

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DILANTIN-125® safely and effectively. See full prescribing information for DILANTIN-125®.

DILANTIN-125® (phenytoin) oral suspension

Initial U.S. Approval: 1953

RECENT MAJOR CHANGES

Warnings and Precautions (5.11)

11/2016

INDICATIONS AND USAGE

DILANTIN is indicated for the treatment of tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures. (1)

DOSAGE AND ADMINISTRATION

- Adult starting dose in patients who have received no previous treatment is 5mL three times daily, with dose adjustments as necessary, up to 25 mL daily. (2.2)
- Pediatric starting dose is 5 mg/kg/day in two to three equally divided doses, with dosage adjustments as necessary, up to a maximum of 300 mg daily. Maintenance dosage is 4 to 8 mg/kg/day. (2.3)
- Serum blood level determinations may be necessary for optimal dosage adjustments—the clinically effective serum total concentration is 10–20 mcg/mL (unbound phenytoin concentration is 1-2 mcg/mL). (2.1)

DOSAGE FORMS AND STRENGTHS

DILANTIN-125 is available as a 125 mg phenytoin/5 mL oral suspension. (3)

CONTRAINDICATIONS

- Hypersensitivity to phenytoin, its ingredients, or other hydantoin (4)
- A history of prior acute hepatotoxicity attributable to phenytoin (4, 5.6)
- Coadministration with delavirdine (4)

WARNINGS AND PRECAUTIONS

- Withdrawal Precipitated Seizure:* May precipitate status epilepticus. Dose reductions or discontinuation should be done gradually. (5.1)
- Suicidal Behavior and Ideation:* Monitor patients for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. (5.2)

- Serious Dermatologic Reactions:* Discontinue DILANTIN 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. (5.3)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity:* If signs or symptoms of hypersensitivity are present, evaluate the patient immediately. Discontinue if an alternative etiology cannot be established. (5.4)
- Hepatic Injury:* Cases of acute hepatotoxicity have been reported with DILANTIN. If this occurs, immediately discontinue. (4, 5.6)
- Hematopoietic Complications:* If occurs, follow-up observation is indicated and an alternative antiepileptic treatment should be used. (5.7)

ADVERSE REACTIONS

The most common adverse reactions are nervous system reactions, including nystagmus, ataxia, slurred speech, decreased coordination, somnolence, and mental confusion. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Multiple drug interactions because of extensive plasma protein binding, saturable metabolism and potent induction of hepatic enzymes (7.1, 7.2).

USE IN SPECIFIC POPULATIONS

- Pregnancy:** Prenatal exposure may increase the risks for congenital malformations and other adverse developmental outcomes. (5.11, 8.1)
- Renal and/or Hepatic Impairment or Hypoalbuminemia:** Monitor unbound phenytoin concentrations in these patients (8.7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DILANTIN is indicated for the treatment of tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

FOR ORAL ADMINISTRATION ONLY; NOT FOR PARENTERAL USE

A calibrated measuring device is recommended to measure and deliver the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device.

2.2 Adult Dosage

The recommended starting dosage for adult patients who have received no previous treatment is 5 mL (125 mg/5 mL), or one teaspoonful, by mouth three times daily. Adjust the dosage to suit individual requirements, up to a maximum of 25 mL daily [*see Dosage and Administration (2.4)*].

2.3 Pediatric Dosage

The recommended starting dosage for pediatric patients is 5 mg/kg/day by mouth in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily in divided doses. A recommended daily maintenance dosage is usually 4 to 8 mg/kg/day in equally divided doses. Children over 6 years and adolescents may require the minimum adult dosage (300 mg/day).

2.4 Dosage Adjustments

Dosage should be individualized to provide maximum benefit. In some cases, serum blood level determinations may be necessary for optimal dosage adjustments. Trough levels provide information about clinically effective serum level range and confirm patient compliance, and are obtained just prior to the patient's next scheduled dose. Peak levels indicate an individual's threshold for emergence of dose-related side effects and are obtained at the time of expected peak concentration. Therapeutic effect without clinical signs of toxicity occurs more often with serum total concentrations between 10 and 20 mcg/mL (unbound phenytoin concentrations of 1 to 2 mcg/mL), although some mild cases of tonic-clonic (grand mal) epilepsy may be controlled with lower serum levels of phenytoin. In patients with renal or hepatic disease, or in those with hypoalbuminemia, the monitoring of unbound phenytoin concentrations may be more relevant [*see Dosage and Administration (2.6)*].

With recommended dosages, a period of seven to ten days may be required to achieve phenytoin steady-state blood levels, and changes in dosage (increase or decrease) should not be carried out at intervals shorter than seven to ten days.

2.5 Switching Between Phenytoin Formulations

The free acid form of phenytoin is used in DILANTIN-125 Suspension and DILANTIN Infatabs. DILANTIN extended capsules and parental DILANTIN are formulated with the sodium salt of phenytoin. Because there is approximately an 8% increase in drug content with the free acid form over that of the sodium salt, dosage adjustments and serum level monitoring may be necessary when switching from a product formulated with the free acid to a product formulated with the sodium salt and vice versa.

2.6 Dosing in Patients with Renal or Hepatic Impairment or Hypoalbuminemia

Because the fraction of unbound phenytoin is increased in patients with renal or hepatic disease, or in those with hypoalbuminemia, the monitoring of phenytoin serum levels should be based on the unbound fraction in those patients [see *Warnings and Precautions* (5.9) and *Use in Specific Populations* (8.6)].

2.7 Geriatric Dosage

Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required [see *Clinical Pharmacology* (12.3)].

2.8 Dosing during Pregnancy

Decreased serum concentrations of phenytoin may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of serum phenytoin concentrations should be performed during pregnancy, and the DILANTIN dosage should be adjusted as necessary. Postpartum restoration of the original dosage will probably be indicated [see *Use in Specific Populations* (8.1)]. Because of potential changes in protein binding during pregnancy, the monitoring of phenytoin serum levels should be based on the unbound fraction.

3 DOSAGE FORMS AND STRENGTHS

DILANTIN-125 is available as a 125 mg phenytoin/5 mL oral suspension of orange color with an orange-vanilla flavor.

4 CONTRAINDICATIONS

DILANTIN is contraindicated in patients with:

- A history of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins [see *Warnings and Precautions* (5.5)].
- A history of prior acute hepatotoxicity attributable to phenytoin [see *Warnings and Precautions* (5.6)].
- Coadministration with delavirdine because of the potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.

5 WARNINGS AND PRECAUTIONS

5.1 Withdrawal Precipitated Seizure, Status Epilepticus

Abrupt withdrawal of phenytoin in epileptic patients may precipitate 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 or hypersensitivity reaction, more rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an anticonvulsant not belonging to the hydantoin chemical class.

5.2 Suicidal Behavior and Ideation

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

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

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

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

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

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

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

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

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

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

5.3 Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with phenytoin treatment. The onset of symptoms is usually within 28 days, but can occur later. DILANTIN 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. If a rash occurs, the patient should be evaluated for signs and symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms [*see Warnings and Precautions (5.4)*].

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502.

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

5.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Multiorgan Hypersensitivity

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

5.5 Hypersensitivity

DILANTIN and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity [*see Contraindications (4)*]. Additionally, consider alternatives to structurally similar drugs such as carboxamides (e.g., carbamazepine), barbiturates, succinimides, and oxazolidinediones (e.g., trimethadione) in these same patients. Similarly, if there is a history of hypersensitivity reactions to these structurally similar drugs in the patient or immediate family members, consider alternatives to DILANTIN.

5.6 Hepatic Injury

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with DILANTIN. These events may be part of the spectrum of DRESS or may occur in isolation [*see Warnings and Precautions (5.4)*]. Other common manifestations include 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, DILANTIN should be immediately discontinued and not readministered.

5.7 Hematopoietic Complications

Hematopoietic complications, some fatal, have occasionally been reported in association with administration of DILANTIN. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs of DRESS [*see Warnings and Precautions (5.4)*].

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.

5.8 Effects on Vitamin D and Bone

The chronic use of phenytoin in patients with epilepsy has been associated with decreased bone mineral density (osteopenia, osteoporosis, and osteomalacia) and bone fractures. Phenytoin induces hepatic metabolizing enzymes. This may enhance the metabolism of vitamin D and decrease vitamin D levels, which may lead to vitamin D deficiency, hypocalcemia, and hypophosphatemia. Consideration should be given to screening with bone-related laboratory and radiological tests as appropriate and initiating treatment plans according to established guidelines.

5.9 Renal or Hepatic Impairment, or Hypoalbuminemia

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

5.10 Exacerbation of Porphyria

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.

5.11 Teratogenicity and Other Harm to the Newborn

DILANTIN may cause fetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse development outcomes [*see Use in Specific Populations (8.1)*].

Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), and abnormalities characteristic of fetal hydantoin syndrome, including dysmorphic skull and facial features, nail and digit hypoplasia, growth abnormalities (including microcephaly), and cognitive deficits, have been reported among

children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have been several reported cases of malignancies, including neuroblastoma.

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

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

5.12 Slow Metabolizers of Phenytoin

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

5.13 Hyperglycemia

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.

5.14 Serum Phenytoin Levels above Therapeutic Range

Serum levels of phenytoin sustained above the therapeutic range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction and/or cerebellar atrophy. Accordingly, at the first sign of acute toxicity, serum levels should be immediately checked. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination is recommended.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Withdrawal Precipitated Seizure, Status Epilepticus [*see Warnings and Precautions (5.1)*]
- Suicidal Behavior and Ideation [*see Warnings and Precautions (5.2)*]
- Serious Dermatologic Reactions [*see Warnings and Precautions (5.3)*]
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity [*see Warnings and Precautions (5.4)*]
- Hypersensitivity [*see Warnings and Precautions (5.5)*]
- Hepatic Injury [*see Warnings and Precautions (5.6)*]
- Hematopoietic Complications [*see Warnings and Precautions (5.7)*]
- Effects on Vitamin D and Bone [*see Warnings and Precautions (5.8)*]
- Exacerbation of Porphyria [*see Warnings and Precautions (5.10)*]
- Teratogenicity and Other Harm to the Newborn [*see Warnings and Precautions (5.11)*]
- Hyperglycemia [*see Warnings and Precautions (5.13)*]

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

Body as a Whole: Allergic reactions in the form of rash and rarely more serious forms and DRESS have been observed [see *Warnings and Precautions* (5.3, 5.4)]. Anaphylaxis has also been reported.

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

Digestive System: Acute hepatic failure, toxic hepatitis, liver damage, nausea, vomiting, constipation, enlargement of the lips, and gingival hyperplasia.

Hematologic and Lymphatic System: Hematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. 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 and Precautions* (5.7)].

Laboratory Test Abnormality: Phenytoin may decrease serum concentrations of T4. It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose [see *Warnings and Precautions* (5.13)], alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Nervous System: The most common adverse reactions encountered with phenytoin therapy are nervous system reactions and are usually dose-related. Reactions include nystagmus, ataxia, slurred speech, decreased coordination, somnolence, and mental confusion. Dizziness, vertigo, insomnia, transient nervousness, motor twitchings, paresthesias, and headaches have also been observed. There have also been rare reports of phenytoin-induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. Cerebellar atrophy has been reported, and appears more likely in settings of elevated phenytoin levels and/or long-term phenytoin use [see *Warnings and Precautions* (5.14)].

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

Skin and Appendages: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis [see *Warnings and Precautions* (5.3)]. There have also been reports of hypertrichosis.

Special Senses: Altered taste sensation including metallic taste.

Urogenital: Peyronie's disease

7 DRUG INTERACTIONS

Phenytoin is extensively bound to plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome P450 enzymes CYP2C9 and CYP2C19 and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity. Monitoring of phenytoin serum levels is recommended when a drug interaction is suspected.

Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes.

7.1 Drugs that Affect Phenytoin Concentrations

Table 1 includes commonly occurring drug interactions that affect phenytoin concentrations. However, this list is not intended to be inclusive or comprehensive. Individual prescribing information from relevant drugs should be consulted.

The addition or withdrawal of these agents in patients on phenytoin therapy may require an adjustment of the phenytoin dose to achieve optimal clinical outcome.

Table 1: Drugs That Affect Phenytoin Concentrations

Interacting Agent	Examples
Drugs that may increase phenytoin serum levels	
Antiepileptic drugs	Ethosuximide, felbamate, oxcarbazepine, methsuximide, topiramate
Azoles	Fluconazole, ketoconazole, itraconazole, miconazole, voriconazole
Antineoplastic agents	Capecitabine, fluorouracil
Antidepressants	Fluoxetine, fluvoxamine, sertraline
Gastric acid reducing agents	H ₂ antagonists (cimetidine), omeprazole
Sulfonamides	Sulfamethizole, sulfaphenazole, sulfadiazine, sulfamethoxazole-trimethoprim
Other	Acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, disulfiram, estrogen, fluvastatin, isoniazid, methylphenidate, phenothiazines, salicylates, ticlopidine, tolbutamide, trazodone, warfarin
Drugs that may decrease phenytoin serum levels	
Antacids ^a	Calcium carbonate, aluminum hydroxide, magnesium hydroxide <i>Prevention or Management:</i> Phenytoin and antacids should not be taken at the same time of day
Antineoplastic agents (usually in combination)	Bleomycin, carboplatin, cisplatin, doxorubicin, methotrexate
Antiviral agents	Fosamprenavir, nelfinavir, ritonavir
Antiepileptic drugs	Carbamazepine, vigabatrin
Other	Chronic alcohol abuse, diazepam, diazoxide, folic acid, reserpine, rifampin, St. John's wort ^b , sucralfate, theophylline
Drugs that may either increase or decrease phenytoin serum levels	
Antiepileptic drugs	Phenobarbital, valproate sodium, valproic acid

^a Antacids may affect absorption of phenytoin.

^b The induction potency of St. John's wort may vary widely based on preparation.

7.2 Drugs Affected by Phenytoin

Table 2 includes commonly occurring drug interactions affected by phenytoin. However, this list is not intended to be inclusive or comprehensive. Individual drug package inserts should be consulted.

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

Table 2: Drugs Affected by Phenytoin

Interacting Agent	Examples
Drugs whose efficacy is impaired by phenytoin	
Azoles	Fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole
Antineoplastic agents	Irinotecan, paclitaxel, teniposide
Delavirdine	Phenytoin can substantially reduce the concentrations of delavirdine. This can lead to loss of virologic response and possible resistance [<i>see Contraindications (4)</i>].
Neuromuscular blocking agents	Cisatracurium, pancuronium, rocuronium and vecuronium: resistance to the neuromuscular blocking action of the nondepolarizing neuromuscular blocking agents has occurred in patients chronically administered phenytoin. Whether or not phenytoin has the same effect on other non-depolarizing agents is unknown. <i>Prevention or Management:</i> Patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected, and infusion rate requirements may be higher.
Warfarin	Increased and decreased PT/INR responses have been reported when phenytoin is coadministered with warfarin
Other	Corticosteroids, doxycycline, estrogens, furosemide, oral contraceptives, paroxetine, quinidine, rifampin, sertraline, theophylline, and vitamin D
Drugs whose level is decreased by phenytoin	
Antiepileptic drugs ^a	Carbamazepine, felbamate, lamotrigine, topiramate, oxcarbazepine
Antilipidemic agents	Atorvastatin, fluvastatin, simvastatin
Antiviral agents	Efavirenz, lopinavir/ritonavir, indinavir, nelfinavir, ritonavir, saquinavir Fosamprenavir: phenytoin when given with fosamprenavir alone may decrease the concentration of amprenavir, the active metabolite. Phenytoin when given with the combination of fosamprenavir and ritonavir may increase the concentration of amprenavir
Calcium channel blockers	Nifedipine, nimodipine, nisoldipine, verapamil
Other	Albendazole (decreases active metabolite), chlorpropamide, clozapine, cyclosporine, digoxin, folic acid, methadone, mexiletine, praziquantel, quetiapine

^aThe effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable

7.3 Drug Enteral Feeding/Nutritional Preparations Interaction

Literature reports suggest that patients who have received enteral feeding preparations and/or related nutritional supplements have lower than expected phenytoin serum levels. It is therefore suggested that phenytoin not be administered concomitantly with an enteral feeding preparation. More frequent serum phenytoin level monitoring may be necessary in these patients.

7.4 Drug/Laboratory Test Interactions

Care should be taken when using immunoanalytical methods to measure serum phenytoin concentrations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as DILANTIN, during pregnancy. Physicians are advised to recommend that pregnant patients taking Dilantin enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>

Risk Summary

In humans, prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. An increased incidence of major malformations (such as orofacial clefts and cardiac defects) and abnormalities characteristic of fetal hydantoin syndrome (dysmorphic skull and facial features, nail and digit hypoplasia, growth abnormalities [including microcephaly], and cognitive deficits) has been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

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

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

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

Clinical Considerations

Disease-associated maternal risk

An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of serum phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage [see Dosage and Administration (2.4, 2.8)]. However, postpartum restoration of the original dosage will probably be indicated [see Clinical Pharmacology (12.3)].

Fetal/Neonatal Adverse Reactions

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

Data

Animal data

Administration of phenytoin to pregnant rats, rabbits, and mice during organogenesis resulted in embryofetal death, fetal malformations, and decreased fetal growth. Malformations (including craniofacial, cardiovascular,

neural, limb, and digit abnormalities) were observed in rats, rabbits, and mice at doses as low as 100, 75, and 12.5 mg/kg, respectively.

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years and adolescents may require the minimum adult dosage (300 mg/day) [*see Dosage and Administration (2.3)*].

8.5 Geriatric Use

Phenytoin clearance tends to decrease with increasing age [*see Clinical Pharmacology (12.3)*]. Lower or less frequent dosing may be required [*see Dosage and Administration (2.7)*].

8.6 Renal and/or Hepatic Impairment or Hypoalbuminemia

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

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

10 OVERDOSAGE

The lethal dose in pediatric patients 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, lethargy, slurred speech, blurred vision, nausea, and vomiting. The patient may become comatose and hypotensive. Death is caused by respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin serum levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL, dysarthria and lethargy appear when the serum concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery. Irreversible cerebellar dysfunction and atrophy have been reported.

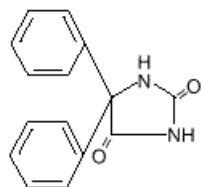
Treatment: Treatment is nonspecific since there is no known antidote.

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

11 DESCRIPTION

DILANTIN (phenytoin) is related to the barbiturates in chemical structure, but has a five-membered ring. The chemical name is 5,5-diphenyl-2,4 imidazolidinedione, having the following structural formula:



Each 5 mL of the oral suspension contains 125 mg of phenytoin, USP; alcohol, USP (maximum content not greater than 0.6 percent); banana flavor; carboxymethylcellulose sodium, USP; citric acid, anhydrous, USP; glycerin, USP; magnesium aluminum silicate, NF; orange oil concentrate; polysorbate 40, NF; purified water, USP; sodium benzoate, NF; sucrose, NF; vanillin, NF; and FD&C yellow No. 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Absorption

For DILANTIN-125 Suspension, peak levels occur 1½–3 hours after administration. Steady-state therapeutic levels are achieved at least 7 to 10 days (5–7 half-lives) after initiation of therapy with recommended doses of 300 mg/day. When serum level determinations are necessary, they should be obtained at least 5–7 half-lives 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.

Distribution

Phenytoin is extensively bound to serum plasma proteins.

Elimination

The plasma half-life in man after oral administration of phenytoin averages 22 hours, with a range of 7 to 42 hours.

Metabolism

Phenytoin is metabolized by hepatic cytochrome P450 enzymes CYP2C9 and CYP2C19. Because phenytoin is hydroxylated in the liver by an enzyme 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 the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

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,

variant CYP2C9 and CYP2C19 alleles, 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.

Excretion

Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine. Urinary excretion of phenytoin and its metabolites occurs partly with glomerular filtration but, more importantly, by tubular secretion.

Specific Populations

Age: Geriatric Population:

Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20-30 years of age). Since phenytoin clearance is decreased slightly in elderly patients, lower or less frequent dosing may be required [see *Dosage and Administration* (2.7)].

Sex/Race:

Gender and race have no significant impact on phenytoin pharmacokinetics.

Renal or Hepatic Impairment:

Increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia has been reported.

Pregnancy:

It has been reported in the literature that the plasma clearance of phenytoin generally increased during pregnancy, reached a peak in the third trimester and returned to the level of pre-pregnancy after few weeks or months of delivery.

Drug Interaction Studies

Phenytoin is metabolized by hepatic cytochrome P450 enzymes CYP2C9 and CYP2C19.

Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes [see *Drug Interactions* (7.1, 7.2)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis [see *Warnings and Precautions* (5.7)]

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

In carcinogenicity studies reported in the literature, phenytoin was administered in the diet for 2 years at doses up to 600 ppm (approximately 90 mg/kg/day) to mice and up to 2400 ppm (approximately 120 mg/kg/day) to rats. The incidences of hepatocellular tumors were increased in female mice at all but the lowest dose tested. No increases in tumor incidence were observed in rats.

Mutagenesis

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

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

Fertility

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DILANTIN-125 Oral Suspension is supplied as follows:

Package Configuration	Strength	NDC
8-oz bottles	125 mg phenytoin/5mL	0071-2214-20

DILANTIN-125 Suspension (phenytoin oral suspension, USP), 125 mg phenytoin/5 mL contains a maximum alcohol content not greater than 0.6 percent in an orange suspension with an orange-vanilla flavor.

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F); see USP controlled room temperature.

Protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Administration Information

Advise patients taking phenytoin 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.

Instruct patients to use an accurately calibrated measuring device when using this medication to ensure accurate dosing.

Withdrawal of Antiepileptic Drugs

Advise patients not to discontinue use of DILANTIN without consulting with their healthcare provider. DILANTIN should normally be gradually withdrawn to reduce the potential for increased seizure frequency and status epilepticus [see *Warnings and Precautions* (5.1)].

Suicidal Ideation and Behavior

Counsel patients, their caregivers, and families that AEDs, including DILANTIN, may increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers [see *Warnings and Precautions* (5.2)].

Potential Signs of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Other Systemic Reactions

Advise patients of the early toxic signs and symptoms of potential hematologic, dermatologic, hypersensitivity, or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy, facial swelling, and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. Advise the patient that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, advise the patient that these signs and symptoms should be reported even if mild or when occurring after extended use [*see Warnings and Precautions (5.3, 5.4, 5.5, 5.6, 5.7)*].

Effects of Alcohol Use and Other Drugs and Over-the-Counter Drug Interactions

Caution patients against the use of other drugs or alcoholic beverages without first seeking their physician's advice [*see Drug Interactions (7.1, 7.2)*].

Inform patients that certain over-the-counter medications (e.g., antacids, cimetidine, and omeprazole), vitamins (e.g., folic acid), and herbal supplements (e.g., St. John's wort) can alter their phenytoin levels.

Hyperglycemia

Advise patients that DILANTIN may cause an increase in blood glucose levels [*see Warnings and Precautions (5.13)*].

Gingival Hyperplasia

Advise patients of the importance of good dental hygiene in order to minimize the development of gingival hyperplasia and its complications.

Neurologic Effects

Counsel patients that DILANTIN may cause dizziness, gait disturbance, decreased coordination and somnolence. Advise patients taking DILANTIN not to drive, operate complex machinery, or engage in other hazardous activities until they have become accustomed to any such effects associated with DILANTIN.

Use in Pregnancy

Inform pregnant women and women of childbearing potential that use of DILANTIN during pregnancy can cause fetal harm, including an increased risk for cleft lip and/or cleft palate (oral clefts), cardiac defects, dysmorphic skull and facial features, nail and digit hypoplasia, growth abnormalities (including microcephaly), and cognitive deficits. When appropriate, counsel pregnant women and women of childbearing potential about alternative therapeutic options. Advise women of childbearing potential who are not planning a pregnancy to use effective contraception while using DILANTIN, keeping in mind that there is a potential for decreased hormonal contraceptive efficacy [*see Drug Interactions (7.2)*].

Instruct patients to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy [*see Use in Specific Populations (8.1, 8.2)*].

Encourage patients to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy [*see Use in Specific Populations (8.1)*].

MEDICATION GUIDE
DILANTIN-125® (Dī LAN' tīn-125) (phenytoin) oral suspension

What is the most important information I should know about DILANTIN?

1. Do not stop taking DILANTIN without first talking to your healthcare provider.

- Stopping DILANTIN suddenly can cause serious problems.
- Stopping a seizure medicine suddenly can cause you to have seizures more often or seizures that will not stop (status epilepticus).

2. Like other antiepileptic drugs, DILANTIN may cause suicidal thoughts or actions in a very small number of people, about 1 in 500. Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- | | | | |
|-----------------------------------|--------------------------------|--|---|
| • Thoughts about suicide or dying | • New or worse anxiety | • Trouble sleeping (insomnia) | • Acting on dangerous impulses |
| • Attempts to commit suicide | • Feeling agitated or restless | • New or worse irritability | • An extreme increase in activity and talking (mania) |
| • New or worse depression | • Panic attacks | • Acting aggressive, being angry, or violent | • Other unusual changes in behavior or mood |

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

3. DILANTIN can cause a type of serious allergic reaction that may affect different parts of the body such as your liver, kidneys, blood, heart, skin or other parts of your body. These can be very serious and cause death. Call your healthcare provider right away if you have any or all of these symptoms:

- | | | |
|---|------------------------------------|--|
| • Fever | • Sore throat | • Not wanting to eat (anorexia) |
| • Rash | • Sores in your mouth | • Nausea |
| • Swollen lymph glands | • Bruise easily | • Vomiting |
| • Swelling of your face, eye, lips, or tongue | • Purple or red spots on your skin | • Yellowing of the skin and the white part of your eyes (jaundice) |
| • Trouble swallowing or breathing | • Increase infections | |

Call your healthcare provider even if the symptoms are mild or if you have been taking DILANTIN for an extended period of time. These symptoms can be a sign of a serious allergic reaction.

What is DILANTIN?

DILANTIN is a prescription medicine used to treat certain types of seizures called tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures.

Do not take DILANTIN if you:

- Are allergic to phenytoin or any of the ingredients in DILANTIN. See the end of this leaflet for a complete list of ingredients in DILANTIN.
- Have had an allergic reaction to CEREBYX (fosphenytoin), PEGANONE (ethotoin), or MESANTOIN (mephenytoin).
- Have had liver problems from taking phenytoin.
- Take delavirdine.

Before taking DILANTIN, tell your healthcare provider about all of your medical conditions, including if you:

- Have or have had depression, mood problems, or suicidal thoughts or behavior
- Have had an allergic reaction to a medicine similar to DILANTIN called carboxamides, barbiturates, succinimides, and oxazolidinediones
- Have or had liver or kidney problems
- Have or had an enzyme problem called porphyria
- Have or had high blood sugar (hyperglycemia)
- Drink alcohol
- Are pregnant or plan to become pregnant. DILANTIN may harm your unborn baby.
 - If you take DILANTIN during pregnancy, your baby is at risk for serious birth defects.
 - If you become pregnant while taking DILANTIN, the level of DILANTIN in your blood may decrease,

- causing your seizures to become worse. Your healthcare provider may change your dose of DILANTIN.
- If you take DILANTIN during pregnancy, your baby is also at risk for bleeding problems right after birth. Your healthcare provider may give you and your baby medicine to prevent this.
- All women of child-bearing age should talk to their healthcare provider about using other possible treatments instead of DILANTIN.
- If you are of childbearing age and are not planning on getting pregnant, you should use effective birth control (contraception) while taking DILANTIN.
- **Pregnancy Registry:** If you become pregnant while taking DILANTIN, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.
- Are breast feeding or plan to breastfeed. DILANTIN can pass into breast milk. You and your healthcare provider should decide if you will take DILANTIN while you are breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. These medicines can change the levels of DILANTIN in your blood.

Taking DILANTIN with certain other medicines can cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take DILANTIN?

- Take DILANTIN exactly as your healthcare provider tells you.
- Your healthcare provider will tell you how much DILANTIN to take and when to take it.
- Your healthcare provider may change your dose if needed. Do not change your dose of DILANTIN without talking to your healthcare provider.
- If your healthcare provider has prescribed DILANTIN oral suspension, ask your pharmacist for a medicine dropper or medicine cup to help you measure the correct amount of DILANTIN. **Do not** use a household teaspoon. Ask your pharmacist for instructions on how to use the measuring device the right way.
- Do not stop taking DILANTIN without first talking to your healthcare provider. Stopping DILANTIN suddenly can cause serious problems.

What should I avoid while taking DILANTIN?

- Do not drink alcohol while you take DILANTIN without first talking to your healthcare provider. Drinking alcohol while taking DILANTIN may change your blood levels of DILANTIN which can cause serious problems.
- Do not drive, operate heavy machinery, or do other dangerous activities until you know how DILANTIN affects you. DILANTIN can slow your thinking and motor skills.

What are the possible side effects of DILANTIN?

See “What is the most important information I should know about DILANTIN?”

DILANTIN may cause other serious side effects including:

- Liver problems.
- Low blood count which could increase your chance of getting infections, bruising, bleeding and increased fatigue.
- Softening of your bones (osteopenia, osteoporosis, and osteomalacia) can cause your bones to break (fractures).
- High blood sugar (hyperglycemia).
- High levels of DILANTIN in your blood that could cause confusion also known as delirium, psychosis or a more serious condition that affects how your brain works (encephalopathy).

Call your healthcare provider right away, if you have any of the symptoms listed above.

The most common side effects of DILANTIN include:

- Irregular movement of the eye (nystagmus)
- Problems with movement and balance (ataxia)
- Slurred speech
- Decrease in coordination
- Drowsiness (somnolence)
- Confusion

DILANTIN can cause overgrowth of your gums. Brushing and flossing your teeth and seeing a dentist regularly while taking DILANTIN can help prevent this from happening.

These are not all of the possible side effects of DILANTIN.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store DILANTIN?

- Store DILANTIN Suspension at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect from light.
- **Do not** freeze.

Keep DILANTIN and all medicines out of the reach of children.

General information about the safe and effective use of DILANTIN.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DILANTIN for a condition for which it was not prescribed. Do not give DILANTIN to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about DILANTIN that is written for health professionals.

What are the ingredients in DILANTIN Suspension?

Active ingredient: phenytoin, USP

Inactive ingredients: alcohol, USP (maximum content not greater than 0.6 percent); banana flavor; carboxymethylcellulose sodium, USP; citric acid, anhydrous, USP; glycerin, USP; magnesium aluminum silicate, NF; orange oil concentrate; polysorbate 40, NF; purified water, USP; sodium benzoate, NF; sucrose, NF; vanillin, NF; and FD&C yellow No. 6.

Distributed by



Parke-Davis

Division of Pfizer Inc, NY, NY 10017

For more information about DILANTIN, visit <http://www.pfizer.com> or call 1 800 438 1985.

This Medication Guide has been approved by the U.S. Food and Drug Administration

LAB-0398-3.2; Revised: November 2016

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DILANTIN® safely and effectively. See full prescribing information for DILANTIN®.

DILANTIN® (phenytoin sodium) injection, for intravenous or intramuscular use

Initial U.S. Approval: 1953

WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH RAPID INFUSION

See full prescribing information for complete boxed warning.

- The rate of intravenous DILANTIN administration should not exceed 50 mg per minute in adults and 1-3 mg/kg/min (or 50 mg per minute, whichever is slower) in pediatric patients because of the risk of severe hypotension and cardiac arrhythmias.
- Careful cardiac monitoring is needed during and after administering intravenous DILANTIN.
- Reduction in rate of administration or discontinuation of dosing may be needed (5.1, 2.1).

RECENT MAJOR CHANGES

Warnings and Precautions (5.11)

11/2016

INDICATIONS AND USAGE

Parenteral DILANTIN is indicated for the treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery. Intravenous DILANTIN can also be substituted, as short-term use, for oral phenytoin. Parenteral DILANTIN should be used only when oral DILANTIN administration is not possible. (1)

DOSAGE AND ADMINISTRATION

For Status Epilepticus and Non-emergent Loading Dose:

- Adult loading dose is 10 to 15 mg/kg at a rate not exceeding 50 mg/min. (2.2)
- Pediatric loading dose is 15-20 mg/kg at a rate not exceeding 1-3 mg/kg/min or 50 mg/min, whichever is slower. (2.8)
- Continuous monitoring of the electrocardiogram, blood pressure, and respiratory function is essential. (2.2)

Maintenance Dosing:

- Initial loading dose should be followed by maintenance doses of oral or intravenous DILANTIN every 6-8 hours. (2.2, 2.3)

Intramuscular Administration:

- Because of erratic absorption and local toxicity, DILANTIN should ordinarily not be given intramuscularly. (2.2, 2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 50 mg phenytoin sodium per milliliter in:

- 2 mL single dose sterile disposable syringes (3)
- 2 mL and 5 mL single dose vials (3)

CONTRAINDICATIONS

- Hypersensitivity to phenytoin, its ingredients, or other hydantoin (4)
- Sinus bradycardia, sino-atrial block, second and third degree A-V block, and Adams-Stokes syndrome (4)
- A history of prior acute hepatotoxicity attributable to phenytoin (4, 5.6)
- Coadministration with delavirdine (4)

WARNINGS AND PRECAUTIONS

- *Withdrawal Precipitated Seizure:* May precipitate status epilepticus. Dose reductions or discontinuation should be done gradually. (5.2)
- *Serious Dermatologic Reactions:* Discontinue Dilantin 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. (5.3)
- *Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity:* If signs or symptoms of hypersensitivity are present, evaluate the patient immediately. Discontinue if an alternative etiology cannot be established. (5.4)
- *Hematopoietic Complications:* If occurs, follow-up observation is indicated and an alternative antiepileptic treatment should be used. (5.7)

ADVERSE REACTIONS

The most common adverse reactions are nervous system reactions, including nystagmus, ataxia, slurred speech, decreased coordination, somnolence, and mental confusion. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Multiple drug interactions because of extensive plasma protein binding, saturable metabolism and potent induction of hepatic enzymes. (7.1, 7.2)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. (5.11, 8.1)
- **Renal and/or Hepatic Impairment or Hypoalbuminemia:** Monitor unbound phenytoin concentrations in these patients. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH RAPID INFUSION

The rate of intravenous DILANTIN administration should not exceed 50 mg per minute in adults and 1-3 mg/kg/min (or 50 mg per minute, whichever is slower) in pediatric patients because of the risk of severe hypotension and cardiac arrhythmias. Careful cardiac monitoring is needed during and after administering intravenous DILANTIN. Although the risk of cardiovascular toxicity increases with infusion rates above the recommended infusion rate, these events have also been reported at or below the recommended infusion rate. Reduction in rate of administration or discontinuation of dosing may be needed [*see Warnings and Precautions (5.1) and Dosage and Administration (2.1)*].

1 INDICATIONS AND USAGE

Parenteral DILANTIN is indicated for the treatment of generalized tonic-clonic status epilepticus, and prevention and treatment of seizures occurring during neurosurgery. Intravenous DILANTIN can also be substituted, as short-term use, for oral phenytoin. Parenteral DILANTIN should be used only when oral DILANTIN administration is not possible [*see Dosage and Administration (2.1, 2.3) and Warnings and Precautions (5.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Because of the increased risk of adverse cardiovascular reactions associated with rapid administration, intravenous administration should not exceed 50 mg per minute in adults. In pediatric patients, the drug should be administered at a rate not exceeding 1-3 mg/kg/min or 50 mg per minute, whichever is slower.

As non-emergency therapy, DILANTIN should be administered more slowly as either a loading dose or by intermittent infusion. Because of the risks of cardiac and local toxicity associated with intravenous DILANTIN, oral phenytoin should be used whenever possible.

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

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

DILANTIN can be given diluted with normal saline. The addition of parenteral DILANTIN to dextrose and dextrose-containing solutions should be avoided due to lack of solubility and resultant precipitation.

Treatment with DILANTIN can be initiated either with a loading dose or an infusion:

Loading Dose: A loading dose of parenteral DILANTIN should be injected slowly, not exceeding 50 mg per minute in adults and 1-3 mg/kg/min (or 50 mg per minute, whichever is slower) in pediatric patients.

Infusion: For infusion administration, parenteral DILANTIN should be diluted in normal saline with the final concentration of DILANTIN in the solution no less than 5 mg/mL. Administration should commence

immediately after the mixture has been prepared and must be completed within 1 to 4 hours (the infusion mixture should not be refrigerated). An in-line filter (0.22-0.55 microns) should be used.

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

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

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

Monitoring Levels: Trough levels provide information about clinically effective serum level range and are obtained just prior to the patient's next scheduled dose. Peak levels indicate an individual's threshold for emergence of dose-related side effects and are obtained at the time of expected peak concentration. Therapeutic effect without clinical signs of toxicity occurs more often with serum total concentrations between 10 and 20 mcg/mL (unbound phenytoin concentrations of 1 to 2 mcg/mL), although some mild cases of tonic-clonic (grand mal) epilepsy may be controlled with lower serum levels of phenytoin. In patients with renal or hepatic disease, or in those with hypoalbuminemia, the monitoring of unbound phenytoin concentrations may be more relevant [*see Dosage and Administration (2.3)*].

2.2 Status Epilepticus

In adults, a loading dose of 10 to 15 mg/kg should be administered slowly intravenously, at a rate not exceeding 50 mg per minute (this will require approximately 20 minutes in a 70-kg patient).

The loading dose should be followed by maintenance doses of 100 mg orally or intravenously every 6-8 hours.

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

Continuous monitoring of the electrocardiogram and blood pressure is essential. The patient should be observed for signs of respiratory depression.

Determination of phenytoin serum levels is advised when using DILANTIN in the management of status epilepticus and in the subsequent establishment of maintenance dosage.

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

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

Intramuscular administration should not be used in the treatment of status epilepticus because the attainment of peak serum levels may require up to 24 hours.

2.3 Non-emergent Loading and Maintenance Dosing

Because of the risks of cardiac and local toxicity associated with intravenous DILANTIN, oral phenytoin should be used whenever possible. In adults, a loading dose of 10 to 15 mg/kg should be administered slowly. The rate of intravenous administration should not exceed 50 mg per minute in adults and 1-3 mg/kg/min (or 50 mg per

minute, whichever is slower) in pediatric patients. Slower administration rates are recommended to minimize the cardiovascular adverse reactions. Continuous monitoring of the electrocardiogram, blood pressure, and respiratory function is essential.

The loading dose should be followed by maintenance doses of oral or intravenous DILANTIN every 6-8 hours.

Ordinarily, DILANTIN should not be given intramuscularly because of the risk of necrosis, abscess formation, and erratic absorption. If intramuscular administration is required, compensating dosage adjustments are necessary to maintain therapeutic serum levels. An intramuscular dose 50% greater than the oral dose is necessary to maintain these levels. When returned to oral administration, the dose should be reduced by 50% of the original oral dose for one week to prevent excessive serum levels due to sustained release from intramuscular tissue sites.

Monitoring serum levels would help prevent a fall into the subtherapeutic range. Serum blood level determinations are especially helpful when possible drug interactions are suspected.

2.4 Parenteral Substitution for Oral Phenytoin Therapy

When treatment with oral phenytoin is not possible, IV DILANTIN can be substituted for oral phenytoin at the same total daily dose. DILANTIN capsules are approximately 90% bioavailable by the oral route. Phenytoin is 100% bioavailable by the IV route. For this reason, serum phenytoin concentrations may increase modestly when IV phenytoin is substituted for oral phenytoin sodium therapy. The rate of administration for IV DILANTIN should be no greater than 50 mg per minute in adults and 1-3 mg/kg/min (or 50 mg per minute, whichever is slower) in pediatric patients.

When intramuscular administration may be required, a sufficient dose must be administered intramuscularly to maintain the serum level within the therapeutic range. Where oral dosage is resumed following intramuscular usage, the oral dose should be properly adjusted to compensate for the slow, continuing IM absorption to minimize toxic symptoms [*see Clinical Pharmacology (12.3)*].

Serum concentrations should be monitored and care should be taken when switching a patient from the sodium salt to the free acid form. DILANTIN extended capsules and parenteral DILANTIN are formulated with the sodium salt of phenytoin. The free acid form of phenytoin is used in 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.

2.5 Dosing in Patients with Renal or Hepatic Impairment or Hypoalbuminemia

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

2.6 Dosing in Geriatrics

Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required [see *Clinical Pharmacology* (12.3)].

2.7 Dosing during Pregnancy

Decreased serum concentrations of phenytoin may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of serum phenytoin concentrations should be performed during pregnancy, and the DILANTIN dosage should be adjusted as necessary. Postpartum restoration of the original dosage will probably be indicated [see *Use in Specific Populations* (8.1)]. Because of potential changes in protein binding during pregnancy, the monitoring of phenytoin serum levels should be based on the unbound fraction.

2.8 Dosing in Pediatrics

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

3 DOSAGE FORMS AND STRENGTHS

DILANTIN Injection: 50 mg phenytoin sodium per milliliter, colorless to slightly yellow solution available as:

- 2-mL single-dose (Steri-Dose[®] 4488) sterile disposable syringes
- 2-mL single-dose Steri-Vials[®]
- 5-mL single-dose Steri-Vials[®]

4 CONTRAINDICATIONS

DILANTIN is contraindicated in patients with:

- A history of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins [see *Warnings and Precautions* (5.5)].
- Sinus bradycardia, sino-atrial block, second and third degree A-V block, and Adams-Stokes syndrome because of the effect of parenteral phenytoin on ventricular automaticity.
- A history of prior acute hepatotoxicity attributable to phenytoin [see *Warnings and Precautions* (5.6)].
- Coadministration with delavirdine because of the potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Risk Associated with Rapid Infusion

Rapid intravenous administration of DILANTIN increases the risk of adverse cardiovascular reactions, including severe hypotension and cardiac arrhythmias. Cardiac arrhythmias have included bradycardia, heart block, ventricular tachycardia, and ventricular fibrillation which have resulted in asystole, cardiac arrest, and death. Severe complications are most commonly encountered in critically ill patients, elderly patients, and patients with hypotension and severe myocardial insufficiency. However, cardiac events have also been reported in adults and children without underlying cardiac disease or comorbidities and at recommended doses and infusion rates.

Intravenous administration should not exceed 50 mg per minute in adults. In pediatric patients, administer the drug at a rate not exceeding 1 to 3 mg/kg/min or 50 mg per minute, whichever is slower.

Although the risk of cardiovascular toxicity increases with infusion rates above the recommended infusion rate, these events have also been reported at or below the recommended infusion rate.

As non-emergency therapy, DILANTIN should be administered more slowly as either a loading dose or by intermittent infusion. Because of the risks of cardiac and local toxicity associated with intravenous DILANTIN, oral phenytoin should be used whenever possible.

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

5.2 Withdrawal Precipitated Seizure, Status Epilepticus

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

5.3 Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with phenytoin treatment. The onset of symptoms is usually within 28 days, but can occur later. DILANTIN 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. If a rash occurs, the patient should be evaluated for signs and symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms [*see Warnings and Precautions (5.4)*].

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502.

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

5.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

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

5.5 Hypersensitivity

DILANTIN and other hydantoin are contraindicated in patients who have experienced phenytoin hypersensitivity [*see Contraindications (4)*]. Additionally, consider alternatives to structurally similar drugs such as carboxamides (e.g., carbamazepine), barbiturates, succinimides, and oxazolidinediones (e.g., trimethadione) in these same patients. Similarly, if there is a history of hypersensitivity reactions to these structurally similar drugs in the patient or immediate family members, consider alternatives to DILANTIN.

5.6 Hepatic Injury

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with DILANTIN. These events may be part of the spectrum of DRESS or may occur in isolation [*see Warnings and Precautions (5.4)*]. Other common manifestations include 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, DILANTIN should be immediately discontinued and not re-administered.

5.7 Hematopoietic Complications

Hematopoietic complications, some fatal, have occasionally been reported in association with administration of DILANTIN. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling DRESS [*see Warnings and Precautions (5.4)*].

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.

5.8 Local toxicity (Including Purple Glove Syndrome)

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

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

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

Intramuscular DILANTIN administration may cause pain, necrosis, and abscess formation at the injection site [*see Dosage and Administration (2.3)*].

5.9 Renal or Hepatic Impairment or Hypoalbuminemia

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

5.10 Exacerbation of Porphyria

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.

5.11 Teratogenicity and Other Harm to the Newborn

DILANTIN may cause fetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse development outcomes [*see Use in Specific Populations (8.1)*].

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

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

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

5.12 Slow Metabolizers of Phenytoin

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

5.13 Hyperglycemia

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

5.14 Serum Phenytoin Levels above Therapeutic Range

Serum levels of phenytoin sustained above the therapeutic range may produce confusional states referred to as "delirium", "psychosis", or "encephalopathy", or rarely irreversible cerebellar dysfunction and/or cerebellar atrophy. Accordingly, at the first sign of acute toxicity, serum levels should be immediately checked. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination is recommended.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Cardiovascular Risk Associated with Rapid Infusion [*see Warnings and Precautions (5.1)*]
- Withdrawal Precipitated Seizure, Status Epilepticus [*see Warnings and Precautions (5.2)*]
- Serious Dermatologic Reactions [*see Warnings and Precautions (5.3)*]
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity [*see Warnings and Precautions (5.4)*]
- Hypersensitivity [*see Warnings and Precautions (5.5)*]

- Hepatic Injury [*see Warnings and Precautions (5.6)*]
- Hematopoietic Complications [*see Warnings and Precautions (5.7)*]
- Local toxicity (Including Purple Glove Syndrome) [*see Warnings and Precautions (5.8)*]
- Exacerbation of Porphyria [*see Warnings and Precautions (5.10)*]
- Teratogenicity and Other Harm to the Newborn [*see Warnings and Precautions (5.11)*]
- Hyperglycemia [*see Warnings and Precautions (5.13)*]

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

The most notable signs of toxicity associated with the intravenous use of this drug are cardiovascular collapse and/or central nervous system depression. Hypotension does occur when the drug is administered rapidly by the intravenous route. The rate of administration is very important; it should not exceed 50 mg per minute in adults, and 1-3 mg/kg/min (or 50 mg per minute, whichever is slower) in pediatric patients [*See Boxed Warning, Dosage and Administration (2.1), and Warnings and Precautions (5.1)*].

Body As a Whole: Allergic reactions in the form of rash and rarely more serious forms (see Skin and Appendages paragraph below) and DRESS [*see Warnings and Precautions (5.4)*] have been observed. Anaphylaxis has also been reported.

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

Cardiovascular: Severe cardiovascular events and fatalities have been reported with atrial and ventricular conduction depression and ventricular fibrillation. Severe complications are most commonly encountered in elderly or critically ill patients [*see Boxed Warning and Warnings and Precautions (5.1)*].

Digestive System: Acute hepatic failure [*see Warnings and Precautions (5.6)*], toxic hepatitis, liver damage, nausea, vomiting, constipation, enlargement of the lips, and gingival hyperplasia.

Hematologic and Lymphatic System: Hematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin [*see Warnings and Precautions (5.7)*]. 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 and Precautions (5.7)*].

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

Nervous System: The most common adverse reactions encountered with phenytoin therapy are nervous system reactions and are usually dose-related. Reactions include nystagmus, ataxia, slurred speech, decreased coordination, somnolence, and mental confusion. Dizziness, vertigo, insomnia, transient nervousness, motor twitchings, paresthesia, and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. Cerebellar atrophy has been reported, and appears more likely in settings of elevated phenytoin levels and/or long-term phenytoin use [*see Warnings and Precautions (5.14)*].

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

Skin and Appendages: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis [see *Warnings and Precautions* (5.3)]. There have also been reports of hypertrichosis.

Local irritation, inflammation, tenderness, necrosis, and sloughing have been reported with or without extravasation of intravenous phenytoin [see *Warnings and Precautions* (5.8)].

Special Senses: Altered taste sensation including metallic taste.

Urogenital: Peyronie’s disease

7 DRUG INTERACTIONS

Phenytoin is extensively bound to plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome P450 enzymes CYP2C9 and CYP2C19 and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity. Monitoring of phenytoin serum levels is recommended when a drug interaction is suspected.

Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes.

7.1 Drugs that Affect Phenytoin Concentrations

Table 1 includes commonly occurring drug interactions that affect phenytoin concentrations. However, this list is not intended to be inclusive or comprehensive. Individual prescribing information from relevant drugs should be consulted.

The addition or withdrawal of these agents in patients on phenytoin therapy may require an adjustment of the phenytoin dose to achieve optimal clinical outcome.

Table 1: Drugs That Affect Phenytoin Concentrations

Interacting Agent	Examples
Drugs that may increase phenytoin serum levels	
Antiepileptic drugs	Ethosuximide, felbamate, oxcarbazepine, methsuximide, topiramate
Azoles	Fluconazole, ketoconazole, itraconazole, miconazole, voriconazole
Antineoplastic agents	Capecitabine, fluorouracil
Antidepressants	Fluoxetine, fluvoxamine, sertraline
Gastric acid reducing agents	H ₂ antagonists (cimetidine), omeprazole
Sulfonamides	Sulfamethizole, sulfaphenazole, sulfadiazine, sulfamethoxazole-trimethoprim
Other	Acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, disulfiram, estrogen, fluvastatin, isoniazid,

	methylphenidate, phenothiazines, salicylates, ticlopidine, tolbutamide, trazodone, warfarin
Drugs that may decrease phenytoin serum levels	
Antineoplastic agents usually in combination	Bleomycin, carboplatin, cisplatin, doxorubicin, methotrexate
Antiviral agents	Fosamprenavir, nelfinavir, ritonavir
Antiepileptic drugs	Carbamazepine, vigabatrin
Other	Chronic alcohol abuse, diazepam, diazoxide, folic acid, reserpine, rifampin, St. John's wort ^b , theophylline
Drugs that may either increase or decrease phenytoin serum levels	
Antiepileptic drugs	Phenobarbital, valproate sodium, valproic acid

^b The induction potency of St. John's wort may vary widely based on preparation.

7.2 Drugs Affected by Phenytoin

Table 2 includes commonly occurring drugs interactions affected by phenytoin. However, this list is not intended to be inclusive or comprehensive. Individual drug package inserts should be consulted. The addition or withdrawal of phenytoin during concomitant therapy with these agents may require adjustment of the dose of these agents to achieve optimal clinical outcome.

Table 2: Drugs Affected by Phenytoin

Interacting Agent	Examples
Drugs whose efficacy is impaired by phenytoin	
Azoles	Fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole
Antineoplastic agents	Irinotecan, paclitaxel, teniposide
Delavirdine	Phenytoin can substantially reduce the concentrations of delavirdine. This can lead to loss of virologic response and possible resistance [<i>see Contraindications (4)</i>].
Neuromuscular blocking agents	Cisatracurium, pancuronium, rocuronium and vecuronium: resistance to the neuromuscular blocking action of the nondepolarizing neuromuscular blocking agents has occurred in patients chronically administered phenytoin. Whether or not phenytoin has the same effect on other non-depolarizing agents is unknown. <i>Prevention or Management:</i> Patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected, and infusion rate requirements may be higher.
Warfarin	Increased and decreased PT/INR responses have been reported when phenytoin is coadministered with warfarin
Other	Corticosteroids, doxycycline, estrogens, furosemide, oral contraceptives, paroxetine, quinidine, rifampin, sertraline, theophylline, and vitamin D
Drugs whose level is decreased by phenytoin	
Antiepileptic drugs ^a	Carbamazepine, felbamate, lamotrigine, topiramate, oxcarbazepine
Antilipidemic agents	Atorvastatin, fluvastatin, simvastatin
Antiviral agents	Efavirenz, lopinavir/ritonavir, indinavir, nelfinavir, ritonavir, saquinavir Fosamprenavir: phenytoin when given with fosamprenavir alone

	may decrease the concentration of amprenavir, the active metabolite. Phenytoin when given with the combination of fosamprenavir and ritonavir may increase the concentration of amprenavir
Calcium channel blockers	Nifedipine, nimodipine, nisoldipine, verapamil
Other	Albendazole (decreases active metabolite), chlorpropamide, clozapine, cyclosporine, digoxin, folic acid, methadone, mexiletine, praziquantel, quetiapine

^aThe effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable

7.3 Drug-Enteral Feeding/Nutritional Preparations Interaction

Literature reports suggest that patients who have received enteral feeding preparations and/or related nutritional supplements have lower than expected phenytoin serum levels. It is therefore suggested that phenytoin not be administered concomitantly with an enteral feeding preparation. More frequent serum phenytoin level monitoring may be necessary in these patients.

7.4 Drug/Laboratory Test Interactions

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as DILANTIN, during pregnancy. Physicians are advised to recommend that pregnant patients taking Dilantin enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves.

Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>

Risk Summary

In humans, prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse development outcomes. An increased incidence of major malformations (such as orofacial clefts and cardiac defects) and abnormalities characteristic of fetal hydantoin syndrome (dysmorphic skull and facial features, nail and digit hypoplasia, growth abnormalities [including microcephaly], and cognitive deficits) has been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

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

In the U.S. general population, the estimated background risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The overall incidence of malformations for children of epileptic women treated with antiepileptic drugs (phenytoin and/or others) during pregnancy is about 10%, or two- to three-fold that in the general population.

Clinical Considerations

Disease-associated maternal risk

An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of serum phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage [see *Dosage and Administration* (2.1, 2.7)]. However, postpartum restoration of the original dosage will probably be indicated.

Fetal/Neonatal adverse reactions

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

Data

Animal data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

A loading dose of 15-20 mg/kg of DILANTIN intravenously will usually produce serum concentrations of phenytoin within the generally accepted serum total concentrations between 10 and 20 mcg/mL (unbound phenytoin concentrations of 1 to 2 mcg/mL). Because of the increased risk of adverse cardiovascular reactions associated with rapid administration DILANTIN should be injected slowly intravenously at a rate not exceeding 1-3 mg/kg/min or 50 mg per minute, whichever is slower [see *Dosage and Administration* (2.8) and *Warnings and Precautions* (5.1)].

8.5 Geriatric Use

Phenytoin clearance tends to decrease with increasing age [see *Clinical Pharmacology* (12.3)]. Lower or less frequent dosing may be required [see *Dosage and Administration* (2.6)].

8.6 Renal and/or Hepatic Impairment or Hypoalbuminemia

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

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

10 OVERDOSAGE

The lethal dose in pediatric patients 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, lethargy, slurred speech, blurred vision, nausea, and vomiting. The patient may become comatose and hypotensive. Death is caused by respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin serum levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL, dysarthria and lethargy appear when the serum concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery. Irreversible cerebellar dysfunction and atrophy have been reported.

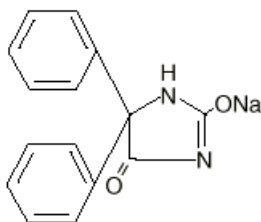
Treatment: Treatment is nonspecific since there is no known antidote.

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

11 DESCRIPTION

DILANTIN (phenytoin sodium) injection, USP is a sterile solution of 50 mg phenytoin sodium per milliliter for intravenous or intramuscular administration. The solution is in a vehicle containing 40% propylene glycol and 10% alcohol in water for injection, adjusted to pH 12 with sodium hydroxide. Phenytoin sodium is related to the barbiturates in chemical structure, but has a five-membered ring. The chemical name is sodium 5,5-diphenyl-2,4-imidazolidinedione represented by the following structural formula:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Absorption

A fall in serum levels may occur when patients are changed from oral to intramuscular administration. The drop is caused by slower absorption, as compared to oral administration, because of the poor water solubility of phenytoin. Intravenous administration is the preferred route for producing rapid therapeutic serum levels.

Patients stabilized on a daily oral regimen of DILANTIN experience a drop in peak blood levels to 50-60 percent of stable levels if crossed over to an equal dose administered intramuscularly. However, the intramuscular depot of poorly soluble material is eventually absorbed, as determined by urinary excretion of 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH), the principal metabolite, as well as the total amount of drug eventually appearing in the blood. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

A short-term (one week) study indicates that patients do not experience the expected drop in blood levels when crossed over to the intramuscular route if the DILANTIN IM dose is increased by 50 percent over the previously established oral dose. To avoid drug accumulation caused by absorption from the muscle depots, it is recommended that for the first week back on oral DILANTIN, the dose be reduced to half of the original oral dose (one-third of the IM dose). Experience for periods greater than one week is lacking and blood level monitoring is recommended.

Therapeutic effect without clinical signs of toxicity occurs most often with serum total concentrations between 10 and 20 mcg/mL (unbound phenytoin concentrations of 1 to 2 mcg/mL).

Distribution

Phenytoin is extensively bound to plasma proteins and is prone to competitive displacement.

Elimination

The serum half-life in man after intravenous administration ranges from 10 to 15 hours.

Metabolism

Phenytoin is metabolized by the cytochrome P450 enzymes CYP2C9 and CYP2C19.

Excretion

Most of the drug is excreted in the bile as inactive metabolites. Urinary excretion of phenytoin and its metabolites occurs partly by glomerular filtration but, more importantly, by tubular secretion.

Specific Populations

Age: Geriatric Population:

Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20-30 years of age). Since phenytoin clearance is decreased slightly in elderly patients, lower or less frequent dosing may be required [see *Dosage and Administration*, (2.6)].

Sex/Race:

Gender and race have no significant impact on phenytoin pharmacokinetics.

Renal or Hepatic Impairment:

Increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia has been reported.

Pregnancy:

It has been reported in the literature that the plasma clearance of phenytoin generally increased during pregnancy, reached a peak in the third trimester and returned to the level of pre-pregnancy after few weeks or months of delivery.

Drug Interaction Studies

Phenytoin is metabolized by the cytochrome P450 enzymes CYP2C9 and CYP2C19.

Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes [see *Drug Interactions* (7.1, 7.2)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis [see *Warnings and Precautions* (5.7)]

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

In carcinogenicity studies reported in the literature, phenytoin was administered in the diet for 2 years at doses up to 600 ppm (approximately 90 mg/kg/day) to mice and up to 2400 ppm (approximately 120 mg/kg/day) to rats. The incidences of hepatocellular tumors were increased in female mice at all but the lowest dose tested. No increases in tumor incidence were observed in rats.

Mutagenesis

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

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

Fertility

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DILANTIN Injection is a colorless to slightly yellow solution supplied as follows:

Package Configuration	Volume	Strength	NDC
Package of 10	2-mL per Steri-Dose [®] 4488 sterile disposable syringes (22 gauge x 1 ¼ inch needle)	Each 2-mL sterile disposable syringe contains 50 mg/mL phenytoin sodium	NDC 0071-4488-47
Package of 25	2-mL Steri-Vials [®]	Each 2-mL vial contains 50 mg/mL phenytoin sodium	NDC 0071-4488-45
Package of 25	5-mL Steri-Vials [®]	Each 5-mL vial contains 50 mg/mL phenytoin sodium	NDC 0071-4475-45

16.2 Storage and Handling

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

Store at controlled room temperature 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

Withdrawal of Antiepileptic Drugs

Advise patients not to discontinue use of DILANTIN without consulting with their healthcare provider. DILANTIN should normally be gradually withdrawn to reduce the potential for increased seizure frequency and status epilepticus [*see Warnings and Precautions (5.2)*].

Potential Signs of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Other Systemic Reactions

Advise patients of the early toxic signs and symptoms of potential hematologic, dermatologic, hypersensitivity, or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy, facial swelling, and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. Advise the patient that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, advise the patient that these signs and symptoms should be reported even if mild or when occurring after extended use [*see Warnings and Precautions (5.3, 5.4, 5.5, 5.6, 5.7)*].

Effects of Alcohol Use and Other Drugs and Over-the-Counter Drug Interactions

Caution patients against the use of other drugs or alcoholic beverages without first seeking their physician's advice [*see Warnings and Precautions (5.9) and Drug Interactions (7.1, 7.2)*].

Inform patients that certain over-the-counter medications (e.g., cimetidine and omeprazole), vitamins (e.g., folic acid), and herbal supplements (e.g., St. John's wort) can alter their phenytoin levels.

Hyperglycemia

Advise patients that DILANTIN may cause an increase in blood glucose levels [*see Warnings and Precautions (5.13)*].

Gingival Hyperplasia

Advise patients of the importance of good dental hygiene in order to minimize the development of gingival hyperplasia and its complications.

Neurologic Effects Counsel patients that DILANTIN may cause dizziness, gait disturbance, decreased coordination and somnolence. Advise patients taking DILANTIN not to drive, operate complex machinery, or engage in other hazardous activities until they have become accustomed to any such effects associated with DILANTIN.

Use in Pregnancy

Inform pregnant women and women of childbearing potential that use of DILANTIN during pregnancy can cause fetal harm, including an increased risk for cleft lip and/or cleft palate (oral clefts), cardiac defects, dysmorphic skull and facial features, nail and digit hypoplasia, growth abnormalities (including microcephaly), and cognitive deficits. When appropriate, counsel pregnant women and women of childbearing potential about alternative therapeutic options. Advise women of childbearing potential who are not planning a pregnancy to use effective contraception while using DILANTIN, keeping in mind that there is a potential for decreased hormonal contraceptive efficacy [*see Drug Interactions (7.2)*].

Instruct patients to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breastfeeding or intend to breastfeed during therapy [*see Use in Specific Populations (8.1, 8.2)*].

Encourage patients to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy [*see Use in Specific Populations (8.1)*].

Caution- Federal law prohibits dispensing without prescription.

Warning- Manufactured with CFC-12, a substance which harms public health and the environment by destroying ozone in the upper atmosphere.

Rx only



LAB-0383-12.4