

**PRESCRIBING INFORMATION**

**DILANTIN<sup>®</sup> INFATABS<sup>®</sup>**  
**(Phenytoin Tablets USP)**

**DILANTIN<sup>®</sup>-30 SUSPENSION**  
**DILANTIN<sup>®</sup>-125 SUSPENSION**  
**(Phenytoin Oral Suspension USP)**

**ANTICONVULSANT**

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Kirkland, Quebec H9J 2M5

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**(Phenytoin Oral Suspension USP)**

## **THERAPEUTIC CLASSIFICATION**

Anticonvulsant

## **ACTION AND CLINICAL PHARMACOLOGY**

**DILANTIN** Infatabs (phenytoin tablets USP) and **DILANTIN-30** Suspension/**DILANTIN-125** Suspension (phenytoin oral suspension) are anticonvulsant drugs which can be useful in the treatment of epilepsy. The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at synapses. 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.

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. Phenytoin is distributed into cerebrospinal fluid, saliva, semen, gastrointestinal fluids, bile, and breast milk. The concentration of phenytoin in cerebrospinal fluid 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. Experiments in human liver microsomes have demonstrated that 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 the net intrinsic clearance). This relative contribution of CYP2C19 to phenytoin metabolism may however increase at higher phenytoin concentrations.

Pharmacokinetic data on six patients (age range: 22-64 years) receiving phenytoin monotherapy showed that ticlopidine (a CYP2C19 inhibitor), administered for two weeks, decreased plasma clearance of phenytoin.

In a human liver microsome study, phenylbutazone (a CYP2C9 inhibitor) decreased clearance of phenytoin (see **PRECAUTIONS-Drug Interactions**).

Clinical studies using **DILANTIN** Infatabs have shown an average plasma half-life of 14 hours with a range of 7 to 29 hours. The plasma half-life of phenytoin in man after oral administration of phenytoin oral suspension averages 22 hours, with a range of 7 to 42 hours. Steady-state therapeutic levels are achieved at least 7 to 10 days after initiation of therapy with recommended doses of 300 mg/day.

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or 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. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

When serum level determinations 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. For **DILANTIN** Infatabs, **DILANTIN**-30 Suspension and **DILANTIN**-125 Suspension, peak serum levels occur 1½- 3 hours after administration.

Most of the drug is eliminated in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine partly with glomerular filtration but more importantly by tubular secretion. Less than 5% of phenytoin is excreted as the parent compound. Because phenytoin is hydroxylated in the liver by a cytochrome system which is saturable at high serum levels, small incremental doses 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.

Clinical studies show that chewed and unchewed **DILANTIN** Infatabs are bioequivalent, yield approximately equivalent plasma levels, and are more rapidly absorbed than **DILANTIN** 100-mg capsules (extended phenytoin capsules, USP).

## **INDICATIONS AND USAGE**

**DILANTIN** Infatabs (phenytoin tablets USP) and **DILANTIN-30** Suspension/**DILANTIN-125** Suspension (phenytoin oral suspension USP) are indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures. Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see **DOSAGE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY**).

## **CONTRAINDICATIONS**

**DILANTIN** Infatabs (phenytoin tablets USP) and **DILANTIN-30** Suspension/**DILANTIN-125** Suspension (phenytoin oral suspension USP) are contraindicated in those patients who are hypersensitive to phenytoin, to other hydantoins or to any of the nonmedicinal ingredients in the formulations.

## **WARNINGS**

### **General**

**DILANTIN** Infatabs (phenytoin tablets USP) or **DILANTIN-30** Suspension/**DILANTIN-125** Suspension (phenytoin oral suspension USP) 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 anticonvulsant medication arises, this should be done gradually. However, in the event of an allergic hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an anticonvulsant drug which does not belong to the hydantoin chemical class.

Anticonvulsant Hypersensitivity Syndrome (AHS) is a rare drug induced, multiorgan syndrome which is potentially fatal and occurs in some patients taking anticonvulsant medication. It is characterized by fever, rash, lymphadenopathy, and other multiorgan pathologies, often hepatic. The mechanism is unknown. The interval between first drug exposure and symptoms is usually 2-4 weeks but has been reported in individuals receiving anticonvulsants for 3 or more months.

Patients at higher risk for developing AHS include black patients, patients who have a family history of or who have experienced this syndrome in the past, and immuno-suppressed patients.

The syndrome is more severe in previously sensitized individuals. If a patient is diagnosed with AHS, discontinue the phenytoin and provide appropriate supportive measures.

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

### **Serious Dermatological Reactions**

#### **Steven's-Johnson Syndrome and Toxic Epidermal Necrolysis**

Serious and sometimes fatal dermatologic reactions, including Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), have been reported with phenytoin. In countries with mainly Caucasian populations, these reactions are estimated to occur in 1 to 6 per 10,000 new users, but in some Asian countries (e.g., Taiwan, Malaysia and the Philippines) the risk is estimated to be much higher.

**HLA-B\*1502:** In studies that included small samples of patients of Asian ancestry a strong association was found between the risk of developing SJS/TEN and the presence of HLA-B\*1502, an inherited allelic variant of the HLA-B gene. The HLA-B\*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia<sup>◇</sup>. Results of these studies suggest that the presence of the HLA-B \*1502 allele may be one of the risk factors for phenytoin-associated SJS/TEN in patients with Asian ancestry. Therefore, physicians should consider HLA-B \*1502 genotyping as a screening tool in these patients. Until further information is available, the use of phenytoin and other anti-epileptic drugs associated with SJS/TEN should also be avoided in patients who test positive for the HLA-B\*1502 allele (see **WARNINGS-Asian Ancestry and Allelic Variation in the HLA-B gene and WARNINGS-Important Limitations of HLA-B Genotyping**).

**Treatment recommendations for dermatological reactions:** phenytoin should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. The use of other anti-epileptic drugs associated with SJS/TEN should be avoided in patients who have shown severe dermatological reactions during phenytoin treatment.

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<sup>◇</sup> The following rates provide a rough estimate of the prevalence of HLA-B\*1502 in various populations. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-B\*1502, averaging 2 to 4%, but this may be higher in some groups. HLA-B\*1502 is present in <1% of the population in Japan and Korea. HLA-B\*1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans). The estimated prevalence rates have limitations due to the wide variability in rates that exist within ethnic groups, the difficulties in ascertaining ethnic ancestry and the likelihood of mixed ancestry.

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. In any of the above instances, caution should be exercised if using structurally similar compounds (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients (see **PRECAUTIONS**).

### **Asian Ancestry and Allelic Variation in the HLA-B Genotyping**

In studies that included small samples of patients of Asian ancestry a strong association was found between the risk of developing SJS/TEN and the presence of HLA-B\*1502, an inherited allelic variant of the HLA-B gene. The HLA-B\*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia. Results of these studies suggest that the presence of the HLA-B \*1502 allele may be one of the risk factors for phenytoin-associated SJS/TEN in patients with Asian ancestry. Therefore, physicians should consider HLA-B \*1502 genotyping as a screening tool in these patients. Until further information is available, the use of phenytoin and other anti-epileptic drugs associated with SJS/TEN should also be avoided in patients who test positive for the HLA-B\*1502 allele.

### **Important Limitations of HLA-B Genotyping**

HLA-B\*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B\*1502-positive Asian patients treated with phenytoin will not develop SJS/TEN, and these reactions can still occur infrequently in HLA-B\*1502-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

In addition, it should be kept in mind that the majority of phenytoin treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration when deciding whether to screen genetically at-risk patients currently on phenytoin.

Should signs and symptoms suggest a severe skin reaction such as SJS or TEN, phenytoin should be withdrawn at once.

### **Hepatic/Immunologic**

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.

### **Hematopoietic**

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, eg, 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.

### **Metabolic**

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.

### **Psychiatric**

#### **Suicidal ideation and behaviour**

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications.

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

An FDA meta-analysis of randomized placebo controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

There were 43892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drug). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

### **Usage in Pregnancy**

Literature reports suggest that phenytoin can cross placental barrier and, if administered during pregnancy, may have an effect on the fetus. Transfer of anticonvulsants is influenced by a variety of factors, including molecular weight and lipophilicity of the agents. Phenytoin is known to be a lipophilic drug which may influence fetal cell growth during the hyperplasia or hypertrophy stage of development.

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; fewer 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 and counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformations, such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other anticonvulsant drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal 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.

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

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 the neonate after birth.

## **PRECAUTIONS**

### **General**

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

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.

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.

### **Hepatic/Immunologic**

The liver is the chief site of biotransformation of **DILANTIN** Infatabs (phenytoin tablets USP) and **DILANTIN-30** Suspension/**DILANTIN-125** Suspension (phenytoin oral suspension USP).

Patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

Toxic hepatitis, liver damage, and hypersensitivity syndrome have been reported and may, in rare cases be fatal (see **ADVERSE REACTIONS**).

### **Serious Dermatological Reactions**

Phenytoin should be discontinued if a skin rash appears (see “**WARNINGS**” section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus or Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered (see **ADVERSE REACTIONS**). 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 reinstatement of therapy, further phenytoin medication is contraindicated.

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. In any of the above instances, caution should be exercised if using structurally similar compounds (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients (see **WARNINGS**).

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.

### **Hematopoietic**

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.

### **Metabolic**

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

### **Musculoskeletal**

Phenytoin and other anticonvulsants that have been shown to induce the CYP450 enzyme are thought to affect bone mineral metabolism indirectly by increasing the metabolism of Vitamin D3. This may lead to Vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcemia, and hypophosphatemia in chronically treated epileptic patients (see **ADVERSE REACTIONS, Post-marketing Experience**).

### **Central Nervous System**

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. 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 phenytoin therapy is recommended (see **WARNINGS**).

### **Driving/Operating Machinery**

Patients should be advised not to drive or operate complex machinery or engage in other hazardous activities until they have gained sufficient experience on phenytoin to gauge whether or not it affects their mental and/or motor performance adversely.

### **Information for Patients**

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, eg, surgery, etc.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without first seeking the 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.

### **Laboratory Tests**

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

### **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:

1. Various drugs may increase phenytoin plasma 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 plasma levels

**Table 1. Drug Classes Which May Increase phenytoin Plasma Levels**

<b>Drug Classes</b>	<b>Drugs in each Class (such as)</b>
Alcohol (acute intake)	
analgesic/anti-inflammatory agents	azapropazone phenylbutazone salicylates
anesthetics	Halothane

<b>Drug Classes</b>	<b>Drugs in each Class (such as)</b>
antibacterial agents	chloramphenicol erythromycin isoniazid sulfonamides (eg. sulfisoxazole)
anticonvulsants	felbamate succinimides (e.g. ethosuximide) valproate sodium topiramate <sup>a</sup>
antifungal agents	amphotericin B fluconazole ketoconazole miconazole itraconazole
benzodiazepines/psychotropic agents	chlordiazepoxide diazepam trazodone disulfiram methylphenidate phenothiazine
calcium channel blockers/ cardiovascular agents	Amiodarone dicumarol diltiazem nifedipine ticlopidine
H <sub>2</sub> -antagonists	cimetidine
hormones	estrogens
oral hypoglycemic agents	tolbutamide
Proton pump inhibitors	omeprazole
serotonin re-uptake inhibitors	fluoxetine paroxetine fluvoxamine sertraline

<sup>a</sup> Coadministration with topiramate reduces serum topiramate levels by 59%, and has the potential to increase phenytoin levels by 25% in some patients. The addition of topiramate therapy to phenytoin should be guided by clinical outcome.

2. Drugs which may decrease phenytoin plasma levels are summarized in **Table 2**.

**Table 2. Drug Classes Which May Decrease Phenytoin Plasma Levels**

<b>Drug Classes</b>	<b>Drugs in each Class (such as)</b>
Alcohol (chronic intake)	
Antibacterial agents/Fluoroquinolones	rifampin ciprofloxacin
Anticonvulsants	carbamazepine vigabatrin <sup>1</sup>
Antiulcer agents	sucralfate
Bronchodilators	theophylline
Calcium preparations	molindone hydrochloride
Cardiovascular agents	reserpine
Hyperglycemic agents	diazoxide
Protease Inhibitors	Nelfinavir

<sup>1</sup>Coadministration with Vigabatrin reduces serum phenytoin levels by 20 to 30%. This may be clinically significant in some patients and may require dosage adjustment.

#### Molindone hydrochloride

Molindone Hydrochloride contains calcium ions which interfere with the absorption of phenytoin.

#### Calcium Preparations

Ingestion times of phenytoin and calcium preparations, including antacid calcium preparations containing calcium should be staggered to prevent absorption problems.

#### Nelfinavir

A pharmacokinetic interaction study between nelfinavir (1,250 mg twice a day ) and phenytoin (300 mg once a day) administered orally showed that nelfinavir reduced AUC values of phenytoin (total) and free phenytoin by 29% and 28% (n=12), respectively. The plasma concentration of nelfinavir was not changed (n=15). Phenytoin concentration should be monitored during coadministration with nelfinavir, as nelfinavir may reduce phenytoin plasma concentration.

3. Drugs which may either increase or decrease phenytoin plasma are summarized in **Table 3**

**Table 3. Drugs Which May Decrease or Increase Phenytoin Plasma Levels**

Drug Classes	Drugs in each class (such as)
Antibacterial Agents	Ciprofloxacin
anticonvulsants	carbamazepine, phenobarbital sodium valproate valproic acid
antineoplastic agents	
Benzodiazepines Psychotropic agents	Chlordiazepoxide diazepam
phenothiazines	

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

4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.
5. Drugs whose blood levels and/or effects may be altered by phenytoin are summarized in **Table 4**

**Table 4. Drugs 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 <sup>a</sup> topiramate <sup>b</sup>
antifungal agents	azoles
antineoplastic agents	teniposide
calcium channel blockers / cardiovascular agents	digitoxin nicardipine nimodipine quinidine verapamil

<b>Drug Classes</b>	<b>Drugs in each Class (such as)</b>
Corticosteroids	
Coumarin anticoagulants	
Diuretics	furosemide
hormones	estrogens oral contraceptives
Hyperglycemic agents	diazoxide
Immunosuppressant	cyclosporine
neuromuscular blocking agents	alcuronium pancuronium vecuronium
opioid analgesics	methadone
oral hypoglycemic agents	chlorpropamide glyburide tolbutamide
Psychotropic agents/Antidepressants	clozapine paroxetine sertraline
Vitamins	Vitamin D

- <sup>a</sup> Coadministration with lamotrigine doubles the plasma clearance and reduces the elimination half life of lamotrigine by 50%. **This clinically important interaction requires dosage adjustment for lamotrigine.** There is no significant change in phenytoin plasma levels in the presence of lamotrigine.
- <sup>b</sup> Coadministration with topiramate reduces serum topiramate levels by 59%, and has the potential to increase phenytoin levels by 25% in some patients. **The addition of topiramate therapy to phenytoin should be guided by 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 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**

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

### **Carcinogenesis**

See **WARNINGS** section.

### **Pregnancy**

See **WARNINGS** section

### **Nursing Mothers**

Infant breast feeding is not recommended for women taking phenytoin.

Phenytoin is secreted into human milk. Limited observations in patients suggest that phenytoin concentration in breast milk is approximately one-third of the corresponding maternal plasma concentration.

### **Pediatric Patients**

See **DOSAGE AND ADMINISTRATION** section.

## **ADVERSE REACTIONS**

### **Body as a whole:**

Anaphylactic reaction and anaphylaxis

### **Central Nervous System:**

The most common manifestations encountered with **DILANTIN** Infatabs (phenytoin tablets USP) and **DILANTIN-30** Suspension/**DILANTIN-125** Suspension (phenytoin oral suspension USP) therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, headaches, paresthesia and somnolence have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

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

### **Gastrointestinal System:**

Nausea, vomiting, constipation, toxic hepatitis, and liver damage (see **PRECAUTIONS**).

### **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, and Stevens-Johnson syndrome and toxic epidermal necrolysis (see **WARNINGS**).

### **Hematopoietic System:**

Hemopoietic 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. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy, including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease has been reported (see **WARNINGS**).

### **Connective Tissue System:**

Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis and Peyronie's Disease.

### **Immunologic:**

Hypersensitivity syndrome (which may include, but is not limited to symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, periarteritis nodosa, and immunoglobulin abnormalities. 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 (see **WARNINGS** and **PRECAUTIONS**).

**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 (see **PRECAUTIONS, Musculoskeletal** ).

### **OVERDOSAGE**

The lethal dose of **DILANTIN** Infatabs (phenytoin tablets USP) and **DILANTIN-30** Suspension/**DILANTIN-125** Suspension (phenytoin oral suspension USP) in pediatric patients is not known. The lethal dose of phenytoin in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, somnolence, drowsiness, lethargy, slurred speech, blurred vision, nausea, 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 plasma levels where toxicity may occur. Nystagmus on lateral gaze, usually appears at 80  $\mu\text{mol/L}$  (20 mcg/mL), ataxia at 119  $\mu\text{mol/L}$  (30 mcg/mL). Dysarthria and lethargy appear when the serum concentration is > 159  $\mu\text{mol/L}$  (40 mcg/mL), but a concentration as high as 198  $\mu\text{mol/L}$  (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 over >396  $\mu\text{mol/L}$  (100 mcg/mL) with complete recovery.

### **Treatment and Management**

For management of a suspected drug overdose, contact your regional Poison Control Center.
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Treatment is nonspecific 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 pressure of other CNS depressants, including alcohol, should be borne in mind.

## **DOSAGE AND ADMINISTRATION**

### **DILANTIN SUSPENSIONS ARE NOT FOR PARENTERAL USE.**

Serum phenytoin concentrations should be monitored and care should be taken when switching a patient from the sodium salt to the free acid form.

**DILANTIN** extended release capsules are formulated with the sodium salt of phenytoin. The free acid form of phenytoin is used in **DILANTIN-30 Suspension** and **DILANTIN-125 Suspension** and **DILANTIN Infatabs**. 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.

#### **General:**

**DILANTIN Infatabs** (phenytoin tablets, USP) and **DILANTIN-30 Suspension/DILANTIN-125 Suspension** (phenytoin oral suspension, USP) are not for once-a-day dosing.

Dosage should be individualized to provide maximum benefit. In some cases, serum blood level determinations may be necessary for optimal dosage adjustments. The clinically effective serum level is usually 40-80  $\mu\text{mol/L}$  (10-20  $\text{mcg/mL}$ ). Serum blood level determinations are especially helpful when possible drug interactions are suspected. With recommended dosage, a period of 7 to 10 days may be required to achieve therapeutic blood levels with **DILANTIN** and changes in dosage (increase or decrease) should not be carried out at intervals shorter than 7 to 10 days.

#### **Adult Dose:**

Patients who have received no previous treatment may be started on 2 **DILANTIN Infatabs** 3 times daily or on 1 teaspoonful (5 mL) of **DILANTIN-125 Suspension** 3 times daily, and the dose then adjusted to suit individual requirements. For some adults, the satisfactory maintenance dosage will be 8 **DILANTIN Infatabs** daily; an increase to 12 **DILANTIN Infatabs** may be made, if necessary. With **DILANTIN-125 Suspension**, an increase to 5 teaspoonfuls (25 mL) daily may be made if necessary.

### **Pediatric Dose**

Initially, 5 mg/kg/day of **DILANTIN** Infatabs, **DILANTIN-30** Suspension or **DILANTIN-125** Suspension may be given in 2 or 3 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 may require the minimum adult dose (300 mg/day). If the daily dosage cannot be divided equally, the larger dose should be given at bedtime.

## PHARMACEUTICAL INFORMATION

### Drug Substance

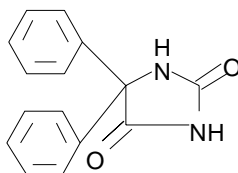
Proper Name: phenytoin

Chemical Name: 5,5-diphenyl-2,4-imidazolidinedione

Empirical Formula:  $C_{15}H_{12}N_2O_2$

Molecular Weight: 252.27

Structural Formula:



Description: phenytoin is related to the barbiturates in chemical structure, but has a 5-membered ring.

### Infatab Composition

Each 50-mg tablet contains 50 mg phenytoin (free acid form). The tablet also contains the following non-medicinal ingredients: alcohol, magnesium stearate, spearmint oil, sugar, and talc.

### DILANTIN-30 Suspension Composition

Each 5 mL of **DILANTIN-30** Suspension contains 30 mg phenytoin (free acid form). The suspension also contains the following non-medicinal ingredients: alcohol, banana oil, citric acid, glycerin, magnesium aluminum silicate, orange oil, polysorbate 40, Red #2 FD&C, sodium benzoate, sodium carboxymethylcellulose, sugar, vanillin, and yellow #6 FD&C.

### **DILANTIN-125 Suspension Composition**

Each 5 mL of **DILANTIN-125 Suspension** contains 125 mg phenytoin (free acid form). The suspension also contains the following non-medicinal ingredients: alcohol, banana oil, citric acid, glycerin, magnesium aluminum silicate, orange oil, polysorbate 40, sodium benzoate, sodium carboxymethylcellulose, sugar, vanillin, and yellow #6 FD&C.

### **Stability and Storage Recommendations**

**DILANTIN Infatabs**: Store at controlled room temperature 15-30°C. Protect from light and moisture.

**DILANTIN-30 Suspension and DILANTIN-125 Suspension**: Store at controlled room temperature 15 - 30°C. Protect from freezing and light.

## **AVAILABILITY OF DOSAGE FORMS**

**DILANTIN INFATABS**: (phenytoin tablets USP)

Each flavoured, triangular shaped, grooved tablet contains: phenytoin 50 mg. Bottles of 100.

**DILANTIN SUSPENSIONS**: (phenytoin oral suspension USP)

Each 5 mL of flavoured, coloured suspension contains: phenytoin (free acid form) 30 mg (red, **DILANTIN-30**) or 125 mg (orange, **DILANTIN-125 Suspension**). Bottles of 250 mL.

Also available as:

**DILANTIN CAPSULES**: (extended phenytoin sodium capsules USP): are available in dosage strengths of 30- and 100-mg capsules.

30 mg: A size 4 hemispherical Coni Snap capsule with a white opaque body and pale pink opaque cap containing a white powder. Capsule is imprinted with black rectified radial print, "PD" on cap and "Dilantin 30 mg" on body. Bottles of 100.

100 mg: No. 3 Coni-Snap white capsule with orange cap, imprinted Parke-Davis and P-D 100 in black ink. Bottles of 100 and 1000, and unit-dose blisters (10 x 10 strips).

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## CONSUMER INFORMATION

DILANTIN\* INFATABS\*

(Phenytoin Tablets USP)

DILANTIN\*-30 SUSPENSION /DILANTIN\*-125 SUSPENSION

(Phenytoin Oral Suspension USP)

Anticonvulsant

### **Information for the patient:**

Please read this information carefully before you start to take your medicine, even if you have taken this drug before. Do not throw away this leaflet until you have finished your medicine as you may need to read it again. For further information or advice, please ask your doctor or pharmacist.

### **ABOUT THIS MEDICATION**

#### **What the medication is used for:**

DILANTIN has been prescribed to you by our doctor to control seizures.

It is specifically used for:

§ the control of generalized tonic-clonic seizures, and psychomotor seizures.

#### **What it does:**

DILANTIN Infatabs and DILANTIN-30 Suspension/DILANTIN-125 Suspension belong to the family of medicines called anticonvulsant. It acts in the brain to block the spread of seizure activity.

#### **When it should not be used:**

If you are allergic to phenytoin, to other medicines of the hydantoin family, or to any of the nonmedicinal ingredients in the formulations (see **What the nonmedicinal ingredients are**).

#### **What the medicinal ingredient is:**

Phenytoin..

#### **What the nonmedicinal ingredients are:**

DILANTIN Infatab; alcohol, magnesium stearate spearmint oil, talc and sugar.

DILANTIN-30 and 125 Suspensions: alcohol, banana oil, citric acid, glycerin, magnesium aluminium silicate, orange oil, polysorbate 40, Red #2 FD&C (30 mg/5mL suspension only), sodium benzoate, sodium carboxymethylcellulose sugar, vanillin, yellow #6 FD&C and water.

#### **What dosage forms it comes in:**

DILANTIN Infatab: 50 mg phenytoin tablet (free acid form).

DILANTIN-30 Suspension: Each 5 mL of flavoured, red suspension contains 30 mg phenytoin (free acid form).

DILANTIN-125 Suspension: Each 5 mL of flavoured, orange suspension contains 125 mg phenytoin (free acid form).

DILANTIN is also available as extended phenytoin sodium 30 mg and 100 mg capsules.

### **WARNINGS AND PRECAUTIONS**

**Do not stop your treatment with DILANTIN without first checking with your doctor as that could cause sudden worsening of your seizure. If you/your child are experiencing any side effects please see “Side Effects and What To Do About Them” section for guidance.**

**BEFORE you use these medicines, tell your doctor if:**

- \$ You/your child are diabetic,
- \$ You/your child are anemic.
- \$ You/your child have low bone density,
- \$ You/your child have or have had any liver disease or blood disorders (including porphyria),
- \$ You/your child have had an allergy to this drug, or other drugs used to treat your condition,
- \$ You are pregnant or thinking about becoming pregnant, or if you are breast-feeding.
- \$ You/your child are taking other drugs (prescription and over-the-counter medicines)
- \$ You consume alcohol on a regular or occasional basis.
- \$ Certain individuals of Asian and /or of black origin may be at an increased risk of developing serious skin reactions during treatment with DILANTIN.
- \$ You/your child have experienced in the past or have a family history of anticonvulsant hypersensitivity syndrome (which may occur rarely in patients treated with anticonvulsant medications and includes symptoms such as fever, rash, hepatitis (such as yellowing of skin and eyes) and lymph node swelling among others).
- \$ You/your child are currently being treated with cranial irradiation and corticosteroids.
- \$ You/your child suffer from absence seizures (petit mal) or seizures caused by low blood sugar (hypoglycemia) or other metabolic causes, as DILANTIN is not effective in controlling these types of seizures.

**When taking DILANTIN:**

Tell your doctor if you develop serious skin reactions such as rash, red skin, blistering of the lips, eyes or mouth, skin peeling and accompanied by fever, tell your doctor immediately. These reactions may be more frequent in patients of Asian origin. Reports of these reactions have been highest in patients from Taiwan, Malaysia and the Philippines. Talk to your doctor about the best way to care for your teeth, gums, and mouth during your treatment with DILANTIN. It is very important that you care for your mouth properly to decrease the risk of gum damage.

**INTERACTIONS WITH THIS MEDICATION**

There are many drugs that may increase or decrease phenytoin levels, or that DILANTIN may affect, tell your doctor or pharmacist about all other prescription and non-prescriptions medication you are taking, as well as dietary supplements, enteral feeding preparations or nutritional drinks, as there may be a need to adjust your medication or monitor you more carefully.

**PROPER USE OF THIS MEDICATION**

It is very important that you take these medicines exactly as your doctor has instructed. Never increase or decrease the dose yourself. Do not stop taking it abruptly unless directed by your doctor as your seizures may increase. Tell your doctor if you cannot take the drug as prescribed, for example if you will be having surgery. You should always check that you have an adequate supply of DILANTIN.

Dilantin Infatabs and oral suspension are not for once-a-day dosing. These medications must be taken 2 or 3 times per day.

Dilantin is also available as Extended Phenytoin Sodium Capsules which can be taken once daily. Dosage adjustments are required when switching from Dilantin Infatabs/oral suspension to the extended phenytoin sodium capsules.

**Usual dose:** The dose is adjusted to suit your/your child response to treatment. In some cases, blood level assessment may be necessary to adjust the dose optimally.

**DILANTIN Infatabs**

- Adult:** *Starting dose:* 2 Infatabs 3 times daily.  
*Maintenance dose:* 8 to 12 Infatabs daily.

Pediatric: **Starting dose:** 5 mg/kg/day in 2 or 3 equally divided doses.

**Maintenance dose:** 4 to 8 mg/kg in 2 or 3 divided doses.

### **DILANTIN-30 Suspension and DILANTIN-125 Suspension**

It is important to use an accurate measuring device when using the oral suspension formulation.

Adult: **Starting dose:** 1 teaspoonful (5 mL) DILANTIN -125 Suspension 3 times daily.

**Maintenance dose:** Up to 5 teaspoonfuls (25 mL) DILANTIN -125 Suspension daily.

Pediatric: **Starting dose:** 5 mg/kg/day, of DILANTIN Infatabs, DILANTIN-30 Suspension or DILANTIN-125 Suspension in 2 or 3 equally divided doses.

**Maintenance dose:** 4 to 8 mg/kg/day.

The maximum dose recommended for children is 300 mg/day. Children over 6 years old may require the minimum adult dose (300 mg/day).

If the daily dosage cannot be divided equally, the larger dose should be given at bedtime.

In case of a drug overdose, immediately go to the nearest emergency room even if you/your child do not feel sick. Make sure you take your medicine bottle with you to show the doctor.

### **Overdose:**

Very high doses can cause toxicity or death.

### **Missed dose:**

If you/your child miss/misses a dose, take it as soon as you remember. But if it is almost time for the next dose, do not take the missed dose. Instead, take the next scheduled dose. Do not try to make up for the missed dose by taking a double dose next time.

## **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Like all medicines, DILANTIN Infatabs and DILANTIN-30 Suspension/ DILANTIN-125 Suspension can cause side effects, although not everybody gets them.

### **Serious Side Effects:**

- If an allergic or hypersensitivity reaction happens such as fever with lymph nodes swelling, hepatitis (such as jaundice , yellowing of skin and eyes), flu-like symptoms with skin rash or skin blistering, you should go to the emergency department at your nearest hospital right away.
- If you notice symptoms suggestive of hepatitis, such as jaundice (yellowing of skin and eyes), tell your doctor right away.

### **Other Side Effects:**

If you experience any side effects such as unusual eye movement, changes in muscle movements or co-ordination, slurred speech, confusion, dizziness, insomnia, lymph node swelling, changes to facial skin or gums, headache, nausea or vomiting, consult your doctor.

***This is not a complete list of side effects. For any unexpected effects, or effects that worry you while taking DILANTIN Infatabs or DILANTIN-30 Suspension/ DILANTIN-125 Suspension, contact your doctor or pharmacist.***

## HOW TO STORE IT

DILANTIN Infatabs: Store at controlled room temperature 15-30°C. Protect from light and moisture.  
DILANTIN-30 Suspension and DILANTIN-125 Suspension: Store at controlled room temperature 15 - 30°C. Protect from freezing and light.  
Keep out of reach of children.

### REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- \$ Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- \$ Call toll-free at 1-866-234-2345
- \$ Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701D  
Ottawa, Ontario  
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:  
<http://www.Pfizer.ca>  
or by contacting the sponsor, Pfizer Canada, at:  
1-800-463-6001

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