Phenytoin
ANTICONVULSANTS, HYDANTOIN (Systemic)

Introduction

Revised: 05/01/00

This monograph includes information on the following:1) Ethotoin b; 2) Fosphenytoin; 3) Mephenytoin b; 4) Phenytoin .

BAN:

Mephenytoin¾Methoin

VA CLASSIFICATION (Primary)
Ethotoin¾CN400
Fosphenytoin¾CN400
Mephenytoin¾CN400
Phenytoin¾CN400/ CV300; MS200

Commonly used brand name(s):Cerebyx2; Dilantin4; Dilantin Infatabs4; Dilantin Kapseals4; Dilantin-1254; Dilantin-304; Mesantoin3; Peganone1; Phenytex4.

Another commonly used name for phenytoin is diphenylhydantoin .

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

b Not commercially available in Canada.

Category

Anticonvulsant¾Ethotoin b; Fosphenytoin b; Mephenytoin b; Phenytoin.

Antiarrhythmic¾Phenytoin.

Antineuralgic (trigeminal neuralgia)¾Phenytoin 13, 14, 15, 16.

Skeletal muscle relaxant¾Phenytoin 35, 36, 37.

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Epilepsy (treatment)¾Hydantoin anticonvulsants are indicated in the suppression and control of tonic-clonic (grand mal) and simple or complex partial (psychomotor or temporal lobe) seizures 94, 95, 96, 97, 98, 99, 104, 105, 106.

Ethotoin may be administered as a second-line agent when seizures have not been adequately controlled by the primary anticonvulsants and before proceeding to more toxic anticonvulsants. 72

Mephenytoin also is used in the treatment of simple partial (focal and Jacksonian) seizures in patients who have not responded to less toxic anticonvulsants 105, 106.

Status epilepticus (treatment)¾Parenteral fosphenytoin and phenytoin are both indicated for the control of tonic-clonic type status epilepticus 71, 100, 101, 102, 103, 180, 235.

Although parenteral benzodiazepines are often used initially for rapid control of status epilepticus, both fosphenytoin and phenytoin are indicated for sustained control of seizure activity 61, 180, 235.

Seizures in neurosurgery (prophylaxis and treatment)¾Fosphenytoin and phenytoin are both indicated for the prevention and treatment of seizures during and following neurosurgery 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 180, 235.

[Arrhythmias, digitalis-induced (treatment)] * 46, 181¾Phenytoin 72 is used in the correction of atrial and ventricular arrhythmias, especially those caused by digitalis glycoside toxicity 196.

[Choreoathetosis, paroxysmal (treatment)] *¾Phenytoin may be effective in treating paroxysmal choreoathetosis, especially the kinesigenic type. This condition, which is considered a form of reflex epilepsy, is characterized by tonic, dystonic, or choreoathetoid contortions of the extremities, trunk, or face, which are usually precipitated by the patient"s initiation of sudden voluntary movement 35, 36, 37.

[Neuralgia, trigeminal (treatment)] * 2¾Phenytoin is used alone or with other anticonvulsants to control paroxysmal pain in some patients with trigeminal neuralgia (tic douloureux) 13, 14, 15, 16.

Carbamazepine is considered the first-line agent 13, 16 , effectively relieving pain in about 66% of patients 15.

However, since phenytoin relieves pain during long-term use in approximately 20% of patients 15 , it may be used alone in some patients or added to carbamazepine therapy when symptoms persist 15.

[Neuromyotonia (treatment)] * 38, 39

[Myotonia congenita (treatment)] * 38 or

[Myotonic muscular dystrophy (treatment)] * 38¾Phenytoin is effective in some patients as a muscle relaxant in the treatment of muscle hyperirritability, characterized by delayed relaxation of muscle after voluntary or mechanically induced contraction and by a state of continuous muscle contraction at rest 38.

Neuromyotonia includes continuous muscle fiber activity syndrome, Isaac"s syndrome, and "stiff man"" syndrome.

[Toxicity, tricyclic antidepressant (treatment adjunct)] *¾Intravenous phenytoin loading has been used to treat quinidine-like conduction defects, bradyarrhythmias, or heart block, in tricyclic antidepressant overdose 42, 50, 69.

Although its use has been supplanted by other agents 225 , in some instances it remains a therapeutic option 200, 221, 222, 223.

Unaccepted

Hydantoin anticonvulsants are not indicated in the treatment of absence (petit mal) seizures 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 180 , or as first-line treatment of febrile 74 , hypoglycemic 180 , or other metabolic 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 180 seizures. When tonic-clonic (grand mal) seizures coexist with absence seizures, combined therapy may be 72 necessary 94, 95, 96, 97, 98, 99, 100, 101, 102, 103.

Although phenytoin has been used in patients with recessive dystrophic epidermolysis bullosa 1, 157 for the treatment of blistering and erosions of the skin that may result from even minor trauma or injury, it is no longer considered preferred therapy 171, 172.

* Not included in Canadian product labeling.

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾Ethotoin: 204.23 182

Fosphenytoin sodium: 406.24 182

Mephenytoin: 218.26 182

Phenytoin: 252.27 182

Phenytoin sodium: 274.26 182

pKa¾Phenytoin: 8.06 to 8.33 108

pH¾Fosphenytoin sodium injection: 8.6 to 9 180.

Phenytoin sodium injection: 12 184, 192.

Note: Fosphenytoin is a water-soluble 10, 12, 180, 186, 187, 192 prodrug 6, 45, 48, 71, 119, 123, 180, 183, 184, 189 that is rapidly converted to phenytoin following parenteral administration 10, 45, 48, 181, 184, 189, 192.

Mechanism of action/Effect:

Anticonvulsant¾The mechanism of action is not completely known, but is thought to involve stabilization of 104 neuronal membranes at the cell body, axon, and synapse and limitation of the spread of neuronal or seizure activity 104, 108, 123.

In neurons, phenytoin decreases sodium and calcium ion influx by prolonging voltage-dependent 221 channel inactivation time during generation of nerve impulses 104, 108.

Phenytoin blocks the voltage-dependent sodium channels of neurons 123, 214 and inhibits the calcium flux across neuronal membranes 123, 180 , thus helping to stabilize neurons 123.

It also decreases synaptic transmission 123, 214 , and decreases post-tetanic potentiation at the synapse 2, 123, 214.

Phenytoin enhances the sodium-potassium ATPase activity of neurons and/or glial cells 214.

It also influences second messenger systems by inhibiting calcium-calmodulin protein phosphorylation 123, 214 and possibly altering cyclic nucleotide production or metabolism 123.

Antiarrhythmic¾Phenytoin may act to normalize influx of sodium and calcium to cardiac Purkinje fibers. Abnormal ventricular automaticity and membrane responsiveness are decreased. Also, phenytoin shortens the refractory period, and therefore shortens the QT interval and the duration of the action potential 46.

Antineuralgic¾Exact mechanism is unknown. Phenytoin may act in the central nervous system (CNS) to decrease synaptic transmission or to decrease summation of temporal stimulation leading to neuronal discharge (antikindling). Phenytoin raises the threshold of facial pain and shortens the duration of attacks by diminishing self-maintenance of excitation and repetitive firing 2, 14.

Skeletal muscle relaxant¾Phenytoin's mechanism of action as a muscle relaxant is thought to be similar to its anticonvulsant action 2.

In movement disorders, the membrane-stabilizing effect reduces abnormal sustained repetitive firing and potentiation of nerve and muscle cells 49.

Other actions/effects:

Therapy with phenytoin significantly increases the amounts and activities of some CYP P450 isoenzymes, the uridine diphosphate glucuronosyltransferase (UDPGT) system, and epoxide hydrolase enzymes, thus enhancing the metabolism of many other drugs 193.

Also, phenytoin may compete with drugs metabolized by the same CYP isoenzymes (CYP2C9 and CYP2C19), thus decreasing the metabolic clearance of those agents 193.

Absorption:

Ethotoin¾ Rapid 104.

Fosphenytoin¾ Intravenous: Immediate.
Intramuscular: Rapid and complete 189.

Note:
Bioavailability from either the intravenous or intramuscular route is essentially 100% 10, 48, 71, 89, 181, 184, 187, 188, 192.

Mephenytoin¾ Rapid.

Phenytoin¾ Oral: Slow and variable among products 120 ; poor in neonates 30.

Intravenous: Immediate.
Intramuscular: Very slow 101, 102, 103 , but complete (92%) 2.

Distribution:

Fosphenytoin¾Most likely distributed in humans to heart, kidneys, small intestine, liver, lungs, and spleen, where it is hydrolyzed by phosphatases to phenytoin 181.

Predominately distributed in the central (plasma) compartment 12, 184.

The volume of distribution (Vol D) ranges from 4.3 to 10.8 liters 180 , and increases with increasing dose and administration rate of fosphenytoin 180.

Phenytoin¾Distributed into cerebrospinal fluid, saliva, semen, gastrointestinal fluids, bile, and breast milk 120 ; also crosses the placenta, with fetal serum concentrations equal to those of the mother 120.

Protein binding:

Fosphenytoin¾Very high (95 to 99%) 6, 180, 184 ; degree of binding is saturable, with the result that the percent bound decreases as the total plasma fosphenytoin concentration increases 180, 189.

Phenytoin¾Very high (90% or more) 2, 14, 108, 120 ; may be lower in neonates (84%) and in hyperbilirubinemic infants (80%) 58 ; also altered in patients with hypoalbuminemia (< 37 mg per dL) 2, 116 , uremia 2, 108, 116, 120 , or acute trauma 116 , and in pregnant patients 116, 120.

Note: Fosphenytoin has a high affinity for phenytoin protein binding sites 6, 10, 180, 183, 184, 189 ; before its conversion to phenytoin, it binds to these sites, retarding the binding of newly formed phenytoin, thus increasing free (unbound) phenytoin concentrations 10, 183, 184, 189.

In the absence of fosphenytoin, approximately 12% of total plasma phenytoin exists in the free (unbound) state over the clinically relevant concentration range 180, 189.

With the administration of fosphenytoin, total free (unbound) phenytoin plasma concentrations may increase up to 30% during the period required for the conversion of fosphenytoin to phenytoin (approximately 30 to 60 minutes postinfusion) 180, 184, 189.

In patients with renal or hepatic function impairment or hypoalbuminemia, fosphenytoin conversion to phenytoin may be increased without a similar increase in the clearance of phenytoin, potentially leading to an increased incidence of adverse effects 180.

Biotransformation:

Hepatic 94, 95, 96, 97, 98, 99, 101, 102, 103, 104, 105, 106 via microsomal oxidative enzymes of the P450 system, specifically the CYP2 family of isozymes 123 ; rate increased in younger children, in pregnant women, in women during menses 25 , and in patients with acute trauma; rate decreases with advancing age 29.

Mephenytoin has an active metabolite, nirvanol (5-ethyl-5-phenylhydantoin) 120, 154.

The metabolism of mephenytoin is genetically determined 123.

Patients who are slow metabolizers of mephenytoin are at risk of increased adverse effects; Oriental and black populations are more likely than white populations to be slow metabolizers of mephenytoin 123.

The major inactive metabolite of phenytoin is 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH) 41, 101, 108.

Phenytoin also may be metabolized slowly in a small number of individuals due to genetic predisposition 102, 103, 120, 180 , which may cause limited enzyme availability and lack of induction 102, 103, 180.

Fosphenytoin undergoes rapid hydrolysis to phenytoin 123, 180, 123.

In vivo , 1.5 mg of fosphenytoin sodium injection liberates 1 mg of phenytoin sodium 123 ; thus, 75 mg of fosphenytoin sodium is essentially equivalent to 50 mg of phenytoin sodium 181.

Conversion of fosphenytoin also yields two additional metabolites, phosphate and formaldehyde 45, 180, 181.

Formaldehyde is subsequently converted to formate 180, 181 , which in turn is metabolized via a folate-dependent mechanism 180.

Biological effects from the production of phosphate and formaldehyde generally occur only at doses exceeding usual clinical doses of fosphenytoin 180.

Phosphatase enzymes probably play a major role in the conversion of fosphenytoin to phenytoin 45, 47, 48, 123, 180, 189 .

Half-life:

Ethotoin¾3 to 9 hours 104.

Fosphenytoin¾The conversion half-life to phenytoin ranges from 8 to 15 minutes 10, 12, 45, 119, 180, 181, 184, 186, 189, 192.

This value is independent of dose 189 , infusion rate 189 , or plasma concentrations of either fosphenytoin or phenytoin 184.

The elimination half-life of fosphenytoin after intravenous or intramuscular injection also is independent of dose 48.

Mephenytoin¾About 7 hours, but for active metabolite, nirvanol, about 95 to 144 hours 2, 154.

Phenytoin¾Because phenytoin exhibits saturable 11, 120, 123 , zero-order 224 , or dose-dependent 11, 120, 123, 125 pharmacokinetics, the apparent half-life of phenytoin changes with dose and serum concentration 120, 122, 125.

This is due to the saturation of the enzyme system responsible for metabolizing phenytoin, which occurs at therapeutic concentrations of the drug 120, 122, 123, 124.

Thus, a constant amount of drug is metabolized 122 (capacity-limited metabolism 126), and small increases in dose may cause disproportionately large increases in serum concentrations 11, 123, 126 and apparent half-life 123, 124 , possibly causing unexpected toxicity 123, 124, 126.

Time to peak concentration:

Fosphenytoin¾ Intravenous: 6 minutes (average) after administration 45, 48, 71, 119, 186.

Intramuscular: 36 minutes (average) after administration 45, 48, 71, 119 ; one dose administered in more than one injection resulted in an increase in time to peak concentration 45, 119.

Mephenytoin¾ 45 minutes to 4 hours.
Nirvanol: 16 to 36 hours 2, 154.

Phenytoin (tablets or oral suspension)¾ 11/2 to 3 hours 95, 96.

Phenytoin sodium¾ Extended capsules: 4 to l2 hours 94, 98, 99, 108.

Prompt capsules: 11/2 to 3 hours 98, 99, 108.

Therapeutic serum concentration

Ethotoin¾ l5 to 50 mcg per mL (74 to 245 micromoles per L) 104.

Mephenytoin¾ 25 to 40 mcg per mL (115 to 183 micromoles per L) (in combination with nirvanol) 120.

Phenytoin¾ l0 to 20 mcg per mL (40 to 80 micromoles per L) 85, 94, 95, 96, 97, 98, 99, 100, 101, 102, 108, 180.

Steady-state serum concentration is usually achieved in 5 75 to 10 days with daily oral dosage of 300 mg 94, 95, 96, 97, 98, 99.

Serum concentrations of 20 to 40 mcg per mL (80 to 159 micromoles per L) usually produce symptoms of toxicity; > 40 mcg per mL (159 micromoles per L) usually produce severe toxicity 94, 95, 96, 97, 108.

The serum concentrations of phenytoin needed for efficacy may be influenced by seizure type. Higher concentrations (23 mcg per mL [91 micromoles per L] or greater 75, 119) may be needed to control simple or complex partial seizures, with or without tonic-clonic seizures, or status epilepticus 84, 119 than are necessary for control of tonic-clonic seizures alone (10 to 20 mcg per mL [40 to 80 micromoles per L]) 22.

Occasionally, a patient may have seizure control with serum phenytoin concentrations of 6 to 9 mcg per mL (24 to 36 micromoles per L) 84, 85.

Effective treatment, therefore, should be guided by clinical response, not drug serum concentrations 84.

In patients who have hypoalbuminemia and/or renal failure 115 , or who are taking other medications that displace phenytoin from binding sites 161 , hydantoin serum concentrations of 5 to 10 mcg per mL (20 to 40 micromoles per L) may be adequate 115.

For cardiac arrhythmias, plasma concentrations of 10 to 18 mcg per mL (40 to 71 micromoles per L) have been reported to be effective 73.

Therapeutic concentrations of free (unbound) phenytoin, which are frequently monitored in patients with altered protein binding (e.g., in neonates and in patients with renal failure, hypoalbuminemia, or acute trauma) 116, 142 , usually fall in the range of 0.8 to 2 mcg per mL 143, 144, 180 (3 to 8 micromoles per L).

Note:
The pharmacokinetic parameters of phenytoin derived from fosphenytoin administered by intravenous or intramuscular injection do not differ from those values for trough concentrations or area under the plasma concentration-time curve (AUC) of orally administered equivalent doses of phenytoin 119.

Elimination:

Ethotoin, mephenytoin, and phenytoin¾Primarily renal as metabolites 94, 95, 96, 97, 98, 99, 108, 120 ; also in feces 120.

Very little phenytoin is excreted in the feces; most is excreted in the bile as metabolites that are reabsorbed in the intestine and excreted in the urine 48.

Phenytoin excretion is enhanced by alkaline urine 120.

Fosphenytoin¾Not excreted in urine 10, 180, 181, 184, 189.

Phenytoin derived from fosphenytoin is excreted in the urine, primarily as metabolites 180 ; little unchanged phenytoin (about 1 to 5% of the fosphenytoin dose) is recovered in the urine 180.

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to one hydantoin anticonvulsant may be sensitive to other hydantoin anticonvulsants also 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 105, 106, 180.

In addition, cross-sensitivity to structurally similar compounds, such as barbiturates, succinimides, and oxazolidinediones, may occur 180.

Tumorigenicity

Phenytoin: There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy 94, 95, 96, 97, 98, 99, 100, 101, 102, 180.

Mutagenicity

Fosphenytoin: Structural chromosome aberration frequency in cultured V79 Chinese hamster lung cells was increased by exposure to fosphenytoin in the presence of metabolic activation 180.

No evidence of mutagenicity of fosphenytoin was observed in bacteria (Ames test) or Chinese hamster lung cells in vitro180.

No evidence of clastogenic activity of fosphenytoin was observed in the in vivo mouse bone marrow micronucleus test 180.

Pregnancy/Reproduction

Pregnancy¾Hydantoin anticonvulsants cross the placenta 120 ; risk-benefit must be considered, although a definite cause and effect relationship has not been established between the hydantoins and teratogenic effects 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104.

Reports in recent years indicate a higher incidence of congenital abnormalities in children whose mothers used anticonvulsant medication during pregnancy, although most epileptic mothers have delivered normal infants 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105.

Reported abnormalities include cleft lip, cleft palate, heart malformations, and the "fetal hydantoin syndrome" (also known as the "fetal anticonvulsant syndrome" and characterized by prenatal growth deficiency, microcephaly, craniofacial abnormalities, hypoplasia of the fingernails, and mental deficiency associated with intrauterine development during therapy) 94, 95, 96, 97, 98, 99, 100, 101, 102.

Medication has not been definitively proven to be the cause of "fetal hydantoin syndrome" 94, 95, 96, 97, 98, 99, 100, 101, 102.

The reports, to date, relate primarily to the more widely used anticonvulsants, phenytoin and phenobarbital 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105.

Pending availability of more precise information, this risk-benefit consideration of anticonvulsant use during pregnancy is extended to the entire family of anticonvulsant medications.

Ethotoin, phenytoin¾FDA Pregnancy Category C 103, 104.

Fosphenytoin¾FDA Pregnancy Category D 180.

Mephenytoin¾FDA pregnancy category not included in product labeling.

Because of altered absorption and protein binding 26, 118 and/or increased metabolic clearance 51, 57 of hydantoin anticonvulsants during pregnancy, pregnant women receiving these medications may experience an increased incidence of seizures 94, 95, 96, 97, 98, 99, 100, 101, 102.

Serum hydantoin concentrations must be monitored and doses increased accordingly 94, 95, 96, 97, 98, 99, 100, 101, 102.

A gradual resumption of the patient's usual dosage may be necessary after delivery 94, 95, 96, 97, 98, 99, 100, 101, 102.

However, some patients may experience a rapid reduction in maternal hepatic phenytoin metabolism at time of delivery, requiring the dosage to be reduced within 12 hours postpartum 24.
Delivery¾Exposure to hydantoins prior to delivery may lead to an increased risk of life-threatening hemorrhage (related to decreased concentrations of vitamin K-dependent clotting factors 123) in the neonate, usually within 24 hours of birth 94, 95, 96, 97, 98, 99, 100, 101, 102, 104, 120.

Hydantoins may also produce a deficiency of vitamin K in the mother, causing increased maternal bleeding during delivery. Risk of maternal and infant bleeding may be reduced by administering vitamin K to the mother during delivery and to the neonate, intramuscularly or subcutaneously, immediately after birth 94, 95, 96, 97, 98, 99, 100, 101, 102, 104, 120, 151.

Breast-feeding

Ethotoin 104 and phenytoin 94, 95, 96, 97, 98, 99, 100, 101, 102 are distributed into breast milk; significant amounts may be ingested by the infant. Information is not available for mephenytoin.

Pediatrics

Children and young adults are more susceptible to gingival hyperplasia than older adults 81, 151.

See Dental section.

Some reports suggest that children may experience decreased school performance during long-term treatment with hydantoin anticonvulsants, especially at high therapeutic or toxic concentrations 2, 52, 151.

Coarsening of facial features 81 and excessive body hair growth 151 may be more pronounced in young patients.

Other anticonvulsants less likely to cause problems should be considered first 74, 81.

Fosphenytoin: Limited pharmacokinetic data in children older than 5 years of age suggest that the conversion of fosphenytoin to phenytoin occurs in a manner similar to that in adults 180, 185.

However, the safety of fosphenytoin in children has not been established 180.

Geriatrics

Geriatric patients tend to metabolize hydantoins slowly, thereby increasing the possibility of the medication reaching toxic serum concentrations 94, 95, 96, 97, 98, 99, 100, 101, 102, 103.

Also, serum albumin may be low in older patients, causing a decrease 61 in protein binding of phenytoin 2, 26.

Lower dosage and subsequent adjustments may be required. The rate of administration of intravenous dosage should be no more than 25 mg per minute 61 , and possibly as low as 5 to 10 mg per minute 2.

Pharmacogenetics

The metabolism of mephenytoin is genetically determined 123.

Patients who are slow metabolizers of mephenytoin are at risk of increased adverse effects; Oriental and black populations are more likely than white populations to be slow metabolizers of mephenytoin 123.

Phenytoin also may be metabolized slowly in a small number of individuals due to genetic predisposition 102, 103, 120, 193 , which may cause limited enzyme availability and lack of induction 102, 103.

Dental

Gingival hyperplasia, a common complication of phenytoin or mephenytoin therapy, usually starts during the first 6 months of treatment as gingivitis or gum inflammation. The incidence is higher in patients up to 23 years of age than in older patients, and severe gingival hyperplasia is less likely to occur with dosage under 500 mg per day. Anterior tissue overgrowth may be greater than posterior overgrowth, creating esthetic and psychological problems for the young patient. A strictly enforced program of teeth cleaning by a professional, combined with plaque control by the patient, if begun within 10 days of initiation of hydantoin anticonvulsant therapy, will minimize growth rate and severity of gingival enlargement. Periodontal surgery may be indicated, and should be followed by careful plaque control to inhibit recurrence of gum enlargement. If gingival hyperplasia cannot be controlled by standard dental procedures, ethotoin may be substituted for phenytoin, without loss of seizure control, usually at doses four to six times greater than those of phenytoin.

In addition, the leukopenic effects of hydantoin anticonvulsants may result in an increased incidence of microbial infection, delayed healing, and gingival bleeding. If leukopenia occurs, dental work should be deferred until blood counts have returned to normal. Patient instruction in proper oral hygiene should include caution in use of regular toothbrushes, dental floss, and toothpicks 33.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Possible interactions of hydantoin anticonvulsants, particularly phenytoin, with medications known to be metabolized by the hepatic cytochrome P450 enzyme system should be considered. Phenytoin therapy significantly increases the amounts and activities of some CYP isoenzymes 63, 193 , the uridine diphosphate glucuronosyltransferase (UDPGT) system 63, 193 , and epoxide hydrolase enzymes 193 , thus enhancing the metabolism of many other drugs 63, 193.

Also, phenytoin may compete with drugs metabolized by the same CYP isoenzymes (CYP2C9 and CYP2C19) 123, 193 , thus decreasing the metabolic clearance of those agents 193.

Metabolism of phenytoin is particularly susceptible to inhibition by other medications using the P450 enzyme system, due to phenytoin's potentially saturable metabolism 180.

In addition, other highly protein-bound medications may displace phenytoin from its serum protein binding sites, increasing serum concentrations of free (unbound) phenytoin and increasing the risk of toxicity 63.

The possibility of significant interactions with hepatic enzyme inducers, hepatic enzyme inhibitors, and medications metabolized by the hepatic P450 isoenzyme system, other than those listed below, should be considered and the patient should be carefully monitored during and following concurrent use.

Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Acetaminophen 112, 120, 155

(risk of hepatotoxicity from a single toxic dose or prolonged use of acetaminophen may be increased and therapeutic efficacy may be decreased in patients regularly taking other hepatic enzyme-inducing agents such as phenytoin)

>> Alcohol 4, 94, 95, 96, 97, 98, 99, 100, 101, 102, 105, 112, 113, 120, 123, 155, 164 or

>> CNS depression-producing medications (see Appendix II)

(CNS depression may be enhanced 47, 105)

(chronic use of alcohol may decrease the serum concentrations and effectiveness of hydantoins; concurrent use of hydantoin anticonvulsants with acute alcohol intake may increase serum hydantoin concentrations 94, 95, 96, 97, 98, 99, 100, 101, 102, 105, 108, 120, 123, 180)

>> Amiodarone 62, 94, 108, 120, 123, 137, 155, 180

(concurrent use with phenytoin and possibly with other hydantoin anticonvulsants may increase plasma concentrations of the hydantoin, resulting in increased effects and/or toxicity)

>> Antacids, aluminum and/or magnesium-containing and calcium carbonate-containing 4, 11, 62, 94, 95, 96, 97, 100, 101, 102, 112, 120, 123, 155, 164

(concurrent use may decrease the bioavailability of phenytoin; doses of antacids and phenytoin should be separated by about 2 to 3 hours)

>> Anticoagulants, coumarin- or indandione-derivative 4, 62, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 108, 120, 123, 156, 180 or

>> Chloramphenicol 4, 62, 94, 95, 96, 97, 98, 99, 100, 101, 102, 108, 112, 113, 120, 123, 155, 156, 164, 180 or

>> Cimetidine 4, 94, 95, 96, 97, 100, 101, 102, 108, 113, 120, 123, 153, 155, 164, 180 or

>> Disulfiram 4, 62, 94, 95, 96, 97, 99, 100, 101, 102, 103, 108, 112, 113, 120, 123, 155, 164, 180 or

Influenza virus vaccine 21, 155 or

>> Isoniazid 4, 62, 63, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 108, 112, 113, 120, 123, 155, 164, 169, 180 or

Methylphenidate 94, 95, 96, 97, 98, 99, 100, 101, 102, 112, 113, 120, 123, 155, 180 or

Metronidazole 123, 180 or

>> Phenylbutazone 4, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 108, 112, 113, 120, 123, 155, 164, 180 or

Ranitidine 123, 152, 153, 155 or

Salicylates 4, 62, 94, 95, 96, 97, 98, 99, 100, 101, 102, 108, 112, 113, 120, 123, 155, 164, 180 or

>> Sulfonamides 62, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 108, 112, 113, 120, 123, 155, 164, 180 or

Trazodone 80, 94, 95, 96, 97, 100, 101, 102, 108, 120, 180 or

Trimethoprim 123, 197, 198

(serum phenytoin concentrations may be increased because of inhibition of its metabolism by these agents, resulting in increased effects and/or toxicity of phenytoin; dosage adjustments may be necessary)

(in addition, the anticoagulant effect of coumarin- or indandione-derivative anticoagulants may be increased initially, but decreased with continued concurrent use)

(phenylbutazone and salicylates also may displace phenytoin from protein binding sites, resulting in increased free [unbound] phenytoin concentrations 4, 123)

(trimethoprim may increase the half-life of phenytoin by up to 50%, and decrease its clearance by 30% through inhibition of metabolism of phenytoin 123, 197, 198)

Anticonvulsants, succinimide 94, 95, 96, 97, 98, 99, 100, 101, 102, 108, 113, 120, 123, 137

(induction of hepatic microsomal enzyme activity may result in decreased serum concentrations of either succinimide or hydantoin anticonvulsants; careful monitoring is suggested, especially when any anticonvulsant is added to or withdrawn from an existing regimen)

>> Corticosteroids, glucocorticoid 63, 94, 95, 96, 97, 98, 99, 100, 101, 102, 108, 112, 120, 123, 156, 180 or

Cyclosporine 62, 63, 113, 120, 123, 156 or

Digitalis glycosides 63, 94, 95, 96, 97, 100, 101, 102, 112, 120, 123, 156, 180 or

Disopyramide 120, 123, 147, 156 or

Doxycycline 4, 94, 95, 96, 97, 100, 101, 102, 112, 120, 123, 156, 180 or

Furosemide 94, 95, 96, 97, 100, 101, 102, 112, 120, 180 or

Levodopa 112, 113 or

Mexiletine 156 or

Quinidine 63, 94, 95, 96, 97, 98, 99, 100, 101, 102, 120, 123, 156, 180

(therapeutic effects of these medications may be decreased because of increased metabolism and decreased plasma concentrations, which may result from hydantoin anticonvulsants' induction of hepatic microsomal enzymes; dosage adjustments of these medications may be necessary)

Antidepressants, tricyclic 60, 63, 69, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 108, 112, 113, 120, 123, 155, 156, 164, 168, 180, 194 or

Bupropion 168 or

Clozapine 168 or

Haloperidol 4, 168 or

Loxapine 112, 168 or

Maprotiline 168 or

Molindone 2, 94, 95, 96, 97, 98, 99, 100, 102, 108, 168 or

Monoamine oxidase (MAO) inhibitors 168 , including furazolidone, procarbazine, and selegiline or

Phenothiazines 4, 94, 95, 96, 97, 98, 99, 100, 101, 102, 108, 112, 113, 123, 168, 180 or

Pimozide 168 or

Thioxanthenes 168

(these medications may lower the seizure threshold and decrease the anticonvulsant effects of hydantoin anticonvulsants; CNS depression may be enhanced; dosage adjustment of the hydantoin anticonvulsant may be necessary)

(concurrent use of phenytoin with tricyclic antidepressants may lower serum concentrations of the antidepressant; dosage increases of the tricyclic antidepressant may be required to produce improvement of the depressed state 60, 63, 76)

(concurrent use of phenytoin with haloperidol may result in significant reductions in haloperidol serum concentrations 4)

(molindone contains calcium ions, which interfere with the absorption of phenytoin 94, 95, 96, 97, 98, 99, 100, 102, 108 ; patients should be advised to take phenytoin and molindone one to three hours apart 225)

(concurrent use of phenothiazines may inhibit phenytoin metabolism, leading to phenytoin intoxication)

Antidiabetic agents, oral 4, 62, 155, 180 or

Insulin 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 120, 180

(hydantoin anticonvulsants may increase serum glucose concentrations and the possibility of hyperglycemia; dosage adjustment of either or both medications may be necessary)

(tolbutamide may displace phenytoin from protein binding sites 4 , resulting in increased plasma phenytoin concentrations 180)

>> Antifungals, azole, including:

>> Fluconazole 62, 63, 123, 130, 131, 132, 133, 155, 164 or

>> Itraconazole 199 or

>> Ketoconazole 134 or

>> Miconazole 62, 108, 120, 123, 135

(concurrent use of any azole antifungal with phenytoin may decrease the metabolism of phenytoin, resulting in increased plasma phenytoin concentrations; a 75% increase in the area under the plasma concentration-time curve [AUC] of phenytoin was found in volunteers given 200 mg of fluconazole per

day; concurrent use has also been reported to decrease the plasma concentration of azole antifungals, which may lead to clinical failure or relapse of the fungal infection; response to both medications should be closely monitored 199)

Antineoplastic agents 78, 114, 123, 204, 227 , such as:

Bleomycin 123, 227

Carmustine (BCNU) 114, 227

Cisplatin 62, 114, 123, 227

Dacarbazine 204, 227

Doxorubicin 123, 227

Ifosfamide 212, 227

Methotrexate 62, 227

Vinblastine 62, 123, 227

(increased metabolism of phenytoin may occur 114, 204 , although other factors such as reduced absorption secondary to chemotherapy-induced gastrointestinal toxicity 204 and concomitant administration of steroids and antacids may contribute to this effect 123)

(phenytoin may induce the metabolism of ifosfamide to its alkylating metabolites, resulting in increased toxicity 212)

Barbiturates 4, 62, 63, 155, 156, 164 or

Primidone 63, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 108, 109, 112, 113, 120, 123, 155

(phenytoin and phenobarbital interact reciprocally through multiple mechanisms 62, 193 ; concurrent use may produce variable and unpredictable effects 180 ; close monitoring of the patient is advised)

(metabolism of primidone to phenobarbital may be increased by phenytoin 62, 123)

>> Calcium 94, 95, 96, 97, 98, 99, 100, 101, 102, 108, 123, 164

(when used as an excipient in phenytoin capsules, calcium sulfate can decrease phenytoin absorption by as much as 20% 11)

(concurrent use of phenytoin with calcium supplements or any tablets or capsules that contain calcium sulfate as an excipient may result in formation of nonabsorbable complexes, thereby decreasing the bioavailability of both calcium and phenytoin; patients should be advised to take these medications 1 to 3 hours apart 5)

Calcium channel blocking agents 63, 216 , including:

Diltiazam 123 or

Nifedipine 108, 155 or

Verapamil 216, 217

(caution is advised when these medications are used concurrently with phenytoin because of their ability to displace phenytoin from its protein binding sites, increasing serum free [unbound] phenytoin concentrations)

(phenytoin also may induce the metabolism of these medications, causing decreased efficacy 63)

Carbamazepine 4, 62, 94, 95, 96, 97, 98, 99, 100, 101, 102, 108, 109, 113, 120, 155, 164, 180

(carbamazepine has complex and variable effects on phenytoin 193 ; it may increase or decrease the clearance of phenytoin 62, 193 ; in most patients, phenytoin metabolism is inhibited and plasma concentrations may increase significantly, resulting in phenytoin toxicity, which can be mistaken for carbamazepine toxicity 193.

In addition, phenytoin may reduce plasma carbamazepine concentrations, mainly by increasing CYP enzymes; in many cases, plasma concentrations of carbamazepine's active metabolite do not change, but the ratio of metabolite to parent drug concentration increases, with a higher contribution of carbamazepine-10,11-epoxide to the overall clinical effects 193.

Monitoring of plasma concentrations is recommended as a guide to dosage, especially when either medication is added to or withdrawn from an existing regimen 62, 193)

Carbonic anhydrase inhibitors 112, 113

(osteopenia induced by hydantoin anticonvulsants may be enhanced; it is recommended that patients receiving concurrent therapy be monitored for early signs of osteopenia and that the carbonic anhydrase inhibitor be discontinued and appropriate treatment initiated if necessary)

Chlordiazepoxide 4, 94, 95, 96, 100, 123, 180 or

Clonazepam 123, 193 or

Diazepam 94, 95, 96, 100, 123, 180, 193

(chlordiazepoxide and diazepam may cause increased plasma concentrations of phenytoin due to inhibition of its metabolism; phenytoin may increase the clearance of clonazepam and diazepam, decreasing their efficacy; careful monitoring is recommended, since the clinical significance of this interaction is controversial 225)

>> Contraceptives, estrogen-containing, oral 4, 18, 19, 23, 63, 94, 95, 96, 97, 98, 99, 100, 101, 102, 108, 113, 120, 123, 136, 156, 180 or

>> Contraceptives, progestin-containing, oral, injection, or subdermal implants 207, 208, 209, 210, 211

(concurrent use of hydantoin anticonvulsants with estrogen- or progestin-containing contraceptives may result in breakthrough bleeding and contraceptive failure due to the increased rate of hepatic enzyme metabolism of steroids induced by hydantoins 2, 123, 136 ; phenytoin has also been shown to increase sex hormone-binding globulin [SHBG], which may lower the amount of free progestin available for biological action and contribute to the lowered effectiveness of the oral contraceptive 2, 18, 19, 123, 136)

>> Diazoxide, oral 62, 112, 113, 120, 155

(concurrent use with hydantoin anticonvulsants may decrease the efficacy of phenytoin and the hyperglycemic effect of diazoxide and is not recommended)

Dopamine 112, 113

(use of intravenous phenytoin in patients maintained on dopamine may produce sudden hypotension and bradycardia; this reaction is considered to be dose-rate dependent; if anticonvulsant therapy is necessary during administration of dopamine, an alternative to phenytoin should be considered)

Enteral feeding solutions 11, 62, 108, 117, 155, 164

(concurrent use with phenytoin may decrease absorption of phenytoin, possibly necessitating an increase in dosage; some clinicians recommend that at least 2 hours should elapse between feeding and phenytoin administration; if phenytoin suspension or capsule contents are administered via nasogastric tubing, flushing the tube with 2 to 4 ounces of water before and after administration has been suggested; phenytoin serum concentrations should be carefully monitored during concurrent therapy)

>> Estrogens 94, 95, 96, 97, 98, 99, 100, 101, 102, 180 or

>> Progestins 207, 208, 209, 210, 211

(therapeutic effects of these medications may be decreased because of increased metabolism and decreased plasma concentrations, which may result from induction of hepatic microsomal enzymes by hydantoin anticonvulsants 94, 95, 96, 180 ; phenytoin plasma concentrations may also be increased 94, 95, 96, 180 ; dosage adjustments of these medications may be necessary)

>> Felbamate 63, 123, 193, 195

(felbamate is a competitive inhibitor of phenytoin metabolism; when felbamate is added to a phenytoin regimen, a decrease of approximately 20 to 33% of the phenytoin dose is necessary 195 ; phenytoin also induces the metabolism of felbamate 63, 123, 193)

>> Fluoxetine 178, 179, 180

(concurrent use of fluoxetine with phenytoin has been reported to cause elevated plasma phenytoin concentrations, resulting in symptoms of toxicity; caution and close monitoring are suggested 178, 179)

Folic acid 4, 11, 62, 104, 108, 110, 112, 113, 120, 146, 151, 155, 156, 164, 180, 219 or

Leucovorin 201, 218

(although hydantoin anticonvulsants deplete the body of folate stores, supplementation with folic acid may result in lowered serum hydantoin concentrations and possible loss of seizure control; therefore, an increase in hydantoin dosage may be necessary in patients who receive folate supplementation 2, 110, 146, 219)

(because leucovorin is a reduced form of folic acid, large doses may counteract the anticonvulsant effects of hydantoin anticonvulsants 201)

Halothane 4, 94, 95, 96, 97, 98, 99, 100, 101, 102, 112 (and possibly enflurane or methoxyflurane)

(chronic use of hydantoin anticonvulsants prior to anesthesia may increase metabolism of anesthetic, leading to increased risk of hepatotoxicity, and may result in increased phenytoin concentrations, leading to increased risk of hydantoin toxicity)

Lamotrigine 4, 27, 28, 63, 193

(effects of lamotrigine may be reduced because of phenytoin's ability to induce the metabolism [specifically, the UDPGT-dependent glucuronidation] of lamotrigine)

Levothyroxine 3, 112, 156

(concurrent use with phenytoin may reduce serum protein binding of levothyroxine and reduce total serum thyroxine [T 4] by 15 to 25%; however, most patients remain euthyroid, and dosage of thyroid hormone does not need to be altered 3)

>> Lidocaine 156 or

Propranolol 156 and probably other beta-adrenergic blocking agents

(concurrent use with intravenous phenytoin may produce additive cardiac depressant effects; hydantoin anticonvulsants may also increase hepatic enzyme metabolism of lidocaine, reducing its concentration)

(in addition, propranolol may inhibit the metabolism of phenytoin, increasing the risk of adverse effects 4)

>> Methadone 63, 112, 120, 155

(long-term use of phenytoin may increase metabolism of methadone, probably by induction of hepatic microsomal enzyme activity, and may precipitate withdrawal symptoms in patients being treated for

opioid dependence; methadone dosage adjustments may be necessary when phenytoin therapy is initiated or discontinued)

Omeprazole 62, 123, 127, 128, 129, 155, 164

(inhibition of the cytochrome P450 enzyme system by omeprazole, especially at higher doses, may cause a decrease in the hepatic metabolism of phenytoin; delayed elimination and increased serum concentrations may result, with considerable interpatient variability)

Paroxetine 205, 206

(concomitant administration with phenytoin may decrease the systemic availability of either agent; also, both medications may exhibit nonlinear pharmacokinetic properties; no initial dosage adjustments are recommended, but subsequent titration should be based on clinical effects)

>> Phenacemide 104

(risk of additive toxicity when phenacemide is used concurrently with hydantoin anticonvulsants 107 ; concurrent use of phenacemide with ethotoin has been reported to cause paranoid symptoms 104, 107 ; extreme caution is recommended during concurrent use of these medications 107)

Praziquantel 123, 170, 173

(one small, single-dose, controlled study found that epileptic patients taking phenytoin had significantly lower plasma concentrations of praziquantel [24% of the control group]; this effect is thought to be due to induction of the cytochrome P450 microsomal enzyme system by phenytoin; patients on phenytoin may require a larger dose of praziquantel)

>> Rifampin 2, 62, 63, 94, 95, 96, 97, 100, 101, 102, 108, 120, 155, 164, 166, 169, 180

(concurrent use with phenytoin may stimulate the hepatic metabolism of phenytoin, increasing its elimination and thus counteracting its anticonvulsant effect; careful monitoring of serum hydantoin concentrations and dosage adjustments may be necessary 2)

>> Streptozocin 202, 203

(phenytoin may protect pancreatic beta cells from the toxic effects of streptozocin, thus reducing streptozocin's therapeutic effects; concurrent use is not recommended)

>> Sucralfate 62, 94, 95, 108, 137, 155

(concurrent use of sucralfate may decrease the absorption of hydantoin anticonvulsants)

Ticlopidine 27, 29, 40, 59

(several cases of elevated phenytoin plasma concentrations with associated somnolence and lethargy have been reported following ticlopidine administration 27, 29, 40)

>> Valproic acid 4, 62, 63, 94, 95, 96, 97, 98, 99, 100, 101, 102, 108, 109, 112, 113, 120, 123, 155, 164, 180, 193

(valproic acid may displace phenytoin from protein-binding sites 4, 62, 74, 109, 120, 193 and may inhibit the metabolism of phenytoin 62, 161, 193 ; phenytoin, through enzyme induction, may lower valproate concentrations 63, 120, 141, 193 ; there may be an increased risk of liver toxicity 91, 123 , especially in infants 91 ; close monitoring of the patient is required since variable serum phenytoin concentrations have resulted 94, 120 ; monitoring of free [unbound] phenytoin concentrations 63, 161 as well as total plasma phenytoin concentrations 63 is advised by some clinicians; dosage of phenytoin should be adjusted as required by clinical situation; caution is advised also for use with other hydantoin anticonvulsants)

Vitamin D 4, 94, 95, 96, 97, 98, 99, 100, 101, 102, 108, 156, 180

(hydantoin anticonvulsants may reduce effect of vitamin D by accelerating metabolism through hepatic microsomal enzyme induction; patients on long-term anticonvulsant therapy may require vitamin D supplementation to prevent osteomalacia, 94, 95, 96, 97, 98, 99, 101, 225 although rickets is rare 123)

Xanthines, such as:

Aminophylline

Caffeine

Oxtriphylline

>> Theophylline 4, 63, 94, 108, 112, 120, 123, 137, 155, 180

(concurrent use may stimulate hepatic metabolism of theophylline [and possibly other xanthines except dyphylline], resulting in increased theophylline clearance, especially if plasma phenytoin concentrations are in the usual therapeutic range for at least 5 days; also, simultaneous use with theophylline may inhibit phenytoin absorption, resulting in decreased serum phenytoin concentrations; serum concentrations of phenytoin and theophylline should be monitored during concurrent therapy; dosage adjustments of both phenytoin and theophylline may be necessary)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

With diagnostic test results

Dexamethasone test 180 or

Metyrapone test 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 112, 113, 119, 120, 123, 180

(results may be inaccurate because of increased dexamethasone or metyrapone metabolism resulting from enzyme induction; dexamethasone or metyrapone doses may need to be increased)

Gallium citrate Ga 67 imaging

(phenytoin may stimulate a benign alteration in lymphoid tissue, which may result in a Ga 67 scintigram similar to that seen in patients with malignant melanoma 64)

Schilling test

(phenytoin in combination with other anticonvulsant medications may cause a reversible malabsorption of vitamin B 12 65)

Thyroid function tests 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 123, 180

(free, circulating thyroxine [FT 4] 86, 120, 123, 151 and total thyroxine [T 4] 86, 120, 123, 151 concentrations are decreased by phenytoin therapy, mainly due to enhanced conversion to triiodothyronine [T 3] 86, 120 ; however, T 3 and thyroid stimulating hormone [TSH] concentrations generally remain unchanged, 86, 120, 123 and most patients remain euthyroid 120, 123)

With physiology/laboratory test values

Alkaline phosphatase and

Gamma-glutamyl transpeptidase (GGT)

(values may be increased 94, 95, 96, 97, 98, 99, 100, 101, 102, 180)

Glucose, serum

(concentrations may be increased 94, 95, 96, 97, 98, 99, 100, 101, 102, 180)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problem exists

>> Cardiac function impairment, such as Adams-Stokes syndrome, second- and third-degree AV block, sino-atrial block, and sinus bradycardia 100, 101, 102, 103, 180, 181

(parenteral phenytoin administration may affect ventricular automaticity and result in ventricular arrhythmias)

Risk-benefit should be considered when the following medical problems exist

Alcoholism, active

(serum phenytoin concentrations may be decreased 94, 95, 96, 97, 98, 99, 100, 105)

>> Blood dyscrasias 104, 105

(risk of serious infections may be increased)

Cardiovascular disease

(intravenous phenytoin administration may result in atrial and ventricular conduction depression 100, 101, 102, 103 , ventricular fibrillation, or reduced cardiac output, especially in the elderly 100, 101, 102, 103 or seriously ill patients 100, 101, 102, 103 ; phenytoin should be administered at a rate of no more than 25 mg per minute, and if necessary, at a slow rate of 5 to 10 mg per minute 2)

Diabetes mellitus

(hyperglycemia may be potentiated 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 120)

Fever or febrile illness¾temperature > 38.2 °C (101 °F) for more than 24 hours

(serum concentrations of hydantoin anticonvulsants may be decreased because of induction of hepatic oxidative enzymes during fever 20, 120)

>> Hepatic function impairment 94, 95, 96, 97, 98, 99, 100, 101, 104, 106

(metabolism of hydantoin anticonvulsants may be reduced, thereby increasing the possibility of toxic serum concentrations; alterations in protein binding are also likely, due to a secondary decrease in albumin concentrations 82)

>> Porphyria

(risk of exacerbation 94, 137, 151, 180)

>> Renal function impairment 97, 106

(excretion and protein binding may be altered)

>> Sensitivity to hydantoin anticonvulsants 88, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 105, 106, 180, 181 , or to structurally similar compounds such as barbiturates, succinimides, and oxazolidinediones 180

Systemic lupus erythematosus 120

(risk of exacerbation 120)

Thyroid function impairment

(free, circulating thyroxine [FT 4] and total thyroxine [T 4] concentrations are decreased by phenytoin therapy 176, 177 ; patients usually 66 remain euthyroid 2, 120)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):

Albumin concentrations, serum 2, 225, 226 and

Calcium concentrations, serum 2, 225, 226 and

>> Complete blood cell and platelet counts 104, 105, 106 and

>> Hepatic function determinations 105, 106

(some or all may be required at periodic intervals during therapy depending on individual needs of the patient; however, these determinations may be necessary only during early weeks or months of treatment 2)

>> Blood pressure determinations 100, 180, 191 and

>> Cardiac function 100, 180, 191 and

>> Respiratory function 100, 180, 191

(patients receiving fosphenytoin or phenytoin intravenously should be carefully monitored; hypotension may occur; severe cardiovascular reactions [including atrial and ventricular conduction depression and ventricular fibrillation] and fatalities have occurred following intravenous administration of phenytoin; severe complications occur most commonly in elderly or seriously ill patients 100, 180)

>> Dental examinations

(recommended at 3-month intervals for teeth cleaning and reinforcement of patient's plaque control for inhibition of gingival hyperplasia 67)

>> Electroencephalograms (EEGs) and

>> Hydantoin concentrations, serum 5, 94, 95, 96, 97, 98, 99, 100, 101, 102

(in patients maintained at steady-state hydantoin concentrations with well-controlled seizures, routine screening usually is not needed 225, 234 ; however, in newly diagnosed patients or in those with poorly controlled seizures, periodic monitoring, possibly with video recording of seizures, and medical and physical reassessment may prevent neurotoxicity 225 and facilitate dosage titration 231)

(when monitoring hydantoin serum concentrations, all blood samples should be drawn at standardized times within the dosing schedule, preferably just before a dose is administered 32 [except for fosphenytoin 180]; since the hepatic metabolism of phenytoin is saturable, a small increment in dose, at

higher doses, will produce a disproportionate and unpredictable increase in serum concentrations to the upper therapeutic ranges, and can lead to clinical toxicity 74, 85, 94, 95, 96, 97, 98, 99.

After administration of fosphenytoin, phenytoin concentrations should not be measured until conversion to phenytoin is essentially complete [i.e., 2 hours after the end of an intravenous infusion or 4 hours after an intramuscular injection] 180, 184, 191.

Prior to complete conversion of fosphenytoin to phenytoin, commonly used immunoanalytical techniques [such as TDxÒ/TDxFLxä (fluorescence polarization) and EmitÒ 2000 (enzyme multiplied)] may significantly overestimate plasma phenytoin concentrations because of cross-reactivity with fosphenytoin. The error is dependent on plasma concentrations of phenytoin and fosphenytoin, which are influenced by the dose, route, and rate of administration of fosphenytoin, the time of sampling relative to dosing, and the analytical method. Chromatographic assay methods accurately quantitate phenytoin concentrations in biological fluids in the presence of fosphenytoin. Prior to complete conversion, blood samples for phenytoin monitoring should be collected in tubes containing EDTA as an anticoagulant to minimize ex vivo conversion of fosphenytoin to phenytoin. However, even with specific assay methods, phenytoin concentrations measured before conversion of fosphenytoin is complete will not accurately reflect phenytoin concentrations ultimately achieved 180, 181, 184, 189)

(free [unbound] hydantoin serum concentrations should be monitored in patients with altered protein binding of phenytoin [e.g., neonates, and patients with renal failure, hypoalbuminemia, or acute trauma] 5, 116, 142 and in patients experiencing adverse reactions who have phenytoin concentrations within the therapeutic or target range 5)

(because of altered metabolism and protein binding 26, 118 , and/or increased metabolic clearance of hydantoin anticonvulsants during pregnancy 51, 57 , monthly measurements of serum hydantoin concentrations are recommended to assess the need for an increase in dosage; weekly measurements are recommended during the postpartum period to ascertain adequate reduction of dosage; some patients may have a significant decrease in hydantoin metabolism at time of delivery; therefore, serum hydantoin concentrations should be followed closely during the immediate postpartum period [within 12 hours] 24)

Folate concentrations, serum

(recommended periodically because of increased folate requirements of patients on long-term phenytoin therapy 2)

Phosphate concentrations in patients with renal insufficiency receiving fosphenytoin 181

(these patients may be prone to phosphate intoxication 181 ; the phosphate load from administration of fosphenytoin is 0.0037 millimoles of phosphate per mg of phenytoin sodium equivalents [PE] 180)

Physical examination, with special attention to lymph glands and skin

(all cases of lymphadenopathy or skin rash should be monitored for an extended period because of possible phenytoin hypersensitivity syndrome with lymphadenopathy or pseudolymphoma 2 ; should these problems occur, every effort should be made to achieve seizure control using alternative anticonvulsants 2, 94, 95, 96, 97, 98, 99, 100, 101, 102, 104)

Thyroid function determinations

(recommended during the first few months of therapy to detect symptoms of hypothyroidism, which may be unmasked by hydantoins; when a patient receiving phenytoin is suspected of having hypothyroidism, T 3 and thyroid-stimulating hormone [TSH] concentrations should be measured rather than T 4 and free T 4 index [FTI], since the latter are both typically depressed in patients receiving phenytoin 86, 213)

Note: Even after patients have been stabilized on a maintenance dose, it is important that they have periodic examinations during therapy since phenytoin (and possibly other hydantoins) may deplete body stores of folic acid and vitamin D, possibly resulting in megaloblastic anemia 94, 95, 96, 97, 98, 99, 100, 101, 102 or osteomalacia 94, 95, 96, 97, 98, 99, 101.

Side/Adverse Effects

Note: Although not all of these side effects have been attributed specifically to each hydantoin anticonvulsant, a potential exists for their occurrence during the use of any hydantoin.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Those indicating need for medical attention

Incidence more frequent

CNS toxicity 94, 95, 96, 97, 98, 99, 100, 101, 102, 105, 106, 120 , including ataxia 47, 180, 181, 184, 187, 188, 191, 232 (clumsiness or unsteadiness); confusion 94, 95, 96, 97, 98, 99, 100, 101, 102, 180; nystagmus 47, 48, 119, 180, 181, 184, 187, 188, 189, 232 (uncontrolled back-and-forth and/or rolling eye movements); slurred speech or stuttering 94, 180; trembling of hands 94, 180; and unusual excitement, nervousness, or irritability 94; gingival hyperplasia 94, 95, 96, 97, 98, 99, 100, 101, 102, 104, 105, 106, 120 (bleeding, tender, or enlarged gums)¾higher incidence in children and young adults; incidence in all age groups rare with ethotoin 120; lupus erythematosus, phenytoin hypersensitivity syndrome, Stevens-Johnson syndrome, or toxic epidermal necrolysis 92, 94, 95, 96, 97, 98, 99, 100, 101, 102, 105, 106, 120 (fever; muscle pain 2; skin rash 72; sore throat)

Note: CNS toxicity usually occurs with long-term use, but may be dose-related 93.

Phenytoin hypersensitivity syndrome may be manifested in many ways 149.

Fever, rash, and lymphadenopathy frequently occur together, and may be part of more than one hypersensitivity syndrome 149.

Skin rash is the most frequent hypersensitivity reaction 149, 151 ; licheniform 149 or maculopapular 149 or morbilliform 109, 121, 150 rash, often pruritic, 121, 149, 151 may present simply or may be prodromal of more serious dermatological reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis149.

Lymphoid syndromes (including lymphoid hyperplasia, pseudolymphomas, and pseudo-pseudolymphomas) occur less commonly and are generally reversible upon discontinuation of phenytoin 149, 150.

Phenytoin-induced hepatitis and hepatic necrosis are other major hypersensitivity reactions 149, 150 , as is eosinophilia, which occurs commonly 137, 138, 150.

Less commonly occurring syndromes include polyarteritis, polymyositis, or systemic lupus erythematosus;149 disseminated intravascular coagulopathy, serum sickness, and renal failure may also occur 149.

Rash usually appears in the first 2 weeks of treatment 2, 151, 162 ; hypersensitivity syndrome usually occurs 3 to 8 weeks after 162 , but may occur as long as 12 weeks after initiation of phenytoin therapy 2, 162.

The syndrome may be life-threatening, but early intervention may prevent renal failure, severe rhabdomyolysis, or hepatic necrosis 17.

Other factors, such as a positive family history for phenytoin hypersensitivity reactions 162 or concomitant administration of cranial radiation therapy 163 , may increase the risk of hypersensitivity syndrome occurring.

Incidence rare

Blood dyscrasias, including agranulocytosis 34, 94, 95, 96, 97, 98, 99, 100, 101, 102, 105, 106, 120, 180 (chills; fever; sore throat; unusual tiredness or weakness); leukopenia 94, 95, 96, 97, 98, 99, 100, 101, 102, 105, 106, 120, 180 (fever; chills; sore throat); pancytopenia 94, 95, 96, 97, 98, 99, 100, 101, 102, 105, 106, 180 (nosebleeds or other unusual bleeding or bruising); and thrombocytopenia 94, 95, 96, 97, 98, 99, 100, 101, 102, 105, 106, 120, 180, 232 (fever; sore throat; unusual bleeding or bruising); cholestatic jaundice or hepatitis 94, 95, 96, 97, 98, 99, 100, 101, 102, 105, 106, 120, 137, 180 (dark urine; light gray-colored stools; loss of appetite and weight; severe stomach pain; yellow eyes or skin; skin rash or itching; dizziness; nausea or vomiting; joint pain; unusual tiredness or weakness); choreoathetoid movements, transient 94, 95, 96, 97, 98, 99, 100, 101, 102, 105, 106, 108 (restlessness or agitation; uncontrolled jerking or twisting movements of hands, arms, or legs; uncontrolled movements of lips, tongue, or cheeks); cognitive impairment 74, 87, 120 (defects in intelligence, short-term memory, learning ability, and attention); periarteritis nodosa 94, 95, 96, 97, 98, 99, 100, 101, 102, 120 (abdominal pain; soreness of muscles; unusual tiredness or weakness; fever with or without chills; headache; loss of appetite and weight); Peyronie's disease 94, 95, 96, 97, 98, 99, 100, 101, 102 (pain of penis on erection); pulmonary infiltrates or fibrosis 105, 106, 109, 111 (fever; troubled or quick, shallow breathing; unusual tiredness or weakness; loss of appetite and weight; chest discomfort); vitamin D and/or calcium imbalance 120, 151 (frequent bone fractures; bone malformations; slowed growth)

Note: Many cases of mephenytoin-induced blood dyscrasias occur in patients given mephenytoin for a second time after a period of abstinence 2.

Choreoathetoid movements may be due to rapid administration of intravenous phenytoin for status epilepticus; the effect usually lasts 24 to 48 hours after discontinuation of phenytoin and may resolve spontaneously; it is unrelated to serum hydantoin toxicity or duration of use 53, 54, 55.

With chronic use

Peripheral polyneuropathy, predominantly sensory 94, 95, 96, 97, 100, 101, 102, 120 (numbness, tingling, or pain in hands or feet)¾with phenytoin

With parenteral use only

Note: Both phenytoin and fosphenytoin may cause hypotension 180, 232 and cardiovascular collapse and/or CNS depression when administered rapidly by the intravenous route 180 , although hypotension and cardiac sequelae are less likely with fosphenytoin 45, 184, 186, 189, 191.

Cardiovascular collapse following rapid intravenous infusion of phenytoin may be primarily attributable to its propylene glycol vehicle 232.

The rate of intravenous infusion of phenytoin should not exceed 50 mg per minute 100, 101, 102, 103 ; the rate of fosphenytoin infusions should not exceed 150 mg phenytoin sodium equivalents (PE) per minute 180.

The incidence of cardiovascular effects may be higher in patients who are hypoxic or who have ischemic heart disease 12.

Phenytoin

Burning pain or irritation at injection site 7, 100, 101, 102, 125, 181, 232¾rarely with necrosis and sloughing 7, 100, 101, 102

Note: Fosphenytoin also may be associated with irritation at injection site45, 47, 180, 181, 186, 188, 232 , but usually to a lesser degree 181, 184, 188, 215, 232 , due to its water-solubility and its more favorable pH 215.

Fosphenytoin

Paresthesias and pruritis 45, 48, 119, 180, 181, 184, 189, 191, 232 (burning; tingling; pain; or itching)¾occurring most commonly in groin areas 45, 48, 119, 181, 184, 189 , but also in face 181, 189 , scalp 119 , head 45, 48, 119, 184 , and neck 45, 48, 119, 184 areas, in lower back 45, 48, 119, 184 , buttocks 119 , and abdominal areas 45, 48, 119, 184

Note: Paresthesias and pruritis may be severe; occurrence and intensity can often be lessened by slowing or temporarily stopping the intravenous infusion 180.

Most alert patients who received intravenous fosphenytoin doses of 15 mg PE per kg or greater at a rate of 150 mg PE per minute experienced some degree of discomfort 180, 181.

Most effects resolved within 10 minutes following completion of the infusion 180 ; however, some patients experienced sensory disturbances for hours 180.

The pharmacologic basis for these effects is not known, but similar symptoms have been reported with other phosphate ester drugs that deliver phosphate loads 180, 181.

These sensory disturbances are seen more frequently following intravenous than intramuscular injections of fosphenytoin 48, 180, 181, 184.

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Constipation 94, 95, 96, 98, 99, 100, 101, 102, 180, 232; mild dizziness 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 180, 232; mild drowsiness 103, 105, 106, 180, 232; nausea and vomiting 94, 95, 96, 98, 99, 100, 101, 102, 104, 105, 106, 180

Incidence less frequent

Diarrhea¾with ethotoin 104; enlargement of facial features, 94, 95, 96, 97, 98, 99, 100, 101, 102, 120 including thickening of lips, widening of nasal tip, and protrusion of jaw; gynecomastia (swelling of breasts)¾in males 56; headache 47, 94, 95, 96, 97, 98, 99, 100, 101, 102, 104, 180, 184; hypertrichosis 94, 95, 96, 97, 100, 101, 102, 120 (unusual and excessive hair growth on body and face)¾primarily with phenytoin; insomnia 94, 95, 96, 97, 98, 99, 100, 101, 102, 104, 105, 106 (trouble in sleeping); muscle twitching

Overdose

For specific information on the agents used in the management of hydantoin anticonvulsant overdose, see the Charcoal, Activated (Oral-Local) monograph.

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Ataxia 12, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 106, 108, 120, 151, 180 (clumsiness or unsteadiness); or staggering walk; blurred or double vision 106, 108, 120, 151; severe confusion 108; severe dizziness or drowsiness 103, 106, 120; dysarthria 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 106, 108, 120, 180 (stuttering); or slurred speech 94, 95, 96, 97, 98, 99, 100, 101, 102, 108, 180; hyperreflexia 94, 95, 96, 97, 98, 99, 100, 101, 102, 108, 180; nausea and vomiting 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 180; nystagmus 12, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 106, 108, 120, 151, 180 (continuous, uncontrolled back-and-forth and/or rolling eye movements); seizures 68, 233; tremor 94, 95, 96, 97, 98, 99, 100, 101, 102, 180; unusual tiredness or weakness 94, 95, 96, 97, 98, 99, 100, 101, 102, 120, 180

Note: The lethal dose of phenytoin in adults is estimated to be 2 to 5 grams. 94, 95, 96, 97, 98, 99, 100, 101, 102, 103 The lethal dose in children is unknown. 94, 95, 96, 97, 98, 99, 100, 101, 102

The formate and phosphate metabolites of fosphenytoin may contribute to toxicity. Formate toxicity is associated with severe anion-gap metabolic acidosis 180.

Large increases in phosphate concentrations may cause hypocalcemia with paresthesias, muscle spasms, and seizures 180, 181.

Treatment of overdose

Since there is no specific antidote for overdose with hydantoin anticonvulsants, treatment is symptomatic and supportive 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 180.

To decrease absorption¾Induction of emesis or gastric lavage. 104, 106, 108 Multiple oral doses of activated charcoal 68, 108, 120, 233 and cathartic 108 may shorten the duration of symptoms.

To enhance elimination¾Forced fluid diuresis, peritoneal dialysis, exchange transfusions, hemodialysis, and plasmapheresis are ineffective; there is little renal elimination and a danger of fluid overload. 200, 225

Monitoring¾If an overdose of fosphenytoin is suspected, ionized free calcium concentrations should be monitored as a sign of phosphate toxicity. 180

Supportive care¾Oxygen, vasopressors, and assisted ventilation may be necessary for CNS, respiratory, or cardiovascular depression 103, 106.

Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Following recovery, careful evaluation of blood-forming organs is advisable 104.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Anticonvulsants, Hydantoin (Systemic) .

In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):

Before using this medication

>> Conditions affecting use, especially:

Sensitivity to hydantoin anticonvulsants 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 105, 106 or to structurally similar compounds, such as barbiturates, succinimides, and oxazolidinediones 180

Pregnancy¾Hydantoin anticonvulsants cross the placenta; risk-benefit should be considered because of possibility of increased birth defects; seizures may increase during pregnancy with need for dose increase; bleeding problems may occur in mother during delivery and in baby immediately after delivery

Breast-feeding¾Ethotoin and phenytoin distributed into breast milk

Use in children¾Bleeding, tender, and enlarged gums more common in children; unusual and excessive hair growth, more noticeable in young girls; decreased performance in school (cognitive impairment) may occur with long-term use of high doses

Use in the elderly¾Side effects more likely to occur in the elderly; hydantoin anticonvulsants metabolized more slowly in elderly, possibly leading to toxicity 94, 95, 96, 97, 98, 99, 100, 101, 102, 103

Dental¾Gingival hyperplasia may appear; good dental hygiene 94, 95, 96, 97, 98, 99, 100 and visits to dentist every 3 months for cleaning recommended; agranulocytosis or thrombocytopenia may cause gingival bleeding, slowed healing, and infections

Other medications, especially alcohol, amiodarone, antacids, anticoagulants, azole antifungals, calcium-containing medicine, chloramphenicol, cimetidine, CNS depressants, corticosteroids, diazoxide, disulfiram, estrogen- or progestin-containing contraceptives, estrogens, felbamate, fluoxetine, isoniazid, lidocaine, methadone, phenacemide, phenylbutazone, progestins, rifampin, streptozocin, sucralfate, sulfonamides, theophylline, or valproic acid

Other medical problems, especially blood dyscrasias, cardiac function impairment, hepatic function impairment, history of hydantoin hypersensitivity, porphyria, or renal function impairment

Proper use of this medication

Proper administration

For liquid dosage forms¾Shaking well; using an accurate measuring device, such as a specially marked measuring spoon, a plastic syringe, or a small graduated cup 2

For chewable tablet dosage form¾Chewing or crushing tablets or swallowing them whole 95

For capsule dosage form¾Swallowing capsule whole

Taking with food to reduce gastrointestinal irritation

>> Compliance with therapy; taking every day exactly as directed 94, 95, 96, 97, 98, 99

>> Proper dosing

Missed dose: If dosing schedule is¾One dose a day: Taking as soon as possible unless next day, then continuing on schedule; not doubling doses

Several doses a day: Taking as soon as possible unless within 4 hours of next scheduled dose, then continuing on regular schedule; not doubling doses

Checking with doctor if doses are missed for 2 or more days in a row

>> Proper storage

Precautions while using this medication

>> Regular visits to physician to check progress of therapy

>> Not taking other medication without physician's advice 94, 95, 96, 97, 98, 99

>> Avoiding the use of alcoholic beverages and other CNS depressants while taking this medicine 94, 95, 96, 97, 98, 99, 105

Not taking within 2 to 3 hours of taking antacids 94, 95, 96, 97, 100, 101, 102 or medication for diarrhea

Not changing brands or dosage forms of phenytoin without checking with physician 94 or pharmacist 160

>> Checking with physician before discontinuing medication; gradual dosage reduction is usually needed to maintain seizure control 94, 95, 96, 97, 98

Carrying medical identification card or bracelet during therapy

Diabetic patients: Checking blood or urine sugar concentrations

Caution if any laboratory tests required; possible interference with test results of dexamethasone, metyrapone, or Schilling tests, thyroid function tests, or gallium citrate Ga 67 imaging

>> Caution if any kind of surgery, dental treatment, or emergency treatment is required

>> Caution when driving, using machines, or doing other jobs requiring alertness 106

>> Using different or additional means of birth control than estrogen- or progestin-containing contraceptives

For phenytoin or mephenytoin only

>> Maintaining good dental hygiene and seeing dentist every 3 months 67 for teeth cleaning, to prevent tenderness, bleeding, and enlargement of gums

Side/adverse effects

Increased incidence of gingival hyperplasia in children and young adults taking phenytoin or mephenytoin

Unusual and excessive hair growth more noticeable in young girls

Signs of potential side effects, especially CNS toxicity, lupus erythematosus, phenytoin hypersensitivity syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, blood dyscrasias, cholestatic jaundice, hepatitis, transient choreoathetoid movements, cognitive impairment, periarteritis nodosa, Peyronie's disease, pulmonary infiltrates or fibrosis, or vitamin D and/or calcium imbalance

General Dosing Information

Dosage must be individualized 94, 95, 96, 97, 98, 105, 180.

Monitoring of serum phenytoin concentrations is recommended 94, 95, 96, 97, 98, 99, 100, 101, 102 because of the great variation of response among patients to the hydantoin anticonvulsants and because of the relatively narrow therapeutic serum concentration range 100, 101, 102, 103, 180.

Geriatric patients, seriously ill patients, or patients with impaired hepatic function may require lower initial dosage with subsequent adjustments, because of slow hydantoin metabolism 2, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103 or decreased protein binding 2.

If phenytoin is administered intravenously, the rate must be slowed to not more than 25 mg a minute 61 , and possibly to as low as 5 to 10 mg a minute 2.

When patients are transferred from hydantoins to other anticonvulsant medication or vice versa, there should be a gradual (over a period of a few weeks) 2 increase in the dosage of the added medication and a gradual decrease in the dosage of the medication to be discontinued 94, 95, 96, 97, 98, 99, 101, 105, 106, 180.

When an enzyme-inducing medication is added to or removed from a regimen, the metabolism of the other medications will be altered 70, 74.

In most patients, changes in enzyme induction may occur over a period of weeks 2.

When single-drug anticonvulsant therapy is to be discontinued in patients with seizure disorders 73 , dosage should be reduced gradually over a period of 6 to 12 months to prevent possible recurrence of seizures 83.

Abrupt withdrawal may lead to status epilepticus 94, 95, 96, 97, 98, 99, 101, 180.

Diet/Nutrition

Oral hydantoin anticonvulsants may be taken with or immediately after meals to lessen gastric irritation 2, 104, 145.

However, the medication should always be taken at the same time in relation to meals to ensure consistent absorption 2, 145.

Patients on long-term hydantoin therapy may have increased folic acid requirements 2, 120, 146.

However, increased hydantoin dosages may be necessary in patients who receive folate supplementation because such supplementation may result in decreased serum hydantoin concentrations and possible loss of seizure control [1, 110, 146].

Patients on long-term hydantoin therapy may also require vitamin D supplementation [123, 225, 226], especially those patients taking high doses of phenytoin [228, 229], those with low dietary intake of vitamin D [228, 229, 230], those with limited sun exposure [228, 229, 230], and those with reduced levels of physical activity [228, 229].

For treatment of adverse effects

Intolerance or allergic reactions¾Hydantoin anticonvulsants should be discontinued immediately. Effects are usually observed within 9 to 14 days after start of therapy. If rash is morbilliform (measles-like) or scarlatiniform (scarlet fever-like), therapy may be restarted after the rash has completely disappeared, but should be discontinued if the rash reappears. If rash is exfoliative, purpuric, bullous, or if lupus erythematosus or Stevens-Johnson syndrome is suspected, hydantoin therapy should not be resumed. Attempts should be made to differentiate lymph gland enlargement from other lymph node pathology. The patient should be monitored closely for an extended length of time, and alternative (nonhydantoin) anticonvulsant therapy initiated [94, 95, 96, 97, 98, 99, 100, 101, 102, 106, 180].

CNS or cerebellar toxicity¾Dosage reduction or discontinuation of hydantoin anticonvulsant may improve or reverse effects [94, 95, 96, 97, 98, 99, 100, 101, 102].

Cerebellar toxicity [93] may occur after long-term administration, usually at serum concentrations above 30 mcg. However, CNS toxicity has also been reported at lower serum concentrations, due to free fraction variability [160].

Gingival or gum enlargement¾Consultation with dentist; following recommendations for care to reduce effects.

ETHOTOIN

Summary of Differences

Pharmacology/pharmacokinetics¾ Half-life:
3 to 9 hours.

Side/adverse effects¾ Diarrhea has been reported.
Drowsiness and sedation are dose related and quite common.
Gum hyperplasia is rare; ethotoin is sometimes substituted for phenytoin therapy when gingival hyperplasia is a problem.
Incidence of ataxia is rare.
Incidence of hypertrichosis is lower than with other hydantoin anticonvulsants.

Additional Dosing Information

See also General Dosing Information.

Ethotoin may be substituted for phenytoin without loss of seizure control for improvement of gum hyperplasia, or other side effects, during anticonvulsant therapy. Ethotoin doses are usually four to six times greater than those of phenytoin.

Oral Dosage Forms

ETHOTOIN TABLETS USP

Usual adult and adolescent dose

Anticonvulsant¾Oral, 500 mg to 1 gram the first day, usually divided into four to six doses, the dosage being gradually increased over several days until seizure control is obtained 104.

Note: Maintenance dosage of less than 2 grams a day has been found to be ineffective in most adults 104.

Debilitated patients may require a lower initial dosage.

Usual adult prescribing limits

Up to 3 grams a day 104.

Usual pediatric dose

Anticonvulsant¾Oral, up to 750 mg a day initially, on the basis of age and weight, the dosage being adjusted as needed and tolerated until seizure control is obtained 104.

Note: A total daily dose of 3 grams may be required for some patients 104.

Usual geriatric dose

See Usual adult and adolescent dose. However, geriatric patients may require a lower initial dosage.

Strength(s) usually available

U.S.¾250 mg (Rx)[Peganone (scored) (lactose)]

500 mg (Rx)[Peganone (scored) (lactose)]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:

- May cause drowsiness.
- Avoid alcoholic beverages.

FOSPHENYTOIN

Summary of Differences

Physicochemical characteristics: Fosphenytoin is a water-soluble [10, 12, 180, 186, 187, 192] prodrug [6, 45, 48, 71, 119, 123, 180, 183, 184, 189] that is rapidly converted to phenytoin following parenteral administration [10, 45, 48, 181, 184, 189, 192].

Pharmacology/pharmacokinetics: Fosphenytoin has no intrinsic pharmacologic activity before its conversion to phenytoin [181, 184].

After conversion, the pharmacologic and toxicologic effects are essentially the same as those of phenytoin [47, 181].

For each millimole of fosphenytoin administered, one millimole of phenytoin is produced [180].

This means that 1.5 mg of fosphenytoin liberates 1 mg of phenytoin [123], or that 75 mg of fosphenytoin sodium is essentially equivalent to 50 mg of phenytoin sodium [181].

To avoid performing molecular weight-based adjustments when converting between fosphenytoin sodium and phenytoin sodium, the amount and concentration of fosphenytoin is expressed in terms of phenytoin sodium equivalents (PE) [180, 181].

Fosphenytoin should always be prescribed and dispensed in phenytoin sodium equivalents (PE) [180, 181].

Pharmacokinetics of fosphenytoin following intravenous administration are complex; when used in an emergent setting, such as status epilepticus, differences in the rate of availability of phenytoin could be critical [180].

Therefore, studies have empirically determined infusion rates for fosphenytoin that produce the rate and extent of systemic phenytoin availability similar to that obtained from a phenytoin sodium infusion of 50 mg per minute [180].

Side/adverse effects: The incidence of adverse reactions following intravenous administration of fosphenytoin tends to increase with dose and infusion rate [180].

Doses of 15 mg PE per kg of body weight administered at 150 mg PE per minute may cause transient pruritis, tinnitus, nystagmus, somnolence, and ataxia to occur two to three times more often than do lower doses or slower administration rates [180].

Additional Dosing Information

See also General Dosing Information.

Dosing of fosphenytoin sodium injection is always expressed in terms of phenytoin sodium equivalents (PE) 180.

Bioequivalence information

In vivo, 1.5 mg of fosphenytoin sodium injection liberates 1 mg of phenytoin sodium 123 ; thus, 75 mg of fosphenytoin sodium is essentially equivalent to 50 mg of phenytoin sodium 181.

Parenteral Dosing Forms

FOSPHENYTOIN SODIUM INJECTION

Note: Dosing for fosphenytoin sodium injection is expressed in terms of phenytoin sodium equivalents (PE) 180.

During intravenous infusion of fosphenytoin, continuous monitoring of the patient"s electrocardiogram (ECG), blood pressure, and respiration is essential 180, 181.

Intramuscular fosphenytoin doses of 20 to 30 mL have been safely administered as a single intramuscular injection, with little or no local irritation reported 191, 220.

Usual adult and adolescent dose

Anticonvulsant in status epilepticus¾Loading: Intravenous, 15 to 20 mg phenytoin sodium equivalents (PE) per kg of body weight 180, 181, 189, 235 , administered at a rate of 100 to 150 mg PE per minute 180, 189, 235.

The infusion rate should not exceed 150 mg PE per minute 181, 189, 191, 235.

Maintenance: Intravenous or intramuscular, initially 4 to 6 mg PE per kg of body weight per day 180, 181.

Note: Because the effect of fosphenytoin is not immediate, other measures including concomitant administration of a benzodiazepine will usually be necessary in status epilepticus 180.

Anticonvulsant for nonemergent conditions ¾Loading: Intravenous or intramuscular, 10 to 20 mg phenytoin sodium equivalents (PE) per kg of body weight 180, 189, 235.

Maintenance: Initially 4 to 6 mg PE per kg of body weight per day 180, 235.

As substitute for oral phenytoin therapy ¾The same total daily dose and frequency as phenytoin sodium has been administered 47, 180, 189, 235.

Since fosphenytoin is 100% bioavailable by both intravenous and intramuscular routes, either route may be used 180, 235.

However, the intramuscular route obviates the need for monitoring and the equipment necessary for intravenous infusion 189, 235.

Since phenytoin sodium delayed-release capsules are approximately 90% bioavailable, plasma concentrations of phenytoin may increase modestly when parenteral fosphenytoin is substituted 47, 180, 181, 188, 189, 235.

Clinical response and therapeutic plasma phenytoin concentrations should be used to guide fosphenytoin therapy after 3 to 5 days 47, 188, 235.

Usual pediatric dose

Anticonvulsant in status epilepticus *¾Loading: Intravenous, 15 to 20 mg phenytoin sodium equivalents (PE) per kg of body weight 190 , administered at up to 3 mg PE per kg of body weight per minute 181, 189, 191, 225.

Maintenance: Intravenous or intramuscular, initially 4 to 6 mg PE per kg of body weight 190, 225.

Usual geriatric dose

Anticonvulsant in status epilepticus¾Loading: Intravenous, 14 mg phenytoin sodium equivalents (PE) per kg of body weight 181.

Note: In patients who require phosphate restriction, such as those with severe renal function impairment, the contribution of fosphenytoin of 0.0037 millimole of phosphate per mg phenytoin sodium equivalent (PE) must be considered 180.

Strength(s) usually available
U.S.¾75 mg per mL, equivalent to 50 mg of phenytoin sodium per mL (Rx)[Cerebyx (Tromethamine USP (TRIS)) (Hydrochloric acid NF) (Sodium hydroxide NF) (Water for injection USP)]

Canada¾75 mg per mL, equivalent to 50 mg of phenytoin sodium per mL (Rx)[Cerebyx (Tromethamine buffer 12 mg/mL) (Hydrochloric acid NF) (Sodium hydroxide NF) (Water for injection USP)]

Packaging and storage:

Store between 2 and 8 °C (36 to 46 °F), unless otherwise specified by manufacturer. Do not store at room temperature for more than 48 hours 180.

Preparation of dosage form:

Prior to intravenous administration, fosphenytoin sodium must be diluted in 5% dextrose injection or 0.9% sodium chloride injection to a concentration of 1.5 to 25 mg phenytoin sodium equivalents (PE) per mL 180, 181.

Stability:

Unopened vials should be refrigerated; however, unopened vials will remain stable for 48 hours at room temperature. Vials that develop particulate matter should not be used 180.

Once diluted for intravenous administration, fosphenytoin sodium solutions are stable for 8 hours at room temperature and 24 hours under refrigeration 181.

Additional information:

Fosphenytoin sodium injection is buffered to a pH of 8.6 to 9 180, 183, 184, 187, 189.

MEPHENYTOIN

Summary of Differences

Pharmacology/pharmacokinetics: Half-life is approximately 7 hours but averages 95 to l44 hours for the active metabolite, nirvanol.

Side/adverse effects: Drowsiness and sedation are dose related 105, 106 and quite common.

Additional Dosing Information

See also General Dosing Information.

Mephenytoin usually is used only after safer anticonvulsants have been tried and have proven unsatisfactory.

Oral Dosage Forms

MEPHENYTOIN TABLETS USP

Usual adult and adolescent dose

Anticonvulsant¾Oral, 50 to 100 mg once a day, the dosage being increased by an additional 50 to 100 mg a day at one-week intervals until seizure control is obtained 105, 106.

Note: Debilitated patients may require a lower initial dosage.

Usual adult prescribing limits

1.2 grams a day 106.

Usual pediatric dose

Anticonvulsant¾Oral, 25 to 50 77 mg a day, the dosage being increased by an additional 25 to 90 50 mg a day at one-week intervals until seizure control is obtained 106.

Usual pediatric prescribing limits

400 mg a day [105], [106].

Note: Dose may be divided and should be based on severity of seizures, age, and serum concentrations [2].

Usual geriatric dose

See Usual adult and adolescent dose. However, geriatric patients may require a lower initial dosage.

Strength(s) usually available

U.S.¾100 mg (Rx)[Mesantoin (scored) (lactose) (sucrose)]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

Auxiliary labeling:

· May cause drowsiness.
· Avoid alcoholic beverages.

PHENYTOIN

Summary of Differences

Category: Also used as an antiarrhythmic, for ventricular arrhythmias, especially when arrhythmia is digitalis-induced or caused by tricyclic antidepressant toxicity; as an antineuralgic in trigeminal neuralgia; and as a muscle relaxant in certain movement disorders.

Pharmacology/pharmacokinetics: Because phenytoin exhibits saturable [120], [123] , zero-order [224] , or dose-dependent [120], [123], [125] pharmacokinetics, the apparent half-life of phenytoin changes with dose and serum concentration [120], [122], [125].

Side/adverse effects: Incidence of hypertrichosis is more frequent than with other hydantoin anticonvulsants.

Additional Dosing Information

See also General Dosing Information.

For oral dosage forms

Extended Phenytoin Sodium Capsules USP is the only dosage form used for once-a-day dosing, and then, only after patients have been stabilized on a divided dosage, generally 300 to 400 73 mg a day 94, 98, 99.

Phenytoin oral suspension is generally not recommended for once-a-day dosing 97 because it is not an extended-release dosage form. The suspension may be adequate for more frequent dosing, if vigorously shaken to avoid inadequate dispersal of phenytoin throughout the vehicle.

For parenteral dosage forms

Intravenous phenytoin sodium should be administered by direct intravenous injection into a large vein through a large-gauge needle or intravenous catheter 41, 100, 101, 102 at a rate not to exceed 50 mg a minute 100, 101, 102, 103.

Faster rates of administration may result in hypotension, cardiovascular collapse, or CNS depression 1, 100, 101, 102, 103, 108 , related to the propylene glycol diluent 160, 164, 165.

Intravenous administration should be monitored by cardiac function and blood pressure readings 100, 101, 102.

To minimize local venous irritation from intravenous injection of phenytoin, each dose must be followed by 0.9% sodium chloride injection through the same in-place needle or catheter 100, 101, 102, 103.

Extravasation should be avoided, as phenytoin injection is caustic to tissues because of its high alkalinity (pH = 12) 100, 101, 102 , and possibly also because of the propylene glycol in the vehicle. Soft tissue injury ranging from irritation to extensive necrosis and sloughing has been reported even when extravasation has not occurred 7, 100, 101, 102.

Some clinicians suggest that, to prevent serious local inflammatory reactions, intermittent phenytoin infusion may be desirable and that such an infusion can be made feasible if all of the following criteria are met:

- Phenytoin injection is admixed only with no more than 50 mL 8 of 0.9% sodium chloride injection.
- The final concentration of phenytoin is between 1 and 10 mg per mL 140, 148.
- Admixture is done immediately before beginning the infusion 140.
- Infusion is completed within 1 hour 8.
- All tubing is flushed with 0.9% sodium chloride injection before and after infusion 148.
- A 0.45- to 0.22-micron filter is placed on the line 44, 125, 140.

When phenytoin injection is administered by infusion, the maximum rate of infusion is 50 mg a minute 100, 101, 102, 103.

However, for patients who may develop hypotension, who are on a sympathomimetic medication, who have cardiovascular disease, or who are older than 65 years of age 2 , the maximum rate of infusion

should be 25 mg a minute and possibly as low as 5 to 10 mg a minute. Vigilant ECG monitoring of cardiovascular status throughout the duration of infusion is required 9.

For rapid control of seizures, concomitant administration of an intravenous benzodiazepine 41, 100, 101, 102 or a short-acting barbiturate 100, 101, 102 may be necessary because of the slow rate of administration necessary for phenytoin injection 41, 100, 101, 102 .

Because of the delayed absorption of intramuscularly administered phenytoin 100, 102 and the high degree of local irritation from the alkaline solution, the intramuscular route of administration is not recommended when the intravenous or oral route is available 100, 101, 103.

Intramuscular administration is not recommended for treatment of status epilepticus since serum concentrations in the therapeutic range cannot be readily achieved for up to 24 hours 41, 100, 101, 102, 103.

Erratic absorption is partly caused by tissue precipitation of phenytoin. Muscle necrosis has also been reported.

Intramuscular administration during neurosurgery, for patients stabilized on oral phenytoin, requires a dose 50% greater than the oral dosage used to maintain serum concentrations 100, 101, 102, 103.

When a patient is returned to the oral route, dosage should be reduced by 50% of the original oral dosage for 1 week to compensate for the sustained release of medication from prior intramuscular injections 100, 101, 102, 103.

If the need for intramuscular administration continues for more than 1 week, alternative routes such as gastric intubation should be considered 100, 101, 102, 103.

Bioequivalence information

For oral dosage forms only¾ The prescribing physician should be consulted before a prescription is changed from one phenytoin dosage form to another because of possible differences in bioavailability, due to varying amounts of calcium sulfate excipient 11 or amount of phenytoin acid contained in the product 94, 95, 96, 97, 98, 99, 100, 101.

Phenytoin dosage forms based on phenytoin acid (oral suspension and chewable tablets) contain 8% more drug on a mg-per-mg basis than those based on phenytoin sodium 94, 95, 96, 97, 100, 101, 102, 164.

Phenytoin intoxication has been reported following weight-for-weight substitution of phenytoin acid for phenytoin sodium 7.

The prescribing physician should be consulted before a product is dispensed that is different from that currently taken by the patient, or from that originally prescribed. Bioavailability may vary enough among oral phenytoin sodium products of different manufacturers to result in either a loss of seizure control or a toxic blood concentration 94, 98.

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

PHENYTOIN ORAL SUSPENSION USP

Note: Phenytoin Oral Suspension USP is not an extended phenytoin product and is not intended for once-a-day dosage.

Usual adult and adolescent dose

Anticonvulsant¾Oral, initially 125 mg 41 three times a day, the dosage being adjusted at seven- to ten-day 2 intervals as needed and tolerated 96, 97.

Note: For seriously ill or debilitated patients, or patients with impaired hepatic function, the total dose is often reduced 96, 97.

Usual pediatric dose

Anticonvulsant¾Initial: Oral, 5 mg per kg of body weight a day, divided into two or three doses, the dosage being adjusted as needed and tolerated 96, 97, 164, 234.

Maintenance: Oral, 4 to 8 mg per kg of body weight 96, 97, 164 or 250 mg per square meter of body surface area a day, divided into two or three doses.

Usual geriatric dose

Anticonvulsant¾Oral, initially 3 mg per kg of body weight a day, in divided doses, the dosage being adjusted according to serum hydantoin concentrations and the patient"s response 29.

Strength(s) usually available

U.S.¾125 mg per 5 mL (Rx)[Dilantin-125 (sucrose)] [Generic]

Canada¾30 mg per 5 mL (Rx)[Dilantin-30]

125 mg per 5 mL (Rx)[Dilantin-125]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container. Protect from freezing.

Auxiliary labeling:

· Shake well.
· Protect from freezing.

· Avoid alcoholic beverages.

Note: Remind patient to shake bottle well before removing each dose.

Advise patient to use an accurate measuring spoon, plastic syringe, or graduated measuring cup 2.

Additional information:

May contain 0.6% alcohol.

PHENYTOIN TABLETS (CHEWABLE) USP

Note: Phenytoin chewable tablets are not intended for once-a-day dosage as they may be too promptly bioavailable. Once-a-day use of phenytoin chewable tablets may result in toxic serum concentrations of phenytoin.

Usual adult and adolescent dose

Anticonvulsant¾Oral, initially 100 95, 97 to 125 41 mg three times a day, the dosage being adjusted at seven- to ten-day 2, 95 intervals as needed and tolerated.

Note: For seriously ill or debilitated patients, or patients with impaired hepatic function, the total dose is often reduced 95, 97.

Usual pediatric dose

Anticonvulsant¾Initial: Oral, 5 mg per kg of body weight a day, divided into two or three doses, the dosage being adjusted as needed and tolerated 95, 97, 164, 234.

Maintenance: Oral, 4 to 8 mg per kg of body weight 95, 97, 164 or 250 mg per square meter of body surface area a day, divided into two or three doses.

Usual geriatric dose

Anticonvulsant¾Oral, initially 3 mg per kg of body weight a day, in divided doses, the dosage being adjusted according to serum hydantoin concentrations and the patient"s response 29.

Strength(s) usually available

U.S.¾50 mg (Rx)[Dilantin Infatabs (saccharin) (sucrose)]

Canada¾50 mg (Rx)[Dilantin Infatabs]

Note: One 100-mg capsule of phenytoin sodium contains 92% phenytoin and is therefore not equivalent to two 50-mg phenytoin chewable tablets containing 100% phenytoin.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

Auxiliary labeling:

· May be chewed or crushed.
· Avoid alcoholic beverages.

EXTENDED PHENYTOIN SODIUM CAPSULES USP

Note: Only phenytoin sodium capsules labeled "Extended"" are to be used for once-a-day dosage. Once-a-day use of capsules labeled "Prompt"" may result in toxic serum phenytoin concentrations.

Usual adult and adolescent dose

Anticonvulsant¾Oral, initially 100 mg three times a day, the dosage being adjusted at seven- to ten-day intervals as needed and tolerated 94, 97, 98, 99.

When established, the daily maintenance dosage may be given on a once-a-day basis in accordance with patient tolerance 94, 97, 98, 99.

Note: An oral loading dose of 1 gram may be given, the dose being divided as follows: Initially 400 mg, then 300 mg after two hours, followed by an additional 300 mg in two hours; normal maintenance dosing is started twenty-four hours after the loading dose 94, 98, 99.

Alternatively, some clinicians recommend an oral loading dose of 20 mg per kg of body weight 160, 161, 164 , divided into three to four doses and administered at two-hour intervals 164.

Patients with a history of renal or liver disease should not receive a loading dose. Use of this regimen should be limited to patients in a clinic or hospital setting where phenytoin serum concentrations can be closely monitored 94, 98, 99.

Once-a-day dosage should be considered only for adult patients whose condition has been stabilized by divided doses of extended phenytoin sodium capsules given as 100 mg three times a day. This single 300-mg daily dosage has the advantage of convenience and improved compliance 94, 98, 99.

For seriously ill patients or for debilitated patients or patients with impaired hepatic function, the total dose is often reduced 94, 97, 98, 99.

[Antineuralgic] *¾Oral, 200 to 600 mg a day 13, 14, 16 , in divided doses, the dose being adjusted as needed and tolerated.

[Skeletal muscle relaxant] *¾Oral, up to 300 to 600 mg a day, as needed and tolerated 49.

Usual pediatric dose

Anticonvulsant¾Initial: Oral, 5 mg per kg of body weight a day, divided into two or three doses, the dosage then being adjusted as needed and tolerated 94, 98, 99, 164, 234.

Maintenance: Oral, 4 to 8 mg per kg of body weight 94, 98, 99, 164 or 250 mg per square meter of body surface area a day, divided into two or three doses.

Usual geriatric dose

Anticonvulsant¾Oral, initially 3 mg per kg of body weight a day, in divided doses, the dosage being adjusted according to serum hydantoin concentrations and the patient"s response 29.

Note: For geriatric patients, the total dose is often reduced 94, 97, 98, 99.

Strength(s) usually available

U.S.¾30 mg (Rx)[Dilantin Kapseals (lactose) (sucrose)] [Generic]

100 mg (Rx)[Dilantin Kapseals (lactose) (sucrose)] [Phenytex] [Generic]

Canada¾30 mg (Rx)[Dilantin (lactose)]

100 mg (Rx)[Dilantin (lactose)]

Note: One 100-mg capsule of phenytoin sodium contains 92% phenytoin and is therefore not equivalent to two 50-mg phenytoin chewable tablets containing 100% phenytoin.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:

· Avoid alcoholic beverages.

Additional information:

The sodium content of phenytoin sodium is 0.35 mEq (8 mg) per 100-mg capsule.

PROMPT PHENYTOIN SODIUM CAPSULES USP

Note: Phenytoin sodium capsules labeled "Prompt"" are not intended for once-a-day dosage because the phenytoin may be too promptly bioavailable and may cause toxic serum concentrations of phenytoin.

Usual adult and adolescent dose

Anticonvulsant¾Oral, 100 mg three times a day, the dosage being adjusted at seven- to ten-day intervals as needed and tolerated.

Note: For seriously ill patients, debilitated patients, or patients with impaired hepatic function, the total dose is often reduced.

Usual pediatric dose

Anticonvulsant¾Initial: Oral, 5 mg per kg of body weight a day, divided into two or three doses, the dosage then being adjusted as needed and tolerated 164, 234.

Maintenance: Oral, 4 to 8 mg per kg of body weight 164 or 250 mg per square meter of body surface area a day, divided into two or three doses in accordance with patient tolerance 234.

Usual geriatric dose

Anticonvulsant¾Oral, initially 3 mg per kg of body weight a day, in divided doses, the dosage being adjusted according to serum hydantoin concentrations and the patient"s response 29.

Note: For geriatric patients, the total dose is often reduced 94, 97, 98, 99.

Strength(s) usually available

U.S.¾30 mg (Rx) [Generic]

100 mg (Rx) [Generic]

Canada¾Not commercially available.

Note: One 100-mg capsule of phenytoin sodium contains 92% phenytoin and is therefore not equivalent to two 50-mg phenytoin chewable tablets containing 100% phenytoin.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:

· Avoid alcoholic beverages.

Additional information:

The sodium content of phenytoin sodium is 0.35 mEq (8 mg) per 100-mg capsule.

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indictions that are not included in U.S. product labeling.

PHENYTOIN SODIUM INJECTION USP

Usual adult and adolescent dose

Anticonvulsant in status epilepticus¾Initial¾ Intravenous, direct, 15 to 20 mg per kg 160, 161, 164, 165, 167 of body weight, administered at a rate not to exceed 50 mg a minute 41, 100, 101, 102, 167.

Note:
For obese patients, the loading dose should be calculated on the basis of ideal body weight plus 1.33 times the excess weight over ideal weight, since phenytoin preferentially distributes into fat 66, 164.

Maintenance¾ Intravenous, direct, 100 mg every six to eight hours, at a rate not to exceed 50 mg a minute 41, 100, 101, 102.

Note:
Maintenance therapy, intravenously, 100 mg every six to eight hours, or orally, 5 mg per kg of body weight a day, divided into two to four doses, should begin about twelve to 61 twenty-four hours after a loading dose is given 2, 41.

[Antiarrhythmic] *¾Intravenous, direct, 50 to 100 mg every ten to fifteen minutes as needed and tolerated to stop arrhythmia, but not to exceed a total dose of 15 mg per kg of body weight, administered slowly at a rate no greater than 50 mg a minute.

Note: For geriatric or seriously ill patients or for debilitated patients or patients with impaired hepatic function, the total dose is often reduced and the rate of intravenous administration slowed to 25 mg a minute, possibly as low as 5 to 10 mg a minute 2 , to lessen the possibility of side effects.

During intravenous infusion of phenytoin, continuous monitoring of the patient"s electrocardiogram (ECG), blood pressure, and respiration is essential 100, 101, 102.

Although the manufacturers recommend that phenytoin not be added to intravenous infusions 100, 101, 102, 103 , some clinicians routinely use such infusions 125, 139.

If phenytoin is administered by infusion, the rate of administration should not exceed 50 mg per minute 44, 125 ; some investigators have suggested rates of 20 to 40 mg per minute 31, 43.

Usual pediatric dose

Anticonvulsant in status epilepticus 7, 41¾Intravenous, direct, 15 to 20 mg per kg of body weight, or 250 mg per square meter of body surface area 103 , administered at a rate of 1 74 mg per kg of body weight per minute, not to exceed 50 mg a minute 7, 41, 100, 101, 102, 234.

Usual geriatric dose

See Usual adult and adolescent dose .

Strength(s) usually available

U.S.¾50 mg per mL (Rx)[Dilantin (alcohol 10%)] [Generic]

Canada¾50 mg per mL (Rx)[Dilantin (alcohol 10%)] [Generic]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F). Protect from freezing.

Stability:

A slight yellowing of the solution will not affect its potency. After being refrigerated, solution may form a precipitate that usually dissolves after being warmed to room temperature; however, do not use if the solution is not clear 100, 101, 102, 103.

Incompatibilities:

The manufacturers recommend that parenteral phenytoin sodium not be added to intravenous infusions or mixed with other medication because precipitation of phenytoin may occur 100, 101, 102, 103.

However, some clinicians routinely use infusion solutions of phenytoin in 0.9% sodium chloride in concentrations of 1 to 10 mg of phenytoin per mL 140, 148 , provided the infusion is started immediately after preparation and is completed within 1 hour 8, 140 ; the admixture must be carefully observed for signs of precipitation 140 , and use of a 0.45- to 0.22-micron in-line filter is recommended 44, 125, 140 ; in addition, flushing of all tubing with 0.9% sodium chloride injection before and after infusion of phenytoin is recommended 148.

Additional information:

The sodium content of phenytoin sodium injection is approximately 0.2 mEq (4.5 mg) per mL.