# Phenytoin

Phenytoin sodium

50 mg/ml solution for injection

Reference Market: UK

AfME Markets using same as LPD: Saudi Arabia

## SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

/

Phenytoin Hospira 50 mg/ml Injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the solution for injection contains 50 mg of phenytoin sodium.

Each 5 ml ampoule contains 250 mg of phenytoin sodium.

For the full list of excipients, see 6.1.

## 3 PHARMACEUTICAL FORM

Solution for Injection

Clear, colourless solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Control of status epilepticus and the prevention of seizures occurring during or following neurosurgery.

Treatment of certain cardiac dysrhythmias, particularly those unresponsive to conventional antidysrhythmic agents or to cardioversion.

### 4.2 Posology and method of administration

Method of administration

Phenytoin Injection should be injected slowly and directly into a large vein through a large-gauge needle or intravenous catheter. It must be administered slowly. Intravenous administration should not exceed 50 mg/minute in adults. In neonates the drug should be administered at a rate not exceeding 1 to 3 mg/kg/min. Each injection should be followed by an injection of 0.9% sodium chloride through the same needle or catheter to avoid local venous irritation due to the alkalinity of the solution.

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 Phenytoin Injection does not terminate seizures, the use of other measures, including general anaesthesia, should be considered.

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 Phenytoin Injection. Following the use of diazepam in patients having continuous seizures and in the initial management of serial

epilepsy, a loading dose of 10-15 mg/kg should be given by slow intravenous injection at a rate not exceeding 50 mg/minute in adults to avoid hypotension (this will require approximately 20 minutes in a 70kg patient). The loading dose is then followed by a maintenance dose of 100 mg given orally or intravenously 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.

Paediatric Population

As for adults, however it has been shown that children tend to metabolise 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.

Determination of phenytoin serum levels is advised when using Phenytoin Injection 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.

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

When given by intramuscular injection, phenytoin precipitates out at the injection site and is absorbed slowly and erratically. This route is not, therefore, recommended for treating status epilepticus. If phenytoin is administered by intramuscular injection to patients unable to take the drug orally, the dose should be increased by 50% over the previously established oral dose. To avoid drug accumulation resulting from eventual absorption from intramuscular injection sites, it is recommended that for the first week back on oral therapy the dose is reduced to one-half the original dose. Monitoring of serum concentrations is also recommended. Intramuscular therapy should generally be limited to 1 week.

Phenytoin sodium can be useful in cardiac arrhythmias, particularly those due to digitalis. The recommended dosage is one intravenous injection of Phenytoin Injection of 3.5 to 5 mg/kg bodyweight initially, repeated once if necessary. The solution should be injected slowly, intravenously and at a uniform rate which should not exceed 1ml (50mg) per minute

## 4.3 Contraindications

1. Hypersensitivity to phenytoin or to any of the excipients listed in 6.1 or other hydantoins.
2. Patients with sinus bradycardia, sino-atrial block, second and third degree AV block or Adams-Stokes syndrome.

3. Intra-arterial administration must be avoided in view of the high pH of the preparation.

## 4.4 Special warnings and precautions for use

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.

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 behaviour emerge.

This drug must be administered slowly, at a rate not exceeding 50 mg/minute intravenously in adults. In neonates, the drug should be administered at a rate not exceeding 1-3 mg/kg/min. The response to phenytoin may be significantly altered by the concomitant use of other drugs (see section 4.5).

Hypotension may occur. Severe cardiotoxic reactions and fatalities have been reported with arrhythmias including bradycardia, atrial and ventricular depression, and ventricular fibrillation. In some cases cardiac arrhythmias have resulted in asystole/ cardiac arrest and death. Severe complications are most commonly encountered in elderly or gravely ill patients. Cardiac adverse events have also been reported in adults and children without underlying cardiac disease or comorbidities and at recommended doses and infusion rates. Therefore, careful cardiac (including respiratory) monitoring is needed when administering IV loading doses of phenytoin. Reduction in rate of administration or discontinuation of dosing may be needed. Phenytoin should be used with caution in patients with hypotension and/or severe myocardial insufficiency.

In these patients, the drug should be administered at a rate not exceeding 25 mg/minute, and if necessary, at a slow rate of 5 to 10 mg/minute.

Serum levels of phenytoin sustained above the optimal range may produce encephalopathy, or confusional states (delirium, psychosis or encephalopathy), or rarely irreversible cerebellar dysfunction. Plasma level determinations are recommended at the first signs of acute toxicity. If plasma levels are excessive, then dosage reduction is indicated. Termination is recommended if symptoms persist.

Abrupt withdrawal of phenytoin in epileptic patients may precipitate the possibility of increased seizure frequency, including status epilepticus. When, in the judgement of the clinician, it is necessary to reduce the dose of phenytoin, discontinuation, or substitution of alternative antiepileptic medication arises this should be done gradually. However, in the event of an allergic or a hypersensitivity reaction, where

rapid substitution of therapy is warranted, the alternative drug should be one not belonging to the hydantoin class of compounds.

Phenytoin may precipitate or aggravate absence seizures and myoclonic seizures.

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 (see section 4.5).

Subcutaneous or perivascular injection should be avoided because of the highly alkaline nature of the solution.

Intramuscular phenytoin administration may cause pain, necrosis, and abscess formation at the injection site (see section 4.2).

Soft tissue irritation and inflammation has occurred at the site of injection with and without extravasation of intravenous phenytoin. Such injection may cause soft tissue irritation of the tissues varying from slight tenderness to extensive necrosis, sloughing and in rare instances has led to amputation.

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.

**Women of Childbearing Potential**
Phenytoin may cause foetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse development outcomes (see section 4.6).

Phenytoin is highly protein bound and extensively metabolised by the liver.

The liver is the principal site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

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.

Patients with renal function impairment should also be carefully observed when prescribing phenytoin, as excretion and protein binding may be altered.

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism appears to be due to limited

enzyme availability and lack of induction, which may be genetically determined.

Phenytoin may affect glucose metabolism and inhibit insulin release.

Hyperglycaemia has been reported. Phenytoin is not indicated for seizures due to hypoglycaemia or other metabolic causes. Phenytoin should be used with caution in diabetic patients as hyperglycaemia may be potentiated.

Measurement of serum phenytoin levels is recommended when using phenytoin in the management of status epilepticus and in establishing a maintenance dose. The usually accepted therapeutic level is 10-20 mg/l, although some patients with tonic-clonic seizures can be controlled with lower serum levels.

Phenytoin is not effective for petit mal seizures. Therefore, combined therapy is required if both tonic-colonic (grand mal) and absence (petit mal) seizures are present.

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.

*Anticonvulsant Hypersensitivity Syndrome:*
Anticonvulsant Hypersensitivity Syndrome (AHS) is a rare drug-induced, multi-organ syndrome that is potentially fatal and occurs in some patients taking anticonvulsant medication. It is characterized by fever, rash, lymphadenopathy, and other multi-organ pathologies, often hepatic. 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. Drug rash with eosinophilia and systemic symptoms (DRESS) reflects a serious hypersensitivity reaction to drugs, characterized by skin rash, fever, lymph node enlargement, and internal organ involvement. Cases of DRESS have been noted in patients taking phenytoin.

Patients at higher risk for developing AHS include black patients, patients who have a family history of or who have experienced this syndrome in the past, and immunosuppressed patients. The syndrome is more severe in previously sensitized individuals. If a patient is diagnosed with AHS, discontinue the phenytoin and provide appropriate supportive measures.

*Serious skin reactions:*
Phenytoin can cause rare, serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and 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. The physician can advise the patient to discontinue or re-institute medication and if further therapy is contraindicated.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, phenytoin 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 phenytoin, phenytoin must not be re-started in this patient at any time.

If the rash is of a milder type (measles-like or scarlantiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Several individual case reports and published literature has suggested that there may be an increased, although still rare, risk of hypersensitivity reactions, including skin rash, SJS, TEN and hepatotoxicity 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. In the Caucasian and Japanese population, the frequency of the HLA-B*1502 allele is extremely low, and thus it is not possible at present to conclude on risk association. Adequate information about risk association in other ethnicities is currently not 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.

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.

Oedema, 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.

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

This product may contain a number of excipients known to have a recognized 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.

Paediatric Population

Phenytoin is used for neonates, infants and children.

## 4.5 Interaction with other medicinal products and other forms of interaction

Phenytoin is extensively bound to serum plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome 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. 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 serum levels of phenytoin include: amiodarone, antifungal agents (such as, but not limited to, amphotericin B fluconazole, ketoconazole, miconazole and itraconazole), chloramphenicol, coumarin anticoagulants, chlordiazepoxide, dicoumarol, diltiazem, fluoxetine, fluvoxamine, sertraline, nifedipine, omeprazole, H2-antagonists e.g. cimetidine, ranitidine, disulfiram, phenylbutazone, isoniazid, salicylates, chlordiazepoxide, phenothiazines, diazepam, oestrogens, ethosuximide, sulthiame, halothane, methylphenidate, trimethadione, mephenytoin, sulphonamides, trazodone, succinimides, tolbutamide, fluorouracil, oxcarbazepine and viloxazine.

Drugs which may decrease serum levels of phenytoin include: carbamazepine, reserpine, bleomycin, carboplatin, carmustine, cisplatin, methotrexate, vinblastine, folic acid, calcium folinate, rifampicin, sucralfate, theophylline and vigabatrin.

The serum levels of phenytoin can also be reduced by concomitant use of the herbal remedy St. John's wort (*Hypericum perforatum*). 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. The patient's physician should be consulted for adjustments in either therapy.

A study showed that nelfinavir reduced AUC values of phenytoin when both were administered orally, therefore, phenytoin concentration should be monitored during co-administration with nelfinavir, as nelfinavir may reduce phenytoin plasma concentration.

Drugs which may either increase or decrease serum levels of phenytoin and vice versa include: barbiturates, valproic acid and sodium valproate, ciprofloxacin, primidone, carbamazepine, phenobarbital, antineoplastic agents, certain antacids.

Acute alcohol intake may increase serum levels of phenytoin while chronic alcohol use may decrease them.

Tricyclic antidepressants, haloperidol, monoamine oxidase inhibitors and thioxanthenes may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

Phenytoin impairs the efficacy of several drugs, including: anticonvulsants (succinimide and lamotrigine), corticosteroids, coumarin anticoagulants (dicoumarol), cyclosporine, vitamin D, digoxin, disopyramide, doxycycline, frusemide, L-dopa, mexiletine, oestrogens, oral contraceptives (see sections 4.4 and 4.6), quinidine, and xanthines. Antifungal agents e.g. azoles, antineoplastic agents (dacarbazine), calcium channel blockers, clozapine, methadone, neuromuscular blockers, paroxetine, sertraline, rifampicin, ticagrelor and theophylline.

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/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. Phenytoin may produce lower than normal values for dexamethasone or metapyrone tests.

Phenytoin may cause raised serum levels of glucose, alkaline phosphatase and gamma glutamyl transpeptidase.

Phenytoin may cause 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 supplements given if necessary.

Caution is advised when nifedipine or verapamil are used concurrently with phenytoin. All are highly protein bound medications and therefore changes in serum concentrations of the free, unbound medications may occur.

Phenytoin may increase serum glucose levels and therefore dosage adjustments for insulin or oral antidiabetic agents may be necessary.

Concurrent use of phenytoin and oral diazoxide may decrease the efficacy of phenytoin and the hyperglycaemic effect of diazoxide and is not recommended.

Use of intravenous phenytoin in patients maintained on dopamine may produce sudden hypotension and bradycardia. This appears to be dose-dependent. If

anticonvulsant therapy is necessary during administration of dopamine, an alternative to phenytoin should be considered.

Concurrent use of intravenous phenytoin with lignocaine or beta-blockers may produce additive cardiac depressant effects. Phenytoin may also increase the metabolism of lignocaine.

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**

*Risk related to antiepileptic medicinal products in general*
When possible, medical advice regarding the potential risks to a foetus caused by both seizures and antiepileptic treatment should be given to all women of childbearing potential taking antiepileptic treatment, and especially to women planning pregnancy and women who are pregnant. Antiepileptic treatment should be reviewed regularly and especially when a woman is planning to become pregnant. In pregnant women being treated for epilepsy, sudden discontinuation of antiepileptic drug (AED) therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. As a general principle, monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AEDs.

*Risk related to phenytoin*
Phenytoin crosses the placenta in humans. Similar concentrations of phenytoin have been reported in the umbilical cord and maternal blood.

Prenatal exposure to phenytoin may increase the risks for congenital malformation 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, dysmorphic facial features, nail and digit hypoplasia, and growth abnormalities (including microencephaly) have been reported among children born to women with epilepsy who took phenytoin during pregnancy. Foetal toxicity, developmental toxicity and teratogenicity were observed in offspring of rats given phenytoin during pregnancy (see section 5.3). Neurodevelopmental disorder has been reported among children born to women with epilepsy who took phenytoin alone or in combination with other AEDs during pregnancy. Studies related to neurodevelopmental risk in children exposed to phenytoin during pregnancy are contradictory and a risk cannot be excluded. There have been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. However, the respective role of antiepileptic drugs and other factors in the increased risk is not determined.

Phenytoin should not be used in women of childbearing potential, women planning pregnancy, and pregnant women, except when there is a clinical need and the woman is made aware of the risks of taking phenytoin during pregnancy.

An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to

appropriate adjustment of dosage (see section 4.2). However, postpartum restoration of the original dosage will probably be indicated.

In women of childbearing potential
Phenytoin should not be used in women of childbearing potential unless other antiepileptic drugs are ineffective or not tolerated and the woman is made aware of the risk of potential harm to the foetus and the importance of planning pregnancy. Women of childbearing potential should use effective contraception during treatment. Pregnancy testing in women of childbearing potential should be considered prior to initiating treatment with phenytoin.

Phenytoin may result in a failure of hormonal contraceptives, hence women of childbearing potential should be counselled regarding the use of other effective contraceptive methods (see section 4.5).

Women planning to become pregnant and in pregnant women
In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception. Phenytoin should not be discontinued prior to reassessment of the treatment. When possible, patients should be informed of the potential harm to the foetus. If based on a careful evaluation of the risks and benefits, phenytoin treatment is continued during the pregnancy, it is recommended to use the lowest effective dose and to institute specialised prenatal monitoring, oriented on the possible occurrence of the described malformations.

In neonates
Haemorrhagic syndrome has been reported in neonates born from epileptic mothers receiving phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother during the last gestational month and to the neonate after birth.

Post-natal monitoring/children
In case of exposure during pregnancy, children should be closely monitored in relation to neurodevelopmental disorders in order to provide specialised care as soon as possible, if necessary.

**Breast-feeding**

It is not known whether phenytoin is excreted in human milk. Following administration of oral phenytoin, phenytoin appears to be excreted in low concentrations in human milk. Therefore, breast-feeding is not recommended for women receiving Phenytoin Injection.

## 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. Phenytoin in appropriate doses may as such impair driving skills but epilepsy itself dictates the practice of driving. Patients affected by drowsiness should not drive or operate machinery.

## 4.8 Undesirable effects

The most notable signs of toxicity are cardiovascular collapse and/or depression of the central nervous system. Hypotension can occur when the drug is administered rapidly by intravenous injection. Toxicity should be minimised by following the appropriate directions (see section 4.2).

*Cardiac disorders:* Asystole/cardiac arrest, bradycardia, atrial and ventricular depression and hypotension have been observed. Severe cardiotoxic reactions and fatalities have been reported with atrial and ventricular conduction depression and ventricular fibrillation. Severe complications are most commonly encountered in the elderly or gravely ill patients (see section 4.4**)**.

*Immune system disorders:* Anaphylactoid reaction, anaphylaxis, drug rash with eosinophilia and systemic symptoms (DRESS). 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. Hypersensitivity syndrome has been reported and may in rare cases be fatal (including but not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash and can be fatal), systemic lupus erythematosus, periarteritis nodosa and immunoglobulin abnormalities.

Drug rash with eosinophilia and systemic symptoms (DRESS) (see **Special warnings and precautions for use, under Anticonvulsant Hypersensitivity Syndrome (AHS)**). 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.

*Nervous System disorder:* The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These are the most common reactions encountered with phenytoin and include nystagmus, ataxia, slurred speech, decreased coordination, mental confusion, paraesthesia, somnolence, drowsiness and vertigo. Cases of dizziness, insomnia, transient nervousness, motor twitching, taste perversion, tonic seizures and headaches have also been reported. These side effects are usually dose related.

There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazines and other neuroleptic drugs. These may be due to sudden intravenous administration for status epilepticus. The effect usually lasts for 24-48 hours after discontinuation.

A predominantly sensory peripheral polyneuropathy has been reported for patients on long-term phenytoin therapy. Tonic seizures have also been reported.

*Gastrointestinal disorders:* Nausea, vomiting, constipation and gingival hyperplasia is common with long-term therapy. Its incidence may be reduced by maintaining good oral hygiene such as frequent brushing, gum massage and appropriate dental care.

*Skin and subcutaneous tissue disorders:* A measle-like rash is the most common dermatological manifestation. Morbilliform rashes and other types of dermatitis, hirsutism, hypertrichosis, and coarsening of the facial features. Rashes including scarlatiniform or morbilliformare sometimes accompanied by fever, and are generally more common in children and young adults.

Other types of rashes are more rare, and more serious forms which may be fatal include bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4).

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, phenytoin should not be resumed. If the rash is mild (measles-like or scarlatiniform), therapy may be resumed when the rash has completely disappeared. However, in the case of the rash recurring upon reinstitution of therapy, further phenytoin medication is contraindicated.

*Blood and lymphatic system disorders:* Some fatal haemopoietic complications have occasionally been reported in association with the use of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression and aplastic anaemia. Although 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 local or generalised lymphadenopathy (local or generalized), including benign lymph node hyperplasia, lymphoma, pseudolymphoma 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 resembling serum sickness e.g. rash, fever and liver involvement. In all cases of lymphadenopathy, seizure control should be sought using alternative antiepileptic drugs and observation of patients for an extended period is recommended.

*General disorders and administrative site conditions:*

*Injection Site:* Soft tissue irritation and inflammation has occurred at the site of the injection with and without extravasation of intravenous phenytoin. Oedema, discoloration and pain distal to the site of injection (described as "purple glove syndrome") have also been reported (see section 4.4 –Local Toxicity (including Purple Glove Syndrome)).

Enlargement of the lips. Local irritation, soft tissue irritation may vary from inflammation, 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.

*Neoplasms benign, malignant and unspecified (incl. cysts and polyps):* Hodgkin's Disease.

*Reproductive system and breast disorders:* Peyronie's disease.

*Musculoskeletal and connective tissue disorders:* Systemic lupus erythematosus, motor twitching, Dupuytren's contracture, decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy, and polyarthropathy.

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.

*Hepatobiliary disorders:* Toxic hepatitis, liver damage.

*Respiratory, thoracic and mediastinal disorders:* Rare reports of pulmonary infiltrates or fibrosis, with symptoms including fever, troubled or quick, shallow breathing, unusual tiredness or weakness, loss of appetite and weight, and chest discomfort have also occurred.

Alterations in respiratory function, respiratory arrest, and pneumonitis.

*Renal and urinary disorders:* Interstitial nephritis.

*Investigations:* Thyroid function test abnormal

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
Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via national reporting system.

**To report side effects:**

The National Pharmacovigilance Centre (NPC)

- SFDA Call center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

## 4.9 Overdose

*Symptoms:*

The lethal dose in adults is considered to be 2 to 5 grams. The lethal dose in children is not known. The initial symptoms are nystagmus, ataxia, and dysarthria. Other

signs are tremor, hyperreflexia, lethargy, slurred speech, nausea and 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

*Treatment:* Treatment is nonspecific since there is no known antidote. The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. (If ingestion has taken place, the stomach should be emptied). If the gag reflex is absent, the airway should be supported. Oxygen and assisted ventilation may be necessary for central nervous system, respiratory and cardiovascular depression. Haemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been utilised 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 normalization 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 Pharmacokinetic 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

There are no preclinical data of relevance to the prescriber additional to the data presented in other sections of this summary.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Propylene glycol

Ethanol absolute

Water for Injections.

### 6.2 Incompatibilities

Incompatible with amikacin sulphate, cephapirin 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
After dilution: Use immediately, complete infusion within 1 hour.

## 6.4 Special precautions for storage

Store below 25°C. Keep container in the outer carton.

After dilution: See 6.3

## 6.5 Nature and contents of container

250 mg/5 ml clear Type 1 glass ampoule, in packs of 5 ampoules.

## 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 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 FURTHER INFORMATION

**MARKETING AUTHORISATION HOLDER**
Pfizer Australia Pty Ltd, Clarence street, Sydney, NSW, Australia
**MANUFACTURER:**
Siegfried Hameln GmbH, Langes Feld 13, Hameln, D-31789, Germany

# 8 DATE OF REVISION OF THE TEXT

October 2019

# Document Approval Record

| | |
|---|---|
| **Document Name:** | Saudi_PHENYTOIN_Pfizer_50 mg-ml_solution_for_injection_LPD |
| **Document Title:** | MAH change to Pfizer Australia |

| Signed By: | Date(GMT) | Signing Capacity |
|---|---|---|
| Ibrahim, Waheed MohammedSageer M. | 25-Nov-2021 10:26:11 | Regulatory Affairs Approval |