SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Phenytoin Sodium Mylan 300 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 300 mg phenytoin sodium.

Excipient with know effect:

Each capsule also contains 53 mg lactose

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Hard capsules (capsules)

A white to off-white powder in a No 1 hard gelatin capsule with a white opaque body and green transparent coloured cap, marked P300 on the cap and P300 (reverse) on the body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Phenytoin Sodium Hard Capsules are indicated for 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.

Phenytoin Sodium Hard Capsules 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

Phenytoin Sodium Hard Capsules contain phenytoin sodium. 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

Dosage should be individualized as there may be wide interpatient variability in phenytoin serum levels with equivalent dosage. Phenytoin Sodium Hard Capsules 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 10-20mg/l (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 ten days may be required to achieve steady state serum levels with Phenytoin Sodium Hard Capsules and changes in dosage should not be carried out at intervals shorter than seven to ten days. Maintenance of treatment should be the lowest dose of anticonvulsant consistent with control of seizures.

Adult Dosage for Seizures:

Initially 3 to 4mg/kg/day with subsequent dosage adjustment if necessary. For most adults, a satisfactory maintenance dose will be 200 to 500mg 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 have been reported in the literature. Dosing should be adjusted based on clinical response. Determination of serum phenytoin level is advised. Levels of total phenytoin should not exceed 20 mcg/ml.

Elderly (over 65 years):

Phenytoin clearance is decreased in elderly patients and lower or less frequent dosing may be required (see section 5.2 Pharmacokinetic properties-Age). As with adults the dosage of Phenytoin Sodium Hard Capsules should be titrated to the patient's individual requirements using the same guidelines. As elderly patients tend to receive multiple drug therapies, the possibility of drug interactions should be borne in mind.

Infants and Children:

Initially, 5mg/kg/day in two divided doses, with subsequent dosage individualised to a maximum of 300mg 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.

Patients with Renal or Hepatic Disease:

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

Method of administration

For oral administration only.

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.

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 may affect glucose metabolism and inhibit insulin release. Hyperglycaemia has been reported in association with toxic levels. Phenytoin is not indicated for seizures due to hypoglycaemia or other metabolic causes.

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.

Phenytoin may precipitate or aggravate absence seizures and myoclonic seizures.

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).

Women of Childbearing Potential

Phenytoin Sodium Hard Capsules may cause foetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse development outcomes (see section 4.6).

Phenytoin Sodium Hard Capsules 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 their physician as soon as they are planning a 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 their doctor immediately if they become pregnant or might be pregnant and are taking phenytoin.

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, Phenytoin Sodium Hard Capsules 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)."

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.

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

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, hematological abnormalities, myocarditis, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leukocytosis, and eosinophilia. The interval between the first drug exposure and symptoms is usually 2 to 4 weeks but has been reported in individuals receiving anticonvulsants for 3 or more months. If such signs and symptoms occur, the patient should be evaluated immediately. Phenytoin should be discontinued if an alternative etiology for the signs and symptoms cannot be established.

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

Serious Dermatologic Reactions

Phenytoin can cause rare, severe cutaneous adverse reactions (SCARs) such as

acute generalised exanthematous pustulosis (AGEP) (see section 4.8 undesirable effects –Skin and subcutaneous tissue disorders), exfoliative dermatitis, Stevens - Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and DRESS which can be fatal. Although serious skin reactions may occur without warning, patients should be alert for the occurrence of rash and other symptoms of HSS/DRESS (see Section 4.4 Special warnings and precautions for use –Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms), and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. The physician should advise the patient to discontinue treatment if the rash appears. If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated. The risk of serious skin reactions and other hypersensitivity reactions to phenytoin may be higher in black patients.

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.

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.

HLAB* 1502 may be associated with an increased risk of developing Stevens Johnson Syndrome (SJS) in individuals of Thai and Han Chinese Origin when treated with phenytoin. If these patients are known to be positive for HLAB*1502, the use of phenytoin should only be considered if the benefits are thought to exceed risks.

In the Caucasian and Japanese population, the frequency of HLAB*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.

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 – Immune system).

Hepatic Injury or use in patients with renal/hepatic impairment

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, unbound phenytoin serum levels will be increased. 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. Therefore, under these circumstances therapeutic control may be achieved with total phenytoin levels below the normal range of 10-20mg/l (40-80 micromoles/l). Unbound phenytoin concentrations may be more useful in these patient populations. Patients with impaired liver function, elderly patients or those who are gravely ill may show early signs of toxicity. 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 Special warnings and precautions for use – Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms). Patients with impaired liver

function, elderly 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.

Hematopoietic System

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

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) 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 HSS/DRESS (see Section 4.4 Special warnings and precautions for use – Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms). 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 anticonvulsant drugs.

While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. If folic acid is added to phenytoin therapy, a decrease in seizure control may occur.

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

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.

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

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 D3. This may lead to Vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcemia, and hypophosphatemia in chronically treated epileptic patients.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions

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

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

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

The most commonly occurring drug interactions are listed below.

Drugs that may increase phenytoin serum levels:

Table 1. Drugs That May Increase Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as)
Alcohol (acute intake)	
Analgesic/Anti-inflammatory agents	Salicylates
Anesthetics	
Antibacterial agents	Chloramphenicol Clarithromycin Isoniazid Sulfadiazine Sulfamethoxazole-trimethoprim Sulfonamides
Anticonvulsants	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
Calcium channel blockers / Cardiovascular agents	Amiodarone Diltiazem Nifedipine
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

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

Drugs that may 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	Ciprofloxacin Rifampin
Anticonvulsants	Vigabatrin
Antineoplastic agent	Bleomycin Carboplatin Cisplatin Doxorubicin
Antiulcer agents	Sucralfate
Antiretrovirals	Fosamprenavir Ritonavir
Bronchodilators	Theophylline
Cardiovascular agents	Reserpine
Folic acid	Folic acid
Hyperglycemic agents	
St. John's Wort	St.John's Wort

a This list is not intended to be inclusive or comprehensive. Individual drug labels 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. 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

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

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

Drugs 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
Anticoagulants	Warfarin Apixaban Dabigatran Edoxaban Rivaroxaban
Anticonvulsants	Carbamazepine Lamotrigine Phenobarbital

	Sodium valproate Valproic acid Lacosamide
Antifungal agents	Posaconazole Voriconazole
Antihelminthics	
Antineoplastic agents	Methotrexate
Antiplatelets	Ticagrelor
Antiretrovirals	Efavirenz Fosamprenavir Indinavir Lopinavir/ritonavir Ritonavir Saquinavir
Bronchodilators	Theophylline
Calcium channel blockers / Cardiovascular agents	Digoxin Disopyramide Mexiletine Nicardipine Nimodipine Verapamil
Corticosteroids	
Cyclosporine	
Diuretics	Furosemide
HMG-CoA reductase inhibitors	Atorvastatin Fluvastatin Simvastatin
Hormones	Oestrogens Oral contraceptives (see sections 4.4 and 4.6)
Hyperglycemic agents	
Immunosuppressant drugs	
Neuromuscular blocking agents	Pancuronium Rocuronium Vecuronium
Opioid analgesics	Methadone
Oral hypoglycemic agents	Tolbutamide

Psychotropic agents / Antidepressants	Clozapine Paroxetine Quetiapine Sertraline
Vitamin D	Vitamin D

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

The effect of phenytoin on warfarin is variable and prothrombin times should be determined when these agents are combined.

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.

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

Drug/Laboratory Test Interactions:

Phenytoin may cause a slight decrease in serum levels of total and free thyroxine, possibly as a result of enhanced peripheral metabolism. These changes do not lead to clinical hypothyroidism and do not affect the levels of circulating TSH. The latter can therefore be used for diagnosing hypothyroidism in the patient on phenytoin. Phenytoin does not interfere with uptake and suppression tests used in the diagnosis of hypothyroidism. It may, however, produce lower than normal values for dexamethasone or metapyrone tests. Phenytoin may cause raised serum levels of glucose, alkaline phosphatase, 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

When possible, 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.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes Studies have shown that phenytoin exposure during pregnancy is associated with an approximate 6% frequency of major malformations, which is higher than the frequency in the general population of 2-3%. Malformations such as orofacial clefts, cardiac defects, craniofacial defects features, nail and digit hypoplasia, and growth abnormalities (including microcephaly and prenatal growth deficiency), have been reported either individually or as part of a Fetal Hydantoin Syndrome among children born to women with epilepsy who used phenytoin during pregnancy.

Neurodevelopmental disorder has been reported among children born to women with epilepsy who took phenytoin alone or in combination with other AEDs during

pregnancy. Studies related to neurodevelopmental risk in children exposed to phenytoin during pregnancy are contradictory and a risk cannot be excluded. A small number of studies have found an increase of serious adverse outcomes compared to control subjects including fetal hydantoin syndrome and below average IQ.

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.

Phenytoin Sodium Hard Capsules should not be used during pregnancy 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.

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.

If based on careful evaluation of the risks and benefits, no alternative treatment option is suitable, and the treatment with Phenytoin Sodium Flynn Hard Capsules 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.

In women of childbearing potential

Phenytoin Sodium Flynn Hard Capsules 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 of 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 Phenytoin Sodium Flynn Hard Capsules.

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment.

Due to enzyme induction, Phenytoin Sodium Flynn Hard Capsules 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 in pregnant women

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception. Phenytoin Sodium Hard Capsules should not be discontinued prior to reassessment of the treatment. When possible, patients should be informed of the potential harm to the foetus. If based on a careful evaluation of the risks and the benefits, Phenytoin Sodium Hard Capsules treatment is continued during the pregnancy, it is recommended to use the lowest effective dose and to institute specialized prenatal monitoring, oriented on the possible occurrence of the described malformations.

In neonates

Haemorrhagic syndrome has been reported in neonates born from epileptic mothers receiving phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother during the last gestational month and to the neonate after birth.

Post-natal monitoring/children

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

Breast-feeding

It is not known whether phenytoin is excreted in human milk. 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 Phenytoin Sodium Hard Capsules

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Immune system reactions: Anaphylactoid reaction, and anaphylaxis.

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, mental confusion. Cerebellar atrophy has been reported and appears more likely in settings of high PHE levels and/or long-term PHE use. (see Section 4.4 Special warnings and precautions for use – Central Nervous System Effect). Dizziness, vertigo, insomnia, transient nervousness, motor twitchings, taste perversion, headache, paresthesia and somnolence 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.

A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Gastrointestinal System:

Vomiting, nausea and constipation.

Hepatobiliary disorders:

Acute hepatic failure, toxic hepatitis and liver damage (see Section 4.4 Special warnings and precautions for use – Hepatic Injury).

Skin and subcutaneous tissue disorders:

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 that may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) (see Section 4.4 Special warnings and precautions for use – Serious Dermatologic Reactions). Urticaria also 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.

Haemopoietic System:

Haemopoietic 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. Macrocytosis and megaloblastic anaemia have occurred. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease have been reported. (see Section 4.4 Special warnings and precautions for use – Hematopoietic Effect)

Immune System:

HSS/DRESS (see Section 4.4 Special warnings and precautions for use – Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms), systemic lupus erythematosus, periarteritis nodosa, and immunoglobulin abnormalities. Angioedema has also been reported (see section 4.4 Special warnings and precautions for use - Angioedema).

Investigations: Thyroid function test abnormal

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. Other disorders of bone metabolism such as hypocalcemia, hypophosphatemia and decreased levels of Vitamin D metabolites have also been reported.

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The 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. The patient then becomes comatose, the pupils are unresponsive and hypotension occurs followed by respiratory depression and apnoea. Bradycardia and asystole/cardiac arrest also have been reported (see Section 4.4 – Cardiac Effects). 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 mg/l, and ataxia at 30 mg/l, dysarthria and lethargy appear when the serum concentration is greater than 40 mg/l, but a concentration as high as 50 mg/l has been reported without evidence of toxicity.

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

Special Populations

Patients with Renal or Hepatic Disease:

Increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia or hyperbilirubinemia has been reported (see section 4.4 Special warnings and precautions for use-General.

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 Posology and method of administration-Dosing in Elderly Patients).

5.3 Preclinical safety data

Reproductive and developmental toxicity:

Phenytoin causes embryofetal death and growth retardation in rats, mice, and rabbits. Phenytoin is teratogenic in rats (craniofacial defects including cleft palate, cardiovascular malformations, neural and renal defects, and limb abnormalities), mice (cleft lip, cleft palate, neural and renal defects, limb abnormalities, and digital and ocular abnormalities) and rabbits (cleft palate, limb abnormalities, and digital and ocular abnormalities). The defects produced are similar to major malformations

observed in humans and abnormalities described for fetal hydantoin syndrome. The teratogenic effects of phenytoin in animals occur at therapeutic exposures, and therefore a risk to the patients cannot be ruled out.

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

Carcinogenesis:

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Lactose monohydrate

Magnesium stearate

Sodium lauril sulfate

Silica, colloidal anhydrous

Shell:

Gelatin

Patent blue V (E131)

Quinoline yellow (E104)

Titanium dioxide (E171)

Printing Ink:

Shellac

Black iron oxide (E172)

Propylene glycol

Strong ammonia solution

Potassium hydroxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

White PVC/PE/PVDC aluminium foil blister pack containing 28 capsules

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Limited t/a Mylan

Station Close

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Hertfordshire

EN6 1TL

United Kingdom

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