MULTIPLE MEDICATION GUIDES ENCLOSED

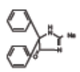
Dilantin®
(extended phenytoin sodium capsules USP)

Dilantin®

(extended phenytoin sodium capsules, USP)

DESCRIPTION

Phenytoin sodium is an antiepileptic drug. 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, having the following structural formula:



Each 30 mg Dilantin (*extended phenytoin sodium capsule, USP*) contains 30 mg phenytoin sodium, USP. Also contains lactose monohydrate, NF; confectioner's sugar, NF; talc, USP; and magnesium stearate, NF. The capsule shell cap and body components contain titanium dioxide (cap and body); gelatin (cap and body); D&C yellow No. 10 (cap); FD&C red No. 3 (cap). Product *in vivo* performance is characterized by a slow and extended rate of absorption with peak blood concentrations expected in 4 to 12 hours as contrasted to *Prompt Phenytoin Sodium Capsules, USP* with a rapid rate of absorption with peak blood concentration expected in 1½ to 3 hours.

Each 100 mg Dilantin (*100 mg extended phenytoin sodium capsule, USP*) contains 100 mg phenytoin sodium. Also contains lactose monohydrate, NF; confectioner's sugar, NF; talc, USP; and magnesium stearate, NF. The capsule body contains titanium dioxide, USP and gelatin, NF. The capsule cap contains FD&C red No. 28; FD&C yellow No. 6; and gelatin, NF. Product *in vivo* performance is characterized by a slow and extended rate of absorption with peak blood concentrations expected in 4 to 12 hours as contrasted to *Prompt Phenytoin Sodium Capsules, USP* with a rapid rate of absorption with peak blood concentration expected in 1½ to 3 hours.

CLINICAL PHARMACOLOGY

Mechanism of Action

Phenytoin is an antiepileptic drug which can be useful in the treatment of epilepsy. The primary site of action appears to be the *motor cortex* where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to *stabilize* the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at synapses. Loss of post-tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of tonic-clonic (grand mal) seizures.

Pharmacokinetics and Drug Metabolism

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

Optimum control without clinical signs of toxicity occurs more often with serum levels between 10 and 20 mcg/mL, although some mild cases of tonic-clonic (grand mal) epilepsy may be controlled with lower serum levels of phenytoin.

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 plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

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. Because phenytoin is hydroxylated in the liver by an enzyme system which is saturable at high plasma levels, small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

Special Populations

Patients with Renal or Hepatic Disease: Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution (see DOSAGE AND ADMINISTRATION). Unbound phenytoin concentrations may be more useful in these patient populations.

Age: 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). Phenytoin dosing requirements are highly variable and must be individualized (see DOSAGE AND ADMINISTRATION).

Gender and Race: Gender and race have no significant impact on phenytoin pharmacokinetics.

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

INDICATIONS AND USAGE

Dilantin is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY sections).

CONTRAINDICATIONS

Phenytoin is contraindicated in those patients with a history of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins.

Coadministration of Dilantin is contraindicated with delavirdine due to potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.

WARNINGS

Effects of Abrupt Withdrawal

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 antiepileptic medication arises, this should be done gradually. 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 antiepileptic drug not belonging to the hydantoin chemical class.

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.

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 **DRESS/Multiorgan hypersensitivity** below).

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.

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, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Dilantin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Hypersensitivity

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

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. 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.

Hematopoietic System

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.

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.

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.

Effects of Alcohol Use on Phenytoin Serum Levels

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

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.

Usage in Pregnancy

Clinical

Risks to Mother. An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage (see PRECAUTIONS, Laboratory Tests). However, postpartum restoration of the original dosage will probably be indicated.

Risks to the Fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential harm to the fetus.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), minor anomalies (dysmorphic facial features, nail and digit hypoplasia), growth abnormalities (including microcephaly), and mental deficiency have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have also been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. 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. However, the relative contributions of antiepileptic drugs and other factors associated with epilepsy to this increased risk are uncertain and in most cases it has not been possible to attribute specific developmental abnormalities to particular antiepileptic drugs.

Patients should consult with their physicians to weigh the risks and benefits of phenytoin during pregnancy.

Postpartum Period. 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.

Preclinical

Increased resorption and malformation rates have been reported following administration of phenytoin doses of 75 mg/kg or higher (approximately 120% of the maximum human loading dose or higher on a mg/m² basis) to pregnant rabbits.

PRECAUTIONS

General: 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.

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

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.

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

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended. (See WARNINGS section.)

Information for Patients

Inform patients of the availability of a Medication Guide, and instruct them to read the Medication Guide prior to taking Dilantin. Instruct patients to take Dilantin only as prescribed.

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

Patients should be made aware of the early toxic signs and symptoms of potential hematologic, dermatologic, hypersensitivity, or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy, and petechial or purpuric hemorrhage, and in the case of

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(Phenytoin sodium)
Chewable Tablets, Extended Oral Capsules

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

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

Stopping DILANTIN suddenly can cause serious problems.

DILANTIN can cause serious side effects including:

1. **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
   - attempts to commit suicide
   - new or worse depression
   - new or worse anxiety
   - feeling agitated or restless
   - panic attacks
   - trouble sleeping (insomnia)
   - new or worse irritability
   - acting aggressive, being angry, or violent
   - acting on dangerous impulses
   - an extreme increase in activity and talking (mania)
   - other unusual changes in behavior or mood

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.

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

Stopping DILANTIN suddenly can cause serious problems. Stopping a seizure medicine suddenly in a patient who has epilepsy can cause seizures that will not stop (status epilepticus).

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.

2. **Dilantin may harm your unborn baby.**
   - If you take DILANTIN during pregnancy, your baby is at risk for serious birth defects.
   - Birth defects may occur even in children born to women who are not taking any medicines and do not have other risk factors
   - 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 the decision is made to use DILANTIN, you should use effective birth control (contraception) unless you are planning to become pregnant.
   - Tell your healthcare provider right away if you become pregnant while taking DILANTIN. You and your healthcare provider should decide if you will take DILANTIN while you are pregnant.
   - **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.
3. **Swollen glands (lymph nodes)**
4. **Allergic reactions or serious problems which may affect organs and other parts of your body like the liver or blood cells.** You may or may not have a rash with these types of reactions. Symptoms can include any of the following:
   - swelling of your face, eyes, lips, or tongue
   - trouble swallowing or breathing
   - a skin rash
   - hives
   - fever, swollen glands (lymph nodes), or sore throat that do not go away or come and go
   - painful sores in the mouth or around your eyes
   - yellowing of your skin or eyes
   - bruising or bleeding
   - severe fatigue or weakness
   - severe muscle pain
   - frequent infections or an infection that does not go away
   - loss of appetite (anorexia)
   - nausea or vomiting

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

What is DILANTIN?

DILANTIN is a prescription medicine used to treat tonic-clonic (grand mal), complex partial (psychomotor or temporal lobe) seizures, and to prevent and treat seizures that happen during or after brain surgery.

Who should not take DILANTIN?

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).
- take delavirdine

What should I tell my healthcare provider before taking DILANTIN?

Before you take DILANTIN, tell your healthcare provider if you:
- Have or had liver disease
- Have or had porphyria
- Have or had diabetes
- Have or have had depression, mood problems, or suicidal thoughts or behavior
- Are pregnant or plan to become pregnant. 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.
- 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 or breastfeed. You should not do both.

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Pfizer PACKAGE DESIGN & DEVELOPMENT

PAR No.	Component Number	Description	
2013 0015184	PAA0422438	Dilantin	
Dimensions	Drawing No.	Country	Item
10" x 26"	DWG-101470-00 / DWG-101470-00	USA	USPI

Additional Info:

Colors: Black, Dieline

(b) (6)

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Taking DILANTIN with certain other medicines can cause side effects or affect how well they work. Do not start or stop other medicines without ta king 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 prescribed. Your healthcare provider wi l tell you how much DILANTIN to take.
- Your healthcare provider may change your dose. Do not change your dose of DILANTIN without talking to your healthcare provider.
- DILANTIN can cause overgrowth of your gums. Brushing and flossing your teeth and seeing a dentist regularly while taking DILANTIN can help prevent this.
- If you take too much DILANTIN, ca l your healthcare provider or local Poison Control Center right away.
- 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:

- Softening of your bones (osteopenia, osteoporosis, and osteomalacia). This can cause broken bones.

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

The most common side effects of DILANTIN include:

- problems w th walking and coordination
- slurred speech
- confusion
- dizziness
- trouble sleeping
- nervousness
- tremor
- headache
- nausea
- vomiting
- constipation
- rash

These are not all the possible side effects of DILANTIN. For more information, ask your healthcare provider or pharmacist.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

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 INFATABS at room temperature between 68°F to 77°F (20°C to 25°C). Protect from moisture.
- Store DILANTIN Capsules at room temperature between 68°F to 77°F (20°C to 25°C) in tight, light-resistant containers. Protect from moisture.

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

General information about 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.

This Medication Guide summarizes the most important information about DILANTIN. If you would like more information, talk with your healthcare provider. You can ask your hea thcare provider or pharmacist for information about DILANTIN that was written for healthcare professionals.

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

What are the ingredients in DILANTIN?

Tablet

Each tablet is a yellow triangular scored chewable tablet.

Active ingredient: 50 mg phenytoin

Inactive ingredients: D & C yellow No. 10, A1 lake, FD&C yellow No. 6, flavor, saccharin sodium, confectioner's sugar, talc, magnesium stearate, and purified water.

Extended Oral Capsule

Dilantin 30mg: Each capsule contains a white powder. The small pale pink opaque cap has "PD" imprinted in black ink and the white, opaque body has "Dilantin 30 mg" printed in black ink.

Active ingredient: 30 mg phenytoin sodium

Inactive ingredients: lactose monohydrate, confectioner's sugar, talc, and magnesium stearate. The capsule shell cap and body contain Titanium Dioxide (cap and body); gelatin (cap and body); D&C ye low No. 10 (cap); FD&C red No. 3 (cap).

Dilantin 100mg: Each capsule contains a white powder. The medium orange cap has "PD" imprinted in black ink and the white, opaque body has "DILANTIN" over "100 mg" printed in black ink.

Active ingredient: 100 mg phenytoin sodium

Inactive ingredients: lactose monohydrate, confectioner's sugar, talc, and magnesium stearate. The capsule body contains titanium dioxide and gelatin. The capsule cap contains FD&C red No. 28, FD&C ye low No. 6, and gelatin.

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

Dist ibuted by

Parke-Davis

Divis on of Pfizer Inc NY NY 10017

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Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

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 ist of them and show it to your hea thcare provider and pharmacist when you get a new medicine.

How should I take DILANTIN?

- Take DILANTIN exactly as prescribed. Your healthcare provider will tell you how much DILANTIN to take.
- Your healthcare provider may change your dose. Do not change your dose of DILANTIN without talking to your healthcare provider.
- DILANTIN can cause overgrowth of your gums. Brushing and flossing your teeth and seeing a dentist regularly while taking DILANTIN can help prevent this.
- If you take too much DILANTIN, call your healthcare provider or local Poison Control Center right away.
- 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 sk lls.

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:

- Softening of your bones (osteopenia, osteoporosis, and osteomalacia). This can cause broken bones.

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

The most common side effects of DILANTIN include:

- problems with walking and coordination
- slurred speech
- confusion
- dizziness
- trouble sleeping
- nervousness
- tremor
- headache
- nausea
- vomiting
- constipation
- rash

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Dilantin 100mg: Each capsule contains a white powder. The medium orange cap has "PD" imprinted in black ink and the white, opaque body has "DILANTIN" over "100 mg" printed in black ink.

Active ingredient: 100 mg phenytoin sodium

Inactive ingredients: lactose monohydrate, confectioner's sugar, talc, and magnesium stearate. The capsule body contains titanium dioxide and gelatin. The capsule cap contains FD&C red No. 28, FD&C yellow No. 6, and gelatin.

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(extended phenytoin sodium capsu es USP)

liver reactions anorexia nausea/vomit ng or aundice The patient shou d be adv sed hat because these signs and symptoms may signal a ser ous reaction hat they must eport any occurrence immed ately to a physic an In addition the patient shou d be advised that hese signs and symptoms shou d be eported even if mi d or when occurr ng a ter extended use

Pat ents should also be cautioned on the use of o her drugs or alcoholic beverages wi hout first seeking the physician's adv ce

The importance of good dental hygiene should be stressed in order to m n mize he development of g ng val hyperplasia and its compl cations

Pat ents their caregivers and fam l es shou d be counseled hat AEDs nclud ng Dilantin may increase he risk of su cidal thoughts and behav or and shou d be adv sed of the need to be alert for he eme gence or worsen ng of symptoms of depression any unusual changes n mood or behav or or the emergence of suic dal thoughts behav or or thoughts about self harm Behav o s of concern should be repo ted immed ately to heal hcare prov de s

Pat ents should be encouraged to enroll in the North Amer can Antiep leptic Drug (NAAED) Pregnancy Registry f they become pregnant Th s eg stry is co lect ng nformat on about he safety of antiepileptic drugs during pregnancy To en o l patients can ca l he toll f ee number 1 888 233 2334 (see PRECAUT ONS Pregnancy sect on)

Do not use capsules which are discolored

Labo ato y Tests Phenyto n serum level determ nations may be necessary to ach eve opt mal dosage adjustments Phenyto n doses are usually selected to attain therapeutic plasma total phenytoin concentrat ons of 10 to 20 mcg/mL (unbound phenyto n concentrat ons of 1 to 2 mcg/mL)

Drug Interactions Phenytoin s extens vely bound to se um plasma prote ns and is prone to competit ve d splacement Phenyto n s metabolized by hepat c cytoch ome P450 enzymes CYP2C9 and CYP2C19 and is particularly suscept ble to inhibito y drug nteract ons because it is sub ect to saturable metabol sm Inhibition of metabolism may p oduce significant nc eases n circulating phenyto n concentrat ons and enhance he isk of drug tox city Phenytoin s a potent nducer of hepatic drug metaboliz ng enzymes Serum level determ nations for phenyto n are especially helpful when possible drug nteractions are suspected

The most commonly occurr ng d ug interact ons a e l sted below

Note The list is not intended to be inclusive or comp ehensive Ind vidual drug package nse ts shou d be consu ted

Drugs that a fect phenytoin concentrations

Drugs that may increase phenyto n se um levels include acute alcohol intake amiodarone anti epilept c agents (ethosux mide fe bamate oxcarbazepine methsux mide topi amate) azoles (fluconazole ketoconazole it aconazole miconazole vo iconazole) capecitab ne chlo amphenicol chlord azepoxide d sulfiram estrogens fluorouracil fluoxet ne fluvastat n fluvoxamine H_2 antagonists (e g cimetidine) halo hane son az d methylphenidate omeprazole pheno h azines salicylates sertral ne succinim des sulfonam des (e g sulfame h zole su faphenazole sulfad az ne sulfamethoxazole trime hopr m) ticlop dine to butamide trazodone and warfar n

Drugs that may decrease phenytoin levels include anticancer drugs usua ly n comb nation (e g bleomycin carboplatin c splatin doxorub cin methotrexate) carbamazepine chron c alcohol abuse diazepam d azox de folic acid fosamp enavir ne finavir eserp ne r fampin itonavir St John's Wort sucralfate theophylline and v gabat in

Adm n strat on of phenytoin wi h prepa ations hat ncrease gast ic pH (e g supplements or antac ds contain ng calc um carbonate aluminum hyd ox de and magnesium hydroxide) may affect the absorpt on of phenyto n In most cases where interact ons were seen he e fect s a decrease in phenyto n levels when the drugs are taken at the same t me When poss ble phenytoin and these products should not be taken at he same t me of day

Drugs hat may ei her increase or decrease phenyto n serum levels include phenobarb tal sodium valproate and valproic acid S mila ly the e fect of phenyto n on phenobarb tal valpro c acid and sodium valproate serum levels s unp ed ctable

The addit on or wi hdrawal of hese agents in pat ents on phenyto n therapy may requ re an adjustment of the phenytoin dose to achieve opt mal clin cal outcome

Drugs affected by phenytoin

Drugs that should not be coadmin stered w th phenyto n Delavirdine (see CONTRAIND CATIONS)

Drugs whose e ficacy is mpaired by phenytoin nclude azoles (fluconazole ketoconazole traconazole vor conazole posaconazole) corticosteroids doxycycl ne estrogens fu osem de rinotecan oral contraceptives paclitaxel pa oxet ne quinid ne r fampin se tral ne ten pos de theophy l ne and vitam n D

Increased and decreased PT/ NR responses have been reported when phenyto n is coadm n stered w th warfar n

Phenytoin decreases plasma concentrations of act ve metabolites of a bendazole certain H V ant virals (efavirenz lop nav r/r tonav r nd nav r nelfinavir ritonav r saquinavi) anti epileptic agents (carbamazepine felbamate lamot igine topiramate oxcarba ep ne quetiap ne) atorvastat n chlorpropamide clozapine cyclospor ne d goxin fluvastat n folic acid methadone mex let ne n fedipine n modipine n so dipine p aziquantel simvastat n and ve apam l

Phenytoin when g ven wi h fosamp enavir alone may decrease the concentration of amp enav r he active metabolite Phenyto n when g ven with the combinat on of fosamp enavir and ritonav r may nc ease the concentration of amprenavir

Resistance to he neuromuscular block ng action of the non depolariz ng neuromuscular blocking agents pancuronium vecuronium rocuronium and cisatracur um has occurred n pat ents ch on ca ly adm nistered phenytoin Whether or not phenyto n has the same effect on other non depolar zing agents s unknown Patients shou d be mon tored closely for more rap d recovery from neu omuscular blockade han expected and nfusion rate requ rements may be higher

The add t on or w thdrawal of phenytoin dur ng concom tant therapy w th these agents may requ re adjustment of the dose of these agents to achieve opt mal cl n cal outcome

Drug Ente al Feeding/Nutritional P eparations Interact on Literatu e reports suggest hat patients who have received enteral feeding preparations and/or related nutr tional supplements have lower than expected phenytoin plasma levels It is therefore suggested hat phenyto n not be adm n stered concom tantly wi h an enteral feeding preparation More frequent serum phenyto n level mon tor ng may be necessary n these patients

Drug/Laboratory Test Inte act ons Phenytoin may decrease se um concentrat ons of T4 t may also produce lower han normal values for dexame hasone or metyrapone tests Phenyto n may cause ncreased serum levels of glucose a kal ne phosphatase and gamma glutamyl transpeptidase (GGT)

Care should be taken when using immunoanalytical methods to measure plasma phenytoin concent ations

Carcinogenesis See WARNINGS sect on for nfo mation on carcinogenes s

Pregnancy Pregnancy Category D See WARNINGS sect on

To prov de informat on rega d ng the effects of n utero exposu e to Dilantin physic ans a e adv sed to ecommend that pregnant patients tak ng Dilantin enroll in the NAAED

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Pregnancy Registry This can be done by ca l ng he toll free number 1 888 233 2334 and must be done by patients hemselves Info mation on the reg stry can also be found at the webs te http //www aedp egnancy eg stry org/

Nursing Mothers Infant breast feed ng is not recommended for women taking th s drug because phenyto n appears to be secreted in low concentrat ons n human mi k

Pediatr c Use See DOSAGE AND ADM N STRATION section

Geriat ic Use Phenyto n clearance tends to decrease with increasing age (see CLINICAL PHARMACOLOGY Special Populations)

ADVERSE REACTIONS

Body as a Whole Allerg c react ons n the form of rash and rarely more serious forms (see Sk n and Appendages paragraph below) and DRESS (see WARNINGS) have been observed Anaphylaxis has also been eported

There have also been reports of coarsening of facial features systemic lupus e y hematosus pe iarte it s nodosa and mmunoglobul n abnormalit es

Nervous System The most common adverse react ons encounte ed with phenyto n therapy a e nervous system react ons and are usua ly dose related React ons nclude nystagmus atax a slurred speech decreased coord nation somnolence and mental confusion D zziness vertigo insomnia transient nervousness motor twitch ngs paresthesias and headaches have also been observed There have also been rare reports of phenyto n nduced dyskinesias nclud ng chorea dystonia tremor and asterix s s milar to hose nduced by phenoth az ne and other neu oleptic drugs

A predom nan ly sensory peripheral polyneuropathy has been observed n pat ents rece ving long term phenytoin therapy

Digestive System Acute hepat c fa lure toxic hepat tis liver damage nausea vom ting const pation enlargement of the lips and g ng val hyperplasia

Skin and Appendages Dermatolog cal man festat ons sometimes accompan ed by fever have ncluded scarlatin form or mo b lliform rashes A morbi liform rash (measles like) is he most common other types of dermatit s are seen more rarely Other more se ious forms which may be fatal have ncluded bullous exfol at ve or purpu ic de matitis Stevens Johnson syndrome and tox c epidermal necrolys s (see WARNINGS section) There have also been reports of hype tr chosis

Hematologic and Lymphatic System Hematopoietic complicat ons some fatal have occasionally been eported in assoc ation wi h admin strat on of phenytoin These have included thrombocytopenia leukopenia granulocytopen a agranulocytos s and pancytopen a with or wi hout bone marrow suppress on While macrocytosis and megaloblastic anemia have occurred these conditions usually respond to fol c ac d therapy Lymphadenopa hy including benign lymph node hyperplas a pseudolymphoma lymphoma and Hodgk n's d sease have been reported (see WARNINGS sect on)

Special Senses A tered taste sensation including meta l c taste

Urogen tal Peyronie's disease

OVERDOSAGE

The lethal dose n ped atric patients s not known The lethal dose n adu ts s estimated to be 2 to 5 grams The n t al symptoms are nystagmus atax a and dysa thria O her s gns are tremor hype reflex a lethargy slur ed speech nausea vomiting The patient may become comatose and hypotensive Death is due to respiratory and circulato y depression

There are marked variat ons among nd viduals w th respect to phenytoin plasma levels where toxic ty may occur Nystagmus on lateral gaze usua ly appears at 20 mcg/mL ataxia at 30 mcg/mL dysarthria and lethargy appear when the plasma concent ation s over 40 mcg/mL but as h gh a concentrat on as 50 mcg/mL has been reported w thout ev dence of toxic ty As much as 25 times he therapeut c dose has been taken to result in a serum concentrat on over 100 mcg/mL wi h complete recovery

T eatment Treatment is nonspec fic since there s no known antidote

The adequacy of he resp ratory and circulatory systems shou d be carefu ly observed and approp iate suppo tive measures employed Hemodialys s can be cons dered s nce phenytoin s not completely bound to plasma prote ns Total exchange transfusion has been used in the treatment of severe ntoxicat on n ped atr c patients

In acute overdosage the possibility of other CNS depressants including alcohol shou d be borne n mind

DOSAGE AND ADMIN STRATION

Serum concentrat ons should be monitored in chang ng from D lant n (extended phenytoin sod um capsules USP) to Prompt Phenyto n Sodium Capsules USP and from he sodium sa t to the free acid fo m

Dilantin (extended phenytoin sodium capsules USP) are formulated wi h the sod um sa t of phenytoin The free acid fo m of phenyto n is used n D lantin 125 Suspens on and Dilantin Infatabs Because there s app ox mately an 8% ncrease in drug content wi h the free acid form over hat of the sodium sa t dosage adjustments and se um level mon toring may be necessary when switch ng from a product formulated w th the f ee ac d to a p oduct formulated with he sod um salt and v ce versa

General Dosage shou d be indiv dualized to prov de max mum benefit In some cases se um blood level dete minations may be necessary for opt mal dosage adjustments the clinically e fect ve serum level is usua ly 10 20 mcg/mL W th ecommended dosage a period of seven to ten days may be requ red to ach eve steady state blood levels w th phenytoin and changes n dosage (increase or decrease) should not be ca ried out at inte vals sho ter han seven to ten days

Adult Dosage

Div ded daily dosage Pat ents who have rece ved no previous treatment may be started on one 100 mg Dilantin (extended phenyto n sod um capsule USP) h ee t mes da ly and the dosage then adjusted to suit indiv dual equ rements For most adu ts the satisfacto y maintenance dosage wi l be one capsule three to four times a day An increase up to two capsules three t mes a day may be made f necessary

Once a day dosage In adults if seizure control s established w th divided doses of three 100 mg Dilant n (extended phenyto n sodium capsules USP) daily once a day dosage w th 300 mg of D lant n (extended phenyto n sodium capsules USP) may be considered Stud es comparing div ded doses of 300 mg wi h a s ngle daily dose of this quantity indicated absorption peak plasma levels biologic ha f life difference between peak and minimum values and ur na y recovery were equ valent Once a day dosage o fers a convenience to the nd v dual pat ent or to nursing personnel for inst tutional zed patients and s intended to be used only for patients requ ring h s amount of d ug da ly A ma or problem in motivat ng noncompliant pat ents may also be lessened when he patient can take this d ug once a day However patients should be caut oned not to m ss a dose inadvertently

Only D lantin (extended phenytoin sodium capsules USP) are recommended for once a day dosing Inherent d ffe ences n d ssolution character stics and resultant absorpt on rates of phenytoin due to di ferent manufacturing procedures and/or dosage forms preclude such recommendat on for o her phenytoin products When a change n he dosage fo m or brand is presc ibed careful monitor ng of phenyto n serum levels should be carr ed out

Loading dose Some authorities have advocated use of an oral loading dose of phenytoin n adu ts who equi e rapid steady state serum levels and whe e int avenous adm n stration is not desirable Th s dos ng reg men should be reserved for pat ents in a cl nic or hospital sett ng whe e phenytoin serum levels can be closely monitored Pat ents wi h a h story of renal or l ver d sease shou d not rece ve he oral load ng reg men

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(ex ended pheny o n sod um capsules USP)

Init ally one gram of Dilantin (extended phenyto n sodium capsules USP) is divided nto three doses (400 mg 300 mg 300 mg) and adm n stered at two hour ntervals Normal maintenance dosage s then inst tuted 24 hours after the loading dose wi h frequent se um level determinat ons

Dosing in Spec al Populations

Pat ents wi h Renal or Hepatic D sease Due to an increased fraction of unbound phenytoin n patients with enal or hepatic d sease or in hose with hypoalbuminemia the nterp etat on of total phenytoin plasma concentrat ons should be made w th caut on Unbound phenyto n concentrat ons may be more useful in hese pat ent populations

Elderly Pat ents Phenyto n clearance is decreased sl gh ly n elderly patients and lower or less frequent dos ng may be requ red

Pediatric Initially 5 mg kg day n two or three equa ly d vided doses wi h subsequent dosage nd v dualized to a max mum of 300 mg daily A ecommended daily maintenance dosage is usually 4 to 8 mg kg Ch ldren over 6 years o d and adolescents may equi e the m n mum adu t dose (300 mg/day)

HOW SUPPLIED

30 mg D lant n (*extended phenytoin sodium capsule* USP)

A s ze 4 hemispherical Coni Snap capsule w th a white opaque body and pale p nk opaque cap conta n ng a white powder Capsule is mprinted with black ectified radial p int "PD" on cap and "Dilant n 30 mg" on body

100's (NDC 0071 3740 66)

100 mg Dilantin *100 mg (extended phenytoin sodium capsule USP)*

Hard fi led No 3 capsules conta ning a wh te powder The med um o ange cap having "PD" pr nted in black ink and he white opaque body having "DILANT N" over "100 mg" p inted n black ink

100's (NDC 0071 0369 24)

1 000's (NDC 0071 0369 32)

Unit Dose 100's (NDC 0071 0369 40)

Sto e at 20 25°C (68 77°F) [See USP Controlled Room Temperature] Preserve n tight light resistant conta ners P otect from mo sture

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