

PRODUCT MONOGRAPH

APO-PHENYTOIN SODIUM

Extended Phenytoin Sodium Capsules

Apotex Standard

100 mg

Anticonvulsant

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Extended capsules 100 mg	Colloidal silicon dioxide, hydroxypropyl methylcellulose, and magnesium stearate. Capsule shells: D&C Red No. 28, D&C Yellow No. 10, FD&C Red No. 40, gelatin, and titanium dioxide. Pharmaceutical ink: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, iron oxide black, propylene glycol, and shellac.

INDICATIONS AND CLINICAL USE

APO-PHENYTOIN SODIUM (extended phenytoin sodium) capsules are indicated for the control of generalized tonic-clonic and psychomotor (grand mal and temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

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

CONTRAINDICATIONS

APO-PHENYTOIN SODIUM capsules are contraindicated to patients who are hypersensitive to phenytoin, to other hydantoin, or to any of the nonmedicinal ingredients in the formulations (see **WARNINGS AND PRECAUTIONS, Hypersensitivity**).

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

WARNINGS AND PRECAUTIONS

General

APO-PHENYTOIN SODIUM capsules should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative anticonvulsant medication arises, this should be done gradually. However, in the event of an allergic hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an anticonvulsant drug which does not belong to the hydantoin chemical class.

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

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

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

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

In patients with renal or hepatic impairment or in those with hypoalbuminemia, there is increased plasma levels of unbound phenytoin. In patients with hyperbilirubinemia, plasma levels of unbound phenytoin may also be elevated. Since unbound phenytoin concentrations may be more useful in these patient populations, it may affect dosing considerations (see **DOSAGE AND ADMINISTRATION, Renal or Hepatic Disease**).

Skin

Serious Dermatological Reactions

Hypersensitivity Syndrome / Drug Reaction with Eosinophilia and Systemic Symptoms

Hypersensitivity Syndrome (HSS) or Drug rash with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking anticonvulsant drugs, including phenytoin. Some of these events have been fatal or life threatening.

HSS/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, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leukocytosis, and eosinophilia. The interval between first drug exposure and symptoms is usually 2 to 4 weeks but has been reported in individuals receiving anticonvulsants for 3 or more months. If such signs and symptoms occur, the patient should be evaluated immediately. Phenytoin should be discontinued if an alternative aetiology for the signs and symptoms cannot be established.

Patients at higher risk for developing HSS/DRESS include black patients, patients who have experienced HSS/DRESS in the past (with phenytoin or other anticonvulsant drugs), those with a family history of HSS/DRESS, and immune-suppressed patients. The syndrome is more severe in previously sensitized individuals.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Serious and sometimes fatal dermatologic reactions, including Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), have been reported with phenytoin. Although serious skin reactions may occur without warning, patients should be alert for the occurrence of rash and other symptoms of DRESS (see **WARNINGS AND PRECAUTIONS, Skin**). In countries with mainly Caucasian populations, these reactions are estimated to occur in 1 to 6 per 10,000 new users, but in some Asian countries (e.g., Taiwan, Malaysia and the Philippines) the risk is estimated to be much higher (see **WARNINGS AND PRECAUTIONS, Skin - Asian Ancestry and Allelic Variation in the HLA-B Genotyping**).

Literature reports suggest that the combination of phenytoin, cranial irradiation and the gradual reduction of corticosteroids may be associated with the development of erythema multiforme, and/or SJS, and/or TEN. In any of the above instances, caution should be exercised if using structurally similar compounds (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Treatment recommendations for dermatological reactions

Phenytoin should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus or SJS or TEN is suspected, use of this drug should not be resumed and alternative therapy should be considered (see **ADVERSE REACTIONS**). If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated. The use of other anti-epileptic drugs associated with SJS/TEN should be avoided in patients who have shown severe dermatological reactions during phenytoin treatment. If a rash occurs and SJS or TEN is not suspected, the patient should be evaluated for signs and symptoms of DRESS (see **WARNINGS AND PRECAUTIONS, Skin**).

Asian Ancestry and Allelic Variation in the HLA-B Genotyping

HLA-B*1502

In studies that included small samples of patients of Asian ancestry a strong association was found between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. The HLA-B*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia¹. Results of these studies suggest that the presence of the HLA-B *1502 allele may be one of the risk factors for phenytoin-associated SJS/TEN in patients with Asian ancestry.

Therefore, physicians should consider HLA-B *1502 genotyping as a screening tool in these patients. Until further information is available, the use of phenytoin and other anti-epileptic drugs associated with SJS/TEN should also be avoided in patients who test positive for the HLA-B*1502 allele.

Important Limitations of HLA-B Genotyping

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

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

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

Hepatic/Biliary/Pancreatic

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents have been associated with a hypersensitivity syndrome characterized by fever, skin eruptions, and lymphadenopathy, and usually occur within the first 2 months of treatment. Other common manifestations include arthralgias, rash, jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, phenytoin should be immediately discontinued and not

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

re-administered.

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 (see **OVERDOSAGE**).

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

Immune

Hypersensitivity

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity (see **CONTRAINDICATIONS**). If there is a history of hypersensitivity reactions to structurally similar drugs, such as carboxamides (e.g., carbamazepine), barbiturates, succinimides, and oxazolidinediones (e.g., trimethadione) in these patients or immediate family members, other alternatives should be considered.

Hematologic

Hematopoietic

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

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling DRESS (see **WARNINGS AND PRECAUTIONS, Skin**). In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative anticonvulsant drugs.

While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. If folic acid is added to phenytoin therapy, a decrease in seizure control may occur.

Carcinogenesis and Mutagenesis

(See **WARNINGS AND PRECAUTIONS, Hematopoietic; WARNINGS AND PRECAUTIONS, Special Populations – Pregnant Women**)

Endocrine and Metabolism

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.

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.

Musculoskeletal

Chronic use of phenytoin by patients with epilepsy has been associated with decreased bone mineral density (osteopenia, osteoporosis, osteomalacia) and bone fractures (see **ADVERSE REACTIONS, Adverse Drug Reaction Overview**).

Phenytoin and other anticonvulsants that have been shown to induce the CYP450 enzyme are thought to affect bone mineral metabolism indirectly by increasing the metabolism of Vitamin D3. This may lead to Vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcemia, and hypophosphatemia in chronically treated epileptic patients. Consideration should be given to monitoring with bone-related laboratory and radiological tests and initiating treatment plans, as appropriate.

Neurologic

Central Nervous System

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium", "psychosis" or "encephalopathy", or rarely irreversible cerebellar dysfunction and/or cerebellar atrophy. Accordingly, at the first sign of acute toxicity, serum drug level determinations are recommended. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination of phenytoin therapy is recommended (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics-Absorption**; **WARNINGS AND PRECAUTIONS, General**).

Driving/Operating Machinery

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

Psychiatric

Suicidal ideation and behaviour

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

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

There were 43,892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for

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

Special Populations

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

Pregnant Women

Risks to mother: An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics-Absorption**). However, postpartum restoration of the original dosage will probably be indicated.

Risks to fetus: APO-PHENYTOIN SODIUM should be used during pregnancy only if the potential benefit outweighs the potential risks. 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 from exposure to phenytoin.

A number of reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Literature reports suggest that phenytoin can cross placental barrier and, if administered during pregnancy, may have an effect on the fetus. In addition to the reports of increased incidence of congenital malformations, such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other anticonvulsant drugs, there have also been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione.

However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes. There have also been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

Postpartum Period: Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and the neonate after birth.

Nursing Women: Infant breast feeding is not recommended for women taking phenytoin. Phenytoin is secreted into human milk. Limited observations in patients suggest that phenytoin concentration in breast milk is approximately one-third of the corresponding maternal plasma concentration.

Geriatrics (> 65 years of age): Phenytoin clearance is decreased slightly in elderly patients (see **DOSAGE AND ADMINISTRATION, Geriatrics**).

Monitoring and Laboratory Tests

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

Information for Patients and Caregivers

Patients and caregivers should be advised to read the Consumer Information sheet for APO-PHENYTOIN SODIUM prior to use. Patients receiving APO-PHENYTOIN SODIUM, and caregivers, should be given the following instructions by the physician and pharmacist:

1. Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing their physician of any clinical condition in which it is not possible to take the drug orally as prescribed, eg, surgery, etc.
2. Patients should be advised of the early toxic signs and symptoms of potential hematologic, dermatologic, hypersensitivity, or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, the patient should be advised that these signs and symptoms should be reported even if mild or when occurring after extended use. Patients should be advised that a history of hypersensitivity reactions with other antiepileptic drugs may be a risk for developing reactions with phenytoin (see **WARNINGS AND PRECAUTIONS, Hematologic; Immune; Skin; Hepatic/Biliary/Pancreatic**).
3. Patients should be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice (see **DRUG INTERACTIONS**).

4. Patients should be instructed to call their physician if skin rash develops.
5. The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.
6. Patients, their caregivers, and families should be counseled that antiepileptic drugs, including APO-PHENYTOIN SODIUM, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers (see **WARNINGS AND PRECAUTIONS, Psychiatric**).
7. Women of child-bearing potential should be warned to consult their physician regarding the discontinuation of the drug due to the potential hazards to themselves and to the fetus if they are pregnant or intend to become pregnant (see **WARNINGS AND PRECAUTIONS, Special Populations – Women of child-bearing potential, Pregnant Women, Nursing Women**).
8. Patients who become pregnant should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients themselves must call the toll free number 1-888-233-2334. Registry information can also be obtained from the Internet at <http://www.aedpregnancyregistry.org/> (see **WARNINGS AND PRECAUTIONS, Special Populations – Pregnant Women**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The following listing of adverse events is based on adverse events reported in clinical trials and/or spontaneous adverse event reports from post-marketing experience. A frequency cannot be estimated from the available data and is therefore classified as ‘not known’.

Body as a whole: Anaphylactic reaction and anaphylaxis

Central Nervous System: The most common manifestations encountered with extended phenytoin sodium capsules therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion. 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, Neurologic**). Dizziness, vertigo, insomnia, transient nervousness, motor twittings, headaches, paresthesia and somnolence have also been observed.

There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

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

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, and Peyronie's Disease.

Gastrointestinal System: Acute hepatic failure, toxic hepatitis, liver damage, vomiting, nausea, constipation. (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

Hematopoietic System: Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy, including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease has been reported (see **WARNINGS AND PRECAUTIONS, Hematologic**).

Immunologic: Drug rash with eosinophilia and systemic symptoms (DRESS) (which may include, but is not limited to symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, periarteritis nodosa, and immunoglobulin abnormalities. Several individual case reports have suggested that there may be an increased, although still rare, incidence of hypersensitivity reactions, including skin rash and hepatotoxicity, in black patients (see **WARNINGS AND PRECAUTIONS, Skin**).

Musculoskeletal System: Bone fractures and osteomalacia have been associated with chronic use of phenytoin by patients with epilepsy. Osteoporosis and other disorders of bone metabolism such as hypocalcemia, hypophosphatemia and decreased levels of Vitamin D metabolites have also been reported (see **WARNINGS AND PRECAUTIONS, Musculoskeletal**).

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

Special Senses: Taste perversion

DRUG INTERACTIONS

Drug-Drug Interactions

Phenytoin is extensively bound to serum plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome (CYP) 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.

Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes and may reduce the levels of drugs metabolized by these enzymes.

There are many drugs which may increase or decrease phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected.

The most commonly occurring drug interactions are listed below.

1. **Table 1** summarizes the drug classes which may potentially increase phenytoin serum levels:

Table 1. Drugs Which May Increase Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as)
Alcohol (acute intake)	
Analgesic/anti-inflammatory agents	azapropazone phenylbutazone salicylates
Anesthetics	halothane
Antibacterial agents	chloramphenicol erythromycin isoniazid sulfadiazine sulfamethizole sulfamethoxazole-trimethoprim sulfaphenazole sulfisoxazole sulfonamides
Anticonvulsants	felbamate oxcarbazepine sodium valproate succinimides (e.g. ethosuximide) valproate sodium topiramate ^a
Antifungal agents	amphotericin B fluconazole itraconazole ketoconazole miconazole voriconazole
Antineoplastic agents	capecitabine

Drug Classes	Drugs in each Class (such as)
	fluorouracil
Benzodiazepines/psychotropic agents	chlordiazepoxide diazepam disulfiram methylphenidate trazodone phenothiazine viloxazine
Calcium channel blockers/ Cardiovascular agents	amiodarone dicumarol diltiazem nifedipine ticlopidine
H ₂ -antagonists	cimetidine
HMG-CoA reductase inhibitors	fluvastatin
Hormones	estrogens
Immunosuppressant drugs	tacrolimus
Oral hypoglycemic agents	tolbutamide
Proton pump inhibitors	omeprazole
Serotonin re-uptake inhibitors	fluoxetine fluvoxamine sertraline

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

2. **Table 2** summarizes drugs which may decrease phenytoin serum levels.

Table 2. Drugs Which May Decrease Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as)
Alcohol (chronic intake)	
Antibacterial agents/Fluoroquinolones	ciprofloxacin rifampin
Anticonvulsants	carbamazepine vigabatrin ^b
Antineoplastic agent	bleomycin carboplatin cisplatin doxorubicin methotrexate
Antiretrovirals	fosamprenavir nelfinavir ritonavir
Antiulcer agents	sucralfate

Drug Classes	Drugs in each Class (such as)
Bronchodilators	theophylline
Calcium preparation	molindone hydrochloride
Cardiovascular agents	reserpine
Folic Acid	folic acid
Hyperglycemic agents	diazoxide
Protease Inhibitors	nelfinavir
St. John's Wort	St. John's Wort

^bCoadministration with vigabatrin reduces serum phenytoin levels by 20 to 30%. This may be clinically significant in some patients and may require dosage adjustment.

Molindone hydrochloride

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

Calcium Preparations

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

Nelfinavir

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

3. **Table 3** summarizes drugs which may either increase or decrease phenytoin serum levels.

Table 3. Drugs Which May Either Decrease or Increase Phenytoin Serum Levels

Drug Classes	Drugs in each class (such as)
Antibacterial agents	ciprofloxacin
Anticonvulsants	carbamazepine phenobarbital sodium valproate valproic acid
Antineoplastic agents	
Psychotropic agents	chlordiazepoxide diazepam phenothiazines

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

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

Table 4. Drugs Whose Blood Serum Levels and/or Effects May be Altered by Phenytoin

Drug Classes	Drugs in each Class (such as)
Antibacterial agents	doxycycline rifampin tetracycline
Anticonvulsants	carbamazepine lamotrigine ^a phenobarbital sodium valproate topiramate ^b valproic acid
Antifungal agents	azoles posaconazole voriconazole
Anthelmintics	albendazole praziquantel
Antineoplastic agents	teniposide
Antiretrovirals	delavirdine efavirenz fosamprenavir indinavir lopinavir/ritonavir nelfinavir ritonavir saquinavir
Bronchodilators	theophylline
Calcium channel blockers / Cardiovascular agents	digitoxin digoxin mexiletine nicardipine nimodipine nisoldipine quinidine verapamil
Corticosteroids	
Coumarin anticoagulants	warfarin
Cyclosporine	
Diuretics	furosemide

HMG-CoA reductase inhibitors	atorvastatin fluvastatin simvastatin
Hormones	estrogens oral contraceptives
Hyperglycemic agents	diazoxide
Immunosuppressant	cyclosporine
Neuromuscular blocking agents	alcuronium cisatracurium pancuronium rocuronium vecuronium
Opioid analgesics	methadone
Oral hypoglycemic agents	chlorpropamide glyburide tolbutamide
Psychotropic agents/Antidepressants	clozapine paroxetine quetiapine sertraline
Vitamins	vitamin D

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

Drug-Food Interactions

Literature reports suggest that patients who have received enteral feeding preparations and/or related nutritional supplements have lower than expected phenytoin plasma levels. It is therefore suggested that phenytoin not be administered concomitantly with an enteral feeding preparation.

More frequent serum phenytoin level monitoring may be necessary in these patients.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

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

Drug-Lifestyle Interactions

Interactions with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

APO-PHENYTOIN SODIUM capsules are formulated with the sodium salt of phenytoin.

Recommended Dose and Dosage Adjustment

General

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

Adults

Patients who have received no previous treatment may be started on one 100 mg extended phenytoin sodium capsule three times daily, and the dose then adjusted to suit individual requirements. For most adults, the satisfactory maintenance dosage will be three to four capsules (300 to 400 mg) daily. An increase to six capsules daily may be made, if necessary.

Pediatrics (< 18 years of age)

APO-PHENYTOIN SODIUM is not available in any pediatric dosage forms i.e. a 30 mg capsule strength, a 50 mg chewable tablet, or an oral suspension of 30 mg in each 5 mL.

Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years old may require the minimum adult dose (300 mg/day). Given that APO-PHENYTOIN SODIUM is available only as a 100 mg capsule, the child must weigh at least 40 kg in order to initiate therapy with this product.

Geriatrics (> 65 years of age)

Phenytoin clearance is decreased slightly in elderly patients. Lower doses than the doses recommended for adults may be required when initiating treatment. Phenytoin dosing requirements are highly variable and must be individualized (see ACTION AND CLINICAL PHARMACOLOGY – Special Populations – Geriatrics).

Renal or Hepatic Disease

In patients with renal or hepatic impairment or in those with hypoalbuminemia, plasma levels of unbound phenytoin are elevated. Unbound phenytoin concentrations may be more useful in these patient populations. This finding should be considered during therapeutic monitoring and following phenytoin serum level determinations, which may be necessary for optimal dosage adjustment (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment; (see WARNINGS AND PRECAUTIONS – General).

Alternative Dose

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

Missed Dose

The patient/caregiver should be advised that if a dose is missed, the missed dose should be taken as soon it is remembered. If it is almost time for the next dose the missed dose should not be taken. Instead, take the next scheduled dose. The patient/caregiver should be advised to not make up for a missed dose by taking a double dose next time.

OVERDOSAGE

The lethal dose of APO-PHENYTOIN SODIUM in pediatric patients is not known. The lethal dose of phenytoin in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, somnolence, drowsiness, lethargy, slurred speech, blurred vision, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus on lateral gaze, usually appears at 80 $\mu\text{mol/L}$ (20 mcg/mL), ataxia at 119 $\mu\text{mol/L}$ (30 mcg/mL). Dysarthria and lethargy appear when the serum concentration is > 159 $\mu\text{mol/L}$ (40 mcg/mL), but a concentration as high as 198 $\mu\text{mol/L}$ (50 mcg/mL) has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over >396 $\mu\text{mol/L}$ (100 mcg/mL) with complete recovery. Irreversible cerebellar dysfunction and atrophy have been reported.

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

Treatment and Management

Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in pediatric patients.

In acute overdosage the possibility of the presence of other CNS depressants, including alcohol, should be kept in mind.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacokinetics

Absorption: Phenytoin is a weak acid and has limited hydrosolubility, even in the intestine. The compound undergoes a slow and somewhat variable absorption after oral administration.

Steady-state therapeutic levels are achieved at least 7 to 10 days after initiation of therapy with recommended doses of 300 mg/day. In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, congenital enzyme deficiency or drug interactions which result in metabolic interference. The patient with large variations in phenytoin serum levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

When serum level determinations are necessary, they should be obtained at least 7 to 10 days after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that equilibrium or steady-state will have been achieved. Trough levels obtained just prior to the patient's next scheduled dose provide information about clinically effective serum level range and confirm patient compliance. Peak drug levels, obtained at the time of expected peak concentration, indicate an individual's threshold for emergence of dose-related side effects. For extended phenytoin sodium capsules, peak serum levels occur 4 to 12 hours after administration.

Distribution: Phenytoin is distributed into cerebrospinal fluid, saliva, semen, gastrointestinal fluids, bile, and breast milk. The concentration of phenytoin in cerebrospinal fluid approximates the level of free phenytoin in plasma.

Metabolism: Phenytoin is biotransformed in the liver by oxidative metabolism. The major pathway involves 4-hydroxylation, which accounts for 80% of all metabolites. Experiments in

human liver microsomes have demonstrated that CYP2C9 plays the major role in the metabolism of phenytoin (90% of net intrinsic clearance), while CYP2C19 has a minor involvement in this process (10% of the net intrinsic clearance). In experiments with human liver microsomes, the relative contribution of CYP2C19 to phenytoin metabolism increased with increasing phenytoin concentrations, above the concentrations considered to be in the therapeutic range (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment**).

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

In a human liver microsome study, phenylbutazone (a CYP2C9 inhibitor) decreased clearance of phenytoin (see **DRUG INTERACTIONS**).

Excretion: Most of the drug is eliminated in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine partly with glomerular filtration but more importantly by tubular secretion. Less than 5% of phenytoin is excreted as the parent compound. Because phenytoin is hydroxylated in the liver by a cytochrome system which is saturable at high serum levels, small incremental doses may increase the half-life and produce very substantial increases in serum levels when these are in or above the upper therapeutic range. The steady state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

Special Populations

Geriatrics (>65 years of 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, Geriatrics**).

STORAGE AND STABILITY

APO-PHENYTOIN SODIUM Capsules: Store at controlled room temperature 15°C-30°C. Protect from light and moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-PHENYTOIN SODIUM Capsules: Extended phenytoin sodium capsule is available in dosage strength of 100 mg capsule.

100 mg: Hard gelatin capsule with white opaque body and orange opaque cap. Imprinted “APO P100” in black ink. Filled with white to off-white, round biconvex tablets. Available in bottles of 100 and 1000 capsules.

Capsule Composition

Each capsule contains 100 mg phenytoin sodium. The capsule also contains the following non-

medicinal ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, and magnesium stearate.

Capsule Shell: D&C Red No. 28, D&C Yellow No. 10, FD&C Red No. 40, gelatin, and titanium dioxide.

Pharmaceutical ink: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, iron oxide black, propylene glycol, and shellac.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

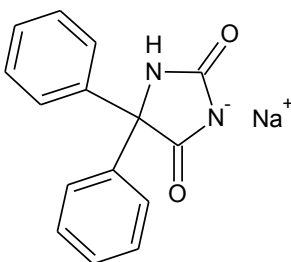
Drug Substance

Proper name: phenytoin sodium

Chemical name: 5,5-Diphenylhydantoin sodium salt

Molecular formula and molecular weight: $C_{15}H_{11}N_2NaO_2$; 274.25 g/mol

Structural formula:



Physicochemical properties: phenytoin sodium is a white powder. It is known to be freely soluble in water; soluble in alcohol; practically insoluble in ether and in chloroform.

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, double-blinded, single dose, standard 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy adult male volunteers. The results obtained from 31 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of phenytoin was measured and compared following a single oral dose (3 x 100 mg capsule) of APO-PHENYTOIN SODIUM (phenytoin sodium) 100 mg capsule (Apotex Inc.) and Dilantin[®] (phenytoin sodium) 100 mg capsule (Warner Lambert Company LLC, Pfizer Canada Inc.).

Phenytoin (3 x 100 mg) From Measured Data				
Geometric Mean [#] Arithmetic Mean (CV %)				
Parameter	Test*	Reference [†]	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC _t (ng•h/mL)	165822.75 170329.9 (22)	160715.94 165519.8 (25)	103.2	96.6 – 110.2
AUC _{inf} (ng•h/mL)	180451.10 187167.3 (27)	175797.84 182909.0 (29)	102.6	96.0-109.8
C _{max} (ng/mL)	4691.19 4769.7 (19)	4306.37 4384.7 (19)	108.9	103.3 – 114.9
T _{max} [§] (h)	5.29 (109)	7.78 (100)		
T _{half} [§] (h)	17.32 (25)	17.53 (26)		

*Apo-Phenytoin Sodium (phenytoin sodium) 100 mg capsules (Apotex Inc.).

[†]Dilantin[®] (phenytoin sodium) 100 mg capsules (Warner Lambert Company LLC, Pfizer Canada Inc.) were purchased in Canada.

[#]For balanced treatment sequence, results are based on Geometric means. For unbalanced treatment sequence, results are based on Least Squares Means (LSM).

[§] Expressed as the arithmetic mean (CV %) only

A randomized, double-blinded, single dose, standard 2-way crossover comparative bioavailability study, conducted under fed conditions, was performed on healthy adult male volunteers. The results obtained from 36 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of phenytoin was measured and compared following a single oral dose (3 x 100 mg capsule) of APO-PHENYTOIN SODIUM (phenytoin sodium) 100 mg capsule (Apotex Inc.) and Dilantin[®] (phenytoin sodium) 100 mg capsule (Warner Lambert Company LLC, Pfizer Canada Inc.).

Phenytoin (3 x 100 mg) From Measured Data Geometric Mean [#] Arithmetic Mean (CV %)				
Parameter	Test*	Reference [†]	- Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC _t (ng•h/mL)	190402.49 197949.0 (29)	203351.83 210883.3 (28)	93.6	90.4 – 97.0
AUC _{inf} (ng•h/mL)	213244.99 227473.5 (39)	229814.91 246218.9 (42)	92.8	89.2 – 96.5
C _{max} (ng/mL)	5910.16 6038.9 (22)	6175.03 6322.1 (21)	95.7	92.1 – 99.4
T _{max} [§] (h)	9.34 (41)	10.11 (40)		
T _{half} [§] (h)	19.26 (43)	19.88 (45)		

*Apo-Phenytoin Sodium (phenytoin sodium) 100 mg capsules (Apotex Inc.).

[†]Dilantin[®] (phenytoin sodium) 100 mg capsules (Warner Lambert Company LLC, Pfizer Canada Inc.) were purchased in Canada.

[#]For balanced treatment sequence, results are based on Geometric means. For unbalanced treatment sequence, results are based on Least Squares Means (LSM).

[§] Expressed as the arithmetic mean (CV %) only

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PART III: CONSUMER INFORMATION

** APO-PHENYTOIN SODIUM**
Extended Phenytoin Sodium Capsules
Apotex Standard
100 mg

This leaflet is part III of a three-part "Product Monograph" published when APO-PHENYTOIN SODIUM was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-PHENYTOIN SODIUM.

Please read this information carefully before you start to take your medicine, even if you have taken this drug before. Do not throw away this leaflet until you have finished your medicine as you may need to read it again. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

APO-PHENYTOIN SODIUM has been prescribed to you by our doctor to control seizures. It is specifically used for:

- the control of generalized tonic-clonic seizures, and psychomotor seizures
- the prevention and treatment of seizures that may begin during or after surgery to the brain or nervous system.

What it does:

APO-PHENYTOIN SODIUM Capsules belong to the family of medicines called anticonvulsant. It acts in the brain to block the spread of seizure activity.

When it should not be used:

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

What the medicinal ingredient is:

Phenytoin sodium.

What the nonmedicinal ingredients are:

The non-medicinal ingredients are: colloidal silicon dioxide, hydroxypropyl methylcellulose, and magnesium stearate.

Capsule shells: D&C Red No. 28, D&C Yellow No. 10, FD&C Red No. 40, gelatin, and titanium dioxide.

Pharmaceutical ink: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, iron oxide black, propylene glycol, and shellac.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:

Extended Phenytoin Sodium Capsules (100 mg).

WARNINGS AND PRECAUTIONS

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

BEFORE you use APO-PHENYTOIN SODIUM talk to your doctor or pharmacist if:

- You/your child are diabetic,
- You/your child are anemic.
- You/your child have low bone density,
- You/your child have or have had any kidney or liver disease, or blood disorders (including porphyria),
- You/your child have had an allergy to this drug, or other drugs used to treat your condition,
- You are pregnant or thinking about becoming pregnant. If you take APO-PHENYTOIN SODIUM during pregnancy your baby is at risk for serious birth defects, such as cleft lip or cleft palate. Birth defects may happen even in children born to women who are not taking any medicines and do not have any other risk factors. All women of child-bearing age who are being treated for epilepsy should talk to their healthcare providers about using other possible treatments instead of APO-PHENYTOIN SODIUM. If the decision is made to use APO-PHENYTOIN SODIUM, you should use effective birth control (contraception) unless you are planning to become pregnant. You should talk to your doctor about the best kind of birth control to use while you are taking APO-PHENYTOIN SODIUM.
- You are breast-feeding.
- You/your child are taking other drugs (prescription and over-the-counter medicines), dietary or herbal supplements.
- You consume alcohol on a regular or occasional basis.
- Certain individuals of Asian and/or of black origin may be at an increased risk of developing serious skin reactions during treatment with APO-PHENYTOIN SODIUM.
- You/your child have experienced in the past or have a family history of anticonvulsant hypersensitivity syndrome. This may occur rarely in patients treated with anticonvulsant medications and includes symptoms such as fever, rash, hepatitis (such as yellowing of skin and eyes) and lymph node swelling, among other symptoms.
- You/your child are currently being treated with cranial irradiation and corticosteroids.
- You/your child suffer from absence seizures (petit mal) or seizures caused by low blood sugar (hypoglycemia) or other metabolic causes, as APO-PHENYTOIN SODIUM is not effective in controlling these types of seizures.

IMPORTANT: PLEASE READ

- You/your child have or have had depression, mood problems, or suicidal thoughts or behavior.

When taking APO-PHENYTOIN SODIUM:

- Always take APO-PHENYTOIN SODIUM as your doctor has prescribed. If it is not possible for you to take APO-PHENYTOIN SODIUM as prescribed, tell your doctor.
- Tell your doctor if you develop a skin rash while taking APO-PHENYTOIN SODIUM.
- Tell your doctor right away if you develop serious skin reactions such as rash, red skin, blistering of the lips, eyes or mouth, skin peeling that may be accompanied by fever. These reactions may be more frequent in patients of Asian origin. Reports of these reactions have been highest in patients from Taiwan, Malaysia and the Philippines.
- Tell your doctor if you become pregnant while taking APO-PHENYTOIN SODIUM. You and your doctor should decide if you will continue to take APO-PHENYTOIN SODIUM while you are pregnant. If you become pregnant while taking APO-PHENYTOIN SODIUM, talk to your doctor 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 medicines during pregnancy. Information about the registry can also be found at the website: <http://www.aedpregnancyregistry.org/>.
- Talk to your doctor about the best way to care for your teeth, gums, and mouth during your treatment with APO-PHENYTOIN SODIUM. It is very important that you care for your mouth properly to decrease the risk of gum damage.
- It is recommended that you **do not** drink alcohol while taking APO-PHENYTOIN SODIUM, without first talking to your doctor. Drinking alcohol while taking APO-PHENYTOIN SODIUM may change your blood levels of APO-PHENYTOIN SODIUM, which can cause serious problems.
- Do not drive, operate heavy machinery or do other dangerous activities until you know how APO-PHENYTOIN SODIUM affects you. APO-PHENYTOIN SODIUM can slow your thinking and motor skills.

INTERACTIONS WITH THIS MEDICATION

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

PROPER USE OF THIS MEDICATION

It is very important that you take APO-PHENYTOIN SODIUM exactly as your doctor has prescribed. Never increase or decrease the dose yourself. Do not stop taking it abruptly unless directed by your doctor as your seizures may increase. Tell your doctor if you cannot take the drug as prescribed, for example if

you will be having surgery. You should always check that you have an adequate supply of APO-PHENYTOIN SODIUM.

Do not use capsules that are discoloured.

Usual dose:

Adult:

Starting dose: One capsule (100 mg) three times daily. The dose is adjusted according to your response to treatment. In some cases, blood level assessment may be necessary to adjust the dose optimally.

Maintenance dose: Usually, 3 to 4 capsules (300 to 400 mg) in divided doses daily. Some adult patients can be maintained on 300 mg once-a-day (3 capsules of 100 mg, taken together once-a-day).

Pediatrics (< 18 years of age):

APO-PHENYTOIN SODIUM is not available in any pediatric dosage forms i.e. a 30 mg capsule strength, a 50 mg chewable tablet, or an oral suspension of 30 mg in each 5 mL.

Starting dose: Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. Given that APO-PHENYTOIN SODIUM is available only as a 100 mg capsule, the child must weigh at least 40 kg in order to initiate therapy with this product. In some cases, blood level assessment may be necessary to adjust the dose optimally.

Maintenance : A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years old may require the minimum adult dose (300 mg/day).

Overdose:

Very high doses can cause toxicity or death.

If you think you have taken too much APO-PHENYTOIN SODIUM, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, APO-PHENYTOIN SODIUM can cause side effects, although not everybody gets them.

IMPORTANT: PLEASE READ

Serious side effects and what to do about them

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Uncommon	Severe skin reactions (rashes, eruptions, skin blistering)			√
	Skin rash and fever with swollen glands, particularly in the first two months of therapy			√
	Sudden wheeziness, difficulty breathing, swelling of eyelids, face or lips, rash or itching			√
	Bruising, fever, looking pale or severe sore throat		√	
	Seizures or fits		√	√
	Suicide, self injury, confusion or disorientation		√	
	Gum disorders (red or bleeding gums)		√	
	Liver failure or disorders (jaundice, yellowing of skin and eyes)		√	√
Unknown	Softening of the bones (bone pain, broken bones)		√	

Other Side Effects:

If you experience any side effects such as unusual eye movement, changes in muscle movements or co-ordination, slurred speech, dizziness, vertigo, trouble sleeping (insomnia), changes to facial skin, rash, headache, nausea or vomiting, consult your doctor.

This is not a complete list of side effects. For any unexpected effects, or effects that worry you while taking APO-PHENYTOIN SODIUM, contact your doctor or pharmacist.

HOW TO STORE IT

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

Keep out of reach and sight of children.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada,
Postal Locator 1908C
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service at:

1-800-667-4708

This leaflet can also be found at:
<http://www.apotex.ca/products>

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