Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Epanutin 100 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains phenytoin sodium 100 mg

Excipient with known effect

Each capsule contains 96.15 mg lactose monohydrate

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsules, hard.

A white powder in a No. 3 hard gelatin capsule with a white opaque body and orange cap, radially imprinted 'EPANUTIN 100'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these, and for the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury. Epanutin has also been employed in the treatment of trigeminal neuralgia but it should only be used as second line therapy if carbamazepine is ineffective or patients are intolerant to carbamazepine.

4.2 Posology and method of administration

For oral administration only.

Dosage:
Dosage should be individualised as there may be wide interpatient variability in phenytoin serum levels with equivalent dosage. Epanutin should be introduced in small dosages with gradual increments until control is achieved or until toxic effects appear. In some cases serum level determinations may be necessary for optimal dosage adjustments - the clinically effective level is usually 10 mcg/ml–20 mcg/ml (40-80 micromoles/l) although some cases of tonic-clonic seizures may be controlled with lower serum levels of phenytoin. With recommended dosage a period of seven to 10 days may be required to achieve steady state serum levels with Epanutin and changes in dosage should not be carried out at intervals shorter than 7 to ten days. Maintenance of treatment should be the lowest dose of anticonvulsant consistent with control of seizures.

Epanutin Capsules, Suspension and Infatabs:
Epanutin Capsules contain 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
Adult Dosage for Seizures:
Initially 3 mg/kg/day to 4 mg/kg/day with subsequent dosage adjustment if necessary. For most adults a satisfactory maintenance dose will be 200 mg to 500 mg daily in single or divided doses.

Exceptionally, a daily dose outside this range may be indicated. Dosage should normally be adjusted according to serum levels where assay facilities exist.

Adult Dosage for Trigeminal Neuralgia:
The clinically effective dose has not been established in clinical trials. In adults, 300-500 mg given in divided daily doses has been reported in the literature. Dosing should be adjusted based on clinical response. Determination of serum phenytoin levels is advised. Levels of total phenytoin should not exceed 20 mcg/ml.

Dosing in Special Populations

Patients with Renal or Hepatic Disease:
See section 4.4.

Elderly:
Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required (see section 5.2 – Special Populations – Age). As with adults the dosage of Epanutin should be titrated to the patient's individual requirements using the same guidelines. As older people tend to receive multiple drug therapies, the possibility of drug interactions should be borne in mind.

Paediatric population Dosage for Seizures:
Initially, 5 mg/kg/day in two divided doses, with subsequent dosage individualised to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 mg/kg to 8 mg/kg.

Neonates:
The absorption of phenytoin following oral administration in neonates is unpredictable. Furthermore, the metabolism of phenytoin may be depressed. It is therefore especially important to monitor serum levels in the neonate.

4.3 Contraindications

Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin, or any of the excipients listed in section 6.1, or other hydantoins.

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
Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence 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.

Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgement of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative anti-epileptic 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 anti-epileptic drug not belonging to the hydantoin chemical class.

Acute alcohol intake may increase phenytoin serum levels while chronic alcoholism may decrease serum levels.

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.

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).

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.

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.

Cardiac Effects
Cases of bradycardia and asystole/cardiac arrest have been reported, most commonly in association with phenytoin toxicity (see section 4.9), but also at recommended phenytoin doses and levels.

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 interval between 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 generalised exanthematous pustulosis (AGEP (see section 4.8)), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (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 4.4-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 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 scarlatiniform), 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 HLAB gene, in patients using carbamazepine.

HLA-B*1502 may be associated with increased risk of developing SJS/TEN in patients of Thai and Han Chinese ancestry taking drugs associated with SJS/TEN, including phenytoin. If these patients are known to be positive for HLA-B*1502, the use of phenytoin should only be considered if the benefits are thought to exceed the risks.

In the Caucasian and Japanese population, the frequency of HLA-B*1502 allele is extremely low, and thus it is not possible at present to conclude on risk association. Adequate information about risk association in other ethnicities is currently not available.

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.

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

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
Phenytoin is highly protein bound and extensively metabolised by the liver. Reduced 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 to 20 mcg/ml (40-80 micromoles/l). Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents usually within the first 2 months of treatment and may be associated with HSS/DRESS (see section 4.4). Patients with impaired liver function, elderly patients or those who are gravely ill may show early signs of toxicity.

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

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

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local and generalised) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling HSS/DRESS (see section 4.4). 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.

While macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy.

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.

Musculoskeletal Effect
Phenytoin and other anticonvulsants that have been shown to induce the CYP450 enzyme are thought to affect bone mineral metabolism indirectly by increasing the metabolism of vitamin D_3. This may lead to vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcemia, and hypophosphatemia in chronically treated epileptic patients.

Metabolic Effect

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

Phenytoin may affect glucose metabolism and inhibit insulin release. Hyperglycaemia has been reported in association with toxic levels.

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).

Epanutin should not be used in women of childbearing potential unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options.

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

Women of childbearing potential should be fully informed of the potential risk to the foetus if they take phenytoin during pregnancy.

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

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, Epanutin may result in a failure of the therapeutic effect of hormonal contraceptives, therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods (see sections 4.5 and 4.6).

Information for the Patient using an Oral Formulation of Phenytoin
Phenytoin may cause lowered serum levels of folic acid. It is recommended that serum folate concentrations be measured at least once every 6 months, and folic acid supplements given if necessary.

Excipient information
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium free'.

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

The most commonly occurring drug interactions are listed below.

Drugs that may increase phenytoin serum levels

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

Table 1 Drugs that may potentially 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	capecitabine fluorouracil
Benzodiazepines /Psychotropic agents	chlordiazepoxide diazepam disulfiram methylphenidate trazodone viloxazine
Calcium channel blockers/Cardiovascular agents	amiodarone dicoumarol diltiazem nifedipine ticlopidine
H2-antagonists	cimetidine
HMG-CoA reductase inhibitors	fluvastatin
Hormones	oestrogens
Immunosuppressant drugs	tacrolimus
Oral hypoglycemic agents	tolbutamide
Proton pump inhibitors	omeprazole
Serotonin re-uptake inhibitors	fluoxetine fluvoxamine sertraline

* 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) [42]	
Antibacterial agents	ciprofloxacin rifampicin
Anticonvulsants	vigabatrin
Antineoplastic agents	bleomycin carboplatin cisplatin doxorubicin methotrexate
Antiulcer agents	sucralfate
Antiretrovirals	fosamprenavir nelfinavir 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 either increase or decrease phenytoin serum levels

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

Table 3 Drugs that may either 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 rifampicin

	tetracycline
Anticoagulants	apixaban dabigatran edoxaban rivaroxaban warfarin
Anticonvulsants	carbamazepine lacosamide lamotrigine phenobarbital sodium valproate valproic acid
Antifungal agents	azoles posaconazole voriconazole
Antihelmintics	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
Immunosuppressant drugs	
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.

H*yperammonaemia 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, and gamma glutamyl transpeptidase and lowered serum levels of calcium and folic acid. It is recommended that serum folate concentrations be measured at least once 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 unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options. The woman should be fully informed of and understand the risks of taking phenytoin during pregnancy.

If based on a careful evaluation of the risks and the benefits, no alternative treatment option is suitable, and treatment with Epanutin is continued, the lowest effective dose of phenytoin should be used. If a woman is 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, she should be referred to a specialist to reassess phenytoin treatment and consider alternative treatment options.

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.

Women of childbearing potential
Epanutin should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options. The woman should be fully informed of and understand the risk of potential harm to the foetus if phenytoin is taken during pregnancy and therefore the importance of planning any pregnancy. Pregnancy testing in women of childbearing potential should be considered prior to initiating treatment with Epanutin.

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, Epanutin may result in a failure of the therapeutic effect of hormonal contraceptives, therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods (see section 4.5).At least one effective method of contraception (such as an intra-uterine device) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, involving the patient in the discussion, when choosing the contraception method.

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.

Breast feeding
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

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

4.8 Undesirable effects

The following adverse reactions have been reported with phenytoin (frequency unknown-cannot be estimated from available data):

Immune system reactions:
Anaphylactoid reaction and anaphylaxis. Angioedema has been reported (see section 4.4).

Central Nervous System:
Adverse reactions in this body system are common and are usually dose-related. Reactions include nystagmus, ataxia, slurred speech, decreased co-ordination and mental confusion. Cerebellar atrophy has been reported, and appears more likely in settings of elevated phenytoin levels and/or long-term phenytoin use (see section 4.4). Dizziness, insomnia, transient nervousness, motor twitchings, taste perversion, headaches paraesthesia, somnolence and vertigo have also been observed.

There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. There are occasional reports of irreversible cerebellar dysfunction associated with severe phenytoin overdosage. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Gastrointestinal System:
Acute hepatic failure, toxic hepatitis, liver damage, vomiting, nausea, constipation (see section 4.4).

Dermatological System:
Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash is the most common; dermatitis is seen more rarely. Other more serious and rare forms 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.

Connective Tissue System:
Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hirsutism, hypertrichosis, Peyronie's Disease and Dupuytren's contracture may occur rarely.

Blood and Lymphatic System Disorders:
Haematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, 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.

Frequent blood counts should be carried out during treatment with phenytoin.

Pure red cell aplasia has also been reported at a frequency of not known.

Immune System:
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), systemic lupus erythematosus, polyarteritis nodosa, and immunoglobulin abnormalities may occur.

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.

Other:
Polyarthropathy, interstitial nephritis, pneumonitis.

Musculoskeletal System:
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. However, phenytoin has been shown to induce the CYP450 enzyme, which can affect bone mineral metabolism indirectly by increasing the metabolism of vitamin D_3. This may lead to vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcemia, and hypophosphatemia in chronically treated epileptic patients.

Endocrine Disorders:
Secondary hyperparathyroidism.

Investigations:
Thyroid function test abnormal.

Paediatric population
The adverse event profile of phenytoin is generally similar between children and adults. Gingival hyperplasia occurs more frequently in paediatric patients and in patients with poor oral hygiene.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after 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 for adults is estimated to be 2 g 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 then becomes comatose, the pupils are unresponsive and hypotension occurs followed by respiratory depression and apnoea. Bradycardia and asystole/cardiac arrest have been reported (see section 4.4). Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin serum levels where toxicity may occur. 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 greater than 40 mcg/ml, but a concentration as high as 50 mcg/ml has been reported without evidence of toxicity.

As much as 25 times therapeutic dose has been taken to result in serum concentration over 100 mcg/ml (400 micromoles/l) with complete recovery. Irreversible cerebellar dysfunction and atrophy have been reported.

Treatment:
Treatment is non-specific since there is no known antidote. If ingested within the previous 4 hours the stomach should be emptied. If the gag reflex is absent, the airway should be supported. Oxygen, and assisted ventilation may be necessary for central nervous system, respiratory and cardiovascular depression. Haemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been utilised in the treatment of severe intoxication in children.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC Code: N03AB02.

Phenytoin is effective in various animal models of generalised convulsive disorders, 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
Phenytoin is absorbed from the small intestine after oral administration. Various formulation factors may affect the bioavailability of phenytoin, however, non-linear techniques have estimated absorption to be essentially complete. After absorption it is distributed into body fluid including the cerebrospinal fluid (CSF). Its volume of distribution has been estimated to be between 0.52 and 1.19 litres/kg, and it is highly protein bound (usually 90% in adults).

Distribution
The plasma half-life of phenytoin in man averages 22 hours with a range of 7 to 42 hours. Steady state therapeutic drug levels are achieved at least 7 to 10 days after initiation of therapy.

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.

Pharmacokinetic Interaction

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 phenytoin by 29% and 28%, respectively (see section 4.5).

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).

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

Core:
Lactose monohydrate
Magnesium stearate

Shell:
Gelatin
Erythrosine (E127)
Quinoline yellow (E104)
Titanium dioxide (E171)
Sodium laurilsulfate

Printing ink:
Shellac
Black iron oxide (E172)
Propylene glycol

Or

Shellac
Black iron oxide (E172)
Propylene glycol
Potassium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

White HDPE container with a white polypropylene child resistant cap, containing 84 capsules. An activated silica gel dessicant, within the HDPE canister, is included in each bottle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park

Mulhuddart
Dublin 15
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01st April 1979

Date of latest renewal: 01st April 2009

10 DATE OF REVISION OF THE TEXT

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