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 contains phenytoin sodium 250 mg (50 mg/ml)
Excipients with known effect:
Each 5 ml also contains 2.072 g propylene glycol and 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 of use in the treatment of cardiac arrhythmias where first line therapy is not effective, such as life-threatening ventricular arrhythmias or arrhythmias secondary to digitalis intoxication, when these have not responded to other available antiarrhythmic treatments or when alternative agents could not be tolerated (see section 4.4). Phenytoin has not been shown to enhance survival in patients with ventricular arrhythmias.

4.2 Posology and method of administration

For parenteral administration.

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

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).

Epanutin Ready Mixed Parenteral should not be mixed with other drugs nor be added to dextrose or dextrose-containing solutions due to the potential for precipitation of phenytoin acid.

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 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)).

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

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.

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.

Posology

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 per minute in adults (this will require approximately 20 minutes in a 70 kg patient). The loading dose should be followed by maintenance doses of 100 mg orally or intravenously every 6 to 8 hours.

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 (10mcg/ml-20 mcg/ml).

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

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

Other clinical conditions:

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

The intravenous route of administration is preferred.

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

Neurosurgery:

In a patient who has not previously received the drug, Parenteral Epanutin 100 mg-200 mg (2-4 ml) may be given intramuscularly at approximately 4-hour intervals prophylactically during neurosurgery and continued during the postoperative

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.

Dosing in Special Populations
Patients with Renal or Hepatic Disease:
See section 4.4.

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

Paediatric population:
It has been shown that children tend to metabolise phenytoin more rapidly than adults. This should be borne in mind when determining dosage regimens; the use of serum level monitoring being particularly beneficial in such cases. The drug should be injected slowly intravenously at a rate of 1 to 3 mg/kg/minute or 50 mg/minute, whichever is slower.

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

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

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 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, sinoatrial 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:
The rate of administration is very important; in adults, intravenous administration should not exceed 50 mg per minute. In neonates and children, the drug should be administered at a rate of 1-3 mg/kg/min or 50 mg/minute (whichever is slower). At this rate, toxicity should be minimised.

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.

Phenytoin may precipitate or aggravate absence seizures and myoclonic seizures.

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.

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 10-20 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 phenytoin plasma concentrations should be made with caution. Unbound concentration of phenytoin may be elevated in patients with hyperbilirubinemia. Unbound phenytoin concentrations may be more useful in these patient populations.

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:
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 Skin Reactions:
Life-threatening severe cutaneous adverse reactions (SCARs) such as Acute generalized exanthematous pustulosis (AGEP (see section 4.8)), SJS, TEN and DRESS have been reported with the use of Epanutin. Although serious skin reactions may occur without warning, patients should be advised of the signs and symptoms of HSS/DRESS (see section 4.4HSS/DRESS) and should be monitored closely for skin reactions. Patients should seek medical advice from their physician immediately when observing any indicative signs or symptoms. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, 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. Phenytoin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur (see section 4.8).
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).

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.

Endocrine disorders:
There have been reports of secondary hyperparathyroidism associated with phenytoin use.

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).

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).

Women of childbearing potential should use effective contraception when taking phenytoin.

Every woman of childbearing potential should be counselled regarding the need to consult her physician as soon as she is planning pregnancy to discuss switching to alternative treatments prior to conception and before contraception is discontinued (see section 4.6).

Every woman of childbearing potential should be counselled to contact her doctor immediately if she becomes pregnant or thinks she may be pregnant and is taking phenytoin.

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

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

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 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 that may increase phenytoin serum levels

Table 1 summarises 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 dicoumarol

	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 summarises the drug classes which 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 summarises 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
Anticoagulants	apixaban dabigatran edoxaban rivaroxaban warfarin
Anticonvulsants	carbamazepine lacosamide lamotrigine phenobarbital sodium valproate valproic acid
Antifungal agents	azoles posaconazole voriconazole
Antihelminthics	albendazole praziquantel
Antineoplastic agents	teniposide
Antiplatelets	ticagrelor
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	
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.

* Coadministration of phenytoin is contraindicated with delavirdine due to the potential to decrease delavirdine plasma concentration due to enzyme induction by phenytoin, and for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors (see section 4.3).

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

Hyperammonaemia with Concomitant Use of Valproate
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.

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

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

Risk related to phenytoin
Phenytoin crosses the placenta in humans. Similar concentrations of phenytoin have been reported in the umbilical cord and maternal blood. Phenytoin is teratogenic in rats, mice and rabbits.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. In humans, phenytoin exposure during pregnancy is associated with a frequency of major malformations 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, 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. Studies related to the risk of neurodevelopmental disorders in children exposed to phenytoin during pregnancy are contradictory and a risk cannot be excluded.

There have been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. However, the respective role of antiepileptic drugs and other factors in the increased risk is not determined.

Epanutin should not be used during pregnancy and in women of childbearing potential except where there is a clinical need following consideration of alternative suitable treatment options. The woman should be fully informed of and understand the risks of taking phenytoin during pregnancy.

An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage (see section 4.2). However, postpartum restoration of the original dosage will probably be indicated.

Risks due to excipient propylene glycol
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. Epanutin should not be used in this population unless other treatments are ineffective or not tolerated (See section 4.4).

Women of childbearing potential
Epanutin should not be used in women of childbearing potential unless other treatments are ineffective or not tolerated. The woman should be fully informed of and understand the risk of potential harm to the foetus and the importance of planning her 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 Epanutin.

Epanutin 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 pregnant women
In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If a woman becomes pregnant while taking phenytoin, all efforts should be made to switch to alternative treatments as soon as possible.

In epilepsy, Epanutin should not be discontinued prior to reassessment of the treatment.

The woman should be informed of and understand the potential harm to the foetus.

If based on a careful evaluation of the risks and the benefits, Epanutin treatment is continued during the pregnancy, it is recommended to use the lowest effective dose and to institute specialized prenatal monitoring, in order to detect the possible occurrence of the described malformations.

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.

Breastfeeding

Following administration of oral phenytoin, phenytoin appears to be excreted in low concentrations in human milk. Therefore, breast feeding is not recommended for women receiving Epanutin.

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

4.7 Effects on ability to drive and use machines

Epanutin Ready Mixed Parenteral has major influence on the ability to drive and use machines.

Patients should be advised not to drive a car or operate potentially dangerous machinery until it is known that this medication does not affect their ability to engage in these activities.

4.8 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. Pure red cell aplasia has also been reported.
Immune system disorders	Not Known	Anaphylactoid reaction and anaphylaxis, periarteritis nodosa, and immunoglobulin abnormalities may occur. Angioedema has been reported (see section 4.4).
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, slurred speech, decreased coordination and mental confusion. Cerebellar atrophy has been reported, and appears

		more likely in settings of elevated phenytoin levels and/or long-term phenytoin use (see section 4.4). Dizziness, insomnia, transient nervousness, motor twitching, taste perversion, headache, paraesthesia, somnolence, drowsiness and vertigo have also been observed. There have also been rare reports of phenytoin-induced dyskinesia, including chorea, dystonia, tremor, and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long term phenytoin therapy. Tonic seizures have also been reported.
Ear and labyrinth disorders	Not Known	Vertigo.
Cardiac disorders	Not Known	Asystole/cardiac arrest, bradycardia, Severe cardiotoxic reactions and fatalities have been reported with atrial and ventricular conduction depression and ventricular fibrillation. Severe complications are most commonly encountered in older people or gravely ill patients.
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 and constipation.
Hepatobiliary disorders	Not Known	Acute hepatic failure, toxic hepatitis, liver damage.
Endocrine Disorders	Not Known	Hyperparathyroidism secondary.
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 forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus. Severe cutaneous adverse reactions (SCARs): AGEP, SJS and TEN have been reported very rarely (see section 4.4). Urticaria has been reported. Coarsening of the facial features, enlargement of the lips, Hirsutism, hypertrichosis, Peyronie's disease and Dupuytren's contracture may occur rarely. Hypersensitivity syndrome/Drug reaction with eosinophilia and systemic symptoms (HSS/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 arthralgias, eosinophilia, fever, liver dysfunction, 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 sloughing of skin 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.

Description of selected adverse reactions
This medicinal product contains propylene glycol (see section 4.4) for use and at a threshold of 500mg/kg/day, 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.

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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

The lethal dose in children is not known. The mean lethal dose in adults is estimated to be 2g to 5 g. The initial symptoms are nystagmus, ataxia and dysarthria. Other signs are tremor, hyperreflexia, somnolence, lethargy, 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.

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. Irreversible cerebellar dysfunction and atrophy have been reported.

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 includingthe 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% ofphenytoin in plasma is bound to albumin. The plasma half-life of phenytoinin 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 inserum levels when these are in the upperrange of therapeutic concentrations.

Elimination
The parameters controlling elimination are also subject to wideinterpatient variation. The serum level achieved by a given dose istherefore also subject to wide variation.

PharmacokineticInteraction
Co-administration of nelfinavir tablets (1 250 mg twice a day) with phenytoin capsule (300 mg once a day) did not change the plasma concentration of nelfinavir. However, co-administration of nelfinavir reduced the AUC values of phenytoin (total) and free phenytoinby29%and28%,respectively.

SpecialPopulations
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 20-30years of age). Phenytoin dosing requirements are highly variable and must be individualized (see section4.2 – Elderly).

5.3 Preclinical safety data

Carcinogenesis
In a transplacental and adult carcinogenicity study, phenytoin was administered in diet at 30 to 600 ppm to mice and 240 to 2400 ppm to rats. Hepatocellular tumors were increased at the higher doses in mice and rats. In additional studies, mice received 10 mg/kg, 25 mg/kg, or 45 mg/kg and rats were given 25 mg/kg, 50 mg/kg, or 100 mg/kg in the diet for 2 years. Hepatocellular tumors in mice increased at 45 mg/kg. No increases in tumor incidence were observed in rats. These rodent tumors are of uncertain clinical significance.

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%
Water for injection
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

Epanutin Ready Mixed Parenteral should not 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

Unopened: 36 months
Once opened, use immediately and discard any unused contents.

6.4 Special precautions for storage

Do not store above 25°C. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Type 1, 6 ml, colourless glass vial sealed with a bromobutyl rubber stopper and an aluminium snap-cap fitted with a polypropylene flip-off cap.

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.

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

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.

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

7 MARKETING AUTHORISATION HOLDER

Upjohn EESV
Rivium Westlaan 142
2909 LD Capelle aan den IJssel
Netherlands

8 MARKETING AUTHORISATION NUMBER

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