For the use of Neurologist only

1. **Generic Name and Brand Name**
   Phenytoin Sodium Extended Release Tablets 300 mg
   Eptoin® 300 ER

2. **Qualitative and Quantitative Composition:**
   Each film coated extended release tablet contains:
   Phenytoin Sodium I.P……300 mg
   Excipients…….q.s.
   Colour: Titanium Dioxide I.P.

3. **Dosage Form & strength**
   Refer section 1 & 2

4. **Clinical particulars**

4.1 Therapeutic indication

For control of generalised tonic clonic (grand-mal) and prevention and treatment of seizures occurring during or following neurosurgery.

4.2 Posology and method of administration:

Serum concentrations should be monitored in changing from Extended Phenytoin Sodium Tablets, to Prompt Phenytoin Sodium Tablets, and from the sodium salt to the free acid form.

General: Dosage of phenytoin sodium should be individualized to provide maximum benefit. In some cases, serum blood level determinations may be necessary for optimal dosage adjustments—the clinically effective serum level is usually 10–20 mcg/mL.

Method of Administration:

Adult Dosage:

Once-a-day dosage: In adults, if seizure control is established with divided doses of three 100-mg Eptoin/Phenytoin sodium Tablets daily, once-a-day dosage with 300 mg of extended phenytoin sodium tablets may be considered. However, patients should be cautioned not to miss a dose, inadvertently.

Only extended phenytoin sodium tablets are recommended for once-a-day dosing. Inherent differences in dissolution characteristics and resultant absorption rates of phenytoin due to different manufacturing procedures and/or dosage forms preclude such recommendation for other phenytoin products. When a change in the dosage form or brand is prescribed, careful monitoring of phenytoin serum levels should be carried outs.

4.3 Contraindications:

Hypersensitivity to phenytoin or other hydantoins.

4.4 Special warnings and precautions for use:

Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin class. There have been reports suggesting a relationship between phenytoin and the development of lymphadenopathy

(local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, e.g., fever, rash, and liver involvement. In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs. Acute alcoholic intake may increase phenytoin serum levels. Chronic alcohol use may decrease serum levels. In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in patients suffering from this disease

C. **Postpartum Period**. A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin in utero. This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth**.**

PRECAUTIONS

General: Patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity. A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Rash: Phenytoin should be discontinued if a skin rash appears. If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity and caution should be exercised if using structurally similar compounds (e.g., barbiturates, succinimides, oxazolidinediones, and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients. Osteomalacia has been

associated with phenytoin therapy and is considered to be due to phenytoin's interference with vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated. Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed. Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended.

Patients should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, e.g., surgery, etc.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice. Patients should be instructed to call their physician if skin rash develops. The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

Laboratory Tests: Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments.

Phenytoin may cause foetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for major congenital malformations and other adverse development outcomes (see Section 4.6). Phenytoin should not be used in women of childbearing potential unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options.

Before the initiation of treatment with phenytoin in a woman of childbearing potential, pregnancy testing should be considered. Women of childbearing potential should be fully informed of the potential risk to the foetus if they take phenytoin during pregnancy. Women of childbearing potential should be counselled regarding the need to consult her physician as soon as she is planning pregnancy to discuss switching to alternative treatments prior to conception and before contraception is discontinued (see Section 4.6).

Women of childbearing potential should be counselled to contact her doctor immediately if she becomes pregnant or thinks she may be pregnant and is taking phenytoin. Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, Phenytoin may result in a failure of the therapeutic effect of hormonal contraceptives, therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods *(see Sections 4.5 and 4.6).*

There is a risk of harm to the unborn child if Phenytoin is used during pregnancy. Women of childbearing age should use effective contraception during treatment with Phenytoin (see Pregnancy and breast-feeding).

Phenytoin can cause major birth defects. If you take Phenytoin during pregnancy your baby has up to 3 times the risk of having a birth defect than women not taking an antiepileptic medication. Major birth defects including growth, skull, facial, nail, finger and heart abnormalities have been reported.

Some of these may occur together as part of a fetal hydantoin syndrome. Problems with neurodevelopment (development of the brain) have been reported in babies born to mothers who used phenytoin during pregnancy. Some studies have shown that phenytoin negatively affects neurodevelopment of children exposed to phenytoin in the womb, while other studies have not found such an effect. The possibility of an effect on neurodevelopment cannot be ruled out.

If you are a woman of childbearing age and are not planning a pregnancy, you should use effective contraception during treatment with Phenytoin. Phenytoin may affect how hormonal contraceptives, such as the contraceptive (birth control) pill, work and make them less effective at preventing pregnancy. Talk to your doctor, who will discuss with you the most suitable type of contraception to use while you are taking Phenytoin. If you are a woman of childbearing age and are planning a pregnancy, talk to your doctor before you stop contraception and before you become pregnant about switching to other suitable treatments in order to avoid exposing the unborn baby to phenytoin. If you are or think you might be pregnant, tell your doctor straight away. You should not stop taking your medicine until you have discussed this with your doctor. Stopping your medication without consulting your doctor could cause seizures which could be dangerous to you and your unborn child. Your doctor may decide to change your treatment.

Case-control, genome-wide association studies in Taiwanese, Japanese, Malaysian and Thai patients have identified an increased risk of SCARs in carriers of the decreased function CYP2C9*3 variant.

CYP2C9 metabolism

Phenytoin is metabolized by the CYP450 CYP2C9 enzyme. Patients who are carriers of the decreased function CYP2C9*2 or CYP2C9*3 variants (intermediate or poor metabolisers of CYP2C9 substrates) may be at risk of increased phenytoin plasma concentrations and subsequent toxicity. In patients who are known to be carriers of the decreased function CYP2C9*2 or *3 alleles, close monitoring of clinical response is advised, and monitoring of plasma phenytoin concentrations may be required

Genetic factors associated with risk of severe cutaneous adverse reactions and toxicity

In view of available data from literature, there is an increased risk of severe cutaneous adverse reactions in carriers of the CYP2C9*3 allele and risk of increased toxicity in intermediate or poor metabolizers of CYP2C9 substrates.

4.5 Drug Interactions:

1. Drugs which may increase phenytoin serum levels include : chloramphenicol, certain sulfonamides, dicoumarol, disulfiram, isoniazid, cimetidine, phenylbutazone and acute alcohol intake. Drugs such as amiodarone, antifungal agents (such as, but not limited to, amphotericin B, fluconazole, ketoconazole, miconazole and itraconazole), chlordiazepoxide, diazepam, diltiazem, estrogens, fluoxetine, fluvoxamine, sertraline, H2-antagonists e.g cimetidine, halothane, isoniazid,

methylphenidate, nifedipine, omeprazole, phenothiazines, phenylbutazone, salicylates, succinimides, tolbutamide, trazodone, fluorouracil and viloxazine may increase phenytoin serum levels.
2. Drugs which may decrease phenytoin serum levels include: carbamazepine and chronic alcohol abuse. Drugs such as folic acid, reserpine, rifampicin, sucralfate, theophylline, vigabatrin may decrease phenytoin serum levels.

3.Serum levels of phenytoin can be reduced by concomitant use of the herbal preparations containing St John's wort. This is due to induction of drug metabolizing enzymes by St John's wort. Herbal preparations containing St John's wort should therefore not be combined with phenytoin. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort. If a patient is already taking St John's wort check the anticonvulsant levels and stop St John's wort. Anticonvulsant levels may increase on stopping St John's wort. The dose of anticonvulsant may need adjusting.

4. A pharmacokinetic interaction study between nelfinavir and phenytoin both administered orally showed that nelfinavir reduced AUC values of phenytoin (total) and free phenytoin by 29% and 28%, respectively. Therefore, phenytoin concentration should be monitored during co-administration with nelfinavir, as nelfinavir may reduce phenytoin plasma concentration.

5. Drugs which may either increase or decrease phenytoin serum levels include phenobarbitone, sodium valproate and certain antacids. Similarly the effect of phenytoin on phenobarbitone and valproic acid serum levels is unpredictable.

6. Although not a true pharmacokinetic interaction, tricyclic antidepressants and phenothiazines may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

7. Drugs whose effect is impaired by phenytoin include: antifungal agents e.g. azoles, antineoplastic agents, calcium channel blockers, clozapine, corticosteroids, ciclosporin, dicoumarol, digitoxin, doxycycline, furosemide, lamotrigine, methadone, neuromuscular blockers, estrogens, oral contraceptives, paroxetine, sertraline, quinidine, rifampicin, theophylline and vitamin D.

8. Drugs whose effect is decreased by phenytoin include: corticosteroids, dicoumarol, oral contraceptives, quinidine, and Vitamin D. Drugs whose effect is enhanced by phenytoin include: warfarin. The effect of phenytoin on warfarin is variable and prothrombin times should be determined when these agents are combined. Serum level determinations are especially helpful, when possible, drug interactions are suspected.

Drug Enteral Feeding/Nutritional Preparations Interaction:

Patients who have received enteral feeding preparations and/or related nutritional supplements have lower than expected phenytoin plasma levels. Phenytoin must not be administered concomitantly with an enteral feeding preparation. More frequent serum phenytoin levels monitoring may be required in these patients.

Drug / laboratory test interactions:

Phenytoin may cause a slight decrease in serum levels of total and free thyroxin, possibly because of enhanced peripheral metabolism. These changes do not lead to clinical hypothyroidism and do not affect the levels of circulating TSH. The latter can therefore be used for diagnosing hypothyroidism in the patient on phenytoin. Phenytoin does not interfere with uptake and suppression tests used in the diagnosis of hyperthyroidism. It may, however, produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause raised serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase and lowered serum levels of calcium and folic acid. It is recommended that serum folate concentrations be measured at least once every 6 months and folic acid supplements given if necessary. Phenytoin may affect blood sugar metabolism tests.

Care should be taken when using immunoanalytical methods to measure plasma phenytoin concentrations.

Concomitant administration of phenytoin and valproate has been associated with an increased risk of valproate-associated hyperammonemia. Patients treated concomitantly with these two drugs should be monitored for signs and symptoms of hyperammonemia.

Drug interactions between phenytoin and dabigatran and phenytoin and rivaroxaban, may lead to reduced plasma concentrations of direct oral anticoagulants.
Phenytoin and enzyme-inducing antiepileptic drugs, including phenytoin, are found to lower the serum lacosamide concentrations.

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use):
Phenytoin crosses the placenta in humans.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. In humans, phenytoin exposure during pregnancy is associated with a frequency of major malformations 2 to 3 times higher than that of the general population, which has a frequency of 2-3%. Malformations such as orofacial clefts, cardiac defects, craniofacial defects, nail and digit hypoplasia, and growth abnormalities (including microcephaly and prenatal growth deficiency), have been reported either individually or as part of a Fetal Hydantoin Syndrome among children born to women with epilepsy who used phenytoin during pregnancy. Neurodevelopmental disorder has been reported among children born to women with epilepsy who used phenytoin alone or in combination with other AEDs during pregnancy. Studies related to the risk of neurodevelopmental disorders in children exposed to phenytoin during pregnancy are contradictory and a risk cannot be excluded.

Phenytoin should not be used during pregnancy unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options. The woman should be fully informed of and understand the risks of taking phenytoin during pregnancy. If based on a careful evaluation of the risks and the benefits, no alternative treatment option is suitable, and treatment with Phenytoin is continued, the lowest effective dose of phenytoin should be used. If a woman is planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued.
If a woman becomes pregnant while taking phenytoin, she should be referred to a specialist to reassess phenytoin treatment and consider alternative treatment options.

Women of childbearing potential:

Phenytoin should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options. The woman should be fully informed of and understand the risk of potential harm to the fetus if phenytoin is taken during pregnancy and therefore the importance of planning any pregnancy.

Pregnancy testing in women of childbearing potential should be considered prior to initiating treatment with Phenytoin.

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, Phenytoin may result in a failure of the therapeutic effect of hormonal contraceptives, therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods (see section 4.5). At least one effective method of contraception (such as an intra-uterine device) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, involving the patient in the discussion, when choosing the contraception method.

Pregnancy Based on human experience, phenytoin is suggested to cause congenital malformations like craniofacial dysmorphia, anomalies of the distal phalanges, pre- and postnatal growth retardation and cardiac defects when administered during pregnancy. For this reason, phenytoin sodium tablet should not be used during pregnancy unless the clinical condition of the woman requires treatment with phenytoin. Women of childbearing potential should be advised that the efficacy of oral contraceptives can be reduced (see section Drug Interactions). If treatment is considered essential, phenytoin should preferably be prescribed as monotherapy and at the lowest effective dose, because the incidence of birth defects rises with increasing dosage.

The plasma concentration of phenytoin may decline during pregnancy, while reaching original levels postpartum. Therefore, periodic measurements of phenytoin plasma concentrations should be performed to guide appropriate dose adjustments for maintaining adequate seizure control. There have been also isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenytoin. Vitamin K1 has been shown to prevent or correct this defect and may be given to the mother before delivery and to the neonate after birth. Lactation Infant breast-feeding is not recommended for women taking phenytoin because phenytoin appears to be secreted in low concentrations in human milk.

4.7 Effects on ability to drive and use machines: Caution is recommended in patients performing skilled tasks (e.g. driving or operating machinery) as treatment with phenytoin may cause central nervous system adverse effects such as dizziness and drowsiness

4.8 Undesirable effects: *Immune system disorders:* Anaphylactoid reaction, and anaphylaxis.

Nervous System disorders: The most common manifestations encountered with phenytoin therapy are preferable to this system and are usually dose related. These include nystagmus, diplopia, ataxia, slurred speech, decreased co-ordination, mental confusion, memory disorder, cognitive disorder, paresthesia, somnolence, drowsiness, and vertigo. Dizziness, insomnia, transient nervousness, increasing irritability, motor twitching, taste perversion and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, high-frequent resting tremor and asterixis, like those induced by phenothiazine and other neuroleptic drugs. There are occasional reports of irreversible cerebellar dysfunction associated with severe phenytoin overdosage or long-term plasma concentrations of phenytoin above 25 μg/ml. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy. Long-term treatment with phenytoin concomitant with other anticonvulsive drugs, especially valproic acid, may lead to signs of encephalopathy: increased seizure frequency, listlessness, stupor, muscular hypotonia, choreiform dyskinesias and severe general changes on the EEG

Gastrointestinal disorders: Nausea, vomiting and constipation, toxic hepatitis, and liver damage.

Skin and subcutaneous tissue disorders: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash is the most common; dermatitis is seen more rarely. Other more serious and rare forms have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Hyperpigmentation (chloasma), severe cutaneous adverse reactions (SCARs) like Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section Warnings and Precautions). Serious Dermatological Reactions Hypersensitivity Syndrome / Drug Reaction with Eosinophilia and Systemic Symptoms Hypersensitivity Syndrome (HSS) or Drug rash with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking anticonvulsant drugs, including phenytoin. Some of these events have been fatal or life threatening. HSS/DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leukocytosis, and eosinophilia. The interval between first drug exposure and symptoms is usually 2-4 weeks but has been reported in individuals receiving anticonvulsants for 3 or more months. If such signs and symptoms occur, the patient should be evaluated immediately. Phenytoin should be discontinued if an alternative aetiology for the signs and symptoms cannot be established. Patients at higher risk for developing HSS/DRESS include black patients, patients who have experienced HSS/DRESS in the past (with phenytoin or other anticonvulsant drugs), those with a family history of HSS/DRESS, and immune-suppressed patients. The syndrome is more severe in previously sensitized individuals

Musculoskeletal and connective tissue disorders: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hirsutism, hypertrichosis, Peyronie's Disease and Dupuytren's contracture may occur rarely. Blood and lymphatic tissue disorders:

Haemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, pancytopenia with or without bone marrow suppression, and

aplastic anaemia. While macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy. There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local and generalised) including benign lymph node hyperplasia, pseudo lymphoma, lymphoma, and Hodgkin's Disease. Although a cause-and-effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, e.g. fever, rash and liver involvement. In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs. A decrease in the number of a type of red blood cell (Pure red cell aplasia) with a frequency not known
Frequent blood counts should be carried out during treatment with phenytoin.

Immune System disorders: Hypersensitivity syndrome has been reported and may in rare cases be fatal (the syndrome may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, polyarteritis nodosa, and immunoglobulin abnormalities may occur. Several individual case reports have suggested that there may be an increased, although still rare, incidence of hypersensitivity reactions, including skin rash and hepatotoxicity, in black patients (see section Warnings and Precautions).

Other:

Poly arthropathy, interstitial nephritis, pneumonitis.

Musculoskeletal System disorders:

Bone fractures and osteomalacia have been associated with long term (>10 years) use of phenytoin by patients with chronic epilepsy. Osteoporosis and other disorders of bone metabolism such as hypocalcemia, hypophosphatemia and decreased levels of Vitamin D metabolites have also been reported. Reversible muscular weakness (myasthenic syndrome).

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with phenytoin. The mechanism by which phenytoin affects bone metabolism has not been identified.

Endocrine disorders:

Disturbance of thyroid function may occur, especially in children Metabolism and nutrition disorders

There is evidence in the literature that phenytoin may trigger attacks of porphyria.

Cardiac disorders:

Rare – asystole due to inhibition of the sinus node, conduction blockade and suppression of the ventricular escape rhythm in patients with total AV block, especially when phenytoin is administered intravenously. Proarrhythmic effects in the form of changes or increases in cardiac arrythmias can occur which can lead to severe impairment of cardiac activity or even cardiac arrest. With intravenous administration in particular, decreased blood pressure, deterioration in existing

heart and respiratory failure can occur. In isolated cases ventricular fibrillation has been triggered. Atrial fibrillation and flutter is not cured by phenytoin. However, as AV node refractory time can be shortened, acceleration in ventricular rate is possible

General disorders and administration site conditions

Exhaustion

In case dose dependent undesirable effects occur, treatment should be reassessed, and the dose reduced, to prevent intoxication

4.9 Overdose: Symptoms

The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression. There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL; dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery.

Treatment:

Treatment is nonspecific. There is no known antidote. The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in pediatric patients. In acute overdosage, the possibility of other CNS depressants, including alcohol, should be borne in mind.

5. Pharmacological properties

5.1 Mechanism of action: The mechanism by which phenytoin exerts its anticonvulsant action has not been fully elucidated, however, possible contributory effects include: 1. Non-synaptic effects to reduce sodium conductance, enhance active sodium extrusion, block repetitive firing and reduce post-tetanic potentiation. 2. Post-synaptic action to enhance GABA-mediated inhibition and reduce excitatory synaptic transmission. 3. Pre-synaptic actions to reduce calcium entry and block release of neurotransmitter.

5.2 Pharmacodynamic Properties: The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post tetanic potentiation at synapses. Loss of post tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of tonic-clonic (grand mal) seizures.

5.3 Pharmacokinetic properties: Phenytoin is highly protein bound. Free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal. Most of the drug is excreted in the bile as inactive metabolites, which is then reabsorbed from the intestinal tract and excreted in the urine. Phenytoin is hydroxylated in the liver by an enzyme system which is saturable at high plasma levels, therefore small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

The plasma half-life in man after oral administration of phenytoin averages 22 hours, with a range of 7 to 42 hours. Steady-state therapeutic levels are achieved at least 7 to 10 days (5–7 half-lives) after initiation of therapy with recommended doses of 300 mg/day.

If serum level determinations are required, they should be obtained at least 5–7 half-lives after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that steady-state will have been achieved. Trough levels should be obtained just prior to the patient's next scheduled dose. Peak levels are obtained at the time of expected peak concentration.

Optimum control without clinical signs of toxicity occurs more often with serum levels between 10 and 20 mcg/mL, although some mild cases of tonic-clonic epilepsy may be controlled with lower serum levels of phenytoin. In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide inter-patient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, congenital enzyme deficiency, or drug interactions, which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be helpful.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology: Phenytoin causes embryofetal death and growth retardation in rats, mice, and rabbits. Phenytoin is teratogenic in rats (craniofacial defects including cleft palate, cardiovascular malformations, neural and renal defects, and limb abnormalities), mice (cleft lip, cleft palate, neural and renal defects, limb abnormalities, and digital and ocular abnormalities) and rabbits (cleft palate, limb abnormalities, and digital and ocular abnormalities). The defects produced are similar to major malformations observed in humans and abnormalities described for fetal hydantoin syndrome. The teratogenic effects of phenytoin in animals occur at therapeutic exposures, and therefore a risk to the patients cannot be ruled out.

Carcinogenesis:

Two- year carcinogenicity studies in mice and rats showed an increased number of hepatocellular adenomas in mice, but no rats, at plasma concentrations relevant for humans. The clinical significance of these rodent tumors is unknown.

Genetic toxicity studies showed that phenytoin was not mutagenic in bacteria or in mammalian cells in vitro. It is clastogenic in vitro but not in vivo.

7. Description

Eptoin 300 ER is supplied for oral administration, as film coated extended-release tablet of Phenytoin Sodium. Each film coated extended - release tablet of Eptoin 300 ER contains Phenytoin Sodium 300 mg.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not known

8.2 Shelf Life

Refer Pack

8.3 Packaging Information

Refer Pack

8.4 Storage condition & handling instructions

Refer Pack

9. Patient Counseling Information: Phenytoin is one of a group of medicines called anti-epileptic drugs; these medicines are used to treat epilepsy. Phenytoin tablets can be used to control a variety of epileptic conditions (tonic-clonic seizures and partial seizures), to control or prevent seizures during or after brain surgery or severe head injury. Phenytoin can also be used to treat trigeminal neuralgia (facial nerve pain). Do not take Phenytoin tablets if -

- You are allergic to phenytoin, or any of the other ingredients of this medicine
- You are allergic to other medicines with a similar chemical structure to phenytoin (e.g. hydantoins)

Your doctor needs to know before you take phenytoin if you suffer from or have suffered in the past from any of the following conditions: • liver disease • kidney disease • Porphyria (an inherited disease that affects hemoglobin biosynthesis)

Serious skin side effects can rarely occur during treatment with phenytoin. There is a risk of harm to the unborn child if Phenytoin Sodium filmcoated tablets are used during pregnancy. Women of childbearing age should use effective contraception during treatment with Phenytoin Sodium film-coated tablets (see Pregnancy and breastfeeding). You should not take Phenytoin tablets if you are breast-feeding. You should be administered phenytoin with caution if you suffer from kidney or liver problems. Phenytoin may cause dizziness or drowsiness, especially during the first few weeks of treatment. If you experience these symptoms do not drive or use any tools or machinery.

10. Details of manufacturer

Refer Pack for manufacturer details
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11. Details of permission or licence number with date

Refer Pack for Permission/License details

12. Date of Revision
Version 1.0, dated 19/09/2024

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com