Phenytoin Oral Suspension USP

DILANTIN® Suspension

1. NAME OF MEDICINAL PRODUCT

DILANTIN SUSPENSION

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 5 mL of oral suspension contains 125 mg of phenytoin I.P.

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

For full list of excipients please see section **6.1**.

3. PHARMACEUTICAL FORM

Oral suspension

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

NOT FOR PARENTERAL USE

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 suspensions (30 mg/5 mL (pediatric) and 125 mg/5 mL). 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 125 mg (5 mL) of the 125 mg/5 mL suspension three times daily, and the dosage then adjusted to suit individual requirements. An increase to 625 mg (25 mL) 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 one gram of phenytoin divided into three doses (400 mg, 300 mg, 300 mg) and administered at two 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 and adolescents may require the minimum adult dose (300 mg/day).

Dosing in Special Populations

Patients with Renal or Hepatic Disease: see Section **4.4 Special Warnings and Precautions for use**.

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**).

Pediatric: 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 and adolescents may require the minimum adult dose (300 mg/day).

Pregnancy: Decreased serum concentrations of phenytoin may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of serum phenytoin concentrations should be performed during pregnancy, and the DILANTIN dosage should be adjusted as necessary. Postpartum restoration of the original dosage will probably be indicated (see Section **4.6 Fertility, Pregnancy, and Lactation**. Because of potential changes in protein binding during pregnancy, the monitoring of phenytoin serum levels should be based on the unbound fraction.

4.3 Contraindications

Phenytoin is contraindicated in patients with

- A history of hypersensitive to phenytoin, or its inactive ingredients, or other hydantoins (see Section **4.4 Special Warnings and Special Precautions for Use**). Reactions have included angioedema.
- A history of prior acute hepatotoxicity attributable to phenytoin (see Section **4.4 Special Warnings and Special Precautions for Use).**
- Co-administration with 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 Special 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.

Slow Metabolizers of Phenytoin:

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be caused by limited enzyme availability and lack of induction; it appears to be genetically determined (polymorphism). If early signs of dose-related central nervous system (CNS) toxicity develop, serum levels should be checked immediately.

Renal or Hepatic Disease or Hypoalbuminemia:

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.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including phenytoin, increase the risk of suicidal thoughts or behavior 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 behavior, and/or any unusual changes in mood or behavior.

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 behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior 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 behavior 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 behavior 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 behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. 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 to100 years) in the clinical trials analyzed.

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 1,000 Patients	Drug Patients with Events Per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1,000 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 behavior 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 the risk of suicidal thoughts or behavior 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 behavior. Should suicidal thoughts and behavior 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 behavior 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 behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

<u>Drug Reaction with Eosinophilia and Systemic Symptoms/Multiorgan Hypersensitivity</u>

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, lymphadenopathy, and/or facial swelling, 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 and 4.4. Special warning and precaution for use**). 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.

Cardiac Effects

Cases of bradycardia and cardiac arrest have been reported in DILANTIN-treated patients, both at recommended phenytoin doses and levels, and in association with phenytoin toxicity (see section **4.9 Overdose**). Most of the reports of cardiac arrest occurred in patients with underlying cardiac disease.

Central Nervous System Effect

Serum levels of phenytoin sustained above the therapeutic 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 should be immediately checked. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination of phenytoin therapy 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 of DRESS (see Section **4.4 Special Warnings and Special Precautions for Use**). 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.

Integumentary Effect

DILANTIN can cause Severe cutaneous adverse reactions (SCARs), such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP) (see section **4.8. Adverse Reactions**), and Drug Reaction with Eosinophilia and Systemic Symptoms (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, or other signs 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 Anticonvulsant Hypersensitivity Syndrome 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 Stevens-Johnson syndrome, and/or toxic epidermal necrolysis.

Angioedema

Angioedema has been reported in patients treated with DILANTIN in the post marketing setting. DILANTIN should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur. DILANTIN should be discontinued permanently if a clear alternative etiology for the reaction cannot be established.

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.

Musculoskeletal Effect

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

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**).

Teratogenicity and Other Harm to the Newborn

DILANTIN may cause fetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes (see Section **4.6 Fertility, pregnancy and lactation).**

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.

A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin *in utero*. This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

Information for the Patient Using an Oral Formulation of Phenytoin

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 advised to use an accurately calibrated measuring device when using the oral suspension formulation to ensure accurate dosing.

Patients should be made aware of the early toxic signs and symptoms of potential hematologic, dermatologic, hypersensitivity, or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, the patient should be advised that these signs and symptoms should be reported even if mild or when occurring after extended use.

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.

Patients, their caregivers, and families should be counseled that AEDs, including phenytoin, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Drug Interactions

There are many drugs which may increase or decrease serum phenytoin levels or which 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.

Drugs that 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) (see Table 2).

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

DRUG CLASSES	DRUGS IN EACH CLASS (SUCH AS)
Alcohol (acute intake)	
Analgesic/Anti-inflammatory agents	azapropazone salicylates
Anesthetics	halothane
Antibacterial agents	chloramphenicol isoniazid sulfonamides (e.g., sulfamethizole, sulfaphenazole, sulfadiazine, sulfamethoxazole-trimethoprim)
Anticonvulsants	felbamate oxcarbazepine topiramate

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

Drugs that may decrease phenytoin plasma levels

Table 3 summarizes the drug classes that may potentially decrease phenytoin plasma levels.

DRUG CLASSES	DRUGS IN EACH CLASS (SUCH AS)
Alcohol (chronic intake)	
Anticancer agents	bleomycin carboplatin cisplatin doxorubicin methotrexate
Vitamins	folic acid
Antiretrovirals	fosamprenavir nelfinavir ritonavir
St. John's Wort	St. John's Wort
Antibacterial agents	rifampin ciprofloxacin
Anticonvulsants	vigabatrin carbamazepine
Antiulcer agents	sucralfate
Bronchodilators	theophylline
Cardiovascular agents	reserpine
Hyperglycemic agents	diazoxide
Benzodiazepines/Psychotropic agents	diazepam

Molindone hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Administration of phenytoin with preparations that increase gastric pH (e.g., supplements or antacids containing calcium carbonate, aluminum hydroxide, and magnesium hydroxide) may affect the absorption of phenytoin. In most cases where interactions were seen, the effect is a decrease in phenytoin levels when the drugs are taken at the same time. When possible, phenytoin and these products should not be taken at the same time of day.

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 that may either increase or decrease phenytoin serum levels

Table 4 summarizes the drug classes that may either increase or decrease phenytoin serum levels:

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

Similarly, 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

Table 5 summarizes the drug classes whose blood levels and/or effects may be altered by phenytoin:

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)
HMG-CoA reductase inhibitors	atorvastatin fluvastatin simvastatin lovastatin
Antineoplastic agents	teniposide irinotecan paclitaxel
Antiretroviral	delavirdine efavirenz lopinavir/ritonavir indinavir nelfinavir ritonavir saquinavir
Bronchodilators	theophylline
Calcium channel blockers/Cardiovascular agents	digitoxin digoxin, mexiletine disopyramide nifedipine nicardipine nimodipine nisoldipine quinidine verapamil
Anthelmintics	praziquantel albendazole
Vitamins	folic acid

Corticosteroids	
Coumarin anticoagulants	warfarin
Cyclosporine	
Diuretics	furosemide
Hormones	estrogens oral contraceptives
Neuromuscular blocking agents	alcuronium pancuronium vecuronium
Opioid analgesics	methadone
Oral hypoglycemic agents	chlorpropamide glyburide tolbutamide
Psychotropic agents/Antidepressants	clozapine paroxetine sertraline
Vitamin D	vitamin D

Increased and decreased PT/INR responses have been reported when phenytoin is co-administered with warfarin.

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

Phenytoin when given with fosamprenavir alone may decrease the concentration of amprenavir, the active metabolite. Phenytoin when given with the combination of fosamprenavir and ritonavir may increase the concentration of amprenavir.

Resistance to the neuromuscular blocking action of the non-depolarizing neuromuscular blocking agents – pancuronium, vecuronium, rocuronium, and cisatracurium has occurred in patients chronically administered phenytoin. Whether or not phenytoin has the same effect on other non-depolarizing agents is unknown. Patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected, and infusion rate requirements may be higher.

The addition or withdrawal of phenytoin during concomitant therapy with these agents may require adjustment of the dose of these agents to achieve optimal clinical outcome.

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 serum 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

Phenytoin may affect blood calcium and blood sugar metabolism rates.

4.6 Fertility, Pregnancy and Lactation

Fertility

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

Usage in Pregnancy

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. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed anticonvulsant drugs. 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 child-bearing potential.

Phenytoin crosses the placenta in humans. If Dilantin is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Prenatal phenytoin exposure is associated with an increased incidence of major

malformations, including orofacial clefts 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 epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. This consists of pre-natal growth deficiency, microcephaly, and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. 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.

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

In the U.S. general population, the estimated background risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

The background risk of major birth defects and miscarriage for the indicated population is unknown.

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.

Data

Animal Data: Administration of phenytoin to pregnant rabbits during organogenesis resulted in embryofetal death, fetal malformations, and decreased fetal growth. Malformations (including craniofacial, cardiovascular, neural, limb, and digit abnormalities) were observed in rats, rabbits, and mice at doses as low as 100, 75, and 12.5 mg/kg respectively.

Lactation

Risk Summary

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.

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 DILANTIN were identified in clinical studies or postmarketing 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: Allergic reactions in the form of rash and rarely more serious forms and DRESS have been observed, as has angioedema (see Section **4.4 Special Warnings and Special Precautions**). Anaphylaxis has also been reported.

There have also been reports of coarsening of facial features, systemic lupus erythematosus, periarteritis nodosa, and immunoglobulin abnormalities.

Cardiac Effects (see section **4.4. Special Warnings and Precautions for use**)

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).

Laboratory Test Abnormality: Phenytoin may decrease serum concentrations of T4. It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose (see Section **4.4 Special Warnings and Special Precautions for Use)**, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Nervous System: The most common adverse reactions encountered with phenytoin therapy are nervous system reactions and are usually dose-related. Reactions include nystagmus, ataxia, slurred speech, decreased coordination, somnolence, and mental confusion. Dizziness, vertigo, insomnia, transient nervousness, motor twitchings, paresthesias, and headaches 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. 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 Special Precautions for Use)**.

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

Skin and Appendages: 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, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see Section **4.4 Special Warnings and Special Precautions for Use)**. There have also been reports of hypertrichosis and urticaria.

Special Senses: Taste perversion.

Post-marketing Experience:

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.

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. Bradycardia and cardiac arrest

have been reported (see section **4.4. Special Warnings and Precautions for use**). Death is caused by 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

The precise mechanism by which phenytoin exerts its therapeutic effect has not been established but is thought to involve the voltage-dependent blockade of membrane sodium channels resulting in a reduction in sustained high-frequency neuronal discharges.

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 absorption is complete, it is rapidly distributed into all tissues.

The plasma half-life of phenytoin in man averages 22 hours with a range of 7 to 42 hours. Steady-state therapeutic drug levels are achieved at least 7 to 10 days after initiation of therapy with recommended doses of 300 mg/day. For oral formulations of phenytoin, peak serum levels occur 1½ - 3 hours after administration. 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 steady-state level may be disproportionately increased with resultant intoxication from an increase in dosage of 10% or more. 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.

In most patients maintained at a steady dosage of an oral formulation, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low serum levels may be non-compliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, congenital enzyme deficiency or drug interactions which result in metabolic interference. The patient with large variations in phenytoin serum levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. When they are necessary, they should be obtained at least 7-10 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. Trough levels, obtained just prior to the patient's next scheduled dose, provide information about clinically effective serum level range and confirm patient compliance. Peak drug levels, obtained at the time of expected peak concentration, indicate an individual's threshold for emergence of dose-related side effects.

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 160 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

Magnesium Aluminium Silicate NF (Grade: Veegum HV), Sodium Benzoate IP, Citric Acid Monohydrate IP, Sodium Carboxymethyl Cellulose IP, Sucrose IP, Glycerin IP, Polysorbate 40 NF, Sunset Yellow FCF, Vanillin IP, Oil Banana Imitation, Oil Orange oil concentrate 16X, Ethanol (95%), Colloidal silicon Dioxide IP, Purified Water IP.

6.2 Incompatibilities

None specific

6.3 Shelf Life

24 months

6.4 Special Precautions for Storage

Keep the bottle tightly closed. Avoid freezing.

6.5 Nature and Contents of Container

100 mL amber glass bottle pack along with graduated measuring cup.

6.6 Instructions for Use/Handling

As directed by the physician.
Special instruction on the label:

Shake well before use.
Dose must be taken with the graduated measuring cup.