parameters	• Monitor for signs of suicidal ideation and behaviors. • ECG prior to start and after titration to steady-state maintenance dose in patients with underlying proarrhythmic conditions.
Drug Interactions	***Risk X: Avoid combination*** Azelastine (Nasal), Bromperidol, Flunarizine, Kratom, Nabilone, Noscapine, Olopatadine (Nasal), Orphenadrine, Oxomemazine, Paraldehyde, Thalidomide. ***Risk D: Consider therapy modification*** Articaine, Blonanserin, Buprenorphine, Chlormethiazole, Daridorexant, Dexmedetomidine, Droperidol, Flunitrazepam, Hydroxyzine, Lemborexant, Loxapine, Mefloquine, Methotrimeprazine, Metyrapone, Opioid Agonists, Oxybate Salt Products, Oxycodone, Suvorexant, Zolpidem, Zuranolone.
Pregnancy and Lactation	**Pregnancy** Inadequate human data. Animal studies have shown fetal harm. Lacosamide should not be used unless clearly necessary. **Lactation** A risk to the infants cannot be excluded. Breastfeeding should be discontinued during treatment with lacosamide.
Administration	**Oral Administration** • Tablets and oral solution may be taken with or without food. • Tablets should be swallowed whole with liquid. Do not divide tablets. • Lacosamide must be taken twice a day, approximately 12 hours apart. **IV Administration** Administered without further dilution or may be mixed with diluents (Sodium Chloride Injection 0.9% (w/v), Dextrose Injection 5% (w/v), Lactated Ringer's Injection). **Rate of infusion** The recommended infusion duration is 30 to 60 minutes. Also, may be infused over 15 minutes for adults. **N.B**. Refer to PIL for other specific considerations.
Warnings/ Precautions	**Suicidal ideation and behavior** Suicidal ideation and behavior have been reported in patients treated with antiepileptic medicinal products. Monitor patients for suicidal behavior and ideation and appropriate treatment should be considered if symptoms have developed.

Lacosamide

	Cardiac rhythm and conduction • Caution in patients with underlying proarrhythmic conditions or on concomitant medications that affect cardiac conduction. In these patients, ECG monitoring is needed before a lacosamide dose increase above 400 mg/day and after lacosamide is titrated to steady-state. • Patients should be made aware of the symptoms of cardiac arrhythmia (e.g. slow, rapid or irregular pulse, palpitations, shortness of breath, feeling lightheaded, fainting). Patients should be counselled to seek immediate medical advice if these symptoms occur. **Dizziness** Lacosamide may cause dizziness and ataxia which could increase the occurrence of accidental injury or falls. Caution. **Potential for new onset or worsening of myoclonic seizures** New onset or worsening of myoclonic seizures has been reported in both adult and pediatric patients with primary generalized tonic-clonic seizures, in particular during titration. **Discontinuation** Lacosamide should be gradually withdrawn to minimize the potential of increased seizure frequency. **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Multi-Organ Hypersensitivity** • Multiorgan hypersensitivity reactions have been reported. Symptoms include fever and rash and can be associated with involvement of different organ systems. • If multiorgan hypersensitivity reaction is suspected, lacosamide should be discontinued if no alternate etiology.
Storage	**Tablet, oral solution**: Store between 15°C and 30°C. Throw away any unused oral solution after first opening the bottle. Do not freeze. **Vial**: Store between 15°C and 30°C. Do not freeze. Use immediately after opening and dilution (not for more than 4 hours at room temperature). **N.B**. Refer to PIL for other specific considerations.

Levetiracetam

Generic Name	Levetiracetam
Dosage Form/Strengths	**Film coated tablets:** 250mg, 500mg, 750mg, 1000mg. **Orally disintegrating tablets**: 500mg. **Modified release tablets**: 500mg, 750mg, 1000mg, 1500mg. **Syrup:** 100mg/ml (100ml, 120ml or 300ml). **Injection:** 500mg/5ml.
Route of Administration	Oral, IV
Pharmacologic Category	Antiseizure Agent, Miscellaneous **ATC:** N03AX14
Indications	**Monotherapy** Partial onset seizures in patients 1 month of age and older (oral immediate release or injection) or 12 years of age and older (oral modified release). **Adjunctive therapy** • Treatment of partial onset seizures in patients 1 month of age and older (oral immediate release or injection) or 12 years of age and older (oral modified release). • Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy (oral or injection). • Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy (oral or injection). **N.B**. Intravenous injection is used only as an alternative for patients when oral administration is temporarily not feasible.
Dosage Regimen	**Dosing (Oral, IV)** **Partial-Onset Seizures (monotherapy or adjunctive therapy)** • **1 Month to < 6 Months** Initial: 7 mg/kg twice daily; increased by 7 mg/kg twice daily in 2 weeks intervals to the recommended dose: 21 mg/kg twice daily. • **6 Months to < 4 Years**: 10 mg/kg twice daily; increased by 10 mg/kg twice daily in 2 weeks intervals to recommended dose of 25 mg/kg twice daily. • **4 Years to < 16 Years**: 10 mg/kg twice daily; increased by 10 mg/kg twice daily in 2 weeks intervals to recommended dose of 30 mg/kg twice daily. • **Adults 16 Years and Older**: 250-500 mg twice daily; increased by 250-500 mg twice daily in 2 weeks intervals to a recommended dose of 1500 mg twice daily. **Myoclonic Seizures (adjunctive therapy)** • **12 Years and Older:** 250-500 mg twice daily; increased by 250-500 mg twice daily in 2 weeks intervals to a recommended dose of 1500 mg twice daily. **Primary Generalized Tonic-Clonic Seizures (adjunctive therapy)** • **6 Years to < 16 Years**: 10 mg/kg twice daily, increased by 10 mg/kg twice daily in 2 weeks intervals to recommended dose of 30 mg/kg twice daily.

Levetiracetam

• **Adults 16 Years and Older**: 250-500 mg twice daily; increased by 250-500 mg twice daily in 2 weeks intervals to the recommended dose of 1500 mg twice daily.

Discontinuation: When needed, it is recommended to withdraw levetiracetam gradually with the same dose intervals as initiation.

Dosage Adjustment

Renal impairment

- **Dosing adjustment for adult and adolescent patients weighing more than 50 kg with impaired renal function**

Group	Creatinine clearance (ml/min/1.73 m^2)	Dose and frequency
Normal	> 80	500 to 1,500 mg twice daily
Mild	50 - 79	500 to 1,000 mg twice daily
Moderate	30 - 49	250 to 750 mg twice daily
Severe	< 30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis	-	500 to 1,000 mg once daily **Loading dose:** 750 mg. **Following dialysis**, a supplemental dose of 250-500 mg is recommended.

- **Dosing adjustment for children and adolescent patients weighing less than 50 kg with impaired renal function**

Group	Creatinine clearance (ml/min/1.73 m^2)	Dose and frequency	
		Infants 1 to less than 6 months	patients 6 months and above
Normal	> 80	7 to 21 mg/kg twice daily	10 to 30 mg/kg twice daily
Mild	50 - 79	7 to 14 mg/kg twice daily	10 to 20 mg/kg twice daily
Moderate	30 - 49	3.5 to 10.5 mg/kg twice daily	5 to 15 mg/kg twice daily
Severe	< 30	3.5 to 7 mg/kg twice daily	5 to 10 mg/kg twice daily
End-stage renal disease patients undergoing dialysis	-	7 to 14 mg/kg once daily. **Loading dose:** 10.5 mg/kg. **Following dialysis**, a supplemental dose of 3.5 to 7 mg /kg is recommended.	10 to 20 mg/kg once daily **Loading dose:** 15mg/kg. **Following dialysis**, a supplemental dose of 5 to 10 mg/kg is recommended.

Levetiracetam

	Dosing: Hepatic Impairment – Mild to moderate hepatic impairment: No dose adjustment is needed. – Severe hepatic impairment: No dose adjustment is needed. If Severe hepatic impairment combined with creatinine clearance < 60 ml/min/1.73 m^2: 50% decrease in the daily maintenance dose is recommended.
Contra-Indications	Hypersensitivity to the active substance or other pyrrolidone derivatives.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Increased blood pressure (diastolic; infants and children <4 years: 17%). **Gastrointestinal**: Vomiting (children and adolescents: 15%). **Infection**: Infection (adults: 13%). **Nervous system**: Asthenia (adults: 15%), behavioral changes (children and adolescents: 7% to 38%; adults: 7% to 13%), drowsiness (8% to 15%), fatigue (children and adolescents: 10% to 11%), headache (14% to 19%), irritability (infants, children, and adolescents: 6% to 12%), psychotic symptoms (infants, children, and adolescents: 2% to 17%; adults: 1%). **Respiratory**: Nasopharyngitis (7% to 15%). **1% to 10%** **Gastrointestinal**: Anorexia (3% to 4%), constipation (children and adolescents: 3%), decreased appetite (children and adolescents: 8%), diarrhea (children and adolescents: 6% to 8%), gastroenteritis (children and adolescents: 2%), nausea (5%), upper abdominal pain (children and adolescents: 9%). **Hematologic & oncologic**: Bruise (children and adolescents: 3%), eosinophilia (children and adolescents: 9%). **Infection**: Influenza (3% to 8%). **Nervous system**: Aggressive behavior (children and adolescents: 10%; adults: 1%), agitation (children and adolescents: 4%), amnesia (adults: 2%), anxiety (2%), ataxia (adult partial-onset seizures: 3%), confusion (children and adolescents: 2% to 3%), depression (3% to 5%), dizziness (5% to 9%), emotional lability (2% to 5%), falling (children and adolescents: 3%), hostility (adults: 2%), insomnia (children and adolescents: 5%), lethargy (children and adolescents: 6%), mood changes (children and adolescents: 3%), nervousness (adults: 4%), pain (adults: 7%), paranoid ideation (children and adolescents: 2%; adults: <1%), paresthesia (adults: 2%), sedated state (children and adolescents: 2%), vertigo (3% to 5%). **Neuromuscular & skeletal**: Arthralgia (children and adolescents: 2%), joint sprain (children and adolescents: 2%), neck pain (children and adolescents: 2% to 8%). **Ophthalmic**: Conjunctivitis (children and adolescents: 2%), diplopia (adults: 2%). **Otic**: Otalgia (children and adolescents: 2%). **Respiratory**: Cough (2% to 9%), nasal congestion (children and adolescents: 9%), pharyngitis (6% to 7%), pharyngolaryngeal pain (children

Levetiracetam

	and adolescents: 7%), rhinitis (2% to 4%), sinusitis (adults: 2%).
Monitoring Parameters	• Renal functions. • Monitor plasma levels during pregnancy • Suicidality (e.g., suicidal thoughts, depression, behavioral changes). • CBC (in patients who experience significant weakness, pyrexia, recurrent infections or coagulation disorders)
Drug Interactions	***Risk X: Avoid combination*** Azelastine (Nasal), Bromperidol, Flunarizine, Kratom, Nabilone, Noscapine, Olopatadine (Nasal), Orphenadrine, Oxomemazine, Paraldehyde, Thalidomide. ***Risk D: Consider therapy modification*** Blonanserin, Brivaracetam, Buprenorphine, Chlormethiazole, Daridorexant, Dexmedetomidine, Droperidol, Flunitrazepam, Hydroxyzine, Lemborexant, Loxapine, Mefloquine, Methotrimeprazine, Metyrapone, Opioid Agonists, Oxybate Salt Products, Oxycodone, Ropeginterferon Alfa-2b, Suvorexant, Zolpidem, Zuranolone.
Pregnancy and Lactation	**Pregnancy** • Levetiracetam can be used during pregnancy, if considered clinically needed. In such case, the lowest effective dose is recommended. • Decrease in levetiracetam plasma concentrations has been observed during pregnancy particularly during third trimester. Monitoring plasma levels during pregnancy may be needed. Dose adjustments may be necessary to maintain clinical response. **Lactation** • Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended. • If levetiracetam medication is required while breastfeeding, benefit versus risk should be evaluated in light of the significance of breastfeeding.
Administration	**N.B** Conversion to or from oral to intravenous administration can be done directly without titration. **IV administration** • The dose must be diluted in at least 100 ml (or to a concentration of 15 mg / mL for pediatrics) of a compatible diluent and administered as IV infusion over 15-minute. • Diluent solutions: Sodium chloride (0.9%), Lactated Ringer, Dextrose 5% injection. **Oral administration** • Administer without regard to meals. • After oral administration a bitter taste may be experienced. • **Oral solution**: it may be diluted in a glass of water or baby's bottle. • **Tablets**: it must be swallowed with a sufficient quantity of liquid. **N.B** Refer to manufacturer PIL if there are specific considerations**.**
Warnings/ Precautions	**Serious Dermatologic Reactions** During treatment, severe and sometimes fatal dermatologic reactions,

Levetiracetam

	including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), may occur early during course of therapy. Levetiracetam should be discontinued at the first sign of a rash, unless it is not drug-related and alternative therapy should be considered. **Renal impairment** Levetiracetam dosage adjustments may be necessary for people with renal impairment. Assessment of renal function is recommended before dose selection in patients with severely impaired hepatic function. **Acute kidney injury** Levetiracetam use has been very rarely associated with acute kidney injury at initiation of the therapy ranging from a few days to several months. **Suicidal ideation** Monitor all patients for any changes in behavior that could indicate suicide ideation or depression; inform healthcare provider immediately if symptoms appear. **Psychiatric disorders** Paranoid and hallucination symptoms, anxiety, agitation may occur. If these behaviors are observed, treatment modification or gradual cessation ought to be taken into consideration. **CNS depression** Patients should be cautioned before performing tasks which need mental alertness. **Worsening of seizures** As with other types of antiepileptic drugs, levetiracetam may rarely exacerbate seizure frequency or severity particularly during first month. It was reversible upon drug discontinuation or dose decrease. Patients should consult their physician immediately. **Electrocardiogram QT interval prolongation** Patients with QTc-interval prolongation, those receiving concurrent treatment with medications that alter the QTc-interval, and those with pertinent pre-existing cardiac illness or electrolyte imbalance should exercise caution when using levetiracetam. **Coordination Difficulties** Monitor for ataxia, abnormal gait, and incoordination.
Storage	• Store between 15°C to 30°C. • Product with particulate matter or discoloration should not be used. • The diluted solution should not be stored for more than 4 hours at controlled room temperature 15-30°C. **N.B** Refer to manufacturer PIL if there are specific considerations**.**

Gabapentin

Generic Name	Gabapentin
Dosage Form/Strengths	**Capsule or Tablets** :100 mg; 300 mg; 400 mg; 600 mg; 800 mg **Extended-release tablets**: 300 mg; 600 mg **Oral solution or Syrup**: 250 mg/5ml.
Route of Administration	***Oral***
Pharmacologic Category	Ant seizure Agent, Miscellaneous; GABA Analog **ATC**: N02BF01
Indications	• Peripheral Neuropathic Pain treatment in adults such as painful diabetic neuropathy and post-herpetic neuralgia (immediate or extended release). • Epilepsy: treatment of partial seizures with and without secondary generalization in adults and pediatric patients 3 years and older (immediate release only).
Dosage Regimen	**Dosing Notes** • The total daily dose should be divided in three single doses. • The maximum time interval between the doses should not exceed 12 hours. • The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is 2 weeks, and to reach 3600 mg/day 3 weeks. **Peripheral Neuropathic Pain in adults** **Immediate release** Dose can be titrated up as needed to a dose of 1800 mg/day ○ Day 1: Single 300 mg dose. ○ Day 2: 300 mg two times a day. ○ Day 3: 300 mg three times a day. ○ Dose can be further increased in 300 mg/day increments every 2-3 days. Alternative dosing: the starting dose is 900 mg/day given in 3 equally divided doses and titrated up to a maximum dose of 3600 mg/day. **Extended release** The starting dose is 300 mg once for 3 days, then increased up to 1800 mg once daily with the evening meal as follows Day 1: 300mg, Day 2: 600 mg, Day 3-6: 900mg, Day 7-10: 1200mg, Days 11–14: 1500mg, Day 15: 1800 mg. **Epilepsy with Partial Onset Seizures** **Patients 3 to 11 years of age** • Initial range: 10 to 15 mg/kg/day, given in three divided doses. Then titrated over 3 days. • Recommended target dose

Gabapentin

- Patients 3 to 4 years: 40 mg/kg/day, given in 3 divided doses.
- Patients 5 to 11 years: 25-35 mg/kg/day, given in 3 divided doses, up to 50 mg/kg/day.

Patients 12 years of age and older: Initial 300 mg three times daily; may be titrated up to 600 mg three times daily.
Dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day.

Discontinuation of gabapentin

If gabapentin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

Dosage Adjustment

- **Elderly patients (over 65 years of age)**
  May need dosage adjustment due to decreased renal function and to avoid adverse effects (Somnolence, peripheral oedema and asthenia).
- **Renal Impairment**

Immediate release formulations

Patients 12 years of age and older

CrCl (mL/minute)	Total Daily Dose (mg/day)
≥ 60	900 to 3600 divided into 3 times daily.
>30 to 59	400 to 1400 divided into 2 times daily.
>15 to 29	200 to 700 (single dose daily).
15	100 to 300 (single dose daily). Reduce daily dose in proportion to creatinine clearance e.g. half the daily dose in case of 7.5 mL/min.
Hemodialysis	As the row above. Supplemental dose after 4 hours: 125 -350.

Alternative dose adjustments

CrCl (mL/minute)	Total Daily Dose (mg/day)
≥ 80	900-3600
50 to 79	600-1800
30 to 49	300-900
15 to 29	150-600
<15	150-300 Reduce daily dose in proportion to creatinine clearance e.g. half the daily dose in case of 7.5 mL/min.

Hemodialysis (intermittent) for anuric patients undergoing hemodialysis who have never received gabapentin

- A loading dose of 300 to 400 mg, then 200 to 300 mg of gabapentin following each 4 hours of hemodialysis. Then maintenance dose as in the table.

Gabapentin

- An additional supplemental dose 200 to 300 mg dose following each 4-hour hemodialysis treatment is recommended.
- On dialysis-free days, there should be no treatment with gabapentin

Children <12 years: The use in patients less than 12 years of age with decreased renal function has not been studied.

Extended release formulations

Creatinine Clearance (mL/min)	Total Daily Dose (mg/day)
≥ 60	1,800 mg
30 - 60	600 mg to 1,800 mg
< 30	should not be administered
Patients receiving hemodialysis	should not be administered

Hepatic Impairment

No dose adjustments needed.

Contra-Indications

Hypersensitivity to gabapentin or any component of the formulation.

Adverse Drug Reactions

>10%

Infection: Viral infection (IR, children: 11%).

Nervous system: Ataxia (IR, adolescents and adults: 1% to 13%), dizziness (IR, adolescents and adults: 17% to 28%; ER, adults: 11%; IR, children: 3%), drowsiness (IR, adolescents and adults: 19% to 21%; IR, children: 8%; ER, adults: 5%), fatigue (IR, adolescents and adults: 11%; IR, children: 3%).

1% to 10%

Cardiovascular: Hypertension, peripheral edema, vasodilation.

Dermatologic: Excoriation of skin, skin rash.

Endocrine & metabolic: Hyperglycemia, weight gain.

Gastrointestinal: Constipation, dental disease, diarrhea, dyspepsia, nausea (IR: ≤8%), viral gastroenteritis, vomiting (IR: ≤8%), xerostomia.

Genitourinary: Erectile dysfunction, urinary tract infection.

Infection: Herpes zoster infection, infection.

Nervous system: Abnormal gait, amnesia, asthenia, changes in thinking, confusion, depression, dysarthria, emotional lability, hostility, lethargy, memory impairment, pain, status epilepticus, tremor, vertigo.

Neuromuscular & skeletal: Back pain, hyperkinetic muscle activity, joint swelling, limb pain.

Ophthalmic: Amblyopia, conjunctivitis, diplopia, nystagmus disorder.

Otic: Otitis media.

Respiratory: Bronchitis, cough, dry throat, nasopharyngitis, pharyngitis, pneumonia, respiratory tract infection, upper respiratory tract infection.

Miscellaneous: Accidental injury, fever.

Monitoring Parameters

- Periodic renal function.
- Suicidality, dependence, mental alertness, symptoms of respiratory depression, dermal toxicity, and sedation.

Gabapentin

Drug Interactions	***Risk X: Avoid combination*** Azelastine (Nasal), Bromperidol, Flunarizine, Kratom, Nabilone, Olopatadine (nasal), Orphenadrine, Oxomemazine, Paraldehyde, Thalidomide. ***Risk D: Consider therapy modification*** Aluminum Hydroxide, Blonanserin, Buprenorphine, Chlormethiazole, Daridorexant, Dexmedetomidine, Droperidol, Flunitrazepam, Hydroxyzine, Lemborexant, Loxapine, Magnesium Salts, Mefloquine, Methotrimeprazine, Metyrapone, Opioid Agonists, Oxycodone, Oxybate Salt Products, Ropeginterferon Alfa-2b, Suvorexant, Zolpidem, Zuranolone.
Pregnancy and Lactation	**Pregnancy** • Based on animal data, may cause fetal harm. • Based on human data, Gabapentin can be used during the first trimester of pregnancy if clinically needed. • Gabapentin should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus. **Lactation** • Gabapentin is secreted in human milk. • No data. Gabapentin should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

Administration	**Oral administration**
	Do not administer within 2 hours of magnesium- or aluminum-containing antacids.
	• **Immediate release**
	  ○ May administer without regard to meals. Swallow whole with sufficient fluid-intake (e.g. a glass of water).
	  ○ Administer the first dose on the first day at bedtime to avoid somnolence and dizziness.
	• **Extended-release**
	  ○ Administer with evening meal.
	  ○ Swallow whole with sufficient fluid-intake (e.g. a glass of water); do not chew, crush, or split.
	• **Oral Liquid Formulations**
	  ○ Measure with calibrated device prior to administration to ensure accurate dosage.
	  ○ May be administered without regard to meals; however, administration with meals may minimize adverse GI effects.
	N.B. Refer to manufacturer PIL if there are specific considerations.

Warnings/ Precautions	**Serious Dermatologic Reactions** During treatment, severe and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), may occur early during course of therapy. Gabapentin should be discontinued at the first sign of a rash, unless it is not drug-related and alternative therapy should be considered.

Gabapentin

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Potentially serious, sometimes fatal reactions. If DRESS is suspected, discontinue the drug. Monitor signs including fever, rash, lymphadenopathy, facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities.

Anaphylaxis and Angioedema

Therapy should be discontinued and evaluate patient immediately.

Suicidal Behavior and Ideation

Patients should be monitored for signs and symptoms. Discontinuation of gabapentin and appropriate treatment should be considered.

Gradual withdrawal

Gradual withdrawal in not less than a week is recommended. Increased seizure frequency if abruptly discontinued. Withdrawal symptoms may occur shortly after discontinuation, usually within 48 hours. Symptoms of withdrawal include anxiety, insomnia, nausea, pains, sweating, tremor, headache, depression, feeling abnormal, dizziness, and malaise.

Concomitant use with opioids

Caution is advised when prescribing gabapentin concomitantly with opioids and other CNS depressants due to risk of CNS depression.

Respiratory depression

Gabapentin has been associated with severe respiratory depression. Risk factors include respiratory or neurological disease, concomitant use of CNS depressants, renal impairment and the elderly. Dose adjustments might be necessary in these patients.

Pediatrics

Long terms (greater than 36 weeks) effects of gabapentin use on learning and development of children have not been adequately studied.

CNS depression

Driving impairment; somnolence, sedation and dizziness may occur. Caution.

Misuse, abuse potential and dependence

Gabapentin can cause drug dependence, which may occur at therapeutic doses. Caution.

Extended release products are not interchangeable with other gabapentin products.

Gabapentin

	Acute pancreatitis It is recommended to stop gabapentin if a patient experiences acute pancreatitis while using it. **Neuropsychiatric Adverse Reactions** in Children 3 to 12 Years of Age: Monitor for such events.
Storage	Capsules and tablets: Store between 15°C to 30°C. Oral solution: Store between 15°C to 30°C. N.B. Refer to manufacturer PIL if there are specific considerations.

Magnesium Sulphate Heptahydrate

Generic Name	Magnesium Sulfate Heptahydrate
Dosage Form/Strengths	• **Solution for IM and IV injection or slow IV infusion**: 1gm/2ml, 0.5gm/5ml (10%). • **Solution for IV injection or infusion:** 1gm/10ml, 2.5gm/25ml. • **Solution for IV infusion:** 1gm/10ml, 10gm/100ml (10%).
Route of Administration	IM, IV
Pharmacologic Category	Antiseizure Agent, Miscellaneous; Electrolyte Supplement, Parenteral Magnesium Salt. ATC: B05XA05
Indications	• Treatment of magnesium deficiency in adults, adolescents and children in hypomagnesaemia. (e.g. children with primary congenital hypomagnesaemia, adults with malabsorption syndrome after persistent diarrhea, chronic alcoholism or long-term parenteral nutrition). • Treatment and prevention of seizures and recurrent seizures in eclampsia of pregnancy or preeclampsia with severe features.
Dosage Regimen	**Adult and pediatric dosing** • **Hypomagnesemia:** Dose should be individualized. ○ **Initial: IV infusion:** Up to 8-12 gm in the first 24 hours. ○ **Maintenance: IV infusion:** 4-6 gm daily for 3-4 days. **Infusion rates** should not exceed 2 g/hour for adults or 10 mg/kg/minute for children. **Target Mg sulphate serum level:** Above 0.4 mmol/l. • **Severe pre-eclampsia or eclampsia** ○ **Initial: IV Loading dose (injection or infusion):** 4-5 gm followed by maintenance dose IV or IM. ○ **IV maintenance regimen:** IV infusion: 1-2 g/hour continued for 24h after the last seizure. ○ **IM maintenance regimen:** IM injections: 4-5 g every 4 hours continued until seizures stop. **Recurrent Convulsions**: A further 2-4g (2g if less than 70Kg) is given IV over 5 min.
Dosage Adjustment	**Renal Impairment** **Renal insufficient patients**: 25-50% of the initial dose. **Severe renal impairment or renal failure**: Contraindicated. The dosage should not exceed 20g in 48 hours. **Hepatic Impairment** No dosage adjustments necessary. **Hepatic failure**: Contraindicated.
Contra-Indications	• Hypersensitivity to magnesium and its salts or to any of the excipients. • Hepatic failure, hepatic encephalopathy. • Renal failure, severe renal impairment, anuria. • Should not be administered parenterally in patients with heart block or myocardial damage and myasthenia gravis.

Magnesium Sulphate Heptahydrate

Adverse Drug Reactions	**Frequency not defined.** **Immune system disorders:** hypersensitivity reactions. Excessive administration of magnesium leads to hypermagnesemia symptoms which may include: **Metabolism and nutrition disorders:** Electrolyte abnormalities (hypophosphatemia, hypertonic dehydration), Maternal and fetal hypocalcemia with high doses. **Nervous system disorders:** Respiratory depression, Nausea, vomiting, drowsiness, confusion, coma, slurred speech, double vision, loss of tendon reflexes due to neuromuscular blockade. **Cardiac disorders:** Cardiac arrhythmias, cardiac arrest, ECG abnormal (prolonged PR, QRS and QT intervals), bradycardia. **Vascular disorders:** Flushing of the skin and hypotension due to peripheral vasodilatation. **Musculoskeletal and connective tissue disorders:** Muscle weakness. **Miscellaneous**: Thirst. **Injection/infusion-related effects** - Too rapid administration: vasodilatation, hypotension. - Local: irritant; extravasation may cause tissue damage. - Intramuscular: pain, redness, swelling, drainage at the injection site, prolonged bleeding, cellulitis, sterile abscess, allergic reactions (such as difficulty breathing or facial swelling), injury to nearby structures (blood vessels, bones, or nerves), tissue necrosis,
Monitoring Parameters	• Serum magnesium level. Normal levels are 1.8-2.5 mg/dl or 0.75-1.05 mmol/l. The presence of the patellar reflex should be checked. • Serum calcium levels. • Monitor respiratory symptoms: breath rate should not be under 16 breaths/min. • Urine volume: should not be under 25 ml/h. • ECG monitoring with high doses and in the elderly.
Drug Interactions	***Risk X: Avoid combination*** Baloxavir Marboxil, Calcium Polystyrene Sulfonate, Levonadifloxacin, Raltegravir, Sodium Polystyrene Sulfonate, Unithiol. ***Risk D: Consider therapy modification*** Alfacalcidol, Alpha-Lipoic Acid, Bictegravir, Bisphosphonate Derivatives, Cabotegravir, Calcitriol (Systemic), Deferiprone, Dolutegravir, Doxercalciferol, Eltrombopag, Elvitegravir, Gabapentin, Levothyroxine, Multivitamins/Fluoride (with ADE), Penicillamine, Phosphate Supplements, Quinolones, Roxadustat (Systemic).
Pregnancy and Lactation	**Pregnancy** • Use for more than 5 to 7 days may induce fetal adverse effects including hypocalcemia, and skeletal adverse effects. use within 2 hours of delivery should be avoided. • Monitoring of neonates for abnormal calcium or magnesium levels and skeletal adverse effects should be considered in long term use.

Magnesium Sulphate Heptahydrate

	Lactation Safety during lactation has not been established. Not recommended unless considered essential.
Administration	**Intramuscular Administration** If the total dose to be administered exceeds 5 ml, the injection volume should be divided between more than one deep intramuscular injection site. If repeating an intramuscular dose, rotate injection sites to avoid injury or discomfort to the muscles. **Intravenous Administration** **Intravenous injection**: 10% concentration can be used without dilution. **Intravenous infusion**: Should be diluted 10- 20% are used. **Infusion rates** should not exceed 2 g/hour for adults or 10 mg/kg/minute for children. Magnesium sulfate can be diluted with Glucose 5% and Sodium chloride 0.9% solutions.
Warnings/ Precautions	**Renal impairment** Used with caution in impaired renal function. Dosage reduction should be made. **Hepatic coma** Magnesium sulfate should not be used in hepatic coma if there is a risk of renal failure. **Antidote** Antidote of injectable calcium gluconate solution should be immediately available. **Aluminum content** The parenteral product may contain aluminum; toxic aluminum concentrations may be seen with high doses, prolonged use, or renal dysfunction. Premature neonates are at higher risk due to immature renal function.
Storage	• Store between 15°C to 30°C. Do not freeze. Refrigeration of solution may result in precipitation or crystallization. • Diluted product in aseptic conditions can be stable for 72 hours at 2 to 8°C or 25°C. **N.B.** Refer to manufacturer PIL if there are specific considerations.

Topiramate

Generic Name	Topiramate
Dosage Form/Strengths	Tablets: 25 mg, 50 mg, 100 mg
Route of Administration	*Oral*
Pharmacologic Category	Antiseizure Agent, Miscellaneous ATC: N03AX11
Indications	**Monotherapy in partial seizures or primary generalized tonic-clonic seizures** (in patients ≥ 2 years of age). **Adjunctive therapy epilepsy** (partial onset seizures with or without secondary generalization, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome) (in patients ≥2 years of age). **Migraine, prevention:** Prophylaxis of migraine in patients ≥ 12 years of age.
Dosage Regimen	***Adult dosing*** **Monotherapy Antiseizure** • **Initial:** 100 mg once or twice daily. • Dose can be increased by increments of 50 mg/day at weekly intervals. • **The maximum recommended dose:** 500 mg/day in 2 divided doses**.** **Adjunctive Antiseizure therapy** • **Initial:** 25-50 mg nightly for one week**.** • Subsequently, dose can be increased by increments of 25-50 mg/day at weekly or bi-weekly intervals. • **The usual daily dose:** 200-400 mg in two divided doses. **Migraine prophylaxis** • **Initial:** 25 mg /day nightly for one week**.** • Dose is increased in increments of 25 mg/day at 1-week intervals. • **The recommended total daily dose:** 100 mg/day in two divided doses. up to 200 mg/day may be tolerated. ***Pediatric dosing*** **Monotherapy Seizures (2-9 years)** • **Initial:** 25 mg/day nightly for the first week. • **Target dose** is 100 mg/day guided by weight. • The dosage should be increased at 1- or 2-week intervals by increments of 25-50 mg /day, administered in two divided doses. • If not tolerated, smaller increments or longer intervals between dose increments can be used.

Topiramate

	<table><tr><th>Weight (kg)</th><th>Minimum Maintenance Total Daily Dose (mg/day)</th><th>Maximum Maintenance Total Daily Dose (mg/day)</th></tr><tr><td>Up to 11</td><td>150</td><td>250</td></tr><tr><td>12 - 22</td><td>200</td><td>300</td></tr><tr><td>23 - 31</td><td>200</td><td>350</td></tr></table> **Adjunctive therapy (2-16 years)** • **Initial:** 25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week. • The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated. • **Recommended daily dose** is 5 to 9 mg/kg/day in two divided doses. • **Maximum daily dose** is 400 mg.
Dosage Adjustment	**Renal impairment** **CrCl <70 mL/minute/1.73 m²**: Reduce dose to 50% of the indication-specific usual dose and titrate more slowly. **Hemodialysis**: A supplemental dose equal to approximately one-half the daily dose should be administered on haemodialysis days given in divided doses at the beginning and completion of the hemodialysis procedure. **Hepatic impairment** **Mild hepatic impairment:** No dose adjustment is needed. **Moderate to severe hepatic impairment**: Caution as the clearance of topiramate is decreased.
Contra-Indications	Hypersensitivity to the active substance or to any of the excipients.
Adverse Drug Reactions	**>10%** **Endocrine & metabolic**: Decreased serum bicarbonate (children and adolescents: 67%; <17 mEq/L and ≥5 mEq/L decrease from pretreatment: 11%; average decrease of 4 mEq/L at dose of 400 mg/day in adults and 6 mg/kg/day in children), hyperammonemia (adolescents: 14% to 26%), weight loss (4% to 17%). **Gastrointestinal:** Abdominal pain (adolescents and adults: 6% to 15%), anorexia (adolescents and adults: 4% to 15%), diarrhea (2% to 11%), dysgeusia (adolescents and adults: 3% to 15%), nausea (adolescents and adults: 8% to 13%). **Nervous system**: Dizziness (dose-related) (adolescents and adults: 6% to 14%), drowsiness (dose-related) (adolescents and adults: 2% to 15%), fatigue (dose-related) (7% to 15%), memory impairment (1% to 11%), paresthesia (adolescents and adults: 19% to 51%; children and adolescents: 3% to 12%). **Neuromuscular & skeletal**: Decreased bone mineral density (children and adolescents: 21%).

Topiramate

Respiratory: Upper respiratory tract infection (13% to 26%).
Miscellaneous: Fever (1% to 12%).

1% to 10%

Cardiovascular: Flushing (children and adolescents: 5%).
Dermatologic: Acne vulgaris (adolescents and adults: 2% to 3%), alopecia (1% to 4%), pruritus (adolescents and adults: 1% to 4%), skin rash (1% to 4%).
Endocrine & metabolic: Decreased libido (adolescents and adults: 3%), intermenstrual bleeding (children and adolescents: 3%), menstrual disease (adolescents and adults: 3%).
Gastrointestinal: Constipation (adolescents and adults: 1% to 4%), dyspepsia (adolescents and adults: 4% to 5%), gastritis (adolescents and adults: 3%), gastroenteritis (adolescents and adults: 3%), xerostomia (adolescents and adults: 1% to 3%).
Genitourinary: Cystitis (adolescents and adults: 1% to 3%), premature ejaculation (adolescents and adults: 3%), urinary frequency (2% to 3%), urinary incontinence (children and adolescents: 1% to 3%), urinary tract infection (adolescents and adults: 4%), vaginal hemorrhage (adolescents and adults: 3%).
Hematologic & oncologic: Anemia (children and adolescents: 1% to 3%), hemorrhage (4% to 5%).
Hepatic: Increased gamma-glutamyl transferase (adolescents and adults: 1% to 3%).
Infection: Infection (2% to 8%), viral infection (3% to 8%).
Nervous system: Anxiety (adolescents and adults: 4% to 6%), asthenia (3% to 6%), ataxia (adolescents and adults: 3% to 4%), behavioral problems (children and adolescents: 3%), cognitive dysfunction (1% to 6%), confusion (3%), depression (adolescents and adults: 7% to 9%; children and adolescents: 3%), disturbance in attention, hypertonia (adolescents and adults: 3%), hypoesthesia (adolescents and adults: 4% to 7%), insomnia (adolescents and adults: 6% to 9%), lack of concentration, language problems (adolescents and adults: 6% to 7%), mood disorder (1% to 8%), nervousness (adolescents and adults: 4%), psychomotor impairment (adolescents and adults: 2% to 5%), vertigo (children and adolescents: 3%).
Neuromuscular & skeletal: Arthralgia (adolescents and adults: 3% to 7%), lower extremity pain (adolescents and adults: 2% to 3%), muscle spasm (3%).
Ophthalmic: Blurred vision (adolescents and adults: 4%), conjunctivitis (adolescents and adults: 7%).
Renal: Nephrolithiasis (adolescents and adults: 3%).
Respiratory: Bronchitis (1% to 5%), cough (adolescents and adults: 2% to 7%), dyspnea (adolescents and adults: 1% to 3%), epistaxis (children and adolescents: 4%), pharyngitis (adolescents and adults: 5% to 6%), rhinitis (2% to 7%), sinusitis (1% to 10%).
Miscellaneous: Accidental injury (adolescents and adults: 6% to 9%).

Topiramate

Monitoring Parameters	• Pregnancy testing should be performed before initiating treatment. • Serum bicarbonate levels, baseline and periodic. • Monitor for signs of suicidal ideation and behavior. • Monitor for weight loss. • Monitor for ophthalmic changes.
Drug Interactions	***Risk X: Avoid combination*** Alcohol (Ethyl), Azelastine (Nasal), Bromperidol, Carbonic Anhydrase Inhibitors, Flunarizine, Kratom, Nabilone, Noscapine, Olopatadine (Nasal), Orphenadrine, Oxomemazine, Paraldehyde, Thalidomide, Ulipristal. ***Risk D: Consider therapy modification*** Articaine, Blonanserin, Buprenorphine, Chlormethiazole, Daridorexant, Dexmedetomidine, Droperidol, Flunitrazepam, Hormonal Contraceptives, Hydroxyzine, Lamotrigine, Lemborexant, Loxapine, Mefloquine, Methenamine, Methotrimeprazine, Metyrapone, Opioid Agonists, Oxybate Salt Products, Oxycodone, Ropeginterferon Alfa-2b, Suvorexant, Zolpidem, Zuranolone.
Pregnancy and Lactation	**Pregnancy**: Avoid use. Use during pregnancy can cause major congenital malformations, including but not limited to cleft lip and/or palate, and fetal growth restriction. **Lactation**: Limited human data. Topiramate is excreted in human milk. A decision must be made whether to suspend breast-feeding or to discontinue/ abstain from topiramate therapy
Administration	**Oral Administration** Topiramate can be taken without regard to meals. It is recommended that film-coated tablets not be broken. N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Acute myopia and secondary angle closure glaucoma** • Symptoms include acute onset of decreased visual acuity and/or ocular pain. Symptoms typically occur within 1 month of initiating topiramate therapy in adults as well as pediatrics. • Treatment includes discontinuation of topiramate, as soon as possible in the judgment of the treating physician, and appropriate measures to reduce intraocular pressure. • Untreated elevated intraocular pressure of any aetiology can lead to permanent vision loss. **Visual field defects** Consider discontinuation if developed. **Metabolic acidosis** • Mild to moderate metabolic acidosis (i.e. decreased serum bicarbonate in the absence of respiratory alkalosis) is associated with topiramate treatment. • Risk factors include renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or certain medicinal products.

Topiramate

- Chronic, untreated metabolic acidosis increases the risk of nephrolithiasis and in paediatric patients can reduce growth rates.
- Symptoms include Kussmaul's deep breathing, dyspnea, anorexia, nausea, vomiting, excessive tiredness, tachycardia or arrhythmia.
- If symptoms developed, reducing the dose or discontinuing topiramate (using dose tapering) is recommended.

Suicidal behavior and ideation

Antiepileptic drugs increase the risk of suicidal behavior or ideation. Patients therefore should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered.

Impairment of cognitive function

Use caution when operating machinery including cars; depression and mood problems may occur. May require reduction in dosage or discontinuation of treatment.

Gradual withdrawal

- Topiramate should be gradually withdrawn to minimise the potential for seizures or increased seizure frequency.
- Daily dosages were decreased in weekly intervals by 50-100 mg in adults with epilepsy and by 25-50 mg in adults receiving topiramate at doses up to 100 mg/day for migraine prophylaxis. In pediatric clinical trials, topiramate was gradually withdrawn over a 2-8-week period.

Negative effects on growth

- Topiramate may slow height increase and weight gain; carefully monitor children receiving prolonged therapy. Also, it may decrease bone mineral density and bone mineral content in pediatric patients.
- A dietary supplement or increased food intake may be considered if the patient is losing weight while on topiramate.

Serious skin reactions

Reactions including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported. Monitor symptoms. If SJS or TEN are suspected, use of topiramate should be discontinued.

Hyperammonemia/encephalopathy

- Hyperammonemia with or without encephalopathy has been reported with topiramate treatment in adults and pediatrics. The risk for hyperammonemia with topiramate appears dose-related. Hyperammonemia has been reported more frequently when topiramate is used concomitantly with valproic acid.

Topiramate

	• Ammonia should be measured if encephalopathic symptoms occur or in patients who develop unexplained lethargy, or changes in mental status. **Kidney stones** • Risk factors include prior stone formation, a family history of nephrolithiasis, hypercalciuria and taking other medicinal products associated with nephrolithiasis. • Associated signs and symptoms such as renal colic or renal pain.
Storage	Store between 15°C to 30°C. Protect from moisture. N.B. Refer to manufacturer PIL if there are specific considerations.

Valproic acid

Generic Name	Valproic acid
Dosage Form/Strengths	**Capsule**: 150, 250, 300 mg. **Syrup:** 250 mg/5ml. **Modified release tablet**: 250, 500 mg. **Oral drops**: 200, 300 mg/ml. **Solution for IV injection**: 500 mg/5ml.
Route of Administration	Oral, IV
Pharmacologic Category	Antimanic Agent; Antiseizure Agent, Miscellaneous; Histone Deacetylase Inhibitor. **ATC**: N03AG01
Indications	• For the treatment of all patients of generalized, partial or other epilepsy. IV: used as alternative for patients in whom oral administration of valproate products is temporarily not feasible. • Manic episode in bipolar disorder only when there is no other effective or tolerated treatment. • Prophylaxis of migraine headaches **N.B**. Use for patients under 55 years only when there is no other effective or tolerated treatment.
Dosage Regimen	**Notes** – Immediate release formulations: Dose may be divided into 2-4 times daily. – Extended release formulations: Dose may be given in once or twice daily dosing. – All formulations: If the total daily dose exceeds 250 mg, it should be given in divided doses. – Children under the age of two years are at higher risk of fatal hepatotoxicity. – Elderly: Lower starting dose should be used and increased more slowly with regular monitoring for fluid and nutritional intake. **Epilepsy oral dosing adults and pediatrics (monotherapy or adjunctive)** – **Initial**: Oral: 10 – 15 mg/kg/day **or** 600mg daily for adults, 400 mg for children. – **Dose adjustment increments**: 5 – 10 mg/kg at weekly intervals. – **Maintenance dose:** 20 – 30 mg/kg/day body weight **or** for adults 1000 – 2000 mg up to 2500 mg daily. – **Maximum dose**: 60 mg/kg/day. – If the response is inadequate, measure plasma valproate levels. Acceptable plasma valproate levels: 50 – 100 mcg/ml. **Epilepsy IV dosing** – **Initial**: IV: 10 – 15 mg/kg/day. – **Dose adjustment increments**: 5 – 10 mg/kg at weekly intervals

Valproic acid

	– **Maximum dose**: 60 mg/kg/day. – Not for more than 14 days. Switch to oral products. – In treatment of complex partial seizures used only for adults and children 10 years of age or older. **Manic episodes in bipolar disorder for adults** – **Initial: Oral:** 750 mg daily in 2 – 3 divided doses or 20 mg/kg body weight. – Adjust dose as rapidly as possible. – **Maintenance dose**: 1000 – 2000 mg. Use the lowest effective dose. – **Maximum dose**: 45 mg/kg/day. – Trough plasma concentration between 50 and 125 mcg/mL **Migraine prophylaxis**: Oral: 250 mg twice daily. Withdrawal of concomitant antiepileptic drugs for conversion to valproate monotherapy – Dose reductions for concomitant antiepileptic drugs by 25% every 2 weeks. – Reduction of dose may be right after starting valproic acid or can be delayed for 1 – 2 weeks after starting treatment with valproate. Monitor for seizures.
Dosage Adjustment	**Renal Impairment** • Dose adjustment may be needed. Dosing should be modified according to clinical monitoring of the patient. **Hepatic Impairment** • Mild to moderate impairment: Adjust dose to reach desired clinical effect. • Severe impairment: Valproic acid is contraindicated. **N.B**. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence.
Contra-Indications	• Known hypersensitivity to Valproic acid or any of its derivatives. • active liver disease, or personal or family history of severe hepatic dysfunction • Porphyria. • Urea cycle disorders. • Pregnancy. • Known mutations in mitochondrial DNA polymerase γ (POLG) in any age group. • Suspected POLG mutations in children 2 years of age or younger.
Adverse Drug Reactions	**>10%** **Dermatologic**: Alopecia (6% to 24%). **Gastrointestinal**: Abdominal pain (oral: 7% to 23%; IV: 1%), anorexia (4%

Valproic acid

to 12%), diarrhea (oral: 7% to 23%; IV: <1%), dyspepsia (7% to 23%), nausea (oral: 15% to 48%; IV: 3% to 6%), vomiting (oral: 7% to 27%; IV: 1%).
Hematologic & oncologic: Thrombocytopenia (1% to 27%).
Infection: Infection (12% to 20%).
Nervous system: Asthenia, dizziness (oral: 12% to 25%; IV: 5% to 7%), drowsiness, headache (oral: 31%; IV: 3% to 4%), insomnia (9% to 15%), nervousness (oral: 7% to 11%; IV: <1%), pain (oral: 11%; IV: 1%), tremor (oral: 9% to 57%; IV: <1%).
Ophthalmic: Diplopia (16%), visual disturbance (4% to 12%; including amblyopia, blurred vision).
Respiratory: Flu-like symptoms (12%).
Miscellaneous: Accidental injury (6% to 11%).

1% to 10%

Cardiovascular: Cardiac arrhythmia, chest pain, edema, hypertension, hypotension, orthostatic hypotension, palpitations, peripheral edema, tachycardia, vasodilation.
Dermatologic: Diaphoresis, ecchymoses, erythema nodosum, furunculosis, maculopapular rash, pruritus, seborrhea, skin rash, vesiculobullous dermatitis, xeroderma.
Endocrine & metabolic: Amenorrhea, weight gain, weight loss.
Gastrointestinal: Constipation, dysgeusia, dysphagia, eructation, fecal incontinence, flatulence, gastroenteritis, gingival hemorrhage, glossitis, hematemesis, hiccups, increased appetite, oral mucosa ulcer, pancreatitis, periodontal abscess, stomatitis, xerostomia.
Genitourinary: Cystitis, dysmenorrhea, dysuria, urinary incontinence, urinary tract infection, vaginal hemorrhage, vaginitis.
Hematologic & oncologic: Anemia, hypoproteinemia, leukopenia, petechia, prolonged bleeding time.
Hepatic: Increased serum alanine aminotransferase, increased serum aspartate aminotransferase.
Hypersensitivity: Facial edema.
Infection: Fungal infection, viral infection.
Local: Injection-site reaction, pain at injection site.
Nervous system: Abnormal dreams, abnormal gait, agitation, amnesia, anxiety, ataxia, catatonia, changes in thinking, chills, confusion, depression, dysarthria, emotional lability, hallucination, hyperreflexia, hypertonia, malaise, myasthenia, paresthesia, personality disorder, psychosis, sleep disturbance, speech disturbance, twitching, vertigo.
Neuromuscular & skeletal: Arthralgia, back pain, discoid lupus erythematosus, hypokinesia, lower limb cramp, myalgia, neck pain, neck stiffness, osteoarthritis, tardive dyskinesia.
Ophthalmic: Conjunctivitis, dry eye syndrome, eye pain, nystagmus disorder, photophobia.
Otic: Deafness, otitis media, tinnitus.
Respiratory: Bronchitis, cough, dyspnea, epistaxis, pharyngitis, pneumonia, rhinitis, sinusitis.

Valproic acid

	Miscellaneous: Fever.
Monitoring Parameters	• Liver function tests at initiation and then frequently during therapy especially first 6 months. • CBC with platelets at initiation and then periodically. • Prothrombin Time and Partial Thromboplastin Time. • Serum ammonia if changes in mental status. • Obtain serum valproate levels as clinically indicated (if the response in inadequate). • Assess for signs of depression, behavioral changes, and suicidal ideation. Assess motor and cognitive function. Monitor therapeutic effectiveness (type of seizure activity, and duration). • Assess for signs of liver toxicity and pancreatitis. • Check pregnancy status and educate patients of childbearing potential to use reliable birth control while on this medicine.
Drug Interactions	***Risk X: Avoid combination*** Azelastine (Nasal), Bromperidol, Cosyntropin, Flunarizine, Kratom, Nabilone, Olopatadine (Nasal), Orphenadrine, Oxomemazine, Paraldehyde, Pivmecillinam, Taurursodiol, Thalidomide. ***Risk D: Consider therapy modification*** Blonanserin, Buprenorphine, Carbapenems, Chlormethiazole, Cholestyramine Resin, Daridorexant, Dexmedetomidine, Droperidol, Felbamate, Flunitrazepam, Hydroxyzine, Lamotrigine, Lemborexant, Lorazepam, Loxapine, Mefloquine, Methotrimeprazine, Metyrapone, Opioid Agonists, Oxybate Salts (calcium, Magnesium, Potassium, And Sodium), Oxycodone, Propofol, Ropeginterferon Alfa-2b, Rufinamide, Sodium Oxybate, Suvorexant, Zolpidem, Zuranolone.
Pregnancy and Lactation	**Pregnancy** • Contraindicated. Valproate has a high teratogenic potential of (11%) congenital malformations and (30-40%) neurodevelopmental disorders which may lead to permanent disability. • Valproic acid should not be used in women of childbearing potential without effective contraception, or in women who plan pregnancy unless other options are inadequate. • There have been reports of male infertility coincident with valproate therapy. **Lactation** Valproate is excreted in breast milk. Hematological disorders have been shown in breastfed infants of treated women. No adverse effects in the nursing infant have been reported. Consider benefit and risk.
Administration	**IV Administration** • Dilute in 50 ml or more of a compatible fluid. • Compatible fluids: 5% dextrose, normal saline, lactated ringer's solution. • Administer over 60 minutes at a rate ≤20 mg/minute.

Valproic acid

	Oral Administration • Valproate may be given with food to avoid gastrointestinal adverse effects. Tablets should be swallowed whole with water, and not crushed or chewed. N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Hepatotoxicity and liver failure** • Valproic acid may cause hepatotoxicity and serious liver damage that can be fatal, usually within 6 months after starting treatment. Risk factors include: – History of liver disease. – The use of multiple anticonvulsants. – Children under the age of 2 years. Risk progressively decreases with increasing age. – Degenerative disease associated with mental retardation. – Congenital metabolic disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, polymerase γ (POLG) mutations. Signs and symptoms of disorders due to POLG mutations include: unexplained encephalopathy, refractory epilepsy, presentation with status epilepticus, delayed development, myopathy, cerebellar ataxia, psychomotor regression, axonal sensorimotor neuropathy or complicated migraine with occipital aura. **Preceding symptoms** of serious fatal hepatotoxicity include malaise, weakness, lethargy, facial edema, anorexia, vomiting and recurrence of seizures. Immediate withdrawal may be needed. • The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity. • Valproate should be discontinued in case of serious liver dysfunction. **Birth defects** Fetal exposure to valproate may result in structural malformations e.g., neural tube defects and decreased IQ. **Pancreatitis** • Life-threatening pancreatitis has been reported rarely in adults and children treated with valproate. Young children are at particular risk; risk decreases with increasing age. • Patients having first signs of pancreatitis include nausea, vomiting or acute abdominal pain should have immediate medical evaluation (including measurement of serum amylase). • Some cases were hemorrhagic and progressed rapidly to death. • If pancreatitis occurs, valproate should be discontinued. • In some cases, pancreatitis recurred after re-challenge. **Hyperammonemia and encephalopathy** • Hyperammonemia has been reported in patients treated with valproate even in the absence of hepatic dysfunction.

Valproic acid

	• Patients develop unexplained lethargy, vomiting, or altered mental status. May be associated with hypothermia. • Fatal hyperammonemic encephalopathy has been reported in patients with urea cycle disorders (UCD). **Suicidal behavior** • Antiepileptic drugs are associated with an increased risk of suicidal behavior. Monitor for the emergence or worsening of depression and suicidal behavior. **Bleeding and hematopoietic disorders** • Dose-related thrombocytopenia occurs with the use of valproate. Monitor blood cell count including platelet counts and coagulation tests prior to therapy and as clinically indicated. • If hemorrhage or coagulopathies occur, valproate should be discontinued, or the dose should be reduced. **Hypersensitivity reactions** Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which can be fatal, has been reported with valproate use. Discontinue. **Carbapenem antibiotics** Carbapenems for example, ertapenem, imipenem, meropenem may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. **Effect on ketone and thyroid function tests** • Valproate is excreted in urine as a ketone metabolite which may result in false urine ketones test results. • Valproate has been reported to alter thyroid function test results. **Abrupt discontinuation** In patients in whom the drug is administered to prevent major seizures abrupt discontinuation may cause life-threatening status epilepticus. **Increased somnolence in the elderly** Elderly patients are more vulnerable to somnolence from valproate use. In case of a poor nutritional status or excessive somnolence, valproate should be discontinued, or the dose should be reduced.
Storage	<u>Tablets, capsules, and oral solution</u> Store between 15 – 30°C. <u>Parenteral products</u> • Store between 15 – 30°C. • Solutions of 5% dextrose, normal saline, and lactated ringer's solution are stable for 24 hours after reconstitution when stored in glass or polyvinyl chloride (PVC) containers. N.B. Refer to manufacturer PIL if there are specific considerations.

Antiparkinsonism

Amantadine

Generic Name	Amantadine
Dosage Form/Strengths	**Capsule:** 100mg. **Tablets:** 100mg. **Solution for IV infusion:** 200mg/500ml.
Route of Administration	*Oral, IV*
Pharmacologic Category	Anti-Parkinson Agent, Dopamine Agonist; Antiviral Agent. **ATC:** N04BB01
Indications	• Treatment of **Parkinsonism** and drug-induced extrapyramidal reactions. • **Influenza A** virus: Prophylaxis and treatment of signs and symptoms of influenza A virus infection. • **Herpes zoster**. Recommended to elderly or debilitated patients. Amantadine can significantly reduce the proportion of patients experiencing long term pain, and a severe and painful rash.
Dosage Regimen	**Dosing: Adults** **Parkinsonism** **Oral**: Initial: 100mg once daily increased to 100mg twice daily at the second week. • The dose may be increased gradually, at intervals of not less than 1 week. • Maximum dose: 400 mg/day. • Doses exceeding 200mg daily may be associated with increasing toxicity, so, closely monitoring is required. • Amantadine effectiveness may be prolonged through withdrawal for 3-4 weeks (as it may lose efficacy within several months). During this time, concomitant antiparkinsonian therapy should be resumed, or low dose L-dopa treatment initiated if clinically necessary. • **Gradual withdrawal**: Half the dose at weekly intervals. • Any anti-Parkinson drug already in use should be continued during initial Amantadine treatment then gradually reduced. **Drug-induced extrapyramidal reactions: Oral** • 100 mg twice a day. • Patients whose responses are not optimal with 200 mg daily may benefit from an increase up to 300 mg daily in divided doses. **Herpes zoster** • **Oral**: 100mg twice daily for 14 days started as soon as possible after diagnosis. • Dose can be continued for a further 14 days if post-herpetic pain persists **Influenza A (treatment and prophylaxis)** • N.B. Amantadine is not a substitute for early vaccination on an annual basis. • **Oral**: 100-200 mg daily for the recommended period. • **Duration of treatment**: 4-10 days. Treatment should start as soon as

Amantadine

	possible and should be continued for 24 to 48 hours after end of signs and symptoms. • **Duration of Prophylaxis**: as required, mostly for 2-6 weeks. • If central nervous system (CNS) effects develop in once-a-day dosage, a split dosage schedule may reduce such complaints. **Dosing: Pediatric** **Prophylaxis/treatment of influenza A** ***Children (10 -15 years):* Oral**: 100 mg once or twice a day.
Dosage Adjustment	**Renal Impairment** • **CrCl > 35 ml/min:** 100mg every day. • **CrCl 15 – 35 ml/min:** 100mg every 2 to 3 days. • **CrCl < 15 ml/min:** Contraindicated. ***Alternative regimens*** • **CrCl 30-50 ml/min/1.73m²:** 200 mg 1st day followed by 100 mg daily. • **CrCl 15-29 ml/min/1.73m²:** 200 mg 1st day followed by 100 mg on alternate days. • **CrCl <15 ml/min/1.73m²:** 200 mg every 7 days. • **Hemodialysis:** 200 mg every 7 days. **Hepatic impairment** There are no dosage adjustments; use with caution. **Elderly** As adult but start with the lowest effective dose as lower renal clearance to avoid adverse effects. Using 2 divided daily doses may minimize CNS effects.
Contra-Indications	• Hypersensitivity to the active substance or to any of the excipients. • Untreated angle closure glaucoma. • Pregnancy. • Severe renal disease.
Adverse Drug Reactions	**>10%** **Cardiovascular:** Orthostatic hypotension (13%; including orthostatic dizziness, syncope, presyncope, and hypotension), peripheral edema (16%). **Gastrointestinal:** Constipation (13%), xerostomia (16%). **Nervous system:** Dizziness (16%), falling (13%), hallucination (21%). **1% to 10%** **Cardiovascular:** Livedo reticularis (6%). **Dermatologic:** Dyschromia (3%). **Gastrointestinal:** Anorexia (1% to 5%), decreased appetite (6%), diarrhea (1% to 5%), nausea (8%), vomiting (3%). **Genitourinary:** Benign prostatic hypertrophy (6%), urinary tract infection (10%). **Hematologic & oncologic:** Bruise (6%). **Nervous system:** Abnormal dreams (4%), agitation (1% to 5%), anxiety

Amantadine

	(7%), apathy (2%), ataxia (3%), confusion (3%), delusion (<3%), depression (6%), drowsiness (<3%), dystonia (3%), fatigue (<3%), headache (6%), illusion (<3%), insomnia (7%), irritability (1% to 5%), nervousness (1% to 5%), paranoid ideation (<3%), suicidal tendencies (≤2%). **Neuromuscular & skeletal:** Joint swelling (3%), muscle spasm (3%). **Ophthalmic:** Blurred vision (4%), cataract (3%), dry eye syndrome (3%). **Respiratory:** Cough (3%), dry nose (1% to 5%).
Monitoring Parameters	• Renal function and hepatic function (baseline and as clinically indicated). • Blood pressure (particularly during escalation of dose) due to risk of orthostatic hypotension. • Advise patient to monitor for any cardiac symptoms (palpitation), CNS changes (dizziness, drowsiness, tremors, hallucinations) or behavioural changes.
Drug Interactions	***Risk X: Avoid combination*** Alcohol (Ethyl), Alizapride, Amisulpride (oral/injection), Methotrimeprazine, Metoclopramide, Sulpiride. ***Risk D: Consider therapy modification*** Antipsychotic Agents (typical, first generation), Antipsychotic Agents (Atypical, second generation), Influenza Virus Vaccine (live/attenuated). ***N.B.*** Avoid administration of live influenza virus vaccine within 2 weeks before or 48 hours after administration of antiviral agents
Pregnancy and Lactation	**Pregnancy:** Amantadine is contra-indicated during pregnancy and in women trying to become pregnant. **Lactation:** Amantadine passes into breast milk. Use is not recommended in nursing mothers.
Administration	**Oral Administration:** May be taken without regard to food. **N.B.** Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Symptomatic orthostatic hypotension** Monitor during dose escalation. **Impulse Control disorders** Patients may experience compulsive behaviors including increased libido, hypersexuality, compulsive buying, and compulsive eating when treated with dopamine agonists including pramipexole. Dose reduction or tapered discontinuation should be considered. **Ophthalmologic effects** If blurred vision occurred, examination should be made to exclude corneal oedema. If corneal oedema is diagnosed, amantadine should be discontinued. **Discontinuation** • Should be gradually (e.g. half the dose at weekly intervals). Abrupt

Amantadine

	discontinuation in Parkinson's disease may cause clinical deterioration of Parkinsonism. It may also precipitate agitation, delusions, hallucinations, paranoid reaction, anxiety, depression and slurred speech. • Abrupt discontinuation might also be associated with Neuroleptic Malignant Syndrome (NMS). Caution and early diagnosis and management are needed (systemic infection must be ruled out due to similar symptoms). **Suicide attempts** Suicide attempts and suicidal ideation have been reported in patients with and without prior history of psychiatric illness. Caution in patients experiencing CNS effects. **CNS effects** May cause CNS depression, which may impair physical or mental abilities. Caution with operating machinery or driving. Increased seizure activity in patient with history of convulsions. **Peripheral edema** May occur during chronic treatment. Use with caution in patients with congestive heart failure. **Liver disease** Caution with hepatic patients. Reversible elevation of liver enzymes may occur. **Dose reduction** The dose may need to be reduced in patients with congestive heart failure, peripheral edema, orthostatic hypotension, or impaired renal function. **Lactose** Some dosage forms may contain Lactose. Use is not recommended in patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose galactose malabsorption.
Storage	Store between 15-30°C. Protect from moisture. N.B Refer to manufacturer PIL if there are specific considerations.

Carbidopa- Levodopa

Generic Name	Carbidopa and Levodopa
Dosage Form/Strengths	**Tablets:** Carbidopa/ Levodopa: 25mg/100mg, 25mg/250mg. **Controlled Release Tablet**: Carbidopa/ Levodopa: 50mg/200mg.
Route of Administration	*Oral*
Pharmacologic Category	Anti-Parkinson Agent, Decarboxylase Inhibitor, Dopamine Precursor. ATC: N04BA02
Indications	• Treatment of Parkinson's disease. • Treatment of post-encephalitic parkinsonism, and symptomatic parkinsonism due to carbon monoxide intoxication or manganese intoxication. **N.B.** Modified release tablets: used in particular to patients who showed motor fluctuations during treatment with immediate-release form. **N.B**. Carbidopa allows patients to use much lower doses of levodopa due to decreased peripheral decarboxylation of levodopa. Carbidopa may also reduce nausea and vomiting and permit more rapid titration of levodopa.
Dosage Regimen	**Adult Dosing** • Immediate release tablets - **Initial dose:** 25 mg / 100 mg every 8 hours. - **Maintenance** ▪ Dosage may be increased by (25mg/100mg) every day or every other day, as needed. **Maximum daily dose**: (200mg/ 800mg) (8 tablets). ▪ When more levodopa is required: 25 mg/250 mg three to four times daily increased by up to (25mg/250mg) every day or every other day, as needed. **Maximum daily dose**: (200mg/2000mg) (8 tablets). - Other antiparkinsonian agents may be resumed when carbidopa-levodopa is introduced with dose adjustments as recommended. • Modified release tablets **Initial dose:** 50mg/200mg two times daily. Adjustments of dose may be needed with intervals of at least 2-4 days up to doses 8 tablets daily divided into 3 or 4 doses. **Pediatrics:** Use is not recommended in patients below the age of 18 as safety has not been established.
Dosage Adjustment	**Renal Impairment** No dosage adjustment is necessary; use with caution. **Hepatic Impairment** No dosage adjustment is necessary; use with caution.
Contra-Indications	• Hypersensitivity to levodopa, carbidopa or any of the excipients. • Concomitant monoamine oxidase (MAO) inhibitors (non-selective or selective type A). Carbidopa/Levodopa must be started at least two weeks after stopping these inhibitors. • Narrow-angle glaucoma.

Carbidopa- Levodopa

	• Patients with suspected undetected skin lesions or a history of melanoma should not take Levodopa since it may trigger a malignant melanoma. • Conditions in which adrenergics are contraindicated e.g. severe CVS diseases, pheochromocytoma, hyperthyroidism, Cushing's syndrome. • Patients with serious psychoses.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Orthostatic hypotension (1% to 68%). **Gastrointestinal**: Constipation (≤6%), nausea (2% to 21%). **Nervous system**: Depression (1% to 2%), dizziness (2% to 19%), headache (1% to 17%). **Neuromuscular & skeletal**: Dyskinesia (2% to 17%). **1% to 10%** **Cardiovascular**: Chest pain (≤1%), ischemia (≤2%). **Endocrine & metabolic**: Increased serum glucose (≥1%). **Gastrointestinal**: Anorexia (1%), diarrhea (≤5%), dyspepsia (≤5%), vomiting (2% to 5%), xerostomia. **Genitourinary**: hematuria (≥1%), urinary frequency (≤1%), urinary tract infection (2%). **Hematologic & oncologic**: Decreased hematocrit (≥1%), decreased hemoglobin (≥1%), leukocyturia (≥1%). **Nervous system**: Abnormal dreams (≤6%), anxiety (2% to 8%), confusion (2% to 8%), hallucination (≤5%, visual and/or auditory), insomnia (1% to 9%), on-off phenomenon (1% to 2%), paresthesia (≤1%), psychosis (≤5%). **Neuromuscular & skeletal**: Back pain (≤2%), dystonia (≤2%), muscle cramps (1%), shoulder pain (≤1%). **Respiratory**: dyspnea (2%), upper respiratory tract infection (1% to 2%).
Monitoring Parameters	• Liver and kidney functions. • Monitor for withdrawal symptoms during discontinuation. • Monitor for potential adverse effects (impulse control disorders, psychic symptoms, cardiac functions, neurologic disorders and ophthalmic symptoms). Monitor closely for melanoma.
Drug Interactions	***Risk X: Avoid combination*** Alcohol (Ethyl), Alizapride, Amisulpride (Injection, Oral), Bromperidol, Macimorelin, Methotrimeprazine, Metoclopramide, Monoamine Oxidase Inhibitors, Sulpiride. ***Risk D: Consider therapy modification*** Amifostine, Antipsychotic Agents (First Generation [Typical], (Second Generation [Atypical]), Iron Preparations, Multivitamins/Fluoride (with ADE), Multivitamins/Minerals (with ADEK, Folate, Iron), Multivitamins/Minerals (with AE, No Iron), Obinutuzumab, Pyridoxine, Reserpine, Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors.
Pregnancy and Lactation	**Pregnancy** Inadequate human data. Skeletal and visceral abnormalities occurred in rabbits. Consider the potential risks of the medication against benefits.

Carbidopa- Levodopa

	Lactation No human data. Due to potential for serious adverse reactions in infants, a decision should be made whether to discontinue breast-feeding or discontinue treatment.
Administration	**Oral Administration** • To be taken with or without food. • Patient should be informed that switching to a high-protein diet, excessive acidity and iron salts could delay Levodopa absorption. • **Modified release tablets**: Administered as whole tablets. When the divided doses are not equal, it is recommended to administer the lowest dose at the end of the day. **N.B** Refer to manufacturer PIL if there are specific considerations**.**
Warnings/ Precautions	**Indications** It is not advised to treat Huntington's chorea or drug-induced extrapyramidal responses with carbidopa and levodopa. **Caution** Caution in patients with severe lung or cardiovascular disease, bronchial asthma, renal, hepatic, or endocrine disorders, or a history of peptic ulcer disease (due to the risk of upper gastrointestinal bleeding). **Cardiovascular considerations** When giving carbidopa with levodopa to individuals who have had a recent myocardial infarction and who still experience ventricular or atrial arrhythmias, caution should be used. Cardiac function should be monitored carefully during initial use and titration of dose. **Sudden onset of sleep and somnolence** Falling asleep during activities of daily living may occur without warning; advise patients to caution during driving or operating machines. **Dyskinesia or dystonia** May be induced or exacerbated. A reduction of the dose or termination of therapy may be considered. **Neuroleptic malignant syndrome symptoms** May occur with abrupt withdrawal including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase. Caution. **Wide-angle glaucoma** Patients with chronic wide-angle glaucoma may be treated cautiously provided the intraocular pressure is well controlled and the patient monitored carefully **Psychotic disorders** All patients taking carbidopa and levodopa should be observed carefully for the development of depression with concomitant suicidal tendencies. Closely monitor patient for any lack of antiparkinsonian efficacy when

Carbidopa- Levodopa

	concurrently administering psychoactive medications such as butyrophenones or phenothiazines. **Impulse Control disorders** Patients may experience compulsive behaviors including increased libido, hypersexuality, compulsive buying, compulsive eating when treated with dopamine agonists including levodopa. Dose reduction or tapered discontinuation should be considered **Melanoma** Regular checking for melanomas when using Carbidopa and Levodopa is recommended.
Storage	Store between 15°C to 30°C. Protect from light and moisture. **N.B** Refer to manufacturer PIL if there are specific considerations**.**

Pramipexole

Generic Name	Pramipexole
Dosage Form/Strengths	Tablets: 0.18 mg, 0.35 mg, 0.7 mg (base). • 0.25 mg pramipexole dihydrochloride monohydrate equivalent to 0.18 mg pramipexole. • 0.5 mg pramipexole dihydrochloride monohydrate equivalent to 0.35 mg pramipexole. • 1 mg pramipexole dihydrochloride monohydrate equivalent to 0.7 mg pramipexole.
Route of Administration	*Oral*
Pharmacologic Category	Anti-Parkinson Agent, Dopamine Agonist. ATC: N04BC05
Indications	- Parkinson's disease. - Moderate to severe primary restless legs syndrome (RLS) in adults.
Dosage Regimen	**Dosing Adult** Gradual escalation of dose is needed to avoid intolerable adverse effects and orthostatic hypotension. **Parkinson's Disease** Week 1: 0.088 (base) three times daily. Week 2: 0.18 (base) three times daily. Week 3: 0.35 (base) three times daily. - Adverse reactions (e.g. somnolence) may increase at doses higher than 1.1 mg (base) daily. - Dose can be increased by a 0.54 mg (base) at weekly intervals up to a **maximum daily dose** of 3.3 mg (base). - If used with levodopa, may need to reduce levodopa dose. - **Gradual withdrawal** is needed at a rate of 0.54 mg (base) per day until the daily dose has been reduced to 0.54 mg (base). Thereafter the dose should be reduced by 0.264 mg (base) per day **Restless Legs Syndrome** Initial: 0.088 mg (base) taken once daily 2-3 hours before bedtime. If needed, dose may be increased every 4-7 days to a maximum of 0.54 mg daily (base) as follow: Step 2 of titration: 0.18 once daily. Step 3 of titration: 0.35 once daily. Step 4 of titration: 0.54 once daily. - Patient response and need of continuation of therapy should be evaluated after 3 months. - If treatment is interrupted for more than a few days, dose titration should be carried out as above. - No need for gradual withdrawal as dose does not exceed 0.54 mg daily. **Pediatrics** Use is not recommended in children and adolescents below 18 years due to a lack of data on safety and efficacy.

Pramipexole

Dosage Adjustment	**Renal impairment** • **Parkinson's Disease** - **CrCl >50 mL/min**: No dose adjustment is needed. - **CrCl: 20 to 50 mL/min:** Initial 0.088 mg of base twice daily. Maximum dose 0.7 mg base twice daily. - **CrCl < 20 ml/min:** 0.088 mg base once daily**.** Maximum dose 1.1 mg base once daily. - If renal function declines during maintenance therapy the pramipexole daily dose should be reduced by the same percentage as the decline in creatinine clearance. • **Restless Legs Syndrome** - CrCl >20 ml/min: No dose adjustment needed. - Hemodialysis patients or severe renal impairment: Not studied. **Hepatic impairment** No dose adjustment is necessary.
Contra-Indications	Hypersensitivity to the active substance or to any of the excipients.
Adverse Drug Reactions	**>10%** **Gastrointestinal**: Constipation (PD: 12% to 14%, RLS: 4%), nausea (PD: 24% to 28%, RLS: 11% to 19%). **Nervous system**: Asthenia (PD: 14%), dizziness (PD: 12% to 25%), drowsiness (PD: 22% to 33%, RLS: 6%), headache (RLS: 16%), insomnia (PD: 4% to 17%). **1% to 10%** **Cardiovascular**: Edema (PD: 5%), orthostatic hypotension, peripheral edema (PD: 5% to 8%). **Endocrine & metabolic**: Decreased libido (PD: 1%), weight loss (PD: 2%) **Gastrointestinal**: Abdominal distress (PD: 1%), anorexia (PD: 4%), diarrhea (RLS: 1% to 3%), dyspepsia (PD: 3%), dysphagia (PD: 2%), increased appetite (PD: 2%), upper abdominal pain (PD: 4%), vomiting (PD: 4%), xerostomia (PD: 4%, RLS: 3%). **Genitourinary**: Erectile dysfunction (PD: 2%). **Infection**: Influenza (RLS: 3% to 4%). **Nervous system**: Akathisia (PD: 2%), amnesia (PD: 4%), balance impairment, changes in thinking (PD: 2%), confusion (PD: 4%), depression, falling (PD: 4%), fatigue (PD: 6%, RLS: 9%), hallucination (PD: 6% to 9%, RLS: <1%), hypoesthesia (PD: 3%), malaise (PD: 2%), myoclonus (PD: 1%), sleep disturbance (PD: 3%), sudden onset of sleep (PD: 6%), tremor (PD: 3%), vertigo (PD: 2%). **Neuromuscular & skeletal**: Dystonia (PD: 2%), limb pain (RLS: 3%), muscle spasm. **Ophthalmic**: Visual disturbance (PD: 3%). **Respiratory**: Cough (PD: 3%), nasal congestion (RLS: 3%). **Miscellaneous**: Fever (PD: 1%).

Pramipexole

Monitoring Parameters	• Renal functions. • Blood pressure (particularly during escalation of dose) due to risk of orthostatic hypotension. • Monitor for adverse effects (impulse control disorders, mania and delirium, ophthalmologic symptoms and withdrawal symptoms during discontinuation).
Drug Interactions	***Risk X: Avoid combination*** Alizapride, Amisulpride (Injection), Amisulpride (Oral), Bromperidol, Methotrimeprazine, Metoclopramide, Sulpiride. ***Risk D: Consider therapy modification*** Amifostine, Antipsychotic Agents (First Generation [Typical]), Antipsychotic Agents (Second Generation [Atypical]), Fexinidazole, Fluorodopa, Obinutuzumab, Risdiplam, Tafenoquine.
Pregnancy and Lactation	**Pregnancy** No human data. May cause fetal harm, based on animal data. Pramipexole should not be used during pregnancy unless clearly necessary. **Lactation** Inhibition of lactation may occur. No human data. Use is not recommended during lactation.
Administration	**Oral Administration** Can be taken with or without food. N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Symptomatic orthostatic hypotension** Monitor during dose escalation. **Impulse Control disorders** Patients may experience compulsive behaviors including increased libido, hypersexuality, compulsive buying, compulsive eating when treated with dopamine agonists including pramipexole. Dose reduction or tapered discontinuation should be considered. **Sudden onset of sleep and somnolence** Falling asleep during activities of daily living may occur without warning; advise patients to caution during driving or operating machines. A reduction of the dose or termination of therapy may be considered. **Dyskinesia or dystonia** May be induced or exacerbated. A reduction of the dose or termination of therapy may be considered. **Hallucinations and Psychotic-like Behavior** May occur; risk increases with age. Coadministration of antipsychotic medicinal products with pramipexole should be avoided.

Pramipexole

	Mania and delirium Caution. A reduction of the dose or termination of therapy should be considered. **Restless legs augmentation syndrome** Patient should be informed to contact their physician if they experience symptoms of augmentation. If augmentation is suspected, dose adjustment to the lowest effective dose, or discontinuation of pramipexole should be considered. **Dopamine agonist withdrawal syndrome** Withdrawal symptoms may include apathy, anxiety, depression, fatigue, sweating and pain. Patients should be closely monitored during tapering and discontinuation. In case of severe symptoms, temporary re-administration of pramipexole at the lowest effective dose may be considered. **Neuroleptic malignant syndrome** May occur with abrupt withdrawal. Symptoms include muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase.
Storage	Store between 15^0C to 30^0C. Protect from light. N.B. Refer to manufacturer PIL if there are specific considerations.

Rasagiline

Generic Name	Rasagiline
Dosage Form /Strengths	Tablets: 0.5 mg, 1 mg.
Route of Administration	Oral
Pharmacologic Category	Anti-Parkinson Agent, MAO Type B Inhibitor ATC code: N04BD02
Indications	Idiopathic Parkinson's disease in adults as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients with end of dose fluctuations.
Dosage Regimen	**Adult dosing** **Monotherapy or as adjunct therapy without levodopa** **Oral:** 1 mg once daily. **As adjunct to levodopa** **Oral:** 0.5 mg once daily. Dose may be increased to 1 mg daily as needed for sufficient clinical response. **Pediatrics** The safety and efficacy in children and adolescents have not been established.
Dosage Adjustment	**Renal Impairment** No dose adjustment is required. **Hepatic Impairment** • **Mild impairment:** 0.5 mg once daily. • **Moderate or severe:** Avoid. **Patients taking CYP1A2 inhibitors** **Oral:** 0.5 mg once daily.
Contra-Indications	• Hypersensitivity to the active substance or to any of the excipients. • Concomitant treatment with other monoamine oxidase (MAO) inhibitors (including medicinal and natural products without prescription e.g. St. John's Wort) or pethidine.
Adverse Drug Reactions	**>10%** **Nervous system:** Headache (14%). **1% to 10%** **Dermatologic:** Ecchymoses (2%). **Gastrointestinal:** Dyspepsia (7%), gastroenteritis (3%). **Nervous system:** Depression (5%), falling (5%), hallucinations (1%), malaise (2%), paresthesia (2%), vertigo (2%). **Neuromuscular & skeletal:** Arthralgia (7%), arthritis (2%), neck pain (2%). **Ophthalmic:** Conjunctivitis (3%). **Respiratory:** Flu-like symptoms (5%), rhinitis (3%). **Miscellaneous:** Fever (3%).

Monitoring Parameters	• Blood pressure. • Monitor for drowsiness, sleepiness and behavioral symptoms.
Drug Interactions	***Risk X: Avoid combination*** Alcohol (Ethyl), Alpha-/Beta-Agonists (Indirect-Acting), Alpha1-Agonists, Amphetamines, Apraclonidine, Atomoxetine, Atropine (Ophthalmic), Bezafibrate, Bromperidol, Buprenorphine, Bupropion, Butorphanol, Carbamazepine, Carbinoxamine, Codeine, Cyproheptadine, Deutetrabenazine, Dexmethylphenidate, Dextromethorphan, Diamorphine, Diethylpropion, Diphenoxylate, Epinephrine (Oral Inhalation), Fenfluramine, Fentanyl, Fluvoxamine, Gepirone, Guanethidine, Indoramin, Iobenguane, Radiopharmaceutical Products, Levomethadone, Linezolid, Maprotiline, Meptazinol, Mequitazine, Methadone, Methotrimeprazine, Methyldopa, Methylene Blue, Methylphenidate, Metoclopramide, Monoamine Oxidase Inhibitors (Antidepressant), Monoamine Oxidase Inhibitors (Type B), Morphine (Systemic), Nefazodone, Nefopam, Normethadone, Opipramol, Opium, Oxymorphone, Ozanimod, Pheniramine, Pholcodine, Pipamperone, Pizotifen, Reboxetine, Selective Serotonin Reuptake Inhibitors, Serotonergic Agents (High Risk, Miscellaneous), Serotonergic Non-Opioid CNS Depressants, Serotonergic Opioids (High Risk), Serotonin/Norepinephrine Reuptake Inhibitors, Solriamfetol, St John's Wort, Sufentanil, Tapentadol, Tetrabenazine, Tricyclic Antidepressants, Tyrosine, Valbenazine, Viloxazine, Ziprasidone. ***Risk D: Consider therapy modification*** Amifostine, Benzhydrocodone, CYP1A2 Inhibitors (Moderate), CYP1A2 Inhibitors (Strong), Dihydrocodeine, Dopamine, Fluorodopa F18, Hydrocodone, Hydromorphone, Iohexol, Iomeprol, Iopamidol, Levonordefrin, Nalbuphine, Obinutuzumab, Oxycodone, Remifentanil, Reserpine.
Pregnancy and Lactation	**Pregnancy** Inadequate data. Animal studies showed decreased survival and reduced body weight. Use is not recommended. **Lactation** No human data Animal studies indicate that rasagiline inhibits prolactin secretion and thus, may inhibit lactation. Caution.
Administration	**Oral Administration** May be taken with or without food. **N.B**. Refer to PIL for other specific considerations.
Warnings/ Precautions	**Effects on blood pressure** • May cause hypertension (including severe hypertensive syndromes) at recommended doses. • May cause orthostatic hypotension. **Serotonin syndrome** • May cause serotonin syndrome when used with antidepressants. Some are fatal. The symptoms of serotonin syndrome have included behavioral and cognitive/mental status changes (e.g., confusion, hypomania, hallucinations, headache, and coma), autonomic effects (e.g., syncope, shivering, sweating, high fever/hyperthermia, hypertension, tachycardia, nausea, diarrhea), and somatic effects (e.g.,

	muscular rigidity, myoclonus, muscle twitching, hyperreflexia manifested by clonus, and tremor). • At least 14 days should elapse between discontinuation of rasagiline and initiation of treatment with a SSRI, SNRI, tricyclic, tetracyclic, or triazolopyridine antidepressant. At least five weeks should elapse between discontinuation of antidepressants (particularly fluoxetine) and initiation of rasagiline. **Adverse effects** • May cause drowsiness, and somnolence during daytime activities, hallucinations and psychotic-like behavior. • May cause or exacerbate dyskinesia. Decreasing the levodopa dose may lessen or eliminate this side effect. **Withdrawal symptoms** Rapid dose reduction may cause elevated temperature, muscular rigidity, altered consciousness, and autonomic instability. **Concomitant use with other agents** • Concomitant administration of rasagiline and sympathomimetics, such as ephedrine or pseudoephedrine, is not recommended. • The concomitant administration of rasagiline and dextromethorphan is not recommended. • The concomitant use of rasagiline and fluoxetine or fluvoxamine should be avoided.
Storage	Store between 15°-30°C. **N.B**. Refer to PIL for other specific considerations.

Trihexyphenidyl

Generic Name	Trihexyphenidyl
Dosage Form/Strengths	Tablets: 5 mg
Route of Administration	*Oral*
Pharmacologic Category	Anti-Parkinson Agent, Anticholinergic ATC: N04AA01
Indications	• Treatment of parkinsonism. • Prevention and control of drug-induced extrapyramidal symptoms (excluding tardive dyskinesia).
Dosage Regimen	**Adult dosing** Initiate at a relatively low level and gradually increase. • **Parkinsonism** **Oral**: usual dose: 6 – 10 mg daily divided into 3-4 times daily at meal times. Doses up to 12 – 15 mg daily may be required. • **Drug-induced Parkinsonism** **Oral**: 5mg and 15 mg per day, although in some cases have been controlled by 1 mg daily. **Pediatrics** Use Safety and effectiveness have not been established in pediatric patients.
Dosage Adjustment	**Renal Impairment.** No dose adjustments necessary. Monitor closely. **Hepatic Impairment.** No dose adjustments necessary. Monitor closely.
Contra-Indications	• Hypersensitivity to the active substance or to any of the excipients. • Narrow angle glaucoma.
Adverse Drug Reactions	**>10%** • **Gastrointestinal**: Nausea (30% to 50%), xerostomia (30% to 50%). • **Nervous system**: Dizziness (30% to 50%), nervousness (30% to 50%). • **Ophthalmic**: Blurred vision (30% to 50%).
Monitoring Parameters	Monitor for adverse effects of anticholinergic effects, psychiatric disorders or abuse.
Drug Interactions	***Risk X: Avoid combination*** Aclidinium, Cimetropium, Eluxadoline, Glycopyrrolate (Oral Inhalation), Glycopyrronium (Topical), Ipratropium (Oral Inhalation), Levosulpiride, Oxatomide, Potassium Chloride, Potassium Citrate, Pramlintide, Revefenacin, Sofpironium, Tiotropium, Umeclidinium. ***Risk D: Consider therapy modification*** Clozapine, Rivastigmine, Secretin.
Pregnancy and Lactation	**Pregnancy** Inadequate data. The potential risk for humans is unknown. During pregnancy, Trihexyphenidyl should not be used unless clearly necessary.

Trihexyphenidyl

	Lactation No data. Trihexyphenidyl should not be used during lactation.
Administration	**Oral Administration** • Taken at divided doses with meals. • Trihexyphenidyl may be taken before or after meals. Taking before meals may decrease dryness of mouth. Taking after meals may decrease nausea. N.B Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Discontinuation** Abrupt discontinuation may result in acute exacerbation- of parkinsonism symptoms. It should be avoided unless there are vital complications. **Abuse** Trihexyphenidyl may be abused due to hallucinogenic and euphoriant properties. Long-term use should be carefully monitored for unwanted effects. **Caution** Patients with cardiac, liver, or kidney disorders, or with hypertension, should be closely monitored. **Parasympatholytic (anticholinergic) activity** May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention). Monitor patients with prolonged use. Caution in patients with glaucoma, obstructive disease of the gastro-intestinal or genito-urinary tracts, and in elderly males with possible prostatic hypertrophy. **Myasthenia gravis** Use should be avoided or used with great caution in patients as trihexyphenidyl has been associated with clinical worsening of myasthenia gravis. **Psychiatric disorders** Nervousness, irritability, confusion, agitation, delusions, hallucinations, insomnia, especially in the elderly and patients with arteriosclerosis. The development of psychiatric disturbances may necessitate discontinuation of treatment. **Lactose** Some dosage forms may contain Lactose. Use is not recommended in patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose galactose malabsorption.
Storage	Store between 15-30°C. N.B Refer to manufacturer PIL if there are specific considerations.

Choline esterase Inhibitors

Neostigmine

Generic Name	Neostigmine
Dosage Form/Strengths	Solution for IM, IV and SC injection: 0.5 mg/ml (1 ml), 1 mg/ml (5 ml), 2.5 mg/ml (5ml) Tablets: 15 mg
Route of Administration	*IM, IV, SC, Oral*
Pharmacologic Category	Acetylcholinesterase Inhibitor ATC: N07AA01
Indications	• Myasthenia Gravis • Antagonist to non-depolarizing neuromuscular blockade • Paralytic Ileus • Post-operative Urinary Retention • Paroxysmal Supraventricular Tachycardia.
Dosage Regimen	**N.B.** An injection of Atropine Sulfate should always be available to counteract severe cholinergic reactions if occurred. **Adult Dosing** **Myasthenia Gravis** **Adults and Children (12 years and above): IM, SC**: 1 – 2.5 mg repeated at suitable intervals along the day. **Usual total daily dose**: 5 – 20 mg. **Antagonist to Non-depolarizing Neuromuscular Blockade** **IV**: 2.5 mg (maximum per dose 5 mg), to be given over 1 minute, after or with glycopyrronium or atropine. Dose can be repeated if necessary. **Paralytic ileus and post-operative urinary retention** **IM, SC:** 0.5 – 2.5 mg. **Paroxysmal supraventricular tachycardia (IV injection).** Treatment should be reserved for severe cases not responding to conventional treatment and under the close supervision of a specialist experienced with its use. **Pediatric Dosing** **Myasthenia Gravis** **Children (1 month to 11 years): IM, SC:** 200 - 500 mcg repeated at suitable intervals along the day. **Neonates (up to 1 month): IM, SC:** 150 mcg/kg every 6 – 8 hours, to be given 30 minutes before feeds, then increased if necessary up to 300 mcg/kg every 4 hours. N.B. In neonates, dose should be reduced until complete withdrawal due to self-limiting nature of disease.

Neostigmine

	Antagonist to Non-depolarizing Neuromuscular Blockade **Children (neonates and up to 17 years): IV:** 50 mcg/kg (maximum per dose 2.5 mg) to be given over 1 minute after or with glycopyrronium or atropine, followed by a further dose of 25 micrograms/kg if required. **Paralytic ileus and post-operative urinary retention** **IM, SC:** 0.125 – 1 mg.
Dosage Adjustment	**Renal Impairment** No adjustments needed. Monitor closely. **Hepatic Impairment** Not studied. No adjustments appear to be needed.
Contra-Indications	• Hypersensitivity to the active substance or to any of the excipients. • Peritonitis or mechanical obstruction of the intestinal or urinary tract.
Adverse Drug Reactions	**1% to 10%** **Cardiovascular**: Atrioventricular block, cardiac arrhythmia (including atrioventricular nodal arrhythmia, bradycardia, tachycardia), flushing, hypotension, syncope. **Dermatologic**: Diaphoresis, pruritus, skin rash, urticaria. **Gastrointestinal**: Flatulence, increased peristalsis, nausea, sialorrhea, vomiting, xerostomia. **Genitourinary**: Urinary frequency. **Hematologic & oncologic**: Oxygen desaturation. **Hypersensitivity**: Anaphylaxis, hypersensitivity reaction. **Nervous system**: Asthenia, dizziness, drowsiness, dysarthria, headache, insomnia, loss of consciousness, postanesthetic shivering, seizure. **Neuromuscular & skeletal:** Arthralgia, muscle cramps, muscle spasm **Ophthalmic**: Miosis, visual disturbance. **Respiratory**: Apnea, bronchospasm, dyspnea, increased bronchial secretions (including pharyngeal secretions), respiratory depression. **Post marketing** **Cardiovascular**: ECG changes (nonspecific). **Gastrointestinal**: Abdominal cramps, diarrhea. **Neuromuscular & skeletal**: Fasciculations.
Monitoring Parameters	Cardiac functions particularly with IV route.
Drug Interactions	***Risk X: Avoid combination*** Fexinidazole, Landiolol ***Risk D: Consider therapy modification*** Ceritinib, Fingolimod, Ponesimod, Siponimod.
Pregnancy and Lactation	**Pregnancy:** Inadequate data. No adverse developmental effects were observed in animal studies. Consider benefit and potential risk before use. **Lactation:** Inadequate data. Consider benefit and potential risk before use.
Administration	IV Administration: taken slowly over 1 minute. N.B Refer to manufacturer PIL if there are specific considerations.

Neostigmine

Warnings/ Precautions

Cardiac disorders

- IV administration may be associated with bradycardia, with the potential for progression to asystole, unless atropine is given simultaneously. Atropine or glycopyrrolate should be taken prior to administration to lessen risk of bradycardia.
- Extreme caution should be employed in patients with pre-existing bradycardia, cardiac arrhythmia or recent coronary occlusion.
- Atropine sulfate should always be available as an antagonist for the muscarinic effects of neostigmine.

Neuromuscular Dysfunction

Large doses administered when neuromuscular blockade is minimal can produce neuromuscular dysfunction. Dose should be reduced if recovery from neuromuscular blockade is nearly complete.

Respiratory effects

Extreme caution in asthma patients is needed as the parasympathomimetic action may cause bronchoconstriction.

Caution

Neostigmine should be used with caution in patients with epilepsy, vagotonia, hyperthyroidism, peptic ulceration or parkinsonism.

Elderly

Elderly may be more susceptible to dysrhythmias than younger patients. Extended monitoring is needed.

Inhaled anaesthetics

Neostigmine should not be given concomitantly with halothane anesthesia; although it may be used after withdrawal of these agents.

Depolarizing muscle relaxants

Neostigmine should not be used in conjunction with depolarizing muscle relaxants such as suxamethonium as neuromuscular blockade may be potentiated.

Cholinergic and myasthenic crisis

- In all patients the possibility of "cholinergic crisis", due to overdose, and its differentiation from "myasthenic crisis", due to increased severity of the disease, must be considered. Both types of crises are manifested by increased muscle weakness.
- But whereas myasthenic crisis may require more intensive anticholinesterase treatment, cholinergic crisis needs immediate discontinuation of this treatment and appropriate supportive measures, including respiratory assistance.

Neostigmine

	Overdosage Neostigmine should be discontinued immediately and 1-4 mg of atropine administered IV. Additional doses of atropine may be given every 5-30 minutes as needed to control muscarinic symptoms. Avoid atropine overdosage. Maintenance of adequate respiration is of primary importance.
Storage	Store between 15° to 30°C. Protect from light. N.B Refer to manufacturer PIL if there are specific considerations.

Pyridostigmine

Generic Name	Pyridostigmine
Dosage Form/Strengths	Tablets: 60 mg Sustained Release Tablets: 180 mg
Route of Administration	*Oral*
Pharmacologic Category	Acetylcholinesterase Inhibitor ATC: N07AA02
Indications	• Myasthenia gravis • Paralytic ileus and post-operative urinary retention.
Dosage Regimen	**Adult dosing** **Myasthenia gravis** **Immediate release tablets: initial:** 30-120 mg given at intervals along the day. • The usual duration of action of a dose is 3 to 4 hours in the daytime but a longer effect (6 hours) is obtained with a dose taken at bedtime. • Dosage should be increased gradually, in increments of 30 mg every 2 days. • **Usual total daily dose**: 300 mg- 1200 mg but higher doses may be needed according to dose titration. **Paralytic ileus, post-operative urinary retention** **Usual dose**: **Immediate release tablets:** 60 – 240 mg per day. **Pediatric dosing** **Myasthenia gravis** **Children under 6 years old: Immediate release tablets: initial**: 30 mg. **Children 6 – 12 years old: Immediate release tablets: initial**: 60mg. • Dosage should be increased gradually, with increments of 30 mg every 2 days, until maximum improvement is obtained. • **Usual total daily dose: Immediate release tablets:** 30 – 360 mg. **Paralytic ileus, post-operative urinary retention** **Usual dose**: **Immediate release tablets:** 15 – 60 mg per day.
Dosage Adjustment	**Renal Impairment** Lower doses may be needed. Treatment should be based on titration of dose to effect. **Hepatic Impairment** No dose adjustments needed.
Contra-Indications	• Hypersensitivity to the active substance, bromides or to any of the excipients. • Mechanical gastro-intestinal or urinary obstruction
Adverse Drug Reactions	**Frequency not defined** **Gastrointestinal**: Increased peristalsis, vomiting.

Pyridostigmine

	Nervous system: Asthenia. **Neuromuscular & skeletal**: Fasciculations. **Ophthalmic**: Miosis. **Postmarketing** **Cardiovascular**: Atrioventricular block, bradycardia, syncope. **Dermatologic**: Diaphoresis, skin rash. **Gastrointestinal**: Abdominal cramps, bloating, diarrhea, flatulence, nausea, sialorrhea. **Genitourinary**: Urinary urgency. **Hypersensitivity**: Hypersensitivity reaction. **Nervous system**: Tingling of extremities (fingers and toes). **Neuromuscular & skeletal**: Muscle cramps, muscle twitching. **Respiratory**: Bronchoconstriction, increased bronchial secretions.
Monitoring Parameters	Cardiac functions monitoring may be needed.
Drug Interactions	***Risk X: Avoid combination*** Landiolol. ***Risk D: Consider therapy modification*** Ceritinib, Fingolimod, Ponesimod, Siponimod.
Pregnancy and Lactation	**Pregnancy:** Inadequate data. Experience showed no unexpected effects during treatment. Since pyridostigmine crosses the placenta barrier excessive dose of pyridostigmine should be avoided; the newborn child should be monitored to possible effects. **Lactation:** Inadequate data. Negligible amounts of pyridostigmine are excreted in breast milk. Regard should be paid to possible effects on the breast-fed infant.
Administration	**Administration: Oral** Should be taken with water. Do not crush modified release tablet. N.B Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Cardiac disorders** • Caution should be employed in patients with pre-existing bradycardia, cardiac arrhythmia or recent coronary occlusion. • Atropine sulfate should always be available as an antagonist for the muscarinic effects of neostigmine. **Respiratory effects** Extreme caution in asthma patients is needed as the parasympathomimetic action may cause bronchoconstriction. **Caution** • Pyridostigmine should be used with caution in patients with epilepsy, vagotonia, hyperthyroidism, peptic ulceration or parkinsonism.

Pyridostigmine

	• The requirement for pyridostigmine is usually markedly decreased after thymectomy or when additional therapy (steroids, immunosuppressant drugs) is given **Cholinergic and myasthenic crisis** • In all patients the possibility of "cholinergic crisis", due to overdose, and its differentiation from "myasthenic crisis", due to increased severity of the disease, must be considered. Both types of crises are manifested by increased muscle weakness. • But whereas myasthenic crisis may require more intensive anticholinesterase treatment, cholinergic crisis needs immediate discontinuation of this treatment and appropriate supportive measures, including respiratory assistance. **Overdosage** • Neostigmine should be discontinued immediately and 1 – 2 mg of atropine administered IV. Additional doses of atropine may be given every 5 – 30 minutes as needed to control muscarinic symptoms. Avoid atropine overdosage. • Maintenance of adequate respiration is of primary importance.
Storage	Store between 15°C and 30°C. Protect from light and moisture. N.B Refer to manufacturer PIL if there are specific considerations.

Multiple Sclerosis

Cladribine

Generic Name	Cladribine
Dosage Form/Strengths	Tablets: 10 mg. Solution for S.C Injection and I.V Infusion: 2 mg/ml.
Route of Administration	Oral, SC, IV
Pharmacologic Category	Antimetabolite (Purine Analog); Antineoplastic Agent, Immunosuppressant Agent. ATC: L01BB04 - L04AA40
Indications	**Injection** • Treatment of hairy cell leukemia. • Treatment of patients with B-cell chronic lymphocytic leukemia (CLL) who had inadequate response to standard alkylating-agent containing regimen. **Oral** Treatment of adult patients with relapsing forms of multiple sclerosis (MS) with active disease. **N.B** Due to its safety profile, indicated for patients that had inadequate response (or unable to tolerate) to other treatments of MS.
Dosage Regimen	**Adult dosing** • **Treatment of adult patients with highly active relapsing multiple sclerosis** ▪ Cumulative dosage of 3.5 mg/kg administered orally over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. ▪ Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. ▪ If medically necessary (e.g., for recovery of lymphocytes), the treatment course in year 2 can be delayed for up to 6 months. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg as a single daily dose, depending on body weight.

Weight range (kg)	Dose in mg (number of tablets) per treatment week	
	Treatment week 1	Treatment week 2
40 to < 50	40 mg (4 tablets)	40 mg (4 tablets)
50 to < 60	50 mg (5 tablets)	50 mg (5 tablets)
60 to < 70	60 mg (6 tablets)	60 mg (6 tablets)
70 to < 80	70 mg (7 tablets)	70 mg (7 tablets)
80 to < 90	80 mg (8 tablets)	70 mg (7 tablets)
90 to < 100	90 mg (9 tablets)	80 mg (8 tablets)
100 to < 110	100 mg (10 tablets)	90 mg (9 tablets)
110 and above	100 mg (10 tablets)	100 mg (10 tablets)

Cladribine

Total number of tablets per week	Day 1	Day 2	Day 3	Day 4	Day 5
4	1	1	1	1	-
5	1	1	1	1	1
6	2	1	1	1	1
7	2	2	1	1	1
8	2	2	2	1	1
9	2	2	2	2	1
10	2	2	2	2	2

- **Treatment of hairy cell leukemia**
  - **SC**: 0.14 mg/kg daily for 5 consecutive days.
  - **Continuous IV infusion:** 0.09 mg/kg/day (3.6 mg/m^2/day) for 7 consecutive days.
  - If neurotoxicity or renal toxicity occurred, delaying or discontinuation should be considered.
- **Treatment of B-cell chronic lymphocytic leukaemia**
  - **Continuous IV infusion:** 0.12 mg/kg/day (4.8 mg/m^2/day) for 2 hours on days 1 to 5 of a 28-day cycle.
  - Evaluate response every two cycles (response is defined as a lymphocyte reduction of 50% or more).
  - Therapy should be discontinued after 2 cycles in non-responding patients.

Pediatrics: Safety and efficacy in children have not been established.

Dosage Adjustment

Renal impairment

- Inadequate data.
- Mild renal impairment: No dosage adjustments.
- Moderate to severe renal impairment (Crcl < 50): Use is not recommended.

Hepatic impairment

- Mild hepatic impairment: No dosage adjustments.
- Moderate or severe hepatic impairment (Child-Pugh score >6): Use is not recommended.

Contra-Indications

Hypersensitivity to cladribine or to any of the excipients.

Adverse Drug Reactions

IV

>10%

Hematologic & oncologic: Anemia (severe: 37%), bone marrow depression (34%; may be delayed onset), febrile neutropenia (47%), neutropenia (severe: 70%), thrombocytopenia (12%).
Infection: Bacterial infection (12%), infection (28%; serious infection: 6% [including pneumonia, septicemia]).
Miscellaneous: Fever (69%; high fever: 11%).

Cladribine

	1% to 10% **Infection**: Fungal infection (6%), herpes zoster infection (4%), viral infection (6%). **Oral** **>10%** **Hematologic & oncologic**: Decreased hemoglobin (26%), decreased neutrophils (27%; severe: 4%), decreased platelet count (11%), lymphocytopenia (24% to 87%). **Hypersensitivity**: Hypersensitivity reaction (11%; severe hypersensitivity reaction: <1%). **Infection**: Infection (49%; including bacterial infection, fungal infection, parasitic infection, serious infection, viral infection). **Nervous system**: Headache (25%). **Respiratory**: Upper respiratory tract infection (38%). **1% to 10%** **Cardiovascular**: Hypertension (5%). **Dermatologic**: Alopecia (3%). **Gastrointestinal**: Nausea (10%), oral herpes simplex infection (3%). **Infection**: Herpes virus infection (6%), herpes zoster infection (2%; serious: <1%). **Nervous system**: Depression (5%), insomnia (6%). **Neuromuscular & skeletal**: Arthralgia (≤7%), arthritis (≤7%), back pain (8%). **Respiratory**: Bronchitis (5%). **Miscellaneous**: Fever (5%).
Monitoring Parameters	• Careful haematologic monitoring especially baseline and after 1-2 months of starting treatment. • Monitor baseline hepatic and renal function and as clinically indicated. • Monitor patients for infections.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Agents that Undergo Intracellular Phosphorylation, Baricitinib, BCG Products , Brivudine, Chikungunya Vaccine (Live), Chloramphenicol (Systemic), Corticosteroids (Systemic), Dengue Tetravalent Vaccine (Live), Deucravacitinib, Etrasimod, Fexinidazole, Filgotinib, Immunosuppressants (Cytotoxic Chemotherapy, Miscellaneous Oncologic Agents, Therapeutic Immunosuppressant Agents), Interferon Beta, Leniolisib, Methotrexate, Mumps- Rubella- or Varicella-Containing Live Vaccines, Myelosuppressive Agents, Nadofaragene Firadenovec, Natalizumab, , Pacritinib, Pimecrolimus, Poliovirus Vaccine (Live/Bivalent/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Sparsentan, Tacrolimus (Topical), Talimogene Laherparepvec, Taurursodiol, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Voxilaprevir, Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** BCRP/ABCG2 Inhibitors, Belumosudil, Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA),

Cladribine

	Deferiprone, Denosumab, Influenza Virus Vaccine, Inhibitors of Equilibrative Nucleoside (ENT1) and Concentrative Nucleoside (CNT3) Transport Proteins, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Sipuleucel-T, Vaccines (Non-Live/Inactivated/Non-Replicating), Zoster Vaccine (Recombinant).
Pregnancy and Lactation	**Pregnancy** • Congenital malformations may occur. Use during pregnancy is not recommended. • Women and men should take precautions to prevent pregnancy during cladribine treatment and for at least 6 months after the last dose. • **Fertility** in men may occur due to therapy with cladribine. **Lactation** Use is not recommended due to potential for serious adverse reactions in nursing infants.
Administration	**Hazardous agent (NIOSH 2016 [group 1]):** Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal**.** **Oral Administration** - The tablets must be taken with water, and swallowed without chewing immediately once removed from the blister. - The tablets can be taken without regard of food. **IV Administration** - The dose must be diluted with 500ml of sodium chloride 0.9% prior to administration over 24 hours. **SC Administration** - The dose is withdrawn into a syringe and injected subcutaneously without dilution. - It should warm up to room temperature prior to administration. **N.B** Refer to manufacturer PIL if there are specific considerations**.**
Warnings/ Precautions	**Hematologic toxicity** Severe bone marrow suppression, including neutropenia, anemia and thrombocytopenia, occurred especially at high doses mostly during the first month after treament. Cautions with infection. **Renal or hepatic insufficiency** Use with cautions due to limited safety studies. Close monitoring is required. Caution in elderly. **Progressive multifocal leukoencephalopathy (PML)** Have been reported including fatal cases. New or worsening neurological, cognitive or behavioural signs or symptoms may indicate PML development. Patients with suspected PML should not receive further treatment with cladribine.

Cladribine

	Secondary malignancies Cladribine may cause secondary malignancies. Therefore, patients treated with it should be regularly monitored. **Neurological toxicity** Appear rarely with a dose relationship. Serious toxicities (including irreversible paraparesis and quadraparesis) have been reported with continuous infusion of cladribine at higher doses than recommended.
Storage	• **Injection:** Stored in refrigerated conditions between (2° to 8°C). Don`t freeze. Protect from light during storage. Precipitated substance can be resolubilized by exposure to room temperature and by vigorous shaking of the vial. • **Tablets:** Store in the original package in order to protect from moisture. **N.B** Refer to manufacturer PIL if there are specific considerations**.**

Dimethyl Fumarate

Generic Name	Dimethyl Fumarate
Dosage Form /Strengths	Delayed Release Capsule: 120 mg, 240 mg
Route of Administration	Oral
Pharmacologic Category	Fumaric Acid Derivative ATC: L04AX07
Indications	Treatment of adult and pediatric patients aged 13 years and older with relapsing remitting multiple sclerosis.
Dosage Regimen	**Initial**: Oral: 120 mg twice a day for 7 days. **Maintenance dose**: 240 mg twice daily.
Dosage Adjustment	**Renal Impairment** No dose adjustment is necessary. Not studied in severe cases. Caution. **Hepatic Impairment** No dose adjustment is necessary. Not studied in severe cases. Caution.
Contra-Indications	Hypersensitivity to dimethyl fumarate or any of the excipients.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Flushing (40%). **Gastrointestinal**: Abdominal pain (18%), diarrhea (14%), nausea (12%). **Infection**: Infection (60%; similar to placebo; including aspergillosis, candidiasis, cytomegalovirus disease, herpes meningoencephalitis, herpes simplex infection, herpes zoster infection, listeriosis, nocardiosis, opportunistic infection, tuberculosis). **1% to 10%** **Dermatologic**: Erythema of skin (5%), pruritus (8%), skin rash (8%). **Endocrine & metabolic**: Albuminuria (6%). **Gastrointestinal**: Dyspepsia (5%), vomiting (9%). **Hematologic & oncologic**: Lymphocytopenia (2% to 6%). **Hepatic**: Increased serum aspartate aminotransferase (4%).
Monitoring Parameters	• Liver functions prior to, and during treatment, as clinically indicated. • CBC, including lymphocyte count, prior to treatment, 6 months after starting treatment, and then yearly thereafter, and as clinically indicated. • Renal function prior to treatment initiation, after 3 and 6 months of treatment, yearly thereafter and as clinically indicated.
Drug Interactions	***Risk X: Avoid combination*** Diroximel Fumarate, Monomethyl Fumarate.
Pregnancy and Lactation	**Pregnancy** Inadequate human data. Animal studies have shown reproductive toxicity. Use is not recommended. **Lactation** No data. Due to potential harm on infant, a decision must be made whether to discontinue breast-feeding or to discontinue dimethyl fumarate therapy.

Dimethyl Fumarate

Administration	**Oral Administration** Capsules should be taken whole and not crushed or chewed. Taken with or without food. **N.B**. Refer to PIL for other specific considerations.
Warnings/ Precautions	**Anaphylactic reactions** • Anaphylaxis and angioedema may occur after the first dose or at any time during treatment. If developed, dimethyl fumarate should be discontinued and immediate medical care should be administered. • Signs and symptoms include difficulty breathing, urticaria, and swelling of the throat and tongue. **Infections** • Herpes zoster and other serious opportunistic infections may occur at any time during treatment. Monitor patients for signs and symptoms. • If a patient develops a serious infection, consider withholding therapy. Appropriate treatment should be administered. Therapy should not be started in patients with active infections. **Lymphopenia** • Dimethyl fumarate may decrease lymphocyte counts. During clinical trials, mean lymphocyte counts decreased by approximately 30% during the first year of treatment and then remained stable. Monitor CBC including lymphocyte count prior to and periodically during treatment. • Therapy should not be initiated in patients with severe lymphopenia (lymphocyte counts<0.5×10^9/L). Consider withholding or discontinuation of treatment if lymphocyte counts <0.5×10^9/L persist for more than 6 months. **Progressive Multifocal Leukoencephalopathy (PML)** • PML is an opportunistic infection caused by John Cunningham virus (JCV), which may be fatal or result in severe disability. PML risk factors are lymphopenia and long duration of treatment. If PML is suspected, MRI should be performed immediately for diagnostic purposes. Withhold dimethyl fumarate at the first sign of PML. • Typical symptoms associated with PML are diverse, progress over days to weeks, including progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and confusion, changes in thinking, memory, and personality changes. **Liver Injury** • Increased hepatic enzymes, within several months after initiation of treatment, have been reported and returned to normal after discontinuation. Monitor liver enzymes and symptoms prior to and periodically during treatment. • Therapy should be discontinued if clinically significant liver injury induced by dimethyl fumarate is suspected.

Dimethyl Fumarate

	Renal Impairment • Changes in renal laboratory tests have been seen in clinical trials. Monitor functions prior to and periodically during treatment. • Concurrent therapy with nephrotoxic medicinal products (such as aminoglycosides, diuretics, non-steroidal anti-inflammatory drugs or lithium) may increase the potential of renal adverse reactions.
Storage	Store between 15°C to 30°C. Protect from light. **N.B**. Refer to PIL for other specific considerations.

Fingolimod

Generic Name	Fingolimod
Dosage Form /Strengths	**Capsules**: 0.5 mg
Route of Administration	Oral
Pharmacologic Category	Sphingosine 1-Phosphate (S1P) Receptor Modulator ATC: L04AE01
Indications	Disease modifying therapy in highly active relapsing remitting multiple sclerosis for adults and pediatrics 10 years and older patient with either • Rapidly evolving severe relapsing remitting multiple sclerosis **or** • Highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy.
Dosage Regimen	**Dosing for adults and pediatric patients (10 years of age and older) weighing more than 40 kg** **Oral**: 0.5 mg orally once daily. N.B. First-Dose Monitoring (including reinitiating after discontinuation) is needed.
Dosage Adjustment	**Renal Impairment** No dose adjustments are needed**.** **Hepatic Impairment** • **Mild or moderate impairment:** No dose adjustments are needed. Caution. • **Severe hepatic impairment:** Avoid use.
Contra-Indications	• Hypersensitivity to fingolimod or its excipients. • Immunodeficiency syndrome and immunocompromised patients. • Severe active infections, active chronic infections (hepatitis, tuberculosis). • Active malignancies. • Severe liver impairment (Child-Pugh class C). • Patients who in the previous 6 months had myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure with hospitalization, or Class III/IV heart failure. • History of Mobitz Type II 2nd degree or 3rd degree AV block or sick sinus syndrome, unless patient has a pacemaker. • Baseline QTc interval ≥ 500 msec. • Cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs. • During pregnancy and in women of childbearing potential not using effective contraception
Adverse Drug Reactions	**>10%** **Gastrointestinal**: Abdominal pain (11%), diarrhea (13%), nausea (13%) **Hepatic**: Increased gamma-glutamyl transferase (≤15%), increased serum alanine aminotransferase (≤15%), increased serum aspartate transaminase (≤15%). **Infection**: Influenza (11%).

Fingolimod

	Nervous system: Headache (25%). **Respiratory**: Cough (12%), sinusitis (11%). **1% to 10%** **Cardiovascular**: Bradycardia (3%), first-degree atrioventricular block (5%), hypertension (8%), second-degree atrioventricular block (4%) Dermatologic: Actinic keratosis (2%), alopecia (3%), basal cell carcinoma of skin (2%), cutaneous papilloma (3%), tinea versicolor (2%). **Endocrine & metabolic**: Increased serum triglycerides (3%). **Hematologic & oncologic**: Leukopenia (2%), lymphocytopenia (7%). **Infection**: Herpes virus infection (9%), herpes zoster infection (2%). **Nervous system**: Asthenia (2%), migraine (6%), seizure (children and adolescents: 6%). **Neuromuscular & skeletal**: Back pain (10%), limb pain (10%). **Ophthalmic**: Blurred vision (4%). **Respiratory**: Bronchitis (8%), dyspnea (9%). **Frequency not defined** **Hepatic**: Increased serum bilirubin. **Infection**: Pneumonia.
Monitoring Parameters	• CBC prior to therapy and periodically during treatment, at month 3 and at least yearly thereafter and at signs of infection. • Liver function prior to and during treatment (every 3 months during first year and periodically thereafter). • Blood pressure regularly. **Monitoring at treatment initiation** • ECG and blood pressure measurement performed prior to and 6 hours after the first dose. • Monitoring hourly heart rate and blood pressure during this 6- hour period is recommended. Observe all patients for bradycardia for at least 6 hours. The same first dose monitoring is recommended when treatment is interrupted for: - 1 day or more during the first 2 weeks of treatment. - More than 7 days during weeks 3 and 4 of treatment. - More than 2 weeks after one month of treatment.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Amiodarone, Baricitinib, BCG Products, Brivudine, Chikungunya Vaccine (Live), Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Etrasimod, Fexinidazole, Filgotinib, Landiolol, Mumps-Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pidotimod, Poliovirus Vaccine (Live/Trivalent/Oral), QT-prolonging Class IA Antiarrhythmics (Highest Risk), QT-prolonging Class III Antiarrhythmics (Highest Risk), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine, Zoster Vaccine (Live/Attenuated).

Fingolimod

	Risk D: Consider therapy modification Bradycardia-Causing Agents, Ceritinib, Coccidioides immitis Skin Test, COVID-19 Vaccine (mRNA), Denosumab, Leflunomide, Polymethylmethacrylate, Ponesimod, Rabies Vaccine, Siponimod, Sipuleucel-T, Vaccines (Non-Live/Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy** Contraindicated, Human data showed a 2-fold increased risk of major congenital malformations. Women must have a negative pregnancy test before treatment and must use effective contraception during treatment and for 2 months after treatment discontinuation. Fingolimod should be stopped 2 months before planning a pregnancy. **Lactation** Fingolimod is excreted in milk of treated animals. Fingolimod should not be used during lactation due to the potential for serious adverse reactions**.**
Administration	**Oral Administration** Capsules can be taken with or without food and should always be swallowed whole. **N.B**. Refer to PIL for other specific considerations.
Warnings/ Precautions	**Infections** • Monitor CBC before and during treatment. Absolute lymphocyte count <$0.2x10^9$ /l should lead to treatment interruption until recovery. • Increased risk of infection. Monitor and evaluate signs during treatment and for 2 months after discontinuation. • If a patient develops a serious infection, consider withholding therapy. Therapy should not be started in patients with active infections. • If herpes encephalitis, meningitis or meningoencephalitis occur, fingolimod should be discontinued and appropriate treatment for the respective infection should be administered. **Progressive Multifocal Leukoencephalopathy (PML)** • PML is an opportunistic infection caused by John Cunningham virus (JCV), which may be fatal or result in severe disability. If PML is suspected, MRI should be performed immediately for diagnostic purposes. Withhold fingolimod at the first sign of PML. • Typical symptoms associated with PML are diverse, progress over days to weeks, including progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and confusion, changes in thinking, memory, and personality changes. **Human papilloma virus infection** Vaccination against HPV should be considered prior to treatment initiation with fingolimod considering vaccination recommendations. **Ophthalmic disorders (Macular Edema)** • Macular edema with or without visual symptoms has been reported

Fingolimod

predominantly in the first 3-4 months of therapy.

- Evaluation of the fundus, including the macula, should be carried out prior to treatment, 3 to 4 months after starting treatment, periodically while on therapy and any time there is a change in vision. Consider discontinuing fingolimod if macular edema develops.
- Diabetes mellitus and uveitis increase the risk.

Liver Injury

- Increased hepatic enzymes, mostly within the first 12 months, have been reported and returned to normal within 2 months after discontinuation of fingolimod. Monitor liver enzymes and symptoms periodically.
- Therapy should be discontinued if there is evidence of liver injury without other cause.

Posterior Reversible Encephalopathy Syndrome (PRES)

- Rare cases have been reported. Symptoms reported included sudden onset of severe headache, nausea, vomiting, altered mental status, visual disturbances and seizure. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage.
- Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, fingolimod should be discontinued.

Respiratory Effects

Evaluate when clinically indicated. Caution in patients with severe respiratory diseases.

Blood pressure effects

Increased Blood Pressure risk. Monitor Blood pressure during treatment. lesions. Discontinuation of fingolimod should be considered on a case-by case basis according to individual benefits and risks.

Potential to Prolong the QT Interval

Fingolimod treatment resulted in a prolongation of QTc. Medicinal products that may prolong QTc interval are best avoided in patients with relevant risk factors, for example, hypokalemia or congenital QT prolongation.

Tumefactive Multiple Sclerosis

MS relapses with tumefactive demyelinating lesions have been reported. In case of severe relapse, MRI should be performed to exclude tumefactive MS.

Rebound after fingolimod discontinuation

Severe exacerbation of disease has been observed rarely in some patients after stopping fingolimod. Patients should be monitored for relevant signs and symptoms and appropriate treatment initiated as required.

Fingolimod

	Malignancies • Skin examination prior to treatment and periodically thereafter is recommended. Suspicious skin lesions should be evaluated. Patients treated with fingolimod should be cautioned against exposure to sunlight without protection. • There have been cases of lymphoma in clinical studies and the post-marketing setting. If lymphoma is suspected, treatment should be discontinued.
Storage	Store between 15°C to 30°C. Protect from moisture. **N.B**. Refer to PIL for other specific considerations.

Glatiramer Acetate

Generic Name	Glatiramer acetate
Dosage Form/Strengths	Prefilled syringe: 20 mg, 40mg.
Route of Administration	Injection (S.C.)
Pharmacologic Category	Antineoplastic and Immunomodulating Agents, Immunostimulant ATC: L03AX13
Indications	- Treatment of relapsing forms of multiple sclerosis (MS) in adults. - Glatiramer acetate is not indicated in primary MS.
Dosage Regimen	**Adult dosing** - The dosing schedule depends on the strength of the product. Doses are not interchangeable. • Glatiramer acetate 20 mg/mL: once per day. **or** • Glatiramer acetate 40 mg/mL: three times per week and at least 48 hours apart. **Pediatrics** The safety and effectiveness have not been established in patients under 18 years of age.
Dosage Adjustment	**Renal impairment** Have not been studied. **Hepatic Impairment** There are no dosage adjustments available. **Elderly** Have not been studied.
Contra-Indications	Hypersensitivity to glatiramer acetate or any of the excipients.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Chest pain (2% to 13%), vasodilation (3% to 20%). **Dermatologic**: Skin rash (2% to 19%). **Gastrointestinal**: Nausea (2% to 15%). **Hypersensitivity**: Type I hypersensitivity reaction (2% to 16%; postinjection). **Immunologic**: Development of IgG antibodies (3 months: ≥3 x baseline: 80%; 12 months: greater than baseline: 90%; ≥3 x baseline: 30%). **Infection**: Infection (30%), influenza (14%). **Local**: Erythema at injection site (22% to 43%), itching at injection site (6% to 27%), pain at injection site (10% to 40%), residual mass at injection site (6% to 26%), swelling at injection site (6% to 19%). **Nervous system**: Anxiety (13%), pain (20%). **Neuromuscular & skeletal**: Asthenia (22%), back pain (12%). **Respiratory**: Dyspnea (3% to 14%), nasopharyngitis (11%). **1% to 10%** **Cardiovascular**: Edema (8%), facial edema (3%), palpitations (9%), peripheral edema (3%), syncope (3%), tachycardia (5%).

Glatiramer Acetate

	Dermatologic: Erythema of skin (2%), hyperhidrosis (7%), pruritus (5%), urticaria (3%). **Endocrine & metabolic**: Weight gain (3%). **Gastrointestinal**: Dysphagia (2%), gastroenteritis (6%), vomiting (7%). **Genitourinary**: Urinary urgency (5%), vulvovaginal candidiasis (4%). **Hematologic & oncologic**: Benign skin neoplasm (2%), lymphadenopathy (7%). **Hypersensitivity**: Hypersensitivity reaction (3%). **Local**: Atrophy at injection site (≤2%), fibrosis at injection site (2%), hypersensitivity reaction at injection site (4%), inflammation at injection site (2% to 9%), lipoatrophy at injection site (≤2%). **Nervous system**: Chills (2% to 3%), migraine (4%), nervousness (2%), speech disturbance (2%). **Neuromuscular & skeletal**: Laryngospasm (2%), tremor (4%). **Ophthalmic**: Diplopia (3%). **Respiratory**: Bronchitis (6%), cough (6%), flu-like symptoms (3%), rhinitis (7%), viral respiratory tract infection (3%). **Miscellaneous**: Fever (3% to 6%).
Monitoring Parameters	• Renal function (regularly during therapy in patients with renal impairment). • Monitor for signs of hepatic injury. • Monitor for serious hypersensitivity reactions and postinjection reactions.
Drug Interactions	There are no known significant interactions. Interactions have not been fully evaluated
Pregnancy and Lactation	**Pregnancy** No adequate and well-controlled studies. Current human data indicate no malformative or feto/neonatal toxicity of glatiramer acetate. As a precautionary measure, it is preferable to avoid use during pregnancy unless the benefit to the mother outweighs the risk to the fetus. **Lactation** Low oral absorption suggests that exposure of newborns/infants to glatiramer acetate via human breast milk is negligible. Glatiramer acetate can be used during breast-feeding.
Administration	**Subcutaneous Administration** • Before use the solution should be warm to room temperature. • Sites for self-injection include the abdomen, arms, hips and thighs. • Rotate sites of injection to reduce irritation and pain at site of injection. • Patients should be instructed about self-injection techniques and should be supervised by a health-care provider the first time they self-inject and for 30 minutes after. • For single use only and any unused portions are to be discarded. **N.B** Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Immediate Post-Injection Reaction** Vasodilatation (flushing), chest pain, palpitations, tachycardia, dyspnea, throat constriction, and/or urticaria) may occur within minutes after

Glatiramer Acetate

	injection and are generally self-limiting. If severe adverse effects, discontinuation is needed. **Lipoatrophy and skin necrosis** Avoid by rotation of injection sites and using proper injection techniques. **Pre-existing cardiac disorders patients** Caution and should be followed up regularly for any reactions during treatment. **Serious hypersensitivity reactions** Bronchospasm, anaphylaxis, Convulsions and urticaria, may rarely occur. If reactions are severe, glatiramer should be discontinued and appropriate treatment should be instituted. **Immune response** Glatiramer acetate-reactive antibodies were detected in patients' sera during treatment. No evidence to suggest effect on clinical efficacy. **Hepatic Injury** If signs or symptoms of hepatic dysfunction occur (including hepatitis with jaundice, liver failure), consider discontinuing glatiramer acetate.
Storage	• Store between 2°C to 8°C. • Do not freeze. If glatiramer acetate syringe freezes, it should be discarded. • Syringe may be stored between 15°C and 25°C, once, for up to one month. After this one-month period, it should be returned to refrigerator if not used. • Store in the original package in order to protect from light. **N.B** Refer to manufacturer PIL if there are specific considerations.

Sources

- The Egyptian Drug Authority database for drugs and pharmaceutical products, available on the official website, https://www.edaegypt.gov.eg/
- The United Kingdom, drug authority, Medicines and Healthcare Products Regulatory Agency (MHRA) https://products.mhra.gov.uk/
- The United States Food and Drug Administration, the federal agency of the Department of Health and Human Services, www.accessdata.fda.gov
- Lexicomp Online, reference handbooks, and desktop software, as a source of drugs full monographs, by Wolters Kluwer Health, www.lexicomp.com
- The searchable version of the complete Anatomical Therapeutic Classification (ATC) index with Defined Daily Dose (DDDs), by the World Health Organization (WHO), www.whocc.no/atc_ddd_index/

Alphabetical List of content