SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epanutin Ready-Mixed Parenteral 250mg/5ml Solution for Injection or Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml ampoule contains phenytoin sodium 250 mg (50 mg/ml).

Excipients with known effect:
Each 5 ml also contains 2.072 g propylene glycol, 400.0 mg ethanol 96% and 22.04 mg of sodium (see section 4.4).

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion.

Clear, colourless, sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

It is also indicated for the treatment of life threatening ventricular arrhythmias or arrhythmias secondary to digitalis intoxication, when these have not responded to other available antiarrhythmic treatments or when other antiarrhythmic agents cannot be used.

4.2 Posology and method of administration

Rapid IV administration may be associated with adverse cardiovascular events (see Section 4.4).

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

Because of the risks of cardiac and local toxicity associated with intravenous phenytoin, oral phenytoin should be used whenever possible.

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

Posology

Adults

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

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

Absorption of phenytoin in neonates is unreliable after oral administration, but a loading dose of 15 mg/kg - 20 mg/kg of Epanutin intravenously will usually produce serum concentrations of phenytoin within the generally accepted therapeutic range (10 mcg/ml - 20 mcg/ml).

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

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

Use in Cardiac Arrhythmias:
Dosage 3.5 mg per kg - 5 mg per kg of bodyweight intravenously initially, repeated once if necessary. The solution should be injected slowly, intravenously and at a uniform rate which should not exceed 1 ml (50 mg/min).

Neurosurgery:
In a patient who has not previously received the drug, Parenteral Epanutin 100 mg - 200 mg (2-4 ml) may be administered intramuscularly at approximately 4-hour

intervals prophylactically during neurosurgery and continued during the post-operative period for 48-72 hrs. The dosage should then be reduced to a maintenance dose of 300 mg and adjusted according to serum level estimations.

If the patient requires more than a week of intramuscular Epanutin, alternative routes should be explored such as gastric intubation. For time periods less than one week, the patient switched from intramuscular administration should receive one half the original oral dose for the same period of time the patient received Epanutin intramuscularly.

Measurement of serum levels is of value as a guide to an appropriate adjustment of dosage.

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

The intravenous route (IV) of administration is preferred. Dosage and dosing interval will, of necessity, be determined by the needs of the individual patient. Factors such as previous antiepileptic therapy, seizure control, age and general medical condition must be considered. Notwithstanding the slow absorption of Epanutin, when given intramuscularly, its use in certain conditions may be appropriate.

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 Epanutin intramuscularly, to prevent excessive serum levels due to continued release from intramuscular tissue sites.

TABLE 1.* ADULTS POSOLOGY

Indication	**Dose**	**Phenytoin Sodium Injection Posology**
Status Epilepticus	Loading	Dosage: 10 - 15 mg/kg intravenously Infusion rate: Not to exceed a rate of 50 mg/min
	Maintenance	Dosage: 100 mg orally or intravenously every 6 to 8 hours Infusion rate: 1 – 3 mg/kg/min intravenously
Neurosurgery	Loading	Dosage: 100 - 200 mg (2 - 4 ml) intramuscularly at approximately 4-hour intervals
	Maintenance	Dosage: 300 mg
Cardiac Arrhythmia	Dosage: 3.5 - 5 mg/kg intravenously Infusion rate: Not to exceed a rate of 50 mg/min	

* The detailed adult posology is outlined under Section 4.2.

Parenteral substitution for oral phenytoin therapy
Epanutin Ready Mixed Parenteral contains phenytoin sodium whereas Epanutin Suspension and Epanutin Infatabs contain phenytoin. Although 100 mg of phenytoin sodium is equivalent to 92 mg of phenytoin on a molecular weight basis, these molecular equivalents are not necessarily biologically equivalent. Physicians should therefore exercise care in those situations where it is necessary to change the dosage form and serum level monitoring is advised.

Dosing in Special Populations

Patients with Renal or Hepatic Disease:
See section 4.4.

Elderly (over 65 years):
Phenytoin clearance may be decreased in elderly patients and lower or less frequent dosing may be required (see section 5.2 – Special Populations – Age). As for adults, however, complications may occur more readily in older people.

Paediatric population:
It has been shown that younger children tend to metabolise phenytoin more rapidly than adults, with metabolism in older children (adolescents) approaching that of adults and absorption of phenytoin in neonates is unreliable after oral administration. This should be borne in mind when determining dosage regimens; the use of serum level monitoring being particularly beneficial in such cases.

TABLE 2.* PAEDIATRIC POPULATION

Indication	**Dose**	**Phenytoin Sodium Injection Posology**
Status Epilepticus	Loading	Dosage: 15 - 20 mg/kg intravenously Infusion rate: 1 - 3 mg/kg/min, not exceeding 50 mg/min, whichev is slower
	Maintenance	Dosage: 2 to 4 mg/kg administered 12 hours after the loading dose and then continued every 12 hours (4 to 8 mg/kg/day) Infusion rate: 1 - 2 mg/kg/min, not exceeding 50 mg/min, whichev is slower
Neurosurgery and/or severe head injury	Loading	Dosage: 10 -15 mg/kg intravenously Infusion rate: 1 - 2 mg/kg/min, not exceeding 50 mg/min, whichev is slower
	Maintenance	Dosage: 2 to 4 mg/kg administered every 12 hours Infusion rate:1 - 2 mg/kg/min, not exceeding 50 mg/min, whiche is slower
Cardiac Arrhythmia	The clinically effective dose has not been established.	

* The detailed paediatric posology is outlined under Section 4.2.

Status Epilepticus:
Loading dose: 15 - 20 mg/kg of Epanutin administered intravenously will usually produce serum concentrations of phenytoin within the generally accepted therapeutic range (10 mcg/ml - 20 mcg/ml). The drug should be injected slowly intravenously at a rate of 1 - 3 mg/kg/min not exceeding 50 mg/min, whichever is slower.

Maintenance Dose: Initial maintenance dose of Epanutin is 2 to 4 mg/kg and should be given 12 hours after the loading dose and then continued every 12 hours (4 to 8 mg/kg/day). The subsequent maintenance doses should be guided by serum phenytoin levels and clinical response. The drug should be injected slowly intravenously at a rate of 1 - 2 mg/kg/min not exceeding 50 mg/min, whichever is slower.

Method of administration

For parenteral administration:
Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Parenteral Epanutin is suitable for use as long as it remains free of haziness and

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

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

Each injection or infusion of intravenous Epanutin 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. Local Toxicity (including Purple Glove Syndrome)).

Parenteral Epanutin 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.

Instructions for dilution:
For infusion administration the parenteral phenytoin should be diluted in 50 - 100 ml of normal saline, with the final concentration of phenytoin in the solution not exceeding 10 mg/ml. Administration should commence immediately after the mixture has been prepared and must be completed within one hour (the infusion mixture should not be refrigerated). An in-line filter (0.22 - 0.50 microns) should be used (Please refer to section 6.6)

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

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

For infusion administration the parenteral phenytoin should be diluted in saline. The infusion mixture should not be refrigerated and an in-line filter (0.22 - 0.50 microns) should be used.

This product contains 2.072g of propylene glycol per 5ml solution, therefore a phenytoin loading dose of 20mg/kg would result in an amount of 165.6mg/kg of propylene glycol. In neonates and infants less than or equal to 1 year of age, this may result in potential adverse reactions (see section 4.4).

4.3 Contraindications

Phenytoin is contraindicated in patients who are hypersensitive to phenytoin, or to any of the excipients listed in section 6.1, or other hydantoins. Intra-arterial administration must be avoided in view of the high pH of the preparation.

Because of its effect on ventricular automaticity, phenytoin is contra-indicated in sinus bradycardia, sino-atrial block, and second and third degree atrioventricular A-V block, and patients with Adams-Stokes syndrome.

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

4.4 Special warnings and precautions for use

General:

In adults, intravenous administration should not exceed 50 mg/min. In the paediatric population, depending on the indication, neonates, the drug should be administered at a rate of between 1 mg/kg/min - 3 mg/kg/min or 50 mg/min (whichever is slower) (refer to section 4.2 Paediatric population).

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

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

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

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

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

Phenytoin may precipitate or aggravate absence seizures and myoclonic seizures.

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus. When, in the judgement of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or

hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

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

Herbal preparations containing St. John's wort (*Hypericum perforatum*) should not be used while taking phenytoin due to the risk of decreased plasma concentrations and reduced clinical effects of phenytoin (see section 4.5).

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

Reduced maintenance dosage to prevent accumulation and toxicity may therefore be required in patients with impaired liver function. Where protein binding is reduced, as in uraemia, total serum phenytoin levels will be reduced accordingly. However, the pharmacologically active free drug concentration is unlikely to be altered. Therefore, under these circumstances therapeutic control may be achieved with total phenytoin levels below the normal range of 10 mcg/mL - 20 mcg/mL. 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.

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

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

Cardiovascular Effects:
Hypotension may occur. Severe cardiotoxic reactions and fatalities have been reported with arrhythmias including bradycardia, atrial and ventricular depression and ventricular fibrillation. In some cases, cardiac arrhythmias have resulted in asystole/ cardiac arrest and death. Severe complications are most commonly encountered in elderly or gravely ill patients. Cardiac adverse events have also been reported in adults and children without underlying cardiac disease or comorbidities and at recommended doses and infusion rates.

Therefore, careful cardiac (including respiratory) monitoring is needed when administering IV loading doses of phenytoin. Reduction in rate of administration or discontinuation of dosing may be needed. Phenytoin should be used with caution in patients with hypotension and/or severe myocardial insufficiency.

Local Toxicity (including Purple Glove Syndrome):
Soft tissue irritation and inflammation have occurred at the site of injection with and without extravasation of intravenous phenytoin.

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

Improper administration including subcutaneous or perivascular injection should be avoided.

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

Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms (HSS/DRESS):
Hypersensitivity Syndrome (HSS) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking anticonvulsant drugs, including phenytoin. Some of these events have been fatal or life threatening.

HSS/DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, haematological abnormalities, myocarditis, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leucocytosis, and eosinophilia. The mechanism is unknown. The interval between 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 aetiology for the signs and symptoms cannot be established.

Patients at higher risk for developing HSS/DRESS include black patients, patients who have experienced this syndrome in the past (with phenytoin or other anticonvulsant drugs), patients who have a family history of this syndrome and immuno-suppressed patients. The syndrome is more severe in previously sensitized individuals.

Serious Cutaneous Adverse Reactions Epanutin can cause severe cutaneous adverse reactions (SCARs) such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and DRESS, which can be fatal (see section 4.8 Skin and subcutaneous tissue disorders).. Although serious skin reactions may occur without warning, patients should be advised of the signs and symptoms of HSS/DRESS (see section 4.4 Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms (HSS/DRESS)), occurrence of rash and should be monitored closely for skin reactions. Patients should seek medical advice from their physician immediately when observing any indicative signs or symptoms. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

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

If the rash is of a milder type (measles-like or scarlantiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated. The risk of serious skin reactions and other hypersensitivity reactions to phenytoin may be higher in black patients.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of human leukocyte antigen 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.

CYP2C9 metabolism:

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 metabolizers 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.

Angioedema:
Angioedema has been reported in patients treated with phenytoin and fosphenytoin. Phenytoin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur (see section 4.8 Immune system disorders).

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

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

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

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

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

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

Metabolic Effect:
Phenytoin may affect glucose metabolism and inhibit insulin release.

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

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

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

Epanutin 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 condition being treated 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, Epanutin may result in a failure of the therapeutic effect of hormonal contraceptives (see sections 4.5 and 4.6).

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

Information on Excipients:
This product contains a number of excipients known to have a recognised action or effect. These are:
Ethanol:
This medicinal product contains400.0mg ethanol, 96% per 5 ml solution.

Harmful for those suffering from alcoholism.

Blood alcohol concentration (BAC) can vary based on indication and population; the following are only two examples in case this medicine is administered for Status Epilepticus in an emergency setting:

- a loading dose of 15 mg/kg for an adult weighing 70 kg would result in exposure to 24 mg/kg of ethanol which may cause a rise in BAC of about 4.0 mg/100 ml
- a loading dose of 20 mg/kg for a child weighing 25 kg would result in exposure to 32 mg/kg of ethanol which may cause a rise in 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.

Propylene glycol:
This medicinal product contains 2.072g propylene glycol per 5ml solution.

In case of propylene glycol content of 1mg/kg/day in babies less than 4weeks and 50mg/kg/day in children less than 5 years, co-administration of any substrate for alcohol dehydrogenase such as ethanol including other medicines that contain propylene glycol, may induce serious adverse effects in neonates and adverse events children less than 5 years respectively and thus the benefit risk balance needs to be assessed on an individual patient basis.

Based on the amount of propylene glycol contained in each 5 ml of parenteral Epanutin solution, the paediatric population would receive 165.6mg/kg of propylene glycol when phenytoin loading dose of 20mg/kg is administered for the treatment of Status Epilepticus (see section 4.2). Due to the specificity of paediatric population, in neonates and infants less than or equal to 1 year the adverse reactions listed under Description of selected adverse reactions for the threshold of 500mg/kg/day (see section 4.8) may occur in this population also for lower threshold. The benefit risk balance needs to be assessed on an individual patient basis.

Propylene glycol at a threshold of 50mg/kg/day may confer additional risks in pregnant and lactating women and Epanutin should not be used in this population unless other treatments are ineffective or not tolerated (see section 4.6).

Prolonged use of >24 hours could result in propylene glycol toxicity (including hemolysis, 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 both osmolar and anion-gap, and/or lactic acid.

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, for propylene glycol threshold of 50 mg/kg/day.

Various adverse events (see section 4.8), have been reported with high doses or prolonged use of propylene glycol at a threshold of 500mg/kg/day.

Sodium:

This medicinal product contains 22.04 mg (0.96 mmol) sodium per 5ml solution.

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.

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

There are many drugs that may increase or decrease serum phenytoin levels or that 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 that may increase phenytoin serum levels

Table 1 summarizes the drug classes that may potentially increase phenytoin serum levels.

Table 1 Drugs That 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
H_2-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

* This list is not intended to be inclusive or comprehensive. Individual product information should be consulted.

Drugs that may decrease phenytoin serum levels

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

Table 2 Drugs That May Decrease Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as*)
Alcohol (chronic intake)	
Antibacterial agents	rifampin ciprofloxacin
Anticonvulsants	vigabatrin
Antineoplastic agents	bleomycin carboplatin cisplatin doxorubicin methotrexate
Antiretrovirals	fosamprenavir nelfinav ritonavir
Bronchodilators	theophylline
Cardiovascular agents	reserpine
Folic Acid	folic acid
Hyperglycemic agents	diazoxide
St. John's wort	St. John's wort

* This list is not intended to be inclusive or comprehensive. Individual product information should be consulted.

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 that may increase or decrease phenytoin serum levels

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

Table 3 Drugs That May Increase or Decrease Phenytoin Serum Levels

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

* This list is not intended to be inclusive or comprehensive. Individual product information should be consulted.

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 disopyramide 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

* This list is not intended to be inclusive or comprehensive. Individual product information should be consulted

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

Drug/Laboratory Test Interactions:

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

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

It may, however, produce lower than normal values for dexamethasone or metapyrone tests. Phenytoin may cause raised serum levels of glucose, alkaline phosphatase, gamma glutamyl transpeptidase and lowered serum levels of calcium and folic acid. It is recommended that

serum folate concentrations be measured at least every 6 months, and folic acid supplements given if necessary. Phenytoin may affect blood sugar metabolism tests.

4.6 Fertility, pregnancy and lactation

Fertility

In animal studies, phenytoin had no direct effect on fertility.

Pregnancy

Phenytoin sodium crosses the placenta.

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

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

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

There is some evidence that phenytoin may produce congenital abnormalities in the offspring of a small number of epileptic patients, therefore it should not be used as the first drug during pregnancy, especially early pregnancy, unless in the judgement of the physician the potential benefits outweigh the risk.

In addition to the reports of increased incidence of congenital malformations, such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other antiepileptic drugs, there have been recent reports of a foetal hydantoin syndrome. This consists of pre-natal growth deficiency, microencephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

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

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

Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated. Neonatal coagulation

defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenytoin. Vitamin K has been shown to prevent or correct this defect and may be given to the mother before delivery and to the neonate after birth.

Phenytoin is teratogenic in rats, mice and rabbits (see section 5.3).

Breast-feeding

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

4.7 Effects on ability to drive and use machines

Caution is recommended in patients performing skilled tasks (e.g. driving or operating machines) as treatment with phenytoin may cause central nervous system adverse effects such as dizziness and drowsiness (see section 4.8).

4.8 Undesirable effects

In the table below all adverse reactions with phenytoin are listed by class and frequency Not Known (cannot be estimated from 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	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 signs and symptoms 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	Not Known	Anaphylactoid reaction, anaphylactic reaction, periarteritis nodosa, immunoglobulin abnormalities may occur.
Psychiatric disorders	Not Known	Insomnia, transient nervousness
Nervous system disorders	Not Known	Adverse reactions in this body system are common and are usually dose-related. Reactions include nystagmus, ataxia, dysarthria, decreased coordination and mental confusion. Cerebellar atrophy has been reported, and appears more likely in settings of elevated phenytoin levels and/or long-term phenytoin use (see section 4.4). Dizziness, motor twitchings, headache, paraesthesia somnolence, drowsiness and dysgeusia have also been observed. There have also been rare reports of phenytoin-induced dyskinesia, including chorea, dystonia, tremor, and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy. Tonic convulsions have also been reported.
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 System	Not Known	Vomiting, nausea, gingival hyperplasia constipation.
Hepatobiliary disorders	Not Known	Acute hepatic failure, hepatitis toxic, liver injury
Skin and subcutaneous tissue disorders	Not Known	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 that may be fatal have bullous, exfoliative or purpuric dermatitis, lupus erythematosus, hirsutism, hypertrichosis, Peyronie's Disease and Dupuytren's contracture may occur rarely, coarsening of the facial features, enlargement of the lips, Severe cutaneous adverse reactions (SCARs): SJS and TEN have been reported very rarely (see section 4.4). 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.
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 – Local Toxicity (including Purple Glove Syndrome)).
Renal and urinary disorders	Not Known	Tubulointerstitial nephritis
General disorders and administration site conditions	Not Known	Local irritation, inflammation, tenderness, necrosis, oedema and skin

		exfoliation have been reported with or without extravasation of intravenous phenytoin.
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 at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The lethal dose in children is not known. The mean lethal dose in adults is estimated to be 2 g to 5 g. 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 and hypotensive (see section 4.4). Death is due to respiratory and circulatory depression.

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

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

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

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

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

In acute overdosage the possibility of the presence of other Central Nervous System (CNS) depressants, including alcohol, should be borne in mind.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC Code: N03AB02.

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.

It appears to stabilise rather than raise the seizure threshold and prevents spread of seizure activity rather than abolish the primary focus of seizure discharge.

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

Absorption
After injection phenytoin is distributed into body fluids including the cerebrospinal fluid (CSF).

Distribution
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 which 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 Dosing in Special Populations – Elderly (over 65 years)).

5.3 Pre-clinical safety data

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 neurodevelopment 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

Each 5ml contains: propylene glycol, ethanol 96%, water for injection, sodium hydroxide

6.2 Incompatibilities

Epanutin Ready Mixed Parenteral 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.

This medicinal product must not be mixed with other medicinal products except those mentioned in sections 4.2 and 6.6.

6.3 Shelf life

Unopened: 30 months.

Once opened, use immediately and discard any unused contents.

6.4 Special precautions for storage

Do not store above 25°C. Keep the ampoule in the outer carton.

6.5 Nature and contents of container

5 ml, colourless neutral glass, Type 1, Ph Eur, with a white colour break band. Each pack contains 10 ampoules.

6.6 Special precautions for disposal and other handling

For single use only.

Epanutin Ready Mixed Parenteral should be used immediately after opening. Discard any unused product once opened. See sections 4.2 and 6.2 for further information.

If the undiluted parenteral Epantin is refrigerated or frozen, a precipitate might form; this will dissolve again after the solution is allowed to stand at room temperature. The product is still suitable for use. Only a clear solution should be used. A faint yellow colouration may develop; however, this has no effect on the potency of this solution.

The product should not be used if a precipitate or haziness develops in the solution in the ampoule.

For infusion administration the parenteral phenytoin should be diluted in 50 - 100 ml of normal saline, with the final concentration of phenytoin in the solution not exceeding 10 mg/ml. Administration should commence immediately after the mixture has been prepared and must be completed within one hour (the infusion mixture should not be refrigerated). An in-line filter (0.22 - 0.50 microns) should be used.

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

7 MARKETING AUTHORISATION HOLDER

Upjohn UK Limited, Sandwich, Kent CT13 9NJ, United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 50622/0025

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