Phenytoin Sodium Injection USP
DILANTIN®

1. NAME OF THE MEDICINAL PRODUCT

DILANTIN®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each mL of the sterile solution contains 50 mg Phenytoin Sodium IP.

Each ml contains:
Phenytoin Sodium IP …….……50 mg

For full list of excipients, please see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and Method of Administration

General: Phenytoin capsules and solution for injection are formulated with the sodium salt of phenytoin. The free acid form of phenytoin is used in the phenytoin suspension (30 mg/5 mL (pediatric) and 125 mg/5 mL) and in the phenytoin tablets. 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*.

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

Optimum control without clinical signs of toxicity occurs most often with serum levels between 10 and 20 mcg/mL.

Parenteral phenytoin should be used only when oral phenytoin administration is not possible.

Parenteral phenytoin may be administered as a slow intravenous (IV) bolus or it may be administered via an IV infusion. Rapid infusion may be associated with adverse cardiovascular events (see section 4.4 **Special warnings and precautions for use** – General).

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

If administered in diluted form, parenteral phenytoin should be diluted with normal saline. Parenteral phenytoin should not be added to dextrose or dextrose-containing solutions due to the potential for precipitation.

Because of the risk of local toxicity, IV phenytoin should be administered directly into a large peripheral or central vein through a large-gauge catheter. Prior to the administration, the patency of the IV catheter should be tested with a flush of sterile saline. Each injection of parenteral phenytoin should then be followed by a flush of sterile saline through the same catheter to avoid local venous irritation due to the alkalinity of the solution (see section 4.4. **Special warnings and precautions for use, - Local Toxicity (including Purple Glove Syndrome)**).

Bolus Administration: A bolus of parenteral phenytoin should be injected slowly, not exceeding 50 mg/minute in adults, into a large vein through a large-gauge needle or intravenous catheter. Each injection of intravenous phenytoin should be preceded by a saline flush and followed by an injection of sterile saline through the same needle or catheter to avoid local venous irritation due to the alkalinity of the solution.

Infusion Administration: For administration by infusion, parenteral phenytoin should be diluted in 50-100 mL of normal saline with the final concentration of phenytoin in the solution not exceeding 10 mg/mL. Administration should commence immediately after the mixture has been prepared and must be completed within one hour (the infusion mixture should not be refrigerated). An in-line filter (0.22 to 0.50 microns) should be used. Each injection of intravenous phenytoin should be preceded by a saline flush and followed by an injection of sterile saline through the same needle or intravenous catheter to help reduce local venous irritation due to the alkalinity of the solution.

Dosage is not to exceed 50 mg/minute, intravenously in adults, and not to exceed 1 – 3 mg/kg/minute in neonates and children or 50 mg/minute, whichever is slower. There is a relatively small margin between full therapeutic effect and minimally toxic doses of this drug (see section 4.4 **Special Warnings and Special Precautions for Use** – General).

On those occasions when intramuscular administration may be required (i.e., Post-operatively in comatose patients), a sufficient dose must be administered intramuscularly to maintain the serum level within the therapeutic range. Where oral dosage is resumed following IM usage, the oral dosage should be adjusted to compensate for the slow, continuing IM absorption to avoid toxic symptoms. To avoid drug accumulation due to absorption from the muscle depots, it is recommended that for the first week back on oral phenytoin, the oral dose be reduced to one-half of the original dose (one-third of the IM dose).

Status Epilepticus: In adults, a loading dose of 10 to 15 mg/kg should be administered slowly intravenously, at a rate not exceeding 50 mg per minute (this will require approximately 20 minutes in a 70 kg patient). The loading dose should be followed by a maintenance dose of 100 mg orally or intravenously every 6 to 8 hours.

Absorption of phenytoin in neonates and children may be unreliable after oral administration.

A loading dose of 15 to 20 mg/kg of phenytoin intravenously will usually produce serum concentrations of phenytoin within the generally accepted serum total concentrations between 10 and 20 mcg/mL (unbound phenytoin concentrations of 1 to 2 mcg/mL). The drug should be injected slowly intravenously at a rate not exceeding 1 to 3 mg/kg/minute or 50 mg/minute, whichever is slower.

Continuous monitoring of the electrocardiogram and blood pressure is essential. The patient should be observed for signs of respiratory depression. Determination of phenytoin serum levels is advised when using phenytoin in the management of status epilepticus and in the subsequent establishment of maintenance dosage.

Other measures including concomitant administration of an intravenous benzodiazepine such as diazepam, or intravenous short-acting barbiturate, will usually be necessary for rapid control of seizures because of the required slow rate of administration of phenytoin.

If administration of parenteral phenytoin does not terminate seizures, the use of other anticonvulsants, intravenous barbiturates, general anesthesia, or other appropriate measures should be considered.

Intramuscular administration should not be used in the treatment of status epilepticus because the attainment of peak serum levels may require up to 24 hours (see section 4.4 **Special Warnings and Special Precautions for Use** – General).

Neurosurgery: Prophylactic dosage - 100 to 200 mg (2 to 4 mL) intramuscularly at approximately 4-hour intervals during surgery and continued during the post-operative period. When intramuscular administration is required for a patient previously stabilized orally, compensating dosage adjustments are necessary to maintain therapeutic serum levels. When intramuscular administration is used, the drug should be given by deep intramuscular injection. An intramuscular dose 50% greater than the oral dose is necessary to maintain these levels. When the patient is returned to oral administration, the dose should be reduced by 50% of the original oral dose for one week to prevent excessive serum levels due to sustained release form intramuscular tissue sites.

If the patient requires more than a week of IM phenytoin, alternative routes should be explored, such as gastric intubation. For time periods less than one week, the patient shifted back from IM administration should receive one-half the original oral dose for the same period of time the patient received IM phenytoin. Monitoring serum levels would help prevent a fall into the sub-therapeutic range. Serum drug level determinations are especially helpful when possible drug interactions are suspected.

4.3 Contraindications

Phenytoin is contraindicated in those patients with

- A history of hypersensitivity to phenytoin, or its inactive ingredients, or other hydantoins (see section 4.4 **Special Warnings and Precautions for Use**).
- Sinus bradycardia, sino-atrial block, second and third degree A-V block, and Adams-Stokes syndrome because of its effect on ventricular automaticity.
- A history of prior acute hepatotoxicity attributable to phenytoin (see section 4.4 **Special Warnings and Precautions for Use**).
- Co-administration of delavirdine because of 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 hypoglycemia or other metabolic causes.

Appropriate diagnostic procedures should be performed as indicated.

The most notable signs of toxicity associated with the intravenous use of this drug are cardiovascular collapse and/or central nervous system depression. Hypotension does occur when the drug is administered rapidly by the intravenous route. The rate of administration is very important; it should not exceed 50 mg per minute in adults, and 1-3 mg/kg/minute or 50 mg/minute (whichever is slower), in neonates and children. At this rate, toxicity should be minimized. As non-emergency therapy, phenytoin should be administered more slowly as either a loading dose or by intermittent infusion. Because of the risks of cardiac and local toxicity associated with intravenous phenytoin, oral phenytoin should be used whenever possible.

Because adverse cardiovascular reactions have occurred during and after infusions, careful cardiac monitoring is needed during and after the administration of intravenous phenytoin. Reduction in rate of administration or discontinuation of dosing may be needed.

Hypotension usually occurs when the drug is administered by the intravenous route.

Phenytoin should be used with caution in patients with hypotension and severe myocardial insufficiency.

The intramuscular route is not recommended for the treatment of status epilepticus since serum levels of phenytoin in the therapeutic range cannot be readily achieved with doses and methods of administration ordinarily used. In the treatment of status epilepticus, the intravenous route is preferred because of the delay in absorption of phenytoin when administered intramuscularly.

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus. When, in the judgement of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

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.

Drug Reaction with Eosinophilia and Systemic Symptoms/Multiorgan Hypersensitivity
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including phenytoin. Some of these events have been fatal or life-threatening. 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, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Phenytoin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Hypersensitivity
Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity (see section 4.3 **Contraindications**). Additionally, consider alternatives to structurally similar drugs such as carboxamides (e.g., carbamazepine), barbiturates, succinimides, and oxazolidinediones (e.g., trimethadione) in these same patients. Similarly, if there is a history of hypersensitivity reactions to these structurally similar drugs in the patient or immediate family members, consider alternatives to phenytoin.

Cardiovascular Effects
Hypotension may occur. Severe cardiotoxic reactions and fatalities have been reported with arrhythmias including bradycardia, atrial and ventricular depression and ventricular fibrillation. In some cases, cardiac arrhythmias have resulted in asystole/cardiac arrest and

death. Severe complications are most commonly encountered in elderly or gravely ill patients. Cardiac adverse events have also been reported in adults and children without underlying cardiac disease or comorbidities and at recommended doses and infusion rates. Therefore, careful cardiac (including respiratory) monitoring is needed when administering IV loading doses of phenytoin. Reduction in rate of administration or discontinuation of dosing may be needed. Phenytoin should be used with caution in patients with hypotension and/or severe myocardial insufficiency.

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.

Hematopoietic Effect

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 symptoms and signs resembling serum sickness - e.g., fever, rash, and liver involvement. In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative 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.

Hepatic/Immunologic Effect

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.

Renal or Hepatic Disease

Because the fraction of unbound phenytoin is increased in patients with renal or hepatic disease, or in those with hypoalbuminemia, the monitoring of phenytoin serum levels should be based on the unbound fraction in those patients.

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.

Local Toxicity (including Purple Glove Syndrome)

Soft tissue irritation and inflammation have occurred at the site of injection with and without extravasation of IV phenytoin.

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

Because of the risk of local toxicity, intravenous Dilantin should be administered directly into a large peripheral or central vein through a large-gauge catheter. Prior to the administration, the patency of the IV catheter should be tested with a flush of sterile saline. Each injection of parenteral Dilantin should then be followed by a flush of sterile saline through the same catheter to avoid local venous irritation due to the alkalinity of the solution.

Intramuscular Dilantin administration may cause pain, necrosis, and abscess formation at the injection site (see section 4.2 **Posology and Method of Administration**).

Integumentary Effect

Phenytoin can cause rare, serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), 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, or other signs of hypersensitivity such as itching, 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. Published literature has suggested that there may be an increased, although still rare, risk of hypersensitivity reactions, including skin rash, SJS, TEN, hepatotoxicity, and AHS 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 HLA-B gene, in patients using another 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.

The use of HLA-B*1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.

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.

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 also may raise serum glucose levels in diabetic 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 **Fertility, Pregnancy and Lactation**).

Information for the Patient

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.

Teratogenicity and Other Harm to the Newborn

Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), and abnormalities characteristic of fetal hydantoin syndrome, including dysmorphic skull and facial features, nail and digit hypoplasia, growth abnormalities (including microcephaly), and cognitive deficits, have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have been several reported cases of malignancies, including neuroblastoma.

The overall incidence of malformations for children of epileptic women treated with antiepileptic drugs, including phenytoin, during pregnancy is about 10%, or two- to three-fold that in the general population

4.5 Interaction with Other Medicinal Products and Other Forms of Interactions

Drug Interactions

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

Drugs which may increase phenytoin serum levels

Various drugs may increase phenytoin serum levels either by decreasing its rate of metabolism by the hepatic CYP450 2C9 and 2C19 enzymatic systems (e.g., dicumarol, disulfiram, omeprazole, ticlopidine), by competing for protein binding sites (e.g., salicylates, sulfisoxazole, tolbutamide), or by a combination of both processes (e.g., phenylbutazone, valproate sodium).

Table 1 summarizes the drug classes which may potentially increase phenytoin serum levels:

TABLE 1

DRUG CLASSES	DRUGS IN EACH CLASS (SUCH AS)
Alcohol (acute intake)	
Analgesic/Anti-inflammatory agents	azapropazone phenylbutazone salicylates
Anesthetics	halothane
Antibacterial agents	chloramphenicol isoniazid sulfonamides sulfamethizole sulfaphenazole sulfadiazine sulfamethoxazole-trimethoprim

Anticonvulsants	felbamate topiramate oxcarbazepine, succinimides (ethosuximide, methsuximide)
Antifungal agents	amphotericin B fluconazole ketoconazole miconazole itraconazole voriconazole
Antineoplastic agents	capecitabine fluorouracil
Benzodiazepines/Psychotropic agents	chlordiazepoxide disulfiram methylphenidate trazodone viloxazine phenothiazines
Calcium channel blockers/Cardiovascular agents	amiodarone dicumarol ticlopidine
H_2-antagonists	cimetidine
HMG-CoA reductase inhibitors	fluvastatin
Hormones	estrogens
Oral hypoglycemic agents	tolbutamide
Proton pump inhibitors	omeprazole
Serotonin re-uptake inhibitors	fluoxetine fluvoxamine sertraline

Drugs which may decrease phenytoin plasma levels

Table 2 summarizes the drug classes which may potentially decrease phenytoin plasma levels:

TABLE 2	
DRUG CLASSES	**DRUGS IN EACH CLASS (SUCH AS)**
Alcohol (chronic intake)	
Antibacterial agents	rifampin ciprofloxacin
Anticonvulsants	vigabatrin carbamazepine
Antineoplastic agents	bleomycin carboplatin cisplatin doxorubicin

	methotrexate
Antiretrovirals	ritonavir fosamprenavir nelfinavir
Psychotropic agents	diazepam
Bronchodilators	theophylline
Cardiovascular agents	reserpine
Folic acid	folic acid
Hyperglycemic agents	diazoxide
St. John's Wort	St. John's Wort

Molindone hydrochloride contains calcium ions which 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.

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 (see section 5.2 **Pharmacokinetic Properties** – Pharmacokinetic Interaction).

Drugs which 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	
DRUG CLASSES	**DRUGS IN EACH CLASS (SUCH AS)**
Anticonvulsants	phenobarbital sodium valproate valproic acid
Antineoplastic agents	
Psychotropic agents	chlordiazepoxide

Similarly, the effect of phenytoin on phenobarbital, valproic acid, and sodium valproate serum levels is unpredictable.

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

Table 4 summarizes the drug classes which blood levels and/or effects may be altered by phenytoin:

TABLE 4	
DRUG CLASSES	**DRUGS IN EACH CLASS (SUCH AS)**
Antibacterial agents	doxycycline praziquantel

	rifampin tetracycline
Anticonvulsants	lamotrigine carbamazepine felbamate topiramate oxcarbazepine quetiapine
Antifungal agents	azoles fluconazole ketoconazole itraconazole voriconazole posaconazole
Antihelmintics	albendazole
Antineoplastic agents	teniposide
Antiretrovirals	delavirdine efavirenz fosamprenavir lopinavir/ritonavir indinavir nelfinavir ritonavir saquinavir
Bronchodilators	theophylline
Calcium channel blockers/Cardiovascular agents	digitoxin digoxin disopyramide mexiletine nicardipine nifedipine nimodipine nisoldipine quinidine verapamil
Corticosteroids	
Coumarin anticoagulants	warfarin
Cyclosporine	
Diuretics	furosemide
HMG-CoA reductase inhibitors	atorvastatin fluvastatin simvastatin
Hormones	estrogens oral contraceptives

Neuromuscular blocking agents	alcuronium pancuronium vecuronium rocuronium cisatracurium
Opioid analgesics	methadone
Oral hypoglycemic agents	chlorpropamide glyburide tolbutamide
Psychotropic agents/Antidepressants	clozapine paroxetine sertraline
Vitamin D	vitamin D
Folic Acid	folic acid

Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and 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.

More frequent serum phenytoin level monitoring may be necessary in these patients.

Drug-laboratory Test Interactions

Care should be taken when using immunoanalytical methods to measure plasma phenytoin concentrations following fosphenytoin administration.

4.6 Fertility, Pregnancy and Lactation

Fertility
Phenytoin has not been adequately assessed for effects on male or female fertility.

Usage in Pregnancy
Phenytoin crosses the placenta in humans. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential harm to the fetus.

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. Less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated

epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans. Genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus 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 or counseling epileptic women of childbearing potential.

In humans, prenatal exposure to phenytoin may increase the risks for congenital malformations and adverse developmental outcomes. Prenatal exposure is associated with an increased incidence of major malformations, including orofacial cleft and cardiac defects. In addition, the fetal hydantoin syndrome, a pattern of abnormalities including dysmorphic skull and facial features, nail and digit hypoplasia growth abnormalities (including microcephaly) and cognitive deficits has been reported among children born to mothers who have took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

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

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

Clinical Considerations

Disease-associated maternal risk
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, post-partum restoration of the original dosage will probably be indicated.

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

Women of childbearing potential who are not planning a pregnancy should be advised regarding 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).

Administration of phenytoin to pregnant animals resulted in teratogenicity (increased incidences of fetal malformations) and other developmental toxicity (including embryofetal death, growth impairment, and behavioral abnormalities) in multiple animal species at clinically relevant doses.

Data

Human Data
Meta-analyses using data from published observational studies and registries have estimated an approximately 2.4-fold increased risk for any major malformation in children with prenatal phenytoin exposure compared to controls. An increased risk of heart defects, facial clefts, and digital hypoplasia has been reported. The fetal hydantoin syndrome is a pattern of congenital anomalies including craniofacial anomalies, nail and digital hypoplasia, prenatal-onset growth deficiency, and neurodevelopmental deficiencies.

Lactation

Phenytoin is secreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DILANTIN and any potential adverse effects on the breastfed infant from DILANTIN or from the underlying maternal condition.

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

The following adverse reactions associated with the use of phenytoin were identified in clinical studies or post-marketing reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Anaphylactoid reaction, and anaphylaxis. Drug rash with eosinophilia and systemic symptoms (DRESS) (see section 4.4 **Special Warnings and Special Precautions for Use** - Drug Reaction with Eosinophilia and Systemic Symptoms /Multiorgan hypersensitivity).

Cardiovascular System: Asystole/cardiac arrest, bradycardia, hypotension have been observed. Severe cardiovascular events and fatalities have been reported with atrial and ventricular conduction depression and ventricular fibrillation. Severe complications are most commonly encountered in elderly or critically ill patients (see section 4.4 **Special**

Warnings and Special Precautions for Use – General and Cardiovascular Effects).

Central Nervous System: The most common adverse reactions encountered with phenytoin therapy are nervous system reactions are usually dose-related. Reactions include nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion (see section 4.4 **Special Warnings and Special Precautions for Use** – Central Nervous System Effect).

Dizziness, vertigo, insomnia, transient nervousness, motor twitching, headache, paresthesia, and somnolence have also been observed.

There have also been rare reports of phenytoin-induced dyskinesia, including chorea, dystonia, tremor, and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. Cerebellar atrophy has been reported, and appears more likely in settings of elevated phenytoin levels and/or long-term phenytoin use. 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: Acute hepatic failure, toxic hepatitis, liver damage, nausea, vomiting, constipation, enlargement of the lips, and gingival hyperplasia (see section 4.4 **Special Warnings and Special Precautions for Use** – Hepatic/Immunologic Effect).

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. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease have been reported (see section 4.4 **Special Warnings and Special Precautions for Use** – Hematopoietic Effect).

Immunologic: Hypersensitivity syndrome, systemic lupus erythematosus, periarteritis nodosa, and immunoglobulin abnormalities (see section 4.4 **Special Warnings and Special Precautions for Use** – Hepatic/Immunologic Effect).

Injection Site: Local irritation, inflammation, tenderness, necrosis, and sloughing have been reported with or without extravasation of intravenous phenytoin [see section 4.4 **Special Warnings and Special Precautions for Use** – Local Toxicity (including Purple Glove Syndrome)].

Integumentary 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. Other more serious forms which may be fatal have included bullous, exfoliative, or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see section 4.4 **Special Warnings and Special Precautions for Use** – Integumentary Effect).

Local irritation, inflammation, tenderness, necrosis, and sloughing have been reported with or without extravasation of intravenous phenytoin.

Investigations: Thyroid function test abnormal.

Special Senses: Taste perversion.

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, and dysarthria. Other signs are tremor, hyperreflexia, somnolence, drowsiness, lethargy, slurred speech, blurred vision, nausea, and vomiting. The patient may become comatose and hypotensive. 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.

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

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

Phenytoin is a weak acid and has limited hydrosolubility, even in the intestine. The compound undergoes a slow and somewhat variable absorption after oral administration. After intramuscular administration, the absorption of phenytoin is slower than after oral administration, due to poor hydrosolubility of the compound and the possibility of its precipitation at the site of injection.

The plasma half-life of phenytoin in man averages 22 hours with a range of 7 to 42 hours. Phenytoin has an apparent volume of distribution of 0.6 L/kg and is highly bound (90%) to plasma proteins, mainly albumin. Free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal. Phenytoin is distributed into cerebrospinal fluid (CSF), saliva, semen, gastrointestinal fluids, bile, and breast milk. The concentration of phenytoin in CSF, brain, and saliva approximates the level of free phenytoin in plasma.

Phenytoin is biotransformed in the liver by oxidative metabolism. The major pathway involves 4-hydroxylation, which accounts for 80% of all metabolites. CYP2C9 plays the major role in the metabolism of phenytoin (90% of net intrinsic clearance), while CYP2C19 has a minor involvement in this process (10% of net intrinsic clearance). This relative contribution of CYP2C19 to phenytoin metabolism may however increase at higher phenytoin concentrations.

Because the cytochrome systems involved in phenytoin hydroxylation in the liver are saturable at high serum concentrations, small incremental doses of phenytoin may increase the half-life and produce very substantial increases in serum levels when these are in or above the upper therapeutic range. The clearance of phenytoin has been shown to be impaired by CYP2C9 inhibitors such as phenylbutazone and sulphaphenazole. Impaired clearance has also been shown to occur in patients administered CYP2C19 inhibitors such as ticlopidine.

Most of the drug is excreted in the bile as inactive metabolites, which are then reabsorbed from the intestinal tract and eliminated in the urine partly through glomerular filtration but, more importantly via tubular secretion. Less than 5% of phenytoin is excreted as the parent compound.

A fall in phenytoin serum levels may occur when patients are switched from oral to intramuscular (IM) administration. The drop is caused by slower absorption, as compared to oral administration, due to the poor hydrosolubility of phenytoin and the possibility of its precipitation at the site of injection. Intravenous administration is the preferred route for producing rapid therapeutic serum levels.

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.

5.3 Preclinical Safety Data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: See section 4.4 **Special Warnings and Special Precautions for Use** – Hematopoietic Effect

In carcinogenicity studies, phenytoin was administered in the diet to mice (10, 25, or 45 mg/kg/day) and rats (25, 50, or 100 mg/kg/day) for 2 years. The incidences of hepatocellular tumors were increased in male and female mice at the highest dose. No increases in tumor incidence were observed in rats. The highest doses tested in these studies were associated with peak serum phenytoin levels below human therapeutic concentrations.

In carcinogenicity studies reported in the literature, phenytoin was administered in the diet for 2 years at doses up to 600 ppm (approximately 90 mg/kg/day) to mice and up to 2,400 ppm (approximately 120 mg/kg/day) to rats. The incidences of hepatocellular tumors were increased in female mice at all but the lowest dose tested. No increases in tumor incidence were observed in rats.

Mutagenesis
Phenytoin was negative in the Ames test and in the *in vitro* clastogenicity assay in Chinese hamster ovary (CHO) cells.

In studies reported in the literature, phenytoin was negative in the *in vitro* mouse lymphoma assay and the *in vivo* micronucleus assay in mouse. Phenytoin was clastogenic in the *in vitro* sister chromatid exchange assay in CHO cells.

Fertility
Phenytoin has not been adequately assessed for effects on male or female fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium Hydroxide
Propylene Glycol
Ethanol (95%)
Water for Injection

6.2 Incompatibilities

Parenteral phenytoin should not be added to dextrose or dextrose-containing solutions due to the potential for precipitation.

6.3 Shelf-life

24 months

6.4 Special Precautions for Storage

Store below 25°C. Avoid Freezing.
(***Do not use the injection if it is hazy or contains a precipitate***)

6.5 Nature and Contents of Container

2 mL clear glass ampoule pack.

6.6 Instructions for Use/Handling

As directed by the physician

For single-use only. After opening, unused product should be discarded

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

Both the undiluted form and the infusion mixture are suitable for use as long as they remain free of haziness and precipitate.

The diluted infusion mixture (phenytoin plus normal saline) should not be refrigerated. If the undiluted parenteral phenytoin is refrigerated or frozen, a precipitate might form; this should dissolve again after the solution is allowed to stand at room temperature, in which case the product is still suitable for use. A faint yellow coloration may develop; however, this should have no effect on the potency of the solution.