PRESCRIBING INFORMATION

PrDILANTIN®

(Extended Phenytoin Sodium Capsules, Manufacturer Standard) 30 mg
(Extended Phenytoin Sodium Capsules USP) 100 mg

ANTICONVULSANT

® Warner-Lambert Company LLC
Pfizer Canada Inc., Licensee

17 300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

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THERAPEUTIC CLASSIFICATION

Anticonvulsant

ACTION AND CLINICAL PHARMACOLOGY

Dilantin (extended phenytoin sodium capsules) is an anticonvulsant drug which can be useful in the treatment of epilepsy. The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at 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**).

The plasma half-life in man after oral administration of phenytoin averages 22 hours, with a range of 7 to 42 hours. Steady-state therapeutic levels are achieved at least 7 to 10 days 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 plasma 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 (extended phenytoin sodium capsules), peak serum levels occur 4-12 hours after administration.
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 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 plasma 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.

INDICATIONS AND USAGE

Dilantin (extended phenytoin sodium capsules) is indicated for the control of generalized tonic-clonic and psychomotor (grand mal and temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery. Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Dilantin (extended phenytoin sodium capsules) is contraindicated in those patients who are hypersensitive to phenytoin or to any of the nonmedicinal ingredients in the formulations or to other hydantoins.

WARNINGS

General

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

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◊. 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.

Asian Ancestry and Allelic Variation in the HLA-B Genotyping

◊ 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.

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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.

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**).

Hepatic/Immunologic

Cases of acute hepatoxicity, 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 with 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, e.g. fever, rash and liver involvement. In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic 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 anticonvulsivants is influenced by a variety of factors, including molecular weight and lipophilicity of the agents. Phenytoin is known to be a lipholiphic 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; less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans. Genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of the increased incidence of congenital malformations, such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other antiepileptic

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 to 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 (extended phenytoin sodium capsules). 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 reinstitution of therapy, further phenytoin medication is contraindicated.

Literature reports suggest that the combination of phenytoin, cranial irradation 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 (e.g. barbiturate, 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, plasma level determinations are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination 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.

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

Do not use capsules which are discoloured.

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 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

Drug Classes	Drugs in each Class (such as)
Alcohol (acute intake)	
analgesic/anti-inflammatory agents	phenylbutazone salicylates
anesthetics	halothane
antibacterial agents	chloramphenicol erythromycin isoniazid sulfonamides (eg. sulfisoxazole)
anticonvulsants	felbamate succinimides (e.g. ethosuximide) valproate sodium topiramate[a]
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 nifefipine ticlopidine
H_2-antagonists	cimetidine
hormones	estrogens
Oral hypoglycemic agents	tolbutamide
Proton pump inhibitors	omeprazole
serotonin re-uptake inhibitors	fluoxetine fluvoxamine sertraline

[a] **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

Drug Classes	**Drugs in each Class (such as)**
Alcohol (chronic intake)	
Antibacterial agents/Fluoroquinolones	rifampin ciprofloxacin
Anticonvulsants	carbamazepine vigabatrin[1]
Antiulcer agents	sucralfate
Bronchodilators	theophylline
Calcium preparation	molindone hydrochloride
Cardiovascular agents	reserpine
Hyperglycemic agents	diazoxide
Protease Inhibitors	nelfinavir

[1]**Coadministration with Vigabatrin reduces serum phenytoin levels by 20 to 30%. This may be clinically significant in some patients and may require dosage adjustment.**

Molidone hyudrochloride

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

Calcium Preparations

Ingestion times of phenytoin and antacid calcium preparations, including antacid 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 ~~Serum~~ Plasma Levels

Drug Classes	**Drugs in each class (such as)**
Antibacterial Agents	ciprofloxacin
Anticonvulsants	carbamazepine, phenobarbital sodium valproate valproic acid
antineoplastic agents	
Psychotropic agents	chlordiazepoxide diazepam
Phenothiazines	

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[a] topiramate[b]
antifungal agents	azoles
antineoplastic agents	teniposide
Bronchodilators	theophylline
calcium channel blockers/ cardiovascular agents	digitoxin nicardipine nimodipine quinidine verapamil
Corticosteroids	
Coumarin anticoagulants	
Diuretics	furosemide
Hormones	estrogens oral contraceptives
Hyperglycemic agents	diazoxide
Immunosuppressant	cyclosporine
neuromuscular blocking agents	pancuronium vecuronium
opioid analgesics	methadone
oral hypoglycemic agents	chlorpropamide glyburide Tolbutamide
Psychotropic agents/Antidepressants	clozapine paroxetine sertraline
Vitamin	Vitamin D

[a] 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.

b 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**.

Pregnancy

See **WARNINGS**.

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**.

ADVERSE REACTIONS

Body as a whole:

Anaphylactic reaction and anaphylaxis.

Central Nervous System:

The most common manifestations encountered with Dilantin (extended phenytoin sodium capsules) 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, and 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 have 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 hepatoxicity, 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, hypophophatemia and decreased levels of Vitamin D metabolites have also been reported (see **PRECAUTIONS, Musculoskeletal**).

OVERDOSAGE

The lethal dose of Dilantin (extended phenytoin sodium capsules) in pediatric patient is not known. The lethal dose 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, 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 µmol/L (20 mcg/mL), ataxia at 119 µmol/L (30 mcg/mL). Dysarthria and lethargy appear when serum concentration is >159 µmol/L (40 mcg/mL), but a concentration as high as 198 µmol/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 µmol/L (100 mcg/mL) with complete recovery.

Treatment and Management

For management of a suspected drug overdose, contact your regional Poison Control Center.

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 presence of other CNS depressants, including alcohol, should be borne in mind.

DOSAGE AND ADMINISTRATION

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

Dilantin capsules are formulated with the sodium salt of phenytoin. The free acid form of phenytoin is used in Dilantin-30 Pediatric and Dilantin-125 Suspensions 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

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 µmol/L (10-20 mcg/mL). Serum blood level determinations are especially helpful when possible drug interactions are suspected. With recommended dosage, a period of seven to ten 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 one 100 mg extended phenytoin sodium capsule three times daily, and the dose then adjusted to suit individual requirements. For most adults, the satisfactory maintenance dosage will be three to four capsules (300-400 mg) daily. An increase to six capsules daily may be made, if necessary.

Pediatric Dose:

Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years old may require the minimum adult dose (300 mg/day). Pediatric dosage forms available include a 30 mg extended phenytoin sodium capsule, a 50 mg palatably flavoured Infatab, or an oral suspension form containing 30 mg of phenytoin in each 5 mL.

Alternative Dose:

Once-a-day dosage for adults with 300 mg of extended phenytoin sodium capsules may be considered if seizure control is established with divided doses of three 100 mg capsules daily. Studies comparing divided doses of 300 mg with a single daily dose of this quantity indicated that absorption, peak plasma levels, biologic half-life, difference between peak and minimum values, and urinary recovery were equivalent. Once-a-day dosage offers a convenience to the individual patient or to nursing personnel for institutionalized patients, and is intended only to be used for patients requiring this amount of drug daily. A major problem in motivating noncompliant patients may also be lessened when the patient can take all of his medication once-a-day. However, patients should be cautioned not to inadvertently miss a dose. Only extended phenytoin sodium capsules are recommended for once-a-day dosing.

PHARMACEUTICAL INFORMATION

Drug Substance

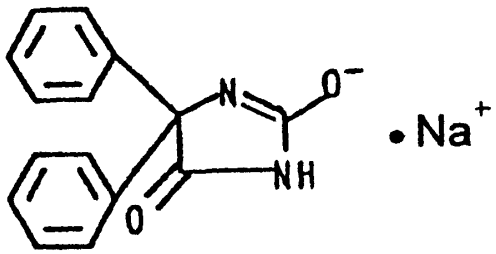
Proper Name: phenytoin sodium

Chemical Name: 2, 4-Imidazolidinedione, 5,5-diphenyl-,monosodium salt

Empirical Formula: $C_{15}H_{11}N_2NaO_2$

Molecular Weight: 274.25

Structural Formula:



Description: Phenytoin sodium is related to the barbiturates in chemical structure, but has a five-membered ring.

Solubility and pKa: Soluble in water.
pKa = 8.3 for phenytoin

Capsule Composition

Each 100 mg capsule contains 100 mg phenytoin sodium. Each 30 mg capsule contains 30 mg phenytoin sodium. The capsules also contain the following non-medicinal ingredients: sugar, talc, lactose, and magnesium stearate.
Capsule Shell (30mg) : D&C Yellow No. 10, FD&C Red No. 3, gelatin, titanium dioxide.
Capsule Shell (100mg) : FD&C Yellow No. 6, D&C red No. 28, gelatin and titanium dioxide.

Stability and Storage Recommendations

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

AVAILABILITY OF DOSAGE FORMS

DILANTIN CAPSULES: Extended phenytoin sodium capsules are available in dosage strengths of 30 and 100 mg capsules.

30 mg: Extended Phenytoin Sodium Capsules, Manufacturer Standard: 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. < 1 mmol (2.52 mg). Energy 3.0 kJ. Bottle of 100.

100 mg: Extended Phenytoin Sodium Capsules USP: Hard, filled No. 3, capsules containing a white powder. The medium orange cap having the Parke-Davis logo printed in black ink and the white, opaque, body having "DILANTIN" over "100 mg" printed in black ink.Sodium < 1 mmol (8.39 mg). Energy 2.6 kJ (0.6 kcal). Bottle of 100 and 1,000.

Also available as:

Dilantin Infatabs:
Each flavoured, triangular shaped, grooved tablet contains: phenytoin 50 mg. Bottle of 100.

Dilantin Suspensions:
Each 5 mL of flavoured, coloured suspension contains: phenytoin 30 mg (red, Dilantin-30) or 125 mg (orange, Dilantin-125). Bottle of 250 mL.

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CONSUMER INFORMATION

DILANTIN
(Extended phenytoin sodium capsules, 30 mg or 100 mg)

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 for you by your doctor to prevent and control seizures.

It is specifically used for:
- the control of generalized tonic-clonic seizures, and psychomotor seizures;
- the prevention and treatment of seizures that may begin during or after surgery to the brain or nervous system.

What it does:
Dilantin capsules belong to the family of medicine called anticonvulsants. 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:
The non-medicinal ingredients are: lactose, magnesium stearate, sugar and talc.
Capsule shells (30mg): D&C Yellow No. 10, FD&C Red No. 3, gelatin and titanium dioxide
Capsule shells (100 mg): FD&C Yellow No. 6, D&C red No. 28, gelatin and titanium dioxide.

What dosage forms it comes in:
Extended Phenytoin Sodium Capsules (30 and 100 mg).

Dilantin is also available in a phenytoin free acid form, as 50 mg flavoured Infatab and an oral suspension of 30 mg /5 mL or 125 mg/5 mL.

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 DILANTIN 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) and 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 over-the counter medication you are talking, 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 DILANTIN 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.

Dosage adjustments are required when switching from the extended phenytoin sodium capsules to DILANTIN Infatabs/oral suspension.
Do not use capsules that are discoloured.

Usual dose:
Adult:
***Starting dose*:** One capsule (100 mg) three times daily. The dose is adjusted to suit your response to treatment. In some cases, blood level assessment may be necessary to adjust the dose optimally.
***Maintenance dose*:** Usually, 3-4 capsules (300-400 mg) in divided doses daily. Some adult patients can be maintained on 300 mg once-a-day.
Pediatric:
***Starting dose*:** 5 mg/kg/day in two or three equally divided doses. The dose is individualized to a maximum of 300 mg daily. In some cases, blood level assessment may be necessary to adjust the dose optimally.
***Maintenance dose*:** 4 to 8 mg/kg/day. Children over 6 years old may require the minimum adult dose (300 mg/day).

Overdose:

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.

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 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, contact your doctor or pharmacist.

HOW TO STORE IT

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

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.

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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