PHENYTOIN INJ 250 MG/5 ML
(Phenytoin sodium)

1. NAME OF THE MEDICINE
Phenytoin sodium

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
DBL Phenytoin Injection BP is a ready mixed solution of Phenytoin Sodium.

Each mL of solution contains phenytoin sodium 50 mg, propylene glycol 0.4 mL and ethanol absolute 0.1 mL in Water for Injections, adjusted to pH 12 with either sodium hydroxide or hydrochloric acid.

Excipient(s) with known effect
Alcohol
For the full list of excipients, see **6.1 List of excipients** .

3. PHARMACEUTICAL FORM
DBL Phenytoin Injection BP is a clear, colourless solution, free from visible particulates.

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
For the control of status epilepticus, tonic-clonic (grand mal), psychomotor seizures and the prevention of seizures occurring during or following neurosurgery. Phenytoin will prevent or effectively decrease the incidence and severity of convulsive seizures in a high percentage of cases, with patients exhibiting little tendency to become resistant to its action. Besides its effectiveness in controlling seizures, phenytoin frequently improves the mental condition and outlook of epileptic patients.

It has also been used in the treatment of certain cardiac arrhythmias, particularly in those patients who do not respond to conventional antiarrhythmic agents or to cardioversion.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see **4.2 Dose and Method of Administration**).

4.2 Dose and Method of Administration
Dosage
Status epilepticus: For the control of status epilepticus in adults, a loading dose of 10 to 15 mg/kg should be administered slowly intravenously, at a rate not exceeding 50 mg/min. 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.

For neonates and children, a loading dose of 10 to 20 mg/kg intravenously will usually provide a plasma concentration of phenytoin within the generally accepted therapeutic range (10 to 20 micrograms/mL). The drug should be administered intravenously at a rate not exceeding 1 to 3 mg/kg/min, maximum of 50 mg/min, (see **4.4 Special Warnings and Precautions for Use**). Children tend to metabolise phenytoin more rapidly than adults, which may affect dosage regimens. Therefore, serum level monitoring may be particularly beneficial in such cases.

In the treatment of status epilepticus, an intravenous benzodiazepine such as diazepam or an intravenous short acting barbiturate, are usually given initially for the rapid control of seizures and are then followed by the slow intravenous administration of phenytoin.

Intramuscular administration of phenytoin is unsuitable for the emergency treatment of status epilepticus due to very slow and erratic absorption from the intramuscular site.

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

Dosage should be individualised to obtain maximum benefit. In some cases, serum blood level determinations may be necessary for optimal dosage adjustments. Serum levels between 10 and 20 micrograms/mL (40 to 80 micromoles/L) are considered to be clinically effective. With the recommended dosage, a period of at least 7 to 10 days may be required to achieve therapeutic blood levels of phenytoin unless therapy is initiated with a loading dose. After the initial dose has been prescribed, plasma levels should be determined and the dosage adjusted if necessary to obtain a level in the therapeutic range; 10 to 20 micrograms/mL (40 to 80 micromoles/L).

Neurosurgery: For the prevention of seizures during or following neurosurgery, cautious intravenous administration of 250 mg every six to twelve hours is recommended until oral dosage is possible. Plasma levels should be monitored to ensure optimal efficacy and to minimise toxicity. Phenytoin should not be given by intramuscular injection for the prevention of seizures following neurosurgery.

Cardiac arrhythmias: Phenytoin sodium can be useful in ventricular arrhythmias, especially those due to digitalis. Although not a cardiac depressant, it has a positive inotropic effect and enhances conduction, though it generally decreases automaticity. The recommended dosage is one intravenous injection of DBL Phenytoin Injection BP of 3 to 5 mg/kg bodyweight initially, repeating if necessary.

Because there is approximately an 8% increase in drug content in the free form over that of the sodium salt, dosage adjustments and serum level monitoring may be necessary when switching from a product formulated with the free acid to a product formulated with the sodium salt to the form or *vice versa*.

Continuous monitoring of the electrocardiogram and blood pressure is essential. The patient should be observed for signs of respiratory depression. Determination of phenytoin plasma levels is advised when using phenytoin in the management of status epilepticus and the subsequent establishment of maintenance dosage. Cardiac resuscitative equipment should be available.

Method of Administration
DBL Phenytoin Injection BP must be administered slowly. Intravenous administration should not exceed 50 mg/min in adults. In neonates and children the drug should be administered at a rate not exceeding 1 to 3 mg/kg/min, maximum of 50 milligrams/min.

Dilution of DBL Phenytoin Injection BP into intravenous infusion is not recommended due to lack of solubility and resultant precipitation.

The solution 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.

DBL Phenytoin Injection BP should be injected slowly and directly into a large vein through a large-gauge needle or intravenous catheter. Prior to the administration, the patency of the IV catheter should be tested with a flush of sterile saline. Each injection should be followed by an injection of sodium chloride intravenous infusion 0.9% through the same needle or catheter to avoid local venous irritation due to the alkalinity of the solution. Continuous infusion should be avoided.

Product is for one dose in one patient only. Discard any remaining contents.

4.3 Contraindications

Phenytoin is contraindicated in patients with:

1. Known hypersensitivity to phenytoin, or any of the excipients (see **6.1 List of excipients**), or other hydantoins.

2. Sinus bradycardia, sino-atrial block, second and third degree AV block or Stokes Adams syndrome due to its effect on ventricular automaticity.

Coadministration of phenytoin with delavirdine is contraindicated due to 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 and Precautions for Use

The mixing of phenytoin sodium with other drugs or with intravenous infusion solutions is not recommended because the solubility of phenytoin sodium is such that crystallisation or precipitation may result if the special vehicle is altered or the pH is lowered.

Local Toxicity (Including Purple Glove Syndrome)

Soft tissue irritation and inflammation, varying from slight tenderness to extensive necrosis and sloughing of the skin, has been noted at the site of injection with and without the extravasation of IV phenytoin. Oedema, discoloration and pain distal to the site of injection (described as "purple glove syndrome") have been reported following peripheral IV phenytoin injection. 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 interventions such as fasciotomies, skin grafting, and, in rare cases, amputation.

DBL phenytoin injection must not be administered improperly, including by subcutaneous or perivascular injection.

Intramuscular administration of phenytoin sodium is not recommended due to erratic absorption and local tissue reactions, such as tissue necrosis, pain and abscess formation at the injection site caused by the alkalinity of the solution. Erratic absorption is partly caused by tissue precipitation of phenytoin (see **4.2. Dose and Method of Administration**).

Cardiovascular Effects

Hypotension usually occurs when phenytoin is administered rapidly by the IV route. Severe cardiotoxic reactions and fatalities have been reported with arrhythmias including bradycardia, atrial and ventricular conduction depression, ventricular fibrillation or reduced cardiac output. 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.

Metabolic Effect

Phenytoin and other anticonvulsants that have been shown to induce the CYP450 enzyme are thought to affect bone mineral metabolism indirectly by increasing the metabolism of Vitamin D3. This may lead to Vitamin D deficiency and heightened risk of osteomalacia, bone fractures,

osteoporosis, hypocalcaemia and hypophosphatemia in chronically treated epileptic patients (see **4.8 Adverse Effects (Undesirable Effects)**).

Caution should be used when administering phenytoin to patients suffering from porphyria. There have been isolated reports linking phenytoin to exacerbation of this disease.

A small percentage of individuals who have been treated with phenytoin have been shown to metabolise the drug slowly. Slow metabolism appears to be due to limited enzyme availability and lack of or defective induction, which may be genetically determined (see **5.2 Pharmacokinetic Properties** - *Elimination*).

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

Anticonvulsant hypersensitivity syndrome (AHS)
Anticonvulsant Hypersensitivity syndrome (AHS) 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.

AHS/DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy in association with multiple-organ pathologies, often hepatic, 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 mechanism is unknown. The interval between the first drug exposure and symptoms is usually 2 to 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 etiology for the signs and symptoms cannot be established.

Patients at higher risk for developing AHS/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 immunosuppressed patients. The syndrome is more severe in previously sensitized individuals.

<u>If a patient is diagnosed with AHS, discontinue the phenytoin and provide appropriate supportive measures.</u>

Serious dermatologic reactions
Phenytoin can cause rare, severe cutaneous adverse reactions (SCARs) such as acute generalized exanthematous pustulosis (AGEP) (see **4.8 Adverse Effects (Undesirable Effects)**, Dermatologic System) exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS, 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, itching or other signs and symptoms of AHS/DRESS, and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. The physician should advise the patient to discontinue treatment if the rash appears. 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.

Published literature has suggested that there may be an increased, although still rare, risk of hypersensitivity reactions, including skin rash, SJS, TEN, hepatotoxicity, and AHS in African American 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 another anticonvulsant, 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 the combination of phenytoin, cranial irradiation and the gradual reduction of corticosteroids may be associated with the development of erythema multiforme and/or Stevens-Johnson syndrome and/or toxic epidermal necrolysis.

Phenytoin should be discontinued if a skin rash appears. If the rash is exfoliative, purpuric or bullous, or if lupus erythematosus, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is suspected, phenytoin should not be resumed. If the rash is mild (measles-like or scarlatiniform), resumption of therapy, after the rash has disappeared completely, will depend on a consideration of the risk-benefit ratio by the treating doctor. However, in the case of the rash recurring upon reinstitution of therapy, further phenytoin medication is contraindicated.

Angioedema
Angioedema has been reported in patients treated with phenytoin. Phenytoin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur (see **4.8 Adverse Effects (Undesirable Effects)**, Immunologic).

General
Phenytoin is not effective for absence (petit mal) seizures as it may increase the frequency of these seizures. Therefore, combined therapy is required if both tonic-clonic (grand mal) and absence (petit mal) seizures are present.

Phenytoin is not indicated for the treatment of seizures due to hypoglycaemia or other metabolic causes. The appropriate diagnostic tests should be performed as indicated (see **4.4 Special Warnings and Precautions for Use,** Diabetes).

Phenytoin should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus, hence any need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication should be implemented gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of an alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

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

Patients should be cautioned on the use of other drugs or alcoholic beverages without first seeking their physician's advice.

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

Patients should be instructed to call their physician if skin rash develops.

Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution. Unbound concentration of phenytoin may be elevated in patients with hyperbilirubinemia. Unbound phenytoin concentrations may be more useful in these patient populations (see **4.4 Special Warnings and Precautions for Use**, Use in hepatic impairment, Use in renal impairment).

The response to phenytoin may be significantly altered by the concomitant use of other drugs (see **4.5 Interactions with Other Medicines and Other Forms of Interactions**).

Each injection of phenytoin should be followed by an injection of sodium chloride intravenous infusion 0.9% through the same needle or catheter to avoid irritation caused by the alkalinity of the solution.

This drug must be administered slowly, at a rate not exceeding 50 milligrams/min in adults. Administration at faster rates may result in cardiac arrhythmias, impaired cardiac conduction, hypotension, cardiovascular collapse or CNS depression, related to the propylene glycol diluent. In children and neonates, the drug should be administered at a rate not exceeding 1 to 3 mg/kg/min, (maximum of 50 mg/min).

Suicidal behaviour and ideation
Antiepileptic drugs, including phenytoin, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any antiepileptic drug (AED) for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% Cl: 1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients were 0.43% compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. This risk did not vary substantially by age (5 – 100 years) in the clinical trials analysed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1: Risk by Indication for antiepileptic drugs in the pooled analysis

Indication	Placebo patients with	Drug patients with	Relative Risk: Incidence of events in Drug	Risk Difference: Additional Drug patients with

	events/1000 patients	events/1000 patients	patients/incidence in Placebo patients	events per 1000 patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing phenytoin or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence of worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

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

There have been a number of reports suggesting a relationship between phenytoin and the development of local or generalised lymphadenopathy, 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 requires differentiation from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms resembling AHS/DRESS or 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.

While macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy. If folic acid is added to phenytoin therapy, a decrease in seizure control may occur (see **4.5 Interactions with Other Medicines and Other Forms of Interactions**).

It is recommended that patients receiving long term phenytoin therapy should undergo regular blood counts as serious adverse haematological reactions have been reported (see **4.8 Adverse Effects (Undesirable Effects)**).

Diabetes
Phenytoin should be used with caution in diabetic patients, as hyperglycaemia may be potentiated. There have been isolated reports of hyperglycaemia occurring in patients receiving phenytoin, resulting from the drug's inhibitory effects on insulin release. Phenytoin may also raise the serum glucose in diabetic patients. Patients with impaired renal function appear to be more susceptible to this effect.

Caution should also be given in patients with hypoalbuminaemia as this condition can lead to potential toxicity through its effect on increasing unbound phenytoin levels (see **5.2 Pharmacokinetic Properties**).

Medicine enteral feeding/nutrition preparations interaction
Patients who must receive continuous enteral feedings should probably receive phenytoin intravenously as enteral feeds may reduce the absorption of oral phenytoin.

Women of childbearing potential
Phenytoin may cause fetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes (See **4.6 Fertility, Pregnancy and Lactation**).

Phenytoin should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following consideration of other suitable treatment options. Women of childbearing potential, women planning pregnancy, and pregnant women should be fully informed of the potential risk to the fetus if they take phenytoin during pregnancy.

Excipients with Known Effect

DBL Phenytoin injection contains the excipient propylene glycol (see **6.1 List of excipients**). Prolonged use could result in propylene glycol toxicity (including hemolysis, Central Nervous System (CNS) depression, hyperosmolality, lactic acidosis, and renal insufficiency), especially in patients with pre-existing renal and/or hepatic dysfunction or when co-administered with any other propylene glycol-containing product or substrate of alcohol dehydrogenase. Patients should be monitored for propylene glycol toxicity, including measurement of the anion-gap.

Hepatic Injury
The liver is the chief site of biotransformation of phenytoin.

Toxic hepatitis, liver damage and hypersensitivity syndrome 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 may be associated with AHS/DRESS (see **4.4 Special Warnings and Precautions for Use**). Patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

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

Use in hepatic impairment
As the main site of biotransformation for phenytoin is in the liver, patients with impaired liver function may show early signs of toxicity on standard dosage. Care should be exercised with dosage adjustment in these patients.

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

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 re-administered.

Use in renal impairment

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

Use in the elderly
Severe complications are most commonly encountered in elderly or gravely ill patients. In these patients, the drug should be administered at a rate not exceeding 25 mg/min, and if necessary, at a slow rate of 5 to 10 mg/min. Elderly patients have an increased frequency of toxicity due to their slower rate of phenytoin metabolism and decreased serum albumin concentration, which decreases the degree of protein binding of phenytoin. Therefore, lower doses and subsequent dosage adjustment may be necessary.

Paediatric use
Refer to Section 4.2 Dose and Method of Administration.

Effects on laboratory tests
Phenytoin increases blood glucose levels due to inhibition of insulin secretion. Raised serum levels of alkaline phosphatase, hypocalcaemia and osteomalacia have been linked with altered vitamin D metabolism. Elevated serum levels of gamma glutamyl transpeptidase (GGT) and alkaline phosphatase may be related to hepatic enzyme induction. Phenytoin may also produce lower than normal values for dexamethasone or metyrapone.

Folic acid, calcium and free thyroxine concentrations and protein bound iodine (PBI) test values may all be reduced.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Mechanisms of drug interactions with phenytoin may be complex. In assessing drug interactions, serum phenytoin concentrations and the clinical status of the patient will be helpful.

In general, phenytoin is an inducer of the hepatic cytochrome P450 microsomal enzymes including CYP3A4, CYP2D6, CYP1A2, CYP2C9 and CYP2C19 isoenzymes. However, a patient's susceptibility to enzyme induction interactions may be influenced by factors such as age, cigarette smoking or the presence of liver disease (see **5.2 Pharmacokinetic Properties**). Phenytoin is metabolised primarily by CYP2C9 (major) and CYP2C19 (minor), thus several drugs may inhibit or induce the metabolism of phenytoin. The activities of some enzymes such as CYP P450 isoenzymes, the uridine diphosphate glucuronosyl transferase (UDPGT) system and epoxide hydrolase enzymes are significantly increased by phenytoin therapy, which in turn enhances the metabolism of many drugs.

In addition, phenytoin is highly plasma-protein bound and may be displaced by other drugs, increasing unbound ('free') phenytoin levels.

Medicines Which May Increase Phenytoin Serum Levels:
Increased phenytoin plasma concentrations have been reported during concomitant use of phenytoin with capecitabine or its metabolite fluorouracil. Formal interaction studies between phenytoin and capecitabine have not been conducted, but the mechanism of interaction is presumed to be inhibition of CYP2C9 isoenzyme system by capecitabine. Serum levels of phenytoin sustained above the optimal range may produce encephalopathy, or confusional states (delirium psychosis), or rarely irreversible cerebellar dysfunction. Therefore, patients taking phenytoin concomitantly with capecitabine or fluorouracil should be regularly monitored for increased phenytoin plasma levels.

Medicine classes	**Medicines in each class (such as[a])**
Alcohol (acute intake)	
Analgesics/anti-inflammatory agents	• phenylbutazone

	• salicylates
Anaesthetics	• halothane
Antibacterial agents	• chloramphenicol • erythromycin • isoniazid • sulphonamides • sulfadiazine • sulfamethoxazole-trimethoprim
Anticonvulsants	• felbamate • succinimides (ethosuximide, methsuximide and phensuximide) • mephenytoin • topiramate • oxcarbazepine • sodium valproate
Antifungal agents	• amphotericin B • fluconazole • itraconazole • ketoconazole • miconazole • voriconazole
Antineoplastic agents	• fluorouracil • capecitabine
Benzodiazepines/psychotropic agents	• chlordiazepoxide • diazepam • methylphenidate • phenothiazines • trazodone • viloxazine
Calcium channel antagonists/cardiovascular agents	• amiodarone • diltiazem • nifedipine • ticlopidine • dicoumarol
H_2 antagonists/proton pump inhibitors	• cimetidine • omeprazole • ranitidine
HMG-CoA reductase inhibitors	• fluvastatin
Hormones	• oestrogens
Immunosuppressant drugs	• tacrolimus
Oral hypoglycaemic agents	• tolbutamide
Serotonin reuptake inhibitors	• fluoxetine • sertraline • fluvoxamine
Other	• azapropazone • clopidogrel • coumarin anticoagulants • disulfiram

[a] This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted.
[b] Sodium valproate and valproic acid are similar medications. The term valproate has been used to represent these medications.

Medicines which may decrease serum levels of phenytoin:	
Medicine classes	**Medicines in each class** (such as[a])
Alcohol (chronic intake)	
Anticonvulsants	• carbamazepine • vigabatrin
Antibacterial agents	• fluoroquinolones (e.g., ciprofloxacin) • rifampicin
Anti-retrovirals	• fosamprenavir • nelfinavir • ritonavir
Cardiovascular agents	• reserpine
Cytotoxic agents	• bleomycin • carboplatin • carmustine • cisplatin • doxorubicin • methotrexate • vinblastine
Dietary supplements	• calcium folinate • folic acid
Hyperglycaemic agents	• diazoxide
Other	• antacids and preparations containing calcium ions • reserpine • sucralfate • theophylline • St. John's Wort (*Hypericum perforatum*)

[a] This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted.

Calcium ions may interfere with the absorption of phenytoin. Ingestion times of phenytoin and calcium preparations, including antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.

Phenytoin levels may be reduced by 20 to 30% when co-administered with vigabatrin; in some patients this may require a dosage adjustment.

Medicines which may either increase or decrease phenytoin serum levels:	
Medicine classes	**Medicines in each class** (such as[a])
Anticonvulsants	• carbamazepine • barbiturates (e.g., phenobarbitone) • primidone • sodium valproate • valproic acid
Benzodiazepines	• chlordiazepoxide
Psychotropic agents Other	• diazepam • phenothiazines
Antibacterial agents	• ciprofloxacin

[a] This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted.
[b] Sodium valproate and valproic acid are similar medications. The term valproate has been used to represent these medications.

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

Medicines whose blood levels and/or effects may be altered by phenytoin: Medicines that should not be coadministered with phenytoin: delavirdine (see **4.3 Contraindications**)	
Medicine classes	**Medicines in each class** (such as[a])
Antibacterial agents	• doxycycline • praziquantel • rifampicin • tetracycline
Anticoagulants	• warfarin • apixaban • dabigatran • edoxaban • rivaroxaban • coumarin anticoagulants
Anticonvulsants	• lamotrigine • succinimide • carbamazepine • phenobarbital • sodium valproate • valproic acid • lacosamide
Antifungal agents	• azoles • posaconazole • voriconazole
Anthelmintics	• albendazole • praziquantel
Antiplatelets	• ticagrelor
Antiretrovirals	• delavirdine • efavirenz • fosamprenavir • indinavir • lopinavir/ritonavir • nelfinavir • ritonavir • saquinavir • amprenavir
Bronchodilators	• xanthines (e.g. theophylline)
Calcium channel antagonists/cardiovascular agents	• diazoxide • digoxin • disopyramide • frusemide • lignocaine • mexiletine • nicardipine • nifedipine • nimodipine • quinidine

	• verapamil
Diuretics	• furosemide
Cytotoxic agents	• dacarbazine
Hormones	• oestrogens • oral contraceptives
HMG-CoA reductase inhibitors	• atorvastatin • simvastatin • fluvastatin
Neuromuscular blocking drugs	• alcuronium • pancuronium • vecuronium • cisatracurium • rocuronium
Opioid analgesics	• methadone
Oral hypoglycaemic agents	• glibenclamide • glyburide • tolbutamide
Other	• corticosteroids • chlorpropamide • cyclosporin • levodopa • sertraline • teniposide • vitamin D • folic acid
Psychotropic agents	• clozapine • quetiapine • paroxetine

[a] This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted.
[b] Sodium valproate and valproic acid are similar medications. The term valproate has been used to represent these medications.

The plasma clearance of lamotrigine is doubled and its elimination half-life is reduced by 50% when given in combination with phenytoin; this requires dosage adjustment.

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

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

Phenytoin sodium, especially in large doses, may increase serum glucose levels; therefore, dosage adjustments for insulin or oral antidiabetic agents may be necessary.

Use of IV phenytoin in patients maintained on dopamine may produce sudden hypotension and bradycardia. This appears to be dose-rate dependent. If anticonvulsant therapy is necessary during administration of dopamine, an alternative to phenytoin should be considered.

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

Concomitant use of fluoxetine in patients stabilised on phenytoin has resulted in elevated plasma phenytoin concentrations and signs and symptoms of phenytoin toxicity. Plasma phenytoin concentrations should be monitored closely during concomitant use of fluoxetine, and the dose of phenytoin adjusted if necessary.

Co-administration of phenytoin and topiramate reduces topiramate levels by 59% and has the potential to increase phenytoin levels by 25% in some patients.

Hyperammonemia with Concomitant Use of Valproate

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.

4.6 Fertility, Pregnancy and Lactation

Effects on Fertility

In studies in which phenytoin sodium was administered orally to female mice and rats for two weeks before breeding and throughout gestation and lactation, no pregnancies occurred at respective doses of 90 mg/kg/day and 240 mg/kg/day; there were no adverse effects at respective doses of 30 and 80 mg/kg/day.

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

Use in Pregnancy –Category D

Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

It is recommended that:

- Women on AEDs receive pre-pregnancy counselling with regards to the risk of congenital malformations or adverse developmental outcomes;
- AEDs should be continued during pregnancy at the lowest effective dose and monotherapy should be used if appropriate as risk of congenital malformations or adverse developmental outcomes is greater in women taking combined medication.
- Adequate folic acid supplementation should be discussed as part of pre-pregnancy and pregnancy counselling;
- Specialist pre-natal diagnosis including detailed mid-trimester ultrasound should be considered.

An increase in seizure frequency during pregnancy occurs in a high 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. Some patients may experience a rapid reduction in maternal hepatic phenytoin metabolism at the time of delivery, requiring the dosage to be reduced within 12 hours postpartum.

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.

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 of approximately 6% compared to a rate in the general population of 2-3%. Malformations such as orofacial clefts, cardiac defects, dysmorphic facial features, nail and digit hypoplasia, and growth abnormalities (including microcephaly) have been reported either individually or as part of a Fetal Hydantoin Syndrome among children born to women with epilepsy who took phenytoin during pregnancy.

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.

In neonates
Phenytoin can also cause coagulation defects with consequent risk of haemorrhage in the foetus and the new-born infant that may be preventable by the prophylactic administration of vitamin K to the mother prior to delivery.

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

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.

Before the initiation of treatment with phenytoin in a woman of childbearing potential, pregnancy testing should be considered.

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.

Contraception
Women 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 **4.5 Interactions with Other Medicines and Other Forms of Interactions**).

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.

Use in Lactation
Breastfeeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in breast milk.

4.7 Effects on Ability to Drive and Use Machines
Patients should be advised not to drive a car or operate potentially dangerous machinery until it is known that this medication does not affect their ability to engage in these activities.

4.8 Adverse Effects (Undesirable Effects)
The most notable signs of toxicity are cardiovascular collapse and/or CNS depression. Nystagmus is the most frequently reported clinical finding of toxicity and tends to occur when the serum phenytoin concentration exceeds 20 microgram/mL. Toxicity should be minimised by following the appropriate directions (see **4.2 Dose and Method of Administration**).

Body as a whole
Anaphylactoid reaction and anaphylaxis.

Cardiovascular
Asystole/cardiac arrest, bradycardia, and hypotension have been observed. Periarteritis nodosa has been reported. Severe cardiotoxic reactions and fatalities have been reported, most commonly in gravely ill patients or the elderly (see **4.4 Special Warnings and Precautions for Use**).

Central Nervous System
These are the most common reactions encountered with phenytoin and include nystagmus, ataxia, slurred speech, decreased co-ordination and mental confusion. Cerebellar atrophy has been reported, and appears more likely in settings of elevated phenytoin levels and/or long-term phenytoin use. These side effects are usually dose related. Cases of dizziness, vertigo, insomnia, transient nervousness, stuttering, trembling of hands, unusual excitement, irritability, toxic amblyopia, cognitive impairment, tonic seizures, motor twitchings, somnolence, drowsiness, paraesthesia, taste perversion and headaches have also been reported.

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

A predominantly sensory peripheral polyneuropathy has been reported for patients on long term phenytoin therapy.

Gastrointestinal
Nausea, vomiting, epigastric pain, dysphagia, loss of taste, anorexia, weight loss and constipation.

Dermatological System
A measles like rash is the most common dermatological manifestation. Rashes are sometimes accompanied by fever, are generally more common in children and young adults. Other types of rashes are more rare, more serious forms which may be fatal, include bullous, exfoliative or purpuric dermatitis, systemic lupus erythematosus, AGEP, SJS, scarlatiniform or morbilliform rashes and TEN (see **4.4 Special Warnings and Precautions for Use**). Urticaria has been reported.

Immunologic
Hypersensitivity syndrome (which may include but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash [DRESS syndrome: drug rash with eosinophilia and systemic symptoms]), systemic lupus erythematosus and immunoglobulin abnormalities. Angioedema has been reported (see **4.4 Special Warnings and Precautions for Use**, Angioedema).

Hepatic System
Acute hepatic failure. Potentially fatal cases of toxic hepatitis and liver damage may occur. This effect may be the result of a hypersensitivity reaction.

Musculoskeletal System
Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with vitamin D metabolism. Some patients on high phenytoin doses with poor dietary intake of vitamin D, limited sun exposure and reduced levels of physical activity may require vitamin D supplementation. Bone fractures and osteomalacia have also been associated with long-term (>10 years) use of phenytoin by patients with chronic epilepsy. Osteoporosis and other disorders of bone metabolism such as hypocalcaemia, hypophosphatemia and decreased serum levels of Vitamin D metabolites have also been reported.

Haematopoietic System
Some fatal haemopoietic complications have occasionally been reported in association with the use of phenytoin. These have included thrombocytopaenia, leukopaenia, granulocytopaenia, agranulocytosis, and pancytopaenia with or without bone marrow suppression. Although macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease has also been reported (see **4.4 Special Warnings and Precautions for Use**). Pure red cell aplasia has also been reported.

Other
Gingival hyperplasia occurs frequently, usually within the first 6 months, beginning as gingivitis or gum inflammation. Children and young adults do appear more susceptible to gingival hyperplasia than adults. The incidence of gum hyperplasia may be reduced by maintaining good oral hygiene, such as frequent brushing, gum massage and appropriate dental care.

Coarsening of the facial features, enlargement or thickening of the lips, widening of the nasal tip, protrusion of the jaw, gynaecomastia, Dupuytren's contracture, hypertrichosis, immunoglobulin abnormalities, hirsutism and Peyronie's Disease may occur.

Younger patients appear more susceptible to bleeding, tender and enlarged gums. Unusual and excessive body hair growth may be more pronounced in young patients.

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

Injection Site
Local irritation, inflammation, tenderness, necrosis and sloughing at the injection site have been reported with or without extravasation of IV phenytoin. Oedema, discoloration and pain distal to the site of injection (described as "purple glove syndrome") have also been reported (see **4.4 Special Warnings and Precautions for Use,** Local Toxicity (Including Purple Glove Syndrome)).

Investigations
Thyroid function test abnormal

Reporting Suspected Adverse Effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

4.9 Overdose

Sign and Symptoms
The mean 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, somnolence, drowsiness, lethargy, slurred speech, blurred vision, nausea and vomiting. The patient may become comatose, hypotensive, severely confused, dizzy or drowsy, unusually tired or weak. The patient's pupils may become unresponsive and blurred or double vision may also occur. Other manifestations of accidental intravenous overdose of phenytoin are bradycardia and heart block. Death is due to respiratory and circulatory depression and apnoea.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus or lateral gaze, usually appears at 20 micrograms/mL, ataxia at 30 micrograms/mL, dysarthria and lethargy appear when the plasma concentration is over 40 micrograms/mL but as high a concentration as 50 micrograms/mL has been reported without evidence of toxicity. Irreversible cerebellar dysfunction and atrophy have been reported.

Treatment of Overdose
Treatment is nonspecific since there is no known antidote. If the gag reflex is absent, the airway should be supported. Oxygen, vasopressors and assisted ventilation may be necessary for CNS, 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 overdose the possibility of other CNS depressants, including alcohol, should be borne in mind.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action
Phenytoin sodium is a hydantoin derivative anticonvulsant. It inhibits the spread of seizure activity in the motor cortex. Epileptic seizures are thought to occur through the development of excessive central excitability due to post tetanic potentiation, which is blocked by phenytoin.

The primary target of phenytoin in the central nervous system appears to be sodium channels in depolarising neurones, where phenytoin binds and blocks sodium influx, reducing neuronal excitability and the spread of electrical activity characteristic of epileptic seizures. Phenytoin may also suppress sodium action potentials by stimulating the sodium pump. Other mechanisms possibly contributing to the antiepileptic activity of phenytoin include inhibition of neuronal calcium influx, enhancement of GABA neurotransmission, block of ionotropic receptors for glutamate (a transmitter implicated in seizure activity) and an action at central sigma binding sites.

The antiarrhythmic action of phenytoin 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.

Clinical Trials
No data available

5.2 Pharmacokinetic Properties

Absorption

Absorption from an intravenous dose of phenytoin is immediate and bioavailability from the intravenous route is essentially 100%. The onset of action after an intravenous dose is 30 to 60 minutes and the effect persists up to 24 hours.

Distribution

Phenytoin is distributed into cerebrospinal fluid, saliva, semen, gastrointestinal fluids, bile, and breast milk; also crosses the placenta, with foetal serum concentrations equal to those of the mother.

Protein Binding

Phenytoin is about 90% protein bound. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal. Protein binding may be lower in neonates and hyperbilirubinaemic infants; also altered in patients with renal or hepatic disease, or in those with hypoalbuminaemia, hyperbilirubinemia, uraemia or acute trauma, and in pregnancy. The interpretation of total phenytoin plasma concentrations should be made with caution. Therapeutic concentrations of free (unbound) phenytoin, which are frequently monitored in patients with altered protein binding, usually fall in the range of 0.8 to 2 micrograms/mL (3 to 8 micromoles/L).

Half-life

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.

Conventionally, with drugs following linear kinetics the half-life is used to determine the dose rate, drug accumulation and the time to reach steady state. Phenytoin, however, demonstrates non-linear kinetics. Therefore, the half-life is affected by the degree of absorption, saturation of metabolic pathways, dose and degree of metabolic enzyme induction. This results in considerable inter- and intra-patient variability in phenytoin pharmacokinetics. As a consequence the clinical relevance of reported phenytoin half-life values are limited and cannot be used in the conventional manner to estimate the dosage regimen.

Therapeutic Serum Concentrations

When administering phenytoin to a patient, it is necessary to measure the serum levels as this provides the most accurate means of deriving a suitable dosage regimen. Serum level determinations should originally be obtained at least 7 to 10 days after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that equilibrium or steady state will have been achieved. Further serum level determinations may be required to further refine the dosage regimen. Trough levels provide information about clinically effective serum level range and confirm patient compliance and are obtained just prior to the patient's next scheduled dose. Peak levels indicate an individual's threshold for emergence of dose related side effects and are obtained at the time of expected peak concentration.

Optimum control without clinical signs of toxicity occurs most often with serum levels between 10 and 20 micrograms/mL. In renal failure or hypoalbuminaemia, 5 to 12 micrograms/mL or even less may be therapeutic. Occasionally a patient may have seizure control with plasma concentrations of 6 to 9 micrograms/mL. Effective treatment, therefore, should be guided by clinical response, not drug concentrations. 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 non-compliant or hypermetabolisers of phenytoin. Unusually high levels of phenytoin 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 particularly helpful.

Metabolism
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 polymorphism, which may cause isoenzyme mutations (e.g. CYP2C9/19), limited enzyme availability and lack of induction (e.g. CYP3A4).

Excretion
Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine. Urinary excretion of phenytoin and its metabolites occurs partly by glomerular filtration but more importantly by tubular secretion.

5.3 Preclinical Safety Data

Genotoxicity
In genotoxicity studies with phenytoin sodium, negative results were obtained in assays for chromosomal damage in mammalian cells *in vitro* and *in vivo* and in a sister chromatid exchange assay *in vivo*. The potential for phenytoin sodium to cause gene mutations has not been investigated.

Phenytoin is teratogenic in rats, mice and rabbits.

Carcinogenicity
In two studies in mice, increased incidences of hepatic adenoma were seen when phenytoin sodium was administered at dietary doses of 45 and 90 mg/kg/day. The incidence of hepatic carcinoma was also increased in one of these studies. These effects were seen at plasma phenytoin concentrations slightly lower than the human therapeutic range. In rats, the incidence of hepatic adenoma was marginally increased at 240 mg/kg/day in one study, but was not affected at 100 mg/kg/day in another. In the latter study, plasma concentrations of phenytoin were slightly lower than the human therapeutic range. In two other studies, no carcinogenic effects were seen at low doses (16 mg/kg/day in mice and 20 mg/kg/day in rats). Phenytoin induced hepatic tumours in rodents may be secondary to hepatic enzyme induction, and are of uncertain clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Propylene glycol
- Ethanol absolute
- Water for Injections
- Sodium hydroxide
- Hydrochloric acid

6.2 Incompatibilities

Dilution of DBL Phenytoin Injection BP into intravenous infusion is not recommended due to lack of solubility and resultant precipitation (see **4.2 Dose and Method of Administration**).

The mixing of phenytoin sodium with other drugs or with intravenous infusion solutions is not recommended because the solubility of phenytoin sodium is such that crystallisation or precipitation may result if the special vehicle is altered or the pH is lowered (see **4.4 Special Warnings and Precautions for Use**).

The response to phenytoin may be significantly altered by the concomitant use of other drugs (see **4.5 Interactions with Other Medicines and Other Forms of Interactions**).

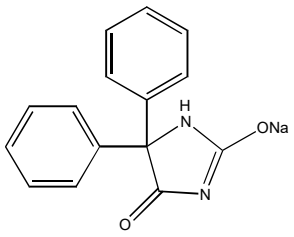
6.3 Shelf Life
Please refer to outer carton for expiry date.

6.4 Special Precautions for Storage
Please refer to outer carton for storage condition.

6.5 Nature and Contents of Container
DBL Phenytoin Injection BP is available as 5 x 5 mL ampoules, each ampoule containing phenytoin sodium 250 mg.

Strength	Pack Size
250 mg/5 mL	5 x 5 mL ampoules

6.6 Physicochemical Properties
Chemical structure



Chemical name: sodium 5,5-diphenyl-2,4-imidazolidinedione
Chemical formula: $C_{15}H_{11}N_2NaO_2$
MW: 274.3

CAS Number

630-93-3

Phenytoin sodium is the sodium salt of phenytoin. It is a white, odourless, slightly hygroscopic crystalline powder. It is soluble in water and alcohol.

Pfizer Corporation Hong Kong Limited
NOV 2022
Version approved: 24 FEB 2023