Phenytoin Capsules I.P.

DILANTIN® Kapseals

1. NAME OF MEDICINAL PRODUCT

DILANTIN KAPSEALS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Phenytoin is an anticonvulsant drug, related to the barbiturates in chemical structure, but has a five-membered ring. The chemical name is 5,5-diphenyl-2,4-imidazolidinedione.

Each phenytoin sodium hard gelatin capsule for oral administration contains 50 mg or 100 mg phenytoin sodium.

All strengths presentations mentioned in this document might not be available in the market.

3. PHARMACEUTICAL FORM

Capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Phenytoin is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

4.2 Posology and Method of Administration

General

Phenytoin capsules are formulated with the sodium salt of phenytoin. Because there is approximately an 8% increase in drug content with the free acid form over that of the sodium salt, dosage adjustments and serum level monitoring may be necessary when switching from a product formulated with the free acid to a product formulated with the sodium salt and *vice versa*.

Dosage should be individualized to provide maximum benefit. In some cases serum drug level determinations may be necessary for optimal dosage adjustments. Optimum control without

clinical signs of toxicity occurs more often with serum levels between 10-20 mcg/mL, although some mild cases of tonic-clonic (grand mal) epilepsy 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, and changes in dosage (increase or decrease) should not be carried out at intervals shorter than seven to ten days.

Adult Dosage

Divided daily dosage

Patients who have received no previous treatment may be started on 300 mg daily, to be taken in three equally divided doses, and the dosage then adjusted to suit individual requirements. For most adults, the satisfactory maintenance dosage will be 300 mg to 400 mg daily to be taken in three to four equally divided doses, respectively. An increase up to 600 mg daily may be made if necessary.

Non-emergency oral loading dose in adult patients

An oral loading dose of phenytoin may be used for non-emergency initiation of therapy in adults who require rapid steady-state serum levels, and for whom intravenous administration is not desirable. This dosing regimen should be reserved for patients in a clinic or hospital setting where phenytoin serum levels can be closely monitored. Patients with a history of renal or liver disease should not receive the oral loading dose regimen.

The recommended oral loading dose is 1 g of phenytoin divided into three doses (400 mg, 300 mg, and 300 mg) and administered at 2 hour intervals. Normal maintenance dosage is then instituted 24 hours after the loading dose, with frequent serum level determinations.

Pediatric Dosage

Initially, 5 mg/kg/day in two or three equally divided doses with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years old and adolescents may require the minimum adult dose (300 mg/day). If the daily dosage cannot be divided equally, the larger dose should be given at bedtime.

Dosing in Special Populations

Patients with Renal or Hepatic Disease: (see Section **4.4 Special Warnings and Precautions for Use -** General).

Elderly Patients: Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required (see Section **5.2 Pharmacokinetic Properties, Special Populations -** Age).

4.3 Contraindications

Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin, or its inactive ingredients, 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 (petit mal) seizures are present, combined drug therapy is needed.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus. When, in the judgment 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 anticonvulsant drug not belonging to the hydantoin chemical class.

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined (polymorphism).

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

Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminaemia, the interpretation of total phenytoin plasma concentrations should be made with caution. Unbound concentration of phenytoin may be elevated in patients with hyperbilirubinaemia. Unbound phenytoin concentrations may be more useful in these patient populations.

Suicidal Behaviour and Ideation

Antiepileptic drugs (AEDs), including phenytoin, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the

risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analysed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing phenytoin or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

Cardiac Effects

Cases of bradycardia and asystole/cardiac arrest have been reported, most commonly in association with phenytoin toxicity (see Section **4.9 Overdose**), 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, 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 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, and appropriate supportive measures provided.

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 sensitised individuals.

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, determination of serum drug levels is recommended. Dose reduction of phenytoin therapy is indicated if plasma drug levels are excessive; if symptoms persist, termination of phenytoin therapy is recommended.

Hematopoietic Effect

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.

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.

It is recommended that patients receiving long-term Dilantin therapy should undergo regular blood counts as serious haematological abnormalities have been reported (see Section **4.8 Undesirable Effects**).

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 Undesirable Effects**, Immunologic).

Hepatic Injury

The liver is the chief site of biotransformation of phenytoin. Patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

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 have been associated with a hypersensitivity syndrome characterized by fever, skin eruptions, and lymphadenopathy, and usually occur within the first 2 months of treatment. Other common manifestations include arthralgias, rash, jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. 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.

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.

Serious Dermatologic Reactions

Phenytoin can cause rare, severe cutaneous adverse reactions (SCARs) such as acute generalized exanthematous pustulosis (AGEP) (see section **4.8 Adverse effects (undesirable effects),** Dermatologic System), 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 signs and symptoms of skin rash and blisters, fever, itching and other signs and symptoms of HSS/DRESS (see Section **4.4 Special Warnings and Precautions for Use -** HSS/DRESS), 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, including skin rash, SJS, TEN, hepatotoxicity, HSS 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 HLA-B*1502, an inherited allelic variant of the human leucocyte antigen B (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.

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.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally caution should be exercised if using structurally similar compounds (e.g., barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Metabolic Effect

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.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise serum glucose levels in diabetic patients.

Hypoalbuminaemia, from any cause, may be potentially toxic through its effect on increasing unbound phenytoin levels.

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.

Women of Childbearing Potential

Phenytoin may cause fetal 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 Pregnancy and Lactation**).

Information for the Patient

Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen and of informing their physician of any clinical condition in which it is not possible to take the drug orally as prescribed - e.g., surgery, etc.

Patients should be cautioned on the use of other drugs or alcoholic beverages without first seeking their physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Drug Interactions

There are many drugs that may increase or decrease serum phenytoin levels or that phenytoin may affect. Determinations of serum phenytoin concentrations are especially helpful when possible drug interactions are suspected. The most commonly occurring drug interactions are listed below.

In general, phenytoin is a potent inducer of the hepatic cytochrome P450 microsomal isoenzymes CYP3A4, CYP2D6, CYP1A2, CYP2C9 and CYP2C19. However, a patient's susceptibility to enzyme-inducing interactions may be influenced by factors such as age, cigarette smoking, or the presence of liver disease. Phenytoin is metabolised primarily by CYP2C9 (major) and CYP2C19 (minor), thus several drugs may inhibit or induce the metabolism of phenytoin.

Oral phenytoin absorption may be reduced by a number of drugs. Phenytoin is highly plasma-protein bound and may be displaced by other drugs, increasing unbound ('free') phenytoin levels. Phenytoin 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.

Drugs that may increase phenytoin serum levels

Table 2 summarizes the drug classes that may potentially increase phenytoin serum levels:

TABLE 2	
DRUG CLASSES	**DRUGS IN EACH CLASS (SUCH AS)***
Alcohol	alcohol (acute intake)
Analgesic/Anti-inflammatory agents	azapropazone salicylates
Anesthetics	halothane
Antibacterial agents	chloramphenicol erythromycin isoniazid

	sulfadiazine sulfamethoxazole-trimethoprim, sulfonamides
Anticonvulsants	felbamate oxcarbazepine sodium valproate succinimides (ethosuximide) topiramate.
Antifungal agents	amphotericin B fluconazole ketoconazole miconazole itraconazole voriconazole
Antineoplastic agents	capecitabine** fluorouracil**
Antiplatelet agents	clopidogrel
Benzodiazepines/Psychotropic agents	chlordiazepoxide diazepam disulfiram methylphenidate trazodone viloxazine
Calcium channel blockers/Cardiovascular agents	amiodarone dicumarol diltiazem nifedipine, ticlopidine
H_2-antagonists	cimetidine
HMG-CoA reductase inhibitors	fluvastatin
Hormones	estrogens
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 drug Product Information should be consulted.

** Increased phenytoin plasma concentrations have been reported during concomitant use of phenytoin with capecitabine or its metabolite fluorouracil (5FU). Formal interaction studies between phenytoin and capecitabine have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme system by capecitabine. Patients taking phenytoin concomitantly with capecitabine or fluorouracil should be regularly monitored for increased phenytoin plasma levels.

Drugs that may decrease phenytoin plasma levels

Error! Reference source not found. Table 3 summarizes the drug classes that may potentially decrease phenytoin plasma levels.

TABLE 3	
DRUG CLASSES	**DRUGS IN EACH CLASS (SUCH AS)***
Alcohol	alcohol (chronic intake)
Antibacterial agents/fluoroquinolones	rifampin ciprofloxacin
Anticonvulsants	vigabatrin
Antineoplastic agent	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	*Hypericum perforatum* (St. John's Wort)
Benzodiazepines/Psychotropic agents	diazepam

* This list is not intended to be inclusive or comprehensive. Individual drug Product Information should be consulted.

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

Molindone hydrochloride contains calcium ions which may interfere with the absorption of phenytoin. Ingestion times of phenytoin and calcium preparations, including antacid preparations containing calcium, should be staggered to prevent absorption problems.

Drugs that may either increase or decrease phenytoin serum levels

Error! Reference source not found. Table 4 summarizes the drug classes that may either increase or decrease phenytoin serum levels:

TABLE 4	
DRUG CLASSES	**DRUGS IN EACH CLASS (SUCH AS)***
Antibacterial agents	ciprofloxacin
Anticonvulsants**	carbamazepine phenobarbital sodium valproate valproic acid
Antineoplastic agents	antineoplastic agents
Psychotropic agents	chlordiazepoxide diazepam phenothiazines

* This list is not intended to be inclusive or comprehensive. Individual drug Product Information should be consulted.

** The effect of phenytoin on carbamazepine, phenobarbital, valproic acid, and sodium valproate serum levels is unpredictable.

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

Error! Reference source not found. Table 5 summarizes the drug classes whose blood levels and/or effects may be altered by phenytoin:

TABLE 5	
DRUG CLASSES	**DRUGS IN EACH CLASS (SUCH AS)***
Antibacterial agents	doxycycline rifampin tetracycline
Anticonvulsants	lamotrigine carbamazepine phenobarbital sodium valproate valproic acid
Antifungal agents	azoles posaconazole voriconazole
Antihelminthics	albendazole praziquantel
Antineoplastic agents	teniposide
Antiretrovirals	delavirdine efavirenz fosamprenavir indinavir lopinavir/ritonavir ritonavir saquinavir
Bronchodilators	theophylline
Calcium channel blockers/Cardiovascular agents	digitoxin digoxin disopyramide mexiletine nicardipine nimodipine quinidine verapamil
Corticosteroids	corticosteroids
Coumarin anticoagulants	warfarin
Cyclosporine	cyclosporine
Diuretics	furosemide
HMG-CoA reductase inhibitors	atorvastatin fluvastatin simvastatin

Hormones	estrogens oral contraceptives (see Sections: **4.4 Special Warnings and Precautions for Use-** Women of Childbearing Potential and **4.6 Pregnancy and Lactation)**
Hyperglycemic agents	diazoxide
Immunosuppressant drugs	immunosuppressant drugs
Neuromuscular blocking agents	alcuronium cisatracurium pancuronium rocuronium vecuronium
Opioid analgesics	methadone
Oral hypoglycemic agents	chlorpropamide glibenclamide tolbutamide
Psychotropic agents/Antidepressants	clozapine paroxetine quetiapine sertraline
Vitamin D	vitamin D
Folic acid	folic acid

* This list is not intended to be inclusive or comprehensive. Individual drug Product Information should be consulted.

Seizure Threshold Lowering Drugs

Although not a pharmacokinetic drug interaction, antidepressants, antipsychotics, tramadol and other seizure threshold lowering drugs may precipitate seizures in susceptible patients by lowering convulsive threshold. Phenytoin dosage may need to be adjusted.

Drug-enteral Feeding/Nutritional Preparations Interaction

Literature reports suggest that patients who have received enteral feeding preparations and/or related nutritional supplements have lower than expected phenytoin plasma levels. It is therefore suggested that phenytoin not be administered concomitantly with an enteral feeding preparation. Conversely, when enteral feedings are halted, phenytoin levels may rise substantially. If the patient can receive intermittent feedings, it is crucial that phenytoin doses be administered at least two hours following a feeding and that the next feeding be delayed until at least two hours after the phenytoin dose is administered. Patients who must receive continuous enteral feedings should probably receive phenytoin intravenously. Any patients receiving phenytoin orally through a feeding tube should have the suspension diluted prior to administration and the tubing flushed following administration. Serum phenytoin levels should be monitored and the dosage should be adjusted to achieve therapeutic concentrations.

Drug-laboratory Test Interactions

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

4.6 Pregnancy and Lactation

Usage in Pregnancy

Phenytoin crosses the placenta in humans.

The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the dangers to the mother and fetus of uncontrolled epilepsy.

It is recommended that:

- Women on antiepileptic drugs (AEDs) receive pre-pregnancy counselling with regard to the risk of fetal abnormalities;
- AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;
- Folic acid supplementation (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception;
- Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

Phenytoin should only be used in women of childbearing potential and pregnant women if the potential benefit outweighs the risk. When appropriate, counsel pregnant women and women of childbearing potential about alternative therapeutic options.

This drug taken during pregnancy has been associated with craniofacial defects, fingernail hypoplasia, developmental disability, growth retardation and less frequently, oral clefts and cardiac anomalies. This clinical pattern is sometimes called the 'fetal hydantoin syndrome'. A number of reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and a higher incidence of birth defects in children born to these women.

The risk of a mother with epilepsy giving birth to a baby with an abnormality is about three times that of the normal population. Some of this risk is due to the anticonvulsant drugs taken.

There have been isolated reports of malignancies including neuroblastoma, in children whose mothers received phenytoin during pregnancy. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant

hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating and counselling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformations such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other anticonvulsant drugs, there have been reports of a fetal hydantoin syndrome. This consists of prenatal dysmorphic facial features, fingernail and digit hypoplasia, developmental disability, growth retardation (including microcephaly) and mental deficiency in children born to mothers who have received phenytoin.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Phenytoin also can cause coagulation defects with consequent risk of haemorrhage in the fetus and the newborn infant which may be preventable by the prophylactic administration of vitamin K to the mother prior to delivery.

Women of childbearing potential who are not planning a pregnancy should be advised on the use of effective contraception during treatment. Phenytoin may result in a failure of the therapeutic effect of hormonal contraceptives (see Section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Usage in Lactation

Breastfeeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk. Phenytoin concentration in breast milk is approximately one-third of the corresponding maternal plasma concentration.

4.7 Effects on 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

Body as a Whole: Anaphylactoid reaction and anaphylaxis.

Central Nervous System: The most common manifestations encountered with phenytoin therapy are nervous system reactions and are usually dose-related. These 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 Special Warnings and Precautions for Use** – Central Nervous System Effect).

Dizziness, vertigo, insomnia, transient nervousness, motor twitchings, 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.

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis, and Peyronie's disease.

Gastrointestinal System: Nausea, vomiting and constipation. To prevent gastric irritation due to alkalinity, Dilantin should be taken with at least half a glass of water. Gastric irritation may often be minimised by administering Dilantin during or following meals.

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. Macrocytosis and megaloblastic anemia have also occurred, these conditions usually respond to folic acid therapy.

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).

Immunologic: HSS/DRESS (which may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, periarteritis nodosa, and immunoglobulin abnormalities (see Section **4.4 Special Warnings and Precautions for Use** – Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms). Angioedema has been reported (see section **4.4 Special warnings and precautions for use,** Angioedema).

Investigations
Thyroid function test abnormal.

Dermatologic System: 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. In general, rashes are more frequent in children and young adults. Other more serious forms that may be fatal have included bullous, exfoliative, or purpuric dermatitis, lupus erythematosus, AGEP, SJS, and TEN (see Section **4.4 Special Warnings and Precautions for Use** – Serious Dermatologic Reactions). Urticaria has been reported.

Hirsutism.

Hepatic System: Potentially fatal cases of acute hepatic failure, toxic hepatitis and liver damage may occur (see Section **4.4 Special Warnings and Precautions for Use –** Hepatic Injury). This effect may be the result of a hypersensitivity reaction.

Special Senses: Taste perversion.

Musculoskeletal System: Bone fractures and osteomalacia have been associated with long-term (>10 years) use of phenytoin by patients with chronic epilepsy. Osteoporosis and other disorders of bone metabolism such as hypocalcemia, hypophosphatemia and decreased levels of Vitamin D metabolites have also been reported.

Miscellaneous: Gingival hyperplasia occurs frequently and its incidence may be reduced by good oral hygiene, including gum massage, frequent brushing and appropriate dental care.

4.9 Overdose

The lethal dose in pediatric patients is not known. The lethal dose in adults is estimated to be 2 to 5 g. The initial symptoms are nystagmus, ataxia, dysarthria and CNS depression. Other signs are tremor, hyperreflexia, somnolence, drowsiness, lethargy, hallucinations, confusion, mental status changes, slurred speech, blurred vision, nausea, vomiting, choreoathetosis, dyskinesias, hyperglycaemia and mild hypoglycaemia. Severe poisoning may result in respiratory depression. Cardiotoxicity has not been reported with oral overdoses. Irreversible cerebellar dysfunction and atrophy has been reported as a delayed effect following severe overdoses. The patient may become comatose and hypotensive. Bradycardia and asystole/cardiac arrest have been reported (see Section **4.4 Special warnings and precautions for use,** 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 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 has been taken to result in a serum concentration >100 mcg/mL with complete recovery. Irreversible cerebellar dysfunction and atrophy have been reported.

Pharmacokinetic Information

In overdose settings, saturation of the hepatic hydroxylation system occurs and zero order kinetics predominate. Elimination follows a Michaelis-Menten model with a prolonged half-life. As phenytoin is continually excreted, elimination changes from zero order to first order kinetics and drug levels decrease more.

Serial plasma phenytoin concentrations should be monitored. In acute overdose, peak levels are frequently delayed for 24 to 48 hours, and occasionally as long as 7 days.

The proportion of phenytoin in plasma not bound to protein is an important measure of potential toxicity with free phenytoin levels of <1.5 µg/mL indicating no signs of toxicity; 1.5 µg/mL to 5 µg/mL seen with mild to moderate intoxication; and levels above 5 µg/mL associated with severe intoxication.

Treatment of Overdosage

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. Hemodialysis 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 pediatric patients.

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

Phenytoin is an anticonvulsant drug, which can be useful in the treatment of epilepsy. The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at the synaptic levels. Loss of post-tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of tonic-clonic (grand mal) seizures.

5.2 Pharmacokinetic Properties

In general the reported plasma half-life of phenytoin averages 22 hours, with a range of 7 to 42 hours. Steady-state therapeutic levels are achieved at least 7 to 10 days (5 to 7 half-lives) after initiation of therapy with recommended doses of 300 mg/day.

Conventionally, with drugs following linear kinetics the half-life is used to determine the dose rate, drug accumulation and the time to reach steady-state. Phenytoin, however, demonstrates non-linear kinetics and therefore the half-life is affected by the degree of absorption, saturation of metabolic pathways, dose and the degree of metabolic enzyme induction. This results in considerable inter- and intra-patient variability in phenytoin pharmacokinetics. As a consequence, the clinical relevance of reported phenytoin half-life values are limited and cannot be used in the conventional manner to estimate the dosage regimen. When administering phenytoin to a patient, it is necessary to measure serum levels as this provides the most accurate means of deriving a suitable dosage regimen.

Serum level determinations should originally be obtained at least 7 to 10 days after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that

equilibrium or steady-state will have been achieved. Further serum level determinations may be required to further refine the dosage regimen. Trough levels provide information about clinically effective serum level range and confirm patient compliance and are obtained just prior to the patient's next scheduled dose. Peak levels indicate an individual's threshold for emergence of dose-related side effects and are obtained at the time of expected peak concentration.

Optimum control without clinical signs of toxicity occurs more often with serum levels between 10 μg/mL and 20 μg/mL. Therapeutic concentrations of free (unbound) phenytoin, which are frequently monitored in patients with altered protein binding, usually fall in the range of 0.8 μg/mL to 2 μg/mL.

In most patients maintained at steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolisers of phenytoin.

Unusually high levels of phenytoin result from liver disease, congenital enzyme deficiency or drug interactions which result in metabolic interference. Patients with large variations in phenytoin plasma levels, despite standard doses, present a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. Phenytoin is about 90% protein bound. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal. Protein binding may be lower in neonates and hyperbilirubinaemic infants; also altered in patients with hypoalbuminaemia, uraemia or acute trauma and in pregnancy.

Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine. Urinary excretion of phenytoin and its metabolites occurs partly with glomerular filtration but more importantly with tubular secretion. Phenytoin is metabolised in the liver primarily by CYP2C9 (major) and CYP2C19 (minor) (see Section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**). The major inactive metabolite is 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH). The rate of metabolism is increased in younger children, pregnant women, in women during menses and in patients with acute trauma. The rate decreased with advancing age. Phenytoin may be metabolised slowly in a small number of individuals due to genetic polymorphism, which may cause isoenzyme mutations (e.g., CYP2C9/19), limited enzyme availability and lack of induction (e.g., CYP3A4). Because phenytoin is hydroxylated in the liver by an enzyme system which is saturable, at high plasma levels small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range.

The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

Special Populations

Patients with Renal or Hepatic Disease: (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 Special Populations–*Elderly Patients*).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

For 50 mg:
Lactose IP
Talc IP
Magnesium Stearate IP

Hard Gelatin Size '3' opaque capsules with white imprint of 'PFIZER' on brown cap and black imprint of "PFIZER' on white body. Hard gelatin capsule shells contains Brilliant Blue, red iron oxide, Ponceau 4R and Titanium dioxide IP as approved colors.

For 100 mg:
Lactose IP
Talc IP
Magnesium Stearate IP

Hard Gelatin Size '3' capsule shells with orange cap, off-white body and 'PFIZER' imprinted in black ink on both body and cap. Hard gelatin capsules shell contains Erythrosine, Sunset yellow FCF and Titanium Dioxide IP as approved colors.

6.2 Incompatibilities

None specific

6.3 Shelf-life

24 months

6.4 Special Precautions for Storage

Keep bottle securely closed at a temperature not exceeding 30°C.

Protect from light and moisture.

6.5 Nature and Contents of Container

Amber Glass Bottle Pack containing 100 capsules.

6.6 Instructions for Use/Handling

As directed by the physician.