SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Phenytoin Sodium 50mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of solution contains phenytoin sodium 250mg.

Excipient(s) with known effect

Each 5ml of solution also contains 404.25 mg of ethanol, 2070 mg of propylene glycol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection.

A clear colourless particle free solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

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

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

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

Determination of phenytoin serum levels is advised during use in the management of status epilepticus and subsequently whilst establishing maintenance dosage. The clinically effective range is usually 10- 20mg/1 although some cases of tonic-clonic seizures may be controlled with lower serum levels of phenytoin.

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

Other clinical conditions: It is not possible to provide a universally applicable dosage schedule.

The intravenous route of administration is preferred. Dosage and dosing interval will be determined by the needs of the individual patient and factors such as previous anti-epileptic therapy, seizure control, age and general medical condition must be considered.

Although absorption of phenytoin is slow following i.m. injection, such use may be appropriate in certain conditions.

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

Neurosurgery: In a patient who has not previously received the drug, Phenytoin Injection 100 - 200mg (2 - 4ml) may be given intramuscularly at approximately 4-hour 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 300mg and adjusted according to serum level estimations.

If possible, intramuscular injections of phenytoin should not be continued for more than one week; after this, alternative routes such as naso-gastric intubation should be considered. For time periods less than one week, the patient switched from intramuscular administration should receive half the original oral dose for the same period of time the patient received phenytoin intramuscularly. Measurement of serum levels is of value as a guide to an appropriate adjustment of dosage.

Elderly: (over 65 years): Phenytoin clearance may be decreased in elderly patients.Lower or less frequent dosing may be required (see section 5.2). It should be noted that complications may occur more readily in elderly patients.

Paediatric population

Neonates: In neonates it has been shown that absorption of phenytoin is unreliable after oral administration, but a loading dose of phenytoin injected slowly intravenously at a rate of 1-3mg/kg/min at a dose of 15-20mg/kg will usually produce serum concentrations of phenytoin within the generally accepted therapeutic range of 10-20mg/l.

Infants and children:. Children tend to metabolize phenytoin more rapidly than adults. This should be considered when determining dosage regimens; monitoring serum levels is therefore particularly beneficial in such cases.

Method of administration: Intravenous. Intramuscular.

Solutions for parenteral administration should be inspected visually for particulate matter and discoloration prior to use. Only a clear solution should be used and the

product should be discarded if a precipitate or haziness develops in the solution. On refrigeration or freezing, a precipitate might form, but this will dissolve when the solution is allowed to stand at room temperature. The product is still suitable for use. Only a clear solution should be used. A faint yellow discoloration may develop, but this does not affect the potency of the solution.

There is a relatively small margin between full therapeutic effect and minimally toxic doses of this drug. Optimum control without clinical signs of toxicity can most often be achieved with serum levels in the range 10 - 20mg/1 (40 - 80 micromoles/1).

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

Each injection or infusion of intravenous phenytoin should be preceded and followed by an injection of sterile saline through the same needle or catheter to avoid local venous irritation due to alkalinity of the solution. (See section 4.4)

For administration by intravenous infusion phenytoin injection should be diluted in 50 - 100 ml of normal saline, and the final concentration of phenytoin in the solution should not exceed 10 mg/ml, the infusion mixture should not be refrigerated. 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.

Phenytoin should neither be mixed with other drugs nor be added to dextrose or dextrose-containing solutions due to the potential for precipitation of phenytoin acid.

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

4.3 Contraindications

Hypersensitivity to the active substance, other hydantoins or to any of the excipients listed in section 6.1.

Because of its effect on ventricular automaticity, it is also contra-indicated in sinus bradycardia, sino-atrial block, and second and third degree A-V block, and patients with Adams-Stokes syndrome. Intra-arterial injection must be avoided because of the high pH of the solution.

Co-administration of phenytoin is contraindicated with delavirdine due to the potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.

4.4. Special warnings and precautions for use

General

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

Hypotension usually occurs with rapid administration of phenytoin by the intravenous route. Irritation and inflammation of soft tissue has occurred at the injection site with and without extravasation of intravenous phenytoin. Soft tissue irritation may vary from slight tenderness to extensive necrosis, sloughing and in rare instances has led to

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

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.

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

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

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

Phenytoin may precipitate or aggravate absence seizures and myoclonic seizures.

Because phenytoin is highly protein bound and extensively metabolised by the liver, reduced maintenance dosage may be required in patients with impaired liver function to prevent accumulation and toxicity. Where protein binding is reduced, as in uraemia, total serum phenytoin levels will be reduced accordingly. However, as the pharmacologically active free drug concentration is unlikely to be altered, under these circumstances therapeutic control may be achieved with total phenytoin levels below the normal range 10 - 20mg/l.

Dosage should not exceed the minimum necessary to control convulsions.

Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total plasma phenytoin 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.

Cardiovascular Effect

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

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

Anticonvulsant Hypersensitivity Syndrome (AHS) is a rare drug-induced, multiorgan syndrome that is potentially fatal and occurs in some patients taking anticonvulsant medication, including phenytoin. AHS/DRESS typically, although not exclusively is characterized by fever, rash, lymphadenopathy, and other multiorgan pathologies, such as hepatitis, nephritis, haematological abnormalities, myocarditis, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leucocytosis, and eosinophilia. The mechanism is unknown. The interval between first drug exposure and symptoms is usually 2-4 weeks, but has been reported in individuals receiving anticonvulsants for 3 or more months. If such signs and symptoms occur, the patient

should be evaluated immediately. Phenytoin should be discontinued if an alternative aetiology for the signs and symptoms cannot be established. 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/DRESS include black patients, patients who have a family history of or who have experienced this syndrome in the past (with phenytoin or other anticonvulsant drugs), and immuno-suppressed 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:

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Phenytoin.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS and TEN is within the first weeks of treatment.

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

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.

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.

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.

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.

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

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 (see section 4.2).

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

Central Nervous System Effect

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as 'delirium', 'psychosis' or 'encephalopathy' or rarely irreversible cerebellar dysfunction and/or cerebellar atrophy. Accordingly, at the first sign of acute toxicity, serum drug level determinations are recommended. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination of therapy with phenytoin is recommended.

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)

Hepatic Injury

Biotransformation of phenytoin occurs mainly in the liver.

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

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents usually occur within the first 2 months of treatment and may be associated with AHS/DRESS (see section 4.4).

Patients with impaired hepatic function, the elderly, or those who are gravely ill may show early signs of toxicity.

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

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

Haematopoietic System

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

Metabolic Effect

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. Caution is advised when treating patients with diabetes.

There are isolated reports associating phenytoin with exacerbation of porphyria, therefore, caution should be exercised when using phenytoin in patients with porphyria.

CYP2C9 metabolism

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

Suicide

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic 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.

Women of childbearing potential

Phenytoin may cause foetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for major congenital malformations and other adverse development outcomes (see Section 4.6). The magnitude of the risk to the foetus is unknown when phenytoin use is of short duration (emergency situations).

Phenytoin Injection should not be used in women of childbearing potential except where there is a clinical need and when possible, the woman should be informed of the potential risk to the foetus associated with the use of phenytoin during pregnancy. In emergency situations, the risk of harm to the foetus should be assessed in view of the risk of status epilepticus of the tonic-clonic (grand mal) type and seizures occurring during or following neurosurgery and/or severe head injury for both the foetus and the pregnant woman.

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

Due to enzyme induction, Phenytoin Injection may result in a failure of the therapeutic effect of hormonal contraceptives (see Sections 4.5 and 4.6).

Laboratory tests: It may be necessary to measure serum phenytoin levels to achieve optimal dosage adjustments.

Excipient

This product contains a number of excipients known to have a recognized action or effect. These are:

- Propylene glycol: This medicine contains 2070 mg propylene glycol in each 5 ml which is equivalent to 414 mg/ml. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.

  While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.

  Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

  Various adverse events, such as hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnoea; liver dysfunction; haemolytic reaction (intravascular haemolysis) and haemoglobinuria; or multisystem organ dysfunction, have been reported with high doses or prolonged use of propylene glycol.

  Therefore doses higher than 500 mg/kg/day may be administered in children > 5 years old but will have to be considered case by case.

  Adverse events usually reverse following weaning off of propylene glycol, and in more severe cases following hemodialysis.

  Medical monitoring is required.

- Sodium: This medicine contains less than 1 mmol sodium (23 mg) per 5ml, that is to say essentially ‘sodium-free’.

- Ethanol: This medicine contains 404.25 mg of alcohol (ethanol) in each 5ml. which is equivalent to 80.85 mg/ml. The amount in 5ml of this medicine is equivalent to 10.11 ml beer or 4.04 ml wine.

  A dose of 20mg/kg of this medicine administered to (a child 5 years of age and weighing 20 kg or an adult weighing 70 kg) would result in exposure to 32 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 5.3 mg/100 ml.

  For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml.

  Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity.

  Because this medicine is usually given slowly, the effects of alcohol may be reduced.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions

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

Sucralfate may decrease phenytoin serum levels.

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

Certain antacids may either increase or decrease phenytoin serum levels.

Phenytoin increases the clearance of quetiapine and thus impairing the effect of it. Neurotoxicity has been reported during concomitant use of phenytoin and lithium.

Drugs whose effect is impaired by phenytoin include: antifungal agents e.g. antifungals, antineoplastic agents, calcium channel blockers, clozapine, corticosteroids, ciclosporin, dicoumarol, digitoxin, doxycycline, furosemide, lamotrigine, methadone, neuromuscular blockers, oestrogens, oral contraceptives, paroxetine, quinidine, rifampicin, theophylline, vitamin D, amprenavir, disopyramide, felodipine, haloperidol, levodopa, methoxsalen, mexiletine, and thyroxine.

Drugs whose effect may be 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.

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

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

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

The most commonly occurring drug interactions are listed below.

Drugs which may increase Phenytoin serum levels

Table 1 summarizes the drug classes which may potentially increase Phenytoin serum levels.

Table 1. Drugs which may increase Phenytoin Serum Levels

Drug Classes	**Drugs in each Class (such as)**
Alcohol (acute intake)	
Analgesic/Anti-inflammatory agents	azapropazone phenylbutazone

	salicylates
Anesthetics	halothane
Antibacterial agents	chloramphenicol erythromycin isoniazid sulfadiazine sulfamethizole sulfamethoxazole-trimethoprim sulfaphenazole sulfisoxazole sulfonamides
Anticonvulsants	felbamate oxcarbazepine sodium valproate succinimides topiramate
Antifungal agents	amphotericin B fluconazole itraconazole ketoconazole miconazole voriconazole
Antineoplastic agents	fluorouracil capecitabine
Benzodiazepines/Psychotropic agents	chlordiazepoxide diazepam disulfiram methylphenidate trazodone viloxazine
Calcium channel blockers/Cardiovascular agents	amiodarone dicumarol diltiazem nifedipine ticlopidine
H2-antagonists	cimetidine
HMG-CoA reductase inhibitors	fluvastatin
Hormones	oestrogens
Immunosuppressant drugs	tacrolimus
Oral hypoglycemic agents	tolbutamide
Proton pump inhibitors	omeprazole
Serotonin re-uptake inhibitors	fluoxetine fluvoxamine sertraline

Drugs which may decrease Phenytoin serum levels

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

Table 2. Drugs which may decrease Phenytoin Serum Levels

Drug Classes	**Drugs in each Class (such as)**
Alcohol (chronic intake)	
Antibacterial agents	rifampin

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

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

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

Drugs which may increase or decrease Phenytoin serum levels

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

Table 3. Drugs which may increase or decrease Phenytoin Serum

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

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

Oral anticoagulants (e.g. rivaroxaban, dabigatran, apixaban, edoxaban)

lacosamide

ticagrelor

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

Table 4 summarizes the drug classes whose serum levels and/or effects may be

altered by Phenytoin.

Table 4. Drugs whose serum levels and/or effects may be altered by Phenytoin

Drug Classes	**Drugs in each Class (such as)**
Antibacterial agents	doxycycline rifampin tetracycline
Anticonvulsants	carbamazepine lamotrigine phenobarbital sodium valproate valproic acid
Antifungal agents	azoles posaconazole voriconazole
Antihelmintics	albendazole praziquantel
Antineoplastic agents	teniposide
Antiretrovirals	delavirdine efavirenz fosamprenavir indinavir lopinavir/ritonavir nelfinavir ritonavir saquinavir
Bronchodilators	theophylline
Calcium channel blockers/Cardiovascular agents	digitoxin digoxin mexiletine nicardipine nimodipine nisoldipine quinidine verapamil
Corticosteroids	
Coumarin anticoagulants	warfarin
Cyclosporine	
Diuretics	furosemide
HMG-CoA reductase inhibitors	atorvastatin fluvastatin simvastatin
Hormones	oestrogens oral contraceptives
Hyperglycemic agents	diazoxide
Neuromuscular blocking agents	alcuronium cisatracurium pancuronium rocuronium vecuronium
Opioid analgesics	methadone
Oral hypoglycemic agents	chlorpropamide glyburide tolbutamide

Psychotropic agents/Antidepressants	clozapine paroxetine quetiapine sertraline
Vitamin D	vitamin D

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

Drug/laboratory test interactions

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

These changes do not lead to clinical hypothyroidism and do not affect the levels of circulating TSH. The latter can therefore be used for diagnosing hypothyroidism in the patient on phenytoin. Phenytoin does not interfere with uptake and suppression tests used in the diagnosis of hypothyroidism.

Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metapyrone tests. Phenytoin may cause raised serum levels of glucose, alkaline phosphatase, gamma glutamyl transpeptidase and lowered serum levels of calcium and folic acid. Phenytoin may affect blood sugar metabolism tests.

It is recommended that serum folate concentrations be measured at least every 6 months, and folic acid supplements given if necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy

The following information should be taken into account when considering the intravenous use of phenytoin in the management of status epilepticus in pregnancy. It is essential to control the condition as quickly as possible in order to reduce the potential adverse effects, specifically hypoxia, of status epilepticus upon the foetus.

There are intrinsic methodologic problems in obtaining meaningful data on drug teratogenicity in humans. Genetic factors or the epileptic condition itself may be more important than drug therapy in the development of birth defects. Most mothers on anticonvulsant therapy deliver normal infants. In patients receiving an anticonvulsant drug to prevent major seizures, it is important that the drug should not be discontinued because of the strong possibility of precipitating status epilepticus and attendant hypoxia and threat to life if the drug was withdrawn. In individual cases, where the frequency and severity of the seizure disorder are such that cessation of therapy does not pose a serious risk to the patient, discontinuation of the drug may be considered prior to and during pregnancy. However, it cannot be stated with certainty that even minor seizures do not pose some hazard to the developing embryo or foetus.

Risk related to antiepileptic medicinal products in general

Medical advice regarding the potential risks to a fetus 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

There is some evidence that phenytoin may produce congenital abnormalities in the offspring of a small number of patients with epilepsy. Therefore, phenytoin should not be used as a first-line drug during pregnancy, especially in early pregnancy, unless the physician considers that the potential benefits outweigh the risk.

In addition to the reports of increased incidence of congenital malformations such as cleft lip/palate and cardiac malformations in children of women who received phenytoin and other antiepileptic agents, there have been reports of foetal hydantoin syndrome. The syndrome consists of prenatal growth deficiency, microencephaly and mental deficiency in the children of women who received phenytoin, alcohol, barbiturates or trimethadione. However, all of these features are interrelated and are frequently associated with intrauterine growth retardation due to other causes.

There are isolated reports of malignancies, including neuroblastoma, in the children of women who received phenytoin during pregnancy. However, the respective role of antiepileptic drugs and other factors in the increased risk is not determined.

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

Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage (see section 4.2). However, postpartum restoration of the original dosage will probably be indicated. Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenytoin. Vitamin K has been shown to prevent or correct this defect and may be given to the mother before delivery and to the neonate after birth.

Reproductive and developmental toxicity has been observed in animals (see section 5.3).

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 malformations and other adverse developmental outcomes. In humans, studies have shown that phenytoin exposure during pregnancy is associated with an approximate 6 % frequency of major malformations, 2 to 3 times higher than that of the general population, which has a frequency of 2-3%. Malformations such as orofacial clefts, cardiac defects, craniofacial defects, dysmorphic facial features, nail and digit hypoplasia, and growth abnormalities (including microcephaly and prenatal growth deficiency), have been reported either individually or as part of a Fetal Hydantoin Syndrome among children born to women with epilepsy who used phenytoin during pregnancy. Neurodevelopmental disorder has been reported among children born to women with epilepsy who used phenytoin alone or in combination with other AEDs during pregnancy. Data related to neurodevelopmental risk in children exposed to phenytoin during pregnancy are inconsistent. However, a small number of studies found an increase of serious adverse outcomes compared to control subjects including fetal hydantoin syndrome and below average IQ. Studies related to the risk of neurodevelopmental disorders in children exposed to phenytoin during pregnancy are contradictory and a risk cannot be excluded.

Phenytoin Injection should not be used in women of childbearing potential, women planning pregnancy and during pregnancy except where there is a clinical need and when possible, the woman is made aware of the risk of potential harm to the foetus.

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 fetus 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 fetus. If based on a careful evaluation of the risks and the benefits, phenytoin treatment is continued during the pregnancy, it is recommended to use the lowest effective dose and to institute specialized 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 specialized care as soon as possible, if necessary.

Breast-feeding

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

Fertility:

No data available.

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 (see Section 4.8).

4.8 Undesirable effects

In the table below all adverse reactions with phenytoin are listed by class and frequency: Rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the available data).

Signs of toxicity are associated with cardiovascular and central nervous system depression.

MedDRA System organ Class	**Frequency**	**Undesirable Effects**
Blood and lymphatic system disorders	Not Known	Pure red cell aplasia, Haematopoietic complications , some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression and aplastic anaemia. While macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy. There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalised) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, e.g. fever, rash and liver involvement. In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Immune system disorders	Rare Not Known	Hypersensitivity syndrome Anaphylactoid reaction, anaphylactic reaction, periarteritis nodosa, immunoglobulin abnormalities may occur.
Psychiatric disorders	Not Known	Insomnia, transient nervousness, confusion.
Nervous system disorders	Rare Not Known	There have also been rare reports of phenytoin-induced dyskinesia, including chorea, dystonia, tremor, and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. Adverse reactions in this body system are common and are usually dose-related. Reactions include nystagmus, ataxia, dysarthria and decreased coordination. Cerebellar atrophy has been reported, and appears more likely in settings of elevated phenytoin levels and/or long-term phenytoin use (see section 4.4). Dizziness, motor twitchings, headache, paraesthesia, somnolence, drowsiness and dysgeusia have also been observed. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy. Tonic convulsions have also been reported. Peripheral sensory neuropathy.
Ear and labyrinth disorders	Not Known	Vertigo
Cardiac disorders	Not Known	Hypotension may occur. Arrhythmias including bradycardia, atrial and ventricular depression and ventricular fibrillation can occur and these have, in some cases, resulted in asystole/ cardiac arrest and death. Severe complications are most commonly encountered in older people or gravely ill patients.
Respiratory, thoracic and mediastinal disorders	Not Known	Pneumonitis, alterations in respiratory function including respiratory arrest may occur.
Gastrointestinal disorders	Not Known	Vomiting, nausea, gingival hyperplasia, constipation.
Hepatobiliary disorders	Not Known	Acute hepatic failure, hepatitis toxic, liver injury, hepatotoxicity, hepatic function abnormal

Skin and subcutaneous tissue disorders	Rare Not Known	Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4) has been reported and may in rare cases be fatal (the syndrome may include, but is not limited to, symptoms such as arthralgia, eosinophilia, pyrexia, hepatic function abnormal, lymphadenopathy or rash). 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. Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles like) is the most common. Other types of dermatitis are seen more rarely. Other more serious and rare forms which may be fatal have bullous, exfoliative or purpuric dermatitis, lupus erythematosus, hirsutism, hypertrichosis, coarsening of the facial features and enlargement of the lips, Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported very rarely (see section 4.4). Skin exfoliation.
Musculoskeletal and connective tissue disorders	Not Known	Systemic lupus erythematosus, arthropathy. 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. Discoloration and pain distal to the site of injection (described as “purple glove syndrome”) have also been reported (see section 4.4). Dupuytren’s contracture. Arthralgia.
Renal and urinary disorders	Not Known	Tubulointerstitial nephritis, Peyronie’s Disease.
General disorders and administration site conditions	Not Known	Local irritation, inflammation, tenderness, necrosis and oedema have been reported with or without extravasation of intravenous phenytoin. Fever.
Investigations	Not Known	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 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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The mean lethal dose in adults is estimated to be 2 to 5 grams. The lethal dose in children is not known. The initial signs are nystagmus, diplopia, ataxia, and dysarthria. Other signs are tremor, hyperflexia, lethargy, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

Attempts to relate serum levels of the drug to toxic effects have shown wide interpatient variation. Nystagmus on lateral gaze usually appears at 20mg/l and ataxia at 30mg/l. Dysarthria and lethargy appear when the serum concentration is above 40mg/l, although a serum concentration as high as 50mg/l has been reported without evidence of toxicity.

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

Treatment: There is no known antidote and treatment is symptomatic and supportive. Particular attention should be paid to circulatory and respiratory function and appropriate supportive measures employed.

Haemodialysis can be considered, since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in children.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC code: N03AB 01

Phenytoin is effective in various animal models of generalised convulsive disorders and reasonably effective in models of partial seizures but relatively ineffective in models of myoclonic seizures.

Phenytoin is an anticonvulsant which appears to stabilise rather than elevate the seizure threshold and to limit the spread of seizure activity rather than abolish the primary focus of seizure discharge. Phenytoin exerts a stabilising effect on excitable membranes of a variety of cells, including neurons and cardiac myocytes.

The mechanism by which phenytoin exerts its anticonvulsant action has not been fully elucidated, however, possible contributory effects include:

1. Non-synaptic effects to reduce sodium conductance, enhance active sodium extrusion, block repetitive firing and reduce post-tetanic potentiation.

2. Post-synaptic action to enhance GABA-mediated inhibition and reduce excitatory synaptic transmission.

3. Pre-synaptic actions to reduce calcium entry and block release of neurotransmitter.

5.2 Pharmacokinetic properties

Distribution

After injection phenytoin is distributed into body fluids including CSF.

Its volume of distribution has been estimated to be between 0.52 and 1.19 litres/kg, and it is highly protein bound (usually 90% in adults).

In serum, phenytoin binds rapidly and reversibly to proteins. About 90% of phenytoin in plasma is bound to albumin. The plasma half-life of phenytoin in man averages 22 hours with a range of 7 to 42 hours.

Biotransformation

Phenytoin is hydroxylated in the liver by an enzyme system that is saturable. Small incremental doses may produce very substantial increases in serum levels when these are in the upper range of therapeutic concentrations.

Elimination

The parameters controlling elimination are also subject to wide interpatient variation. The serum level achieved by a given dose is therefore also subject to wide variation.

Special Populations

Patients with Renal or Hepatic Disease: see section 4.4.

Age: Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20-30 years of age). Phenytoin dosing requirements are highly variable and must be individualized (see section 4.2).

5.3 Preclinical safety data

Reproductive and developmental toxicity:

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

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

Carcinogenesis:

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene Glycol

Ethanol 96% w/v

Sodium Hydroxide Solution 10% w/v

Water for Injections

6.2 Incompatibilities

Phenytoin has a pH in the range of 10 - 12.3. It will only stay in solution when the pH is considerably alkaline (about 10 - 12). The mixing of phenytoin sodium injection with other drugs is not recommended.

Phenytoin should neither be mixed with other drugs nor be added to dextrose or dextrose-containing solutions due to the potential for precipitation of phenytoin acid.

6.3 Shelf life

3 years.

If only part used, discard the remaining solution.

6.4 Special precautions for storage

Do not store above 30°C.

Keep the ampoule in the outer carton in order to protect from light.

6.5 Nature and contents of container

5ml, clear glass ampoules, glass type I, Ph. Eur. packed in cardboard cartons to contain 10 x 5ml ampoules.

6.6 Special precautions for disposal

For I.V. and I.M. administration.

Use as directed by the physician.

Solutions in which a haziness or precipitate develops should not be used.

Do not mix with other drugs because of precipitation of phenytoin acid.

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

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Limited

Dashwood House,

69 Old Broad Street,
London, EC2M 1QS,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0597

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 29 November 1991

10 DATE OF REVISION OF THE TEXT

07/02/2024