

Summary of Product Characteristics

1. Name of the Medical Product

Fentex 250mg /5ml solution for injection.

2. Qualitative & Quantitative Composition:

Each 1mL solution for injection contains;
Phenytoin.....50mg

Excipients with known effect:

Propylene glycol
Sodium

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form:

Solution for injection.

4. Clinical Particulars

4.1 Therapeutic Indications:

Parenteral Fentex is indicated for the control of status epilepticus of the tonic-clonic (grand mal) type and prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.

It is also indicated for the 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.

4.2 Posology and Method of administration:

For parenteral administration

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Parenteral Fentex is suitable for use as long as it remains free of haziness and precipitate. Upon refrigeration or freezing a precipitate might form; this will dissolve again after the solution is allowed to stand at room temperature. The product is still suitable for use. Only a clear solution should be used. A faint yellow colouration may develop, however, this has no effect on the potency of this solution.

There is a relatively small margin between full therapeutic effect and minimally toxic doses of this drug. Optimum control without clinical signs of toxicity occurs most often with serum levels between 10 and 20 mg/l (40-80 micromoles/l).

Because of the risk of local toxicity, intravenous phenytoin should be injected slowly directly into a large vein through a large-gauge needle or intravenous catheter.

Each injection or infusion of intravenous Fentex should be preceded and followed by an injection of sterile saline through the same needle or catheter to avoid local venous irritation due to alkalinity of the solution. For infusion administration the parenteral phenytoin should be diluted in 50-100 ml of normal saline, with the final concentration of phenytoin in the solution not exceeding 10 mg/ml. Administration should commence immediately after the mixture has been prepared and must be

completed within one hour (the infusion mixture should not be refrigerated). An in-line filter (0.22-0.50 microns) should be used.

The diluted form is suitable for use as long as it remains free of haziness and precipitate.

Continuous monitoring of the electrocardiogram and blood pressure is essential. Cardiac resuscitative equipment should be available. The patient should be observed for signs of respiratory depression. If administration of intravenous Fentex does not terminate seizures, the use of other measures, including general anaesthesia, should be considered.

Although 100 mg of phenytoin sodium is equivalent to 92 mg of phenytoin on a molecular weight basis, these molecular equivalents are not necessarily biologically equivalent. Physicians should therefore exercise care in those situations where it is necessary to change the dosage form and serum level monitoring is advised.

Status Epilepticus:

In a patient having continuous seizure activity, as compared to the more common rapidly recurring seizures, i.e. serial epilepsy, injection of intravenous diazepam or a short acting barbiturate is recommended because of their rapid onset of action, prior to administration of Fentex.

Following the use of diazepam in patients having continuous seizures and in the initial management of serial epilepsy a loading dose of Fentex 10-15 mg/kg should be injected slowly intravenously, at a rate not exceeding 50 mg per minute in adults (this will require approximately 20 minutes in a 70 kg patient). The loading dose should be followed by maintenance doses of 100 mg orally or intravenously every 6 to 8 hours.

Recent work in neonates has shown that absorption of phenytoin is unreliable after oral administration, but a loading dose of 15-20 mg/kg of Fentex intravenously will usually produce serum concentrations of phenytoin within the generally accepted therapeutic range (10-20 mg/l). The drug should be injected slowly intravenously at a rate of 1-3 mg/kg/min.

Determination of phenytoin serum levels is advised when using Fentex in the management of status epilepticus and in the subsequent establishing of maintenance dosage. The clinically effective level is usually 10-20 mg/l although some cases of tonic-clonic seizures may be controlled with lower serum levels of phenytoin.

Intramuscular administration should not be used in the treatment of status epilepticus because the attainment of peak plasma levels may require up to 24 hours.

Use in Cardiac Arrhythmias:

3.5-5 mg per kg of bodyweight intravenously initially, repeated once if necessary. The solution should be injected slowly, intravenously and at a uniform rate which should not exceed 1 ml (50 mg) per minute.

Other clinical conditions:

It is not possible to set forth a universally applicable dosage schedule.

The intravenous route of administration is preferred.

Dosage and dosing interval will, of necessity, be determined by the needs of the individual patient. Factors such as previous antiepileptic therapy, seizure control, age and general medical condition must be considered. Notwithstanding the slow

absorption of Fentex, when given intramuscularly, its use in certain conditions may be appropriate.

When short-term intramuscular administration is necessary for a patient previously stabilized orally, compensating dosage adjustments are essential to maintain therapeutic serum levels. An intramuscular dose 50% greater than the oral dose is necessary to maintain these levels. When returned to oral administration, the dose should be reduced by 50% of the original oral dose, for the same period of time the patient received Fentex intramuscularly, to prevent excessive serum levels due to continued release from intramuscular tissue sites. *Neurosurgery:*

In a patient who has not previously received the drug, Parenteral Fentex 100-200 mg (2-4 ml) may be given intramuscularly at approximately 4-hour intervals prophylactically during neurosurgery and continued during the post-operative period for 48-72 hrs. The dosage should then be reduced to a maintenance dose of 300 mg and adjusted according to serum level estimations.

If the patient requires more than a week of intramuscular Fentex, alternative routes should be explored such as gastric intubation. For time periods less than one week, the patient switched from intramuscular administration should receive one half the original oral dose for the same period of time the patient received Fentex intramuscularly. Measurement of serum levels is of value as a guide to an appropriate adjustment of dosage.

Older people (over 65 years):

As for adults, however, complications may occur more readily in older people.

Paediatric population:

It has been shown that children tend to metabolize phenytoin more rapidly than adults. This should be borne in mind when determining dosage regimens; the use of serum level monitoring being particularly beneficial in such cases.

Neonates:

Recent work in neonates has shown that absorption of phenytoin is unreliable after oral administration, but a loading dose of 15-20 mg/kg of Fentex intravenously will usually produce serum concentrations of phenytoin within the generally accepted therapeutic range (10-20 mg/l).

The drug should be injected slowly intravenously at a rate of 1-3 mg/kg/min.

4.3 Contraindications:

Phenytoin is contraindicated in patients who are hypersensitive to phenytoin, or any of its excipients, or other hydantoins. Intra-arterial administration must be avoided in view of the high pH of the preparation. Because of its effect on ventricular automaticity, phenytoin is contra-indicated in sinus bradycardia, sinoatrial block, and second and third degree A-V block, and patients with Adams-Stokes syndrome. Co-administration of phenytoin is contraindicated with delavirdine due to the potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.

4.4 Special warnings & precautions for use

General:

In adults, intravenous administration should not exceed 50 mg per minute. In neonates, the drug should be administered at a rate of 1-3 mg/kg/min.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present together, combined drug therapy is needed.

Phenytoin is not indicated for seizures due to hypoglycaemia or other metabolic causes.

The most notable signs of toxicity associated with the intravenous use of this drug are cardiovascular collapse and/or central nervous system depression. Severe cardiotoxic reactions and fatalities due to depression of atrial and ventricular conduction and ventricular fibrillation, respiratory arrest and tonic seizures have been reported particularly in older people or gravely ill patients, if the preparation is given too rapidly or in excess.

Hypotension usually occurs when the drug is administered rapidly by the intravenous route. Soft tissue irritation and inflammation has occurred at the site of injection with and without extravasation of intravenous phenytoin. Soft tissue irritation may vary from slight tenderness to extensive necrosis, sloughing and in rare instances has led to amputation. Subcutaneous or perivascular injection should be avoided because of the highly alkaline nature of the solution.

Intravenous Fentex should be used with caution in patients with hypotension and severe myocardial insufficiency.

The intramuscular route is not recommended for the treatment of status epilepticus because of slow absorption. Serum levels of phenytoin in the therapeutic range cannot be rapidly achieved by this method.

Phenytoin may precipitate or aggravate absence seizures and myoclonic seizures.

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus. When, in the judgement of the clinician, 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 chemical class.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

Herbal preparations containing St. John's Wort (*Hypericum perforatum*) should not be used while taking phenytoin due to the risk of decreased plasma concentrations and reduced clinical effects of phenytoin. Phenytoin is highly protein bound and extensively metabolised by the liver.

Reduced maintenance dosage to prevent accumulation and toxicity may therefore be required in patients with impaired liver function. Where protein binding is reduced, as in uraemia, total serum phenytoin levels will be reduced accordingly. However, the pharmacologically active free drug concentration is unlikely to be altered. Therefore, under these circumstances therapeutic control may be achieved with total phenytoin levels below the normal range of 10-20 mg/l. Dosage should not exceed the minimum necessary to control convulsions.

Suicide:

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for phenytoin sodium. Therefore patients should be monitored for signs of suicidal ideation and

behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.

Cardiovascular Effect:

Severe cardiotoxic reactions and fatalities have been reported with atrial and ventricular depression and ventricular fibrillation. Severe complications are most commonly encountered in elderly or gravely ill patients.

Local Toxicity (including Purple Glove Syndrome):

Soft tissue irritation and inflammation have occurred at the site of injection with and without extravasation of intravenous phenytoin.

Edema, discoloration and pain distal to the site of injection (described as “purple glove syndrome”) have been reported following peripheral intravenous phenytoin injection. Soft tissue irritation may vary from slight tenderness to extensive necrosis, and sloughing of skin. The syndrome may not develop for several days after injection. Although resolution of symptoms may be spontaneous, skin necrosis and limb ischemia have occurred and required such interventions as fasciotomies, skin grafting, and, in rare cases, amputation.

Improper administration including subcutaneous or perivascular injection should be avoided.

Intramuscular phenytoin administration may cause pain, necrosis, and abscess formation at the injection site.

Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms (HSS/DRESS):

Hypersensitivity Syndrome (HSS) or Drug Reaction 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, haematological abnormalities, myocarditis, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leucocytosis, and eosinophilia. The mechanism is unknown. 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 this syndrome in the past (with phenytoin or other anticonvulsant drugs), patients who have a family history of this syndrome and immuno-suppressed patients. The syndrome is more severe in previously sensitized individuals.

Serious Skin Reactions:

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of phenytoin. Although serious skin reactions may occur without warning, patients should be advised of the signs and symptoms of HSS/DRESS, occurrence of rash and should be monitored closely for skin reactions. Patients should seek medical advice from their

physician immediately when observing any indicative signs or symptoms. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment. If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Fentex treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed SJS or TEN with the use of Fentex, Fentex must not be restarted in this patient at any time.

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. The risk of serious skin reactions and other hypersensitivity reactions to phenytoin may be higher in black patients.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding use of drugs associated with SJS/TEN, including phenytoin, in HLA-B*1502 positive patients when alternative therapies are otherwise equally available. Literature reports suggest that the combination of phenytoin, cranial irradiation, and the gradual reduction of corticosteroids may be associated with the development of erythema multiforme and/or SJS and/or TEN.

Hepatic Injury:

The liver is the chief site of biotransformation of phenytoin.

Toxic hepatitis and liver damage have been reported and may, in rare cases, be fatal.

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents usually occur within the first 2 months of treatment and may be associated with HSS/DRESS.

Patients with impaired liver function, older patients, or those who are gravely ill may show early signs of toxicity.

The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, phenytoin should be immediately discontinued and not readministered.

The risk of hepatotoxicity and other hypersensitivity reactions to phenytoin may be higher in black patients.

Haematopoietic System:

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

Central Nervous System Effect:

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 and/or cerebellar atrophy. Accordingly, at the first sign of acute toxicity, serum drug level determinations are recommended.

Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination of therapy with phenytoin is recommended.

Metabolic Effect:

Phenytoin may affect glucose metabolism and inhibit insulin release.

Hyperglycaemia has been reported. Caution is advised when treating diabetic patients.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Laboratory Tests:

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

This product contains a number of excipients known to have a recognised action or effect. These are: Propylene glycol (may cause alcohol-like symptoms) Sodium (1.1 mmol per 5 ml ampoule). Ethanol (440.4 mg per 5 ml ampoule). This may be harmful for those suffering from alcoholism and should be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease.

4.5 Interactions with other medicinal products and other forms of Interactions

Drug interactions: *Drug Interactions:*

Phenytoin is extensively bound to serum plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome (CYP) P450 enzymes CYP2C9 and CYP2C19 and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity.

Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes and may reduce the levels of drugs metabolized by these enzymes.

There are many drugs which may increase or decrease serum phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected.

The most commonly occurring drug interactions are listed below.

Drugs which may increase phenytoin serum levels

Table 1 summarizes the drug classes which may potentially increase phenytoin serum levels. **Table 1 Drugs Which May Increase Phenytoin Serum Levels**

Drug Classes	Drugs in each Class (such as)
Alcohol (acute intake)	
Analgesic/Anti-inflammatory agents	azapropazone phenylbutazone salicylates
Anesthetics	halothane
Antibacterial agents	chloramphenicol erythromycin isoniazid sulfadiazine sulfamethizole

	sulfamethoxazole-trimethoprim sulfaphenazole sulfisoxazole sulfonamides
Anticonvulsants	felbamate oxcarbazepine sodium valproate succinimides topiramate
Antifungal agents	amphotericin B fluconazole itraconazole ketoconazole miconazole voriconazole
Antineoplastic agents	fluorouracil capecitabine
Benzodiazepines/Psychotropic agents	chlordiazepoxide diazepam disulfiram methylphenidate trazodone viloxazine
Calcium channel blockers/Cardiovascular agents	amiodarone dicumarol diltiazem nifedipine ticlopidine
H2-antagonists	cimetidine
HMG-CoA reductase inhibitors	fluvastatin
Hormones	oestrogens
Immunosuppressant drugs	tacrolimus
Oral hypoglycemic agents	tolbutamide

Proton pump inhibitors	omeprazole
Serotonin re-uptake inhibitors	fluoxetine fluvoxamine sertraline

Drugs which may decrease phenytoin serum levels

Table 2 summarizes the drug classes which may potentially decrease phenytoin serum levels.

Table 2 Drugs Which May Decrease Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as)
Alcohol (chronic intake)	

Antibacterial agents	rifampin ciprofloxacin
Anticonvulsants	vigabatrin
Antineoplastic agents	bleomycin carboplatin cisplatin doxorubicin methotrexate
Antiretrovirals	fosamprenavir nelfinav ritonavir
Bronchodilators	theophylline
Cardiovascular agents	reserpine
Folic Acid	folic acid
Hyperglycemic agents	diazoxide
St. John's Wort	St. John's wort

Serum levels of phenytoin can be reduced by concomitant use of the herbal preparations containing St. John's wort (*Hypericum perforatum*).

This is due to induction of drug metabolising enzymes by St. John's wort. Herbal preparation 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.

Drugs which may increase or decrease phenytoin serum levels

Table 3 summarizes the drug classes which may either increase or decrease phenytoin serum levels.

Table 3 Drugs Which May Increase or Decrease Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as)
Antibacterial agents	ciprofloxacin
Anticonvulsants	carbamazepine phenobarbital sodium valproate valproic acid
Antineoplastic agents	
Psychotropic agents	chlordiazepoxide diazepam phenothiazines

Drugs whose serum levels and/or effects may be altered by phenytoin

table 4 summarizes the drug classes whose serum levels and/or effects may be altered by phenytoin.

table 4 drugs whose serum levels and/or effects may be altered by phenytoin

Drug Classes	Drugs in each Class (such as)
Antibacterial agents	doxycycline
	rifampin tetracycline
Anticonvulsants	carbamazepine lamotrigine phenobarbital sodium valproate valproic acid
Antifungal agents	azoles posaconazole voriconazole
Anthelmintics	albendazole praziquantel
Antineoplastic agents	teniposide
Antiretrovirals	delavirdine efavirenz fosamprenavir indinavir lopinavir/ritonavir nelfinavir ritonavir saquinavir
Bronchodilators	theophylline
Calcium channel blockers/Cardiovascular agents	digitoxin digoxin mexiletine nicardipine nimodipine nisoldipine quinidine verapamil
Corticosteroids	

Coumarin anticoagulants	warfarin
Cyclosporine	
Diuretics	furosemide
HMG-CoA reductase inhibitors	atorvastatin fluvastatin simvastatin
Hormones	oestrogens oral contraceptives
Hyperglycemic agents	diazoxide
Neuromuscular blocking agents	alcuronium cisatracurium

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

Drug/Laboratory Test Interactions:

Phenytoin may cause a slight decrease in serum levels of total and free thyroxine, possibly as a result 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 hypothyroidism.

It may, however, produce lower than normal values for dexamethasone or metapyrone tests. Phenytoin may cause raised serum levels of glucose, alkaline phosphatase, gamma glutamyl transpeptidase and lowered serum levels of calcium and folic acid. It is recommended that serum folate concentrations be measured at least every 6 months, and folic acid supplement given if necessary. Phenytoin may affect blood sugar metabolism tests.

4.6 Pregnancy and Lactation

Use during pregnancy and lactation:

Pregnancy

In considering the use of Fentex intravenously in the management of status epilepticus in pregnancy, the following information should be weighed in assessing the risks and the benefits. The potential adverse effects upon the foetus of status epilepticus, specifically hypoxia, make it imperative to control the condition in the shortest possible time.

There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans. Genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects.

The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus and attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or foetus.

There is some evidence that phenytoin may produce congenital abnormalities in the offspring of a small number of epileptic patients, therefore it should not be used as the first drug during pregnancy, especially early pregnancy, unless in the judgement of the physician the potential benefits outweigh the risk. In addition to the reports of increased incidence of congenital malformations, such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other antiepileptic drugs, there have been recent reports of a foetal hydantoin syndrome. This consists of pre-natal growth deficiency, microencephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a proportion of patients, because of altered phenytoin absorption or metabolism.

Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated. Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenytoin. Vitamin K has been shown to prevent or correct this defect and may be given to the mother before delivery and to the neonate after birth.

Breast-feeding

Infant breast-feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

4.7 Effects on ability to drive and use machine*:

Caution is recommended in patients performing skilled tasks (e.g. driving or operating machines) as treatment with phenytoin may cause central nervous system adverse effects such as dizziness and drowsiness.

4.8 Undesirable Effects

The following adverse reactions have been reported with phenytoin (frequency unknown – cannot be estimated from available data): Signs of toxicity are associated with cardiovascular and central nervous system depression. *Central Nervous System:* Adverse reactions in this body system are common and are usually dose-related. Reactions include nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Cerebellar atrophy has been reported, and appears more likely in settings of elevated phenytoin levels and/or long-term phenytoin use. Dizziness, vertigo, insomnia, transient nervousness, motor twitchings, headache, paraesthesia somnolence drowsiness and taste perversion have also been observed

There have also been rare reports of phenytoin-induced dyskinesia, including chorea, dystonia, tremor, and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy. Tonic seizures have also been reported.

Cardiovascular System:

Severe cardiotoxic reactions and fatalities have been reported with atrial and ventricular conduction depression and ventricular fibrillation. Severe complications are most commonly encountered in older people or gravely ill patients. *Immune system reactions:* Anaphylactoid reaction and anaphylaxis. *Respiratory:* Alterations in respiratory function including respiratory arrest may occur. *Injection Site:* Local irritation, inflammation, tenderness, necrosis, and sloughing of skin have been reported with or without extravasation of intravenous phenytoin. Edema, discoloration and pain distal to the site of injection (described as “purple glove syndrome”) have also been reported.

Dermatological System:

Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common. Other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus. Severe cutaneous adverse reactions (SCARs): StevensJohnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported very rarely.

Haematopoietic System:

Haematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, and 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 or generalised) 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. *Gastrointestinal System:* Acute hepatic failure, toxic hepatitis, liver damage, vomiting, nausea, constipation. *Connective Tissue System:*

Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hirsutism, hypertrichosis, Peyronie's disease and Dupuytren's contracture may occur rarely.

Immune System:

Hypersensitivity syndrome/Drug reaction with eosinophilia and systemic symptoms (HSS/DRESS) 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, periarteritis 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. *Musculoskeletal System:*

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. *Other:* Polyarthropathy, interstitial nephritis, pneumonitis.

Paediatric population

The adverse event profile of phenytoin is generally similar between children and adults. Gingival hyperplasia occurs more frequently in paediatric patients and in patients with poor oral hygiene.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>.

4.9 Overdose:

The lethal dose in children is not known. The mean lethal dose in adults is estimated to be 2 to 5 g. The initial symptoms are nystagmus, ataxia and dysarthria. Other signs are tremor, hyperflexia, lethargy, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression. Attempts to relate serum levels of the drug to toxic effects have shown wide interpatient variation.

Nystagmus on lateral gaze usually appears at 20 mg/l, and ataxia at 30 mg/l, dysarthria and lethargy appear when the serum concentration is >40 mg/l, but a concentration as high as 50 mg/l has been reported without evidence of toxicity.

As much as 25 times the therapeutic dose, which resulted in a serum concentration of 100 mg/l, was taken with complete recovery. Irreversible cerebellar dysfunction and atrophy have been reported.

Treatment:

Treatment is non-specific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed.

Haemodialysis 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 children.

In acute overdosage the possibility of the presence of other CNS depressants, including alcohol, should be borne in mind.

5. Pharmacological properties:

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: Antiepileptics, ATC-code: N03AB02

Phenytoin sodium inhibits the spread of seizure activity in the motor cortex. It appears that by promoting sodium efflux from neurons, phenytoin sodium tends to stabilise the threshold against hyperexcitability caused by environmental changes or excessive stimulation capable of reducing membrane sodium gradient. This includes the reduction of post tetanic potentiation of synapses. Loss of post tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin thereby reduces the over-activity of brain stem centres responsible for the tonic phase of grand mal seizures.

Phenytoin sodium's antiarrhythmic action may be attributed to the normalisation of influx of sodium and calcium to cardiac Purkinje fibres. Abnormal ventricular automaticity and membrane responsiveness are decreased. It also shortens the

refractory period, and therefore shortens the QT-interval and the duration of the action potential.

Hydantoins induce production of liver microsomal enzymes, thereby accelerating the metabolism of concomitantly administered drugs

5.2 Pharmacokinetics Properties*:

Absorption

The onset of action after an intravenous dose is 30 to 60 minutes and the effect persists up to 24 hours. Phenytoin is about 90% protein bound. Protein binding may be lower in neonates and hyperbilirubinemic infants; also altered in patients with hypalbuminaemia, uraemia or acute trauma, and in pregnancy. Optimum control without clinical signs of toxicity occurs most often with serum levels between 10 and 20 microgram/ml. In renal failure or hypalbuminaemia, 5 to 12 microgram/ml or even less may be therapeutic.

Elimination

Phenytoin is metabolised in the liver, the major inactive metabolite is 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH). The rate of metabolism is increased in younger children, pregnant women, in women during menses and in patients with acute trauma. The rate decreases with advancing age. Phenytoin may be metabolised slowly in a small number of individuals due to genetic factors, which may cause limited enzyme availability and lack of induction.

Pharmacokinetic/pharmacodynamic relationship(s)

The plasma half-life is normally from 10 to 15 hours. Because phenytoin exhibits saturable or dose-dependent pharmacokinetics, the apparent half-life of phenytoin changes with dose and serum concentration. At therapeutic concentrations of the drug, the enzyme system responsible for metabolising phenytoin becomes saturated. Thus a constant amount of drug is metabolised, and small increases in dose may cause disproportionately large increases in serum concentrations and apparent half-life, possibly causing unexpected toxicity.

5.3 Preclinical safety data

Reproductive and developmental toxicity:

Phenytoin causes embryofoetal 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. Published data report adverse neurodevelopmental effects in the offspring of animals exposed to clinically relevant exposures of phenytoin during pregnancy.

Carcinogenesis:

Two-year carcinogenicity studies in mice and rats showed an increased number of hepatocellular adenomas in mice, but not rats, at plasma concentrations relevant for humans. The clinical significance of these rodent tumours 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.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Propylene glycol, Ethyl alcohol, Sodium hydroxide and Water for injection Ifuric acid , Sodium Citrate , Sodium Metabisulfate, Water for Injection.

6.2 Incompatibilities:

Incompatible with amikacin sulphate, cephalixin sodium, clindamycin phosphate, and many other drugs.

It is recommended that phenytoin sodium not be mixed with other drugs or with any infusion solution other than sodium chloride 0.9%.

6.3 Shelf life:

24 months

6.4 Special Precautions for storage:

Do not store above 30°C. Keep the vial in the outer carton.

6.5 Nature and contents of container:

Each vial contains 5ml/250mg Phenytoin Sodium EP packed in a glass vial with a rubber cork. 10 vials of Phenytoin Sodium EP are packed in a unit box with leaflet.

6.6 Special precautions for disposal:

For single use. Discard any unused contents.

The product should be visually inspected for particulate matter and discolouration prior to administration.

Phenytoin Injection BP is suitable for use as long as it remains free of haziness and precipitate. A precipitate might form if the product has been kept in a refrigerator or freezer. This precipitate will dissolve if allowed to stand at room temperature. The product will then be suitable for use. For infusion administration, the parenteral phenytoin should be diluted in 50 – 100 ml of normal saline, with the final concentration of phenytoin in the solution not exceeding 10 mg/ml. Administration should commence immediately after the mixture has been prepared and must be completed within one hour (the infusion mixture should not be refrigerated). An in-line filter (0.22 – 0.50 microns) should be used. The diluted form is suitable for use as long as it remains free of haziness and precipitate.

Use in the paediatric population

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder:

Ms Pharma-Jordan

King Abdullah (II) Bin Al-Hussein industrial Estate, Amman Jordan

Manufacturing Site Address:

MS PHARMA JORDAN

8. Marketing Authorization Number:

H2024/CTD7578/14752

9. Date of first registration /renewal of the registration:

2024 March 06

10. Date of revision of text:

2024 March 06