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DILANTIN® READY-MIXED

1. Name of the Medicinal Product

1.1 Product name

Dilantin® Ready-Mixed

1.2 Strength

250 mg/5 mL

1.3 Pharmaceutical dosage form

Solution for injection

2. Qualitative and Quantitative Composition

2.1 Qualitative declaration

Phenytoin sodium is an anticonvulsant drug, related to the barbiturates in chemical structure, but has a five-membered ring. The chemical name is sodium 5, 5-diphenyl-2,4-imidazolidinedione.

2.2 Quantitative declaration

Each 5 mL of the sterile solution contains 250 mg phenytoin sodium.

For the full list of excipients, see Section 6.1 List of Excipients.

3. Pharmaceutical Form

Solution for injection

4. Clinical Particulars

4.1 Therapeutic indications

Phenytoin is indicated for:

- The control of the tonic-clonic (grand-mal) type.
- The control of status epilepticus, because of the required slow rate of administration of phenytoin, concomitant administration of an intravenous rapid onset anticonvulsant, such as diazepam or rapid onset barbiturate will usually be necessary.
- Prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.

It also has been used in the treatment of cardiac arrhythmias, such as life-threatening ventricular arrhythmias or arrhythmias secondary to digitalis intoxication, when these have not responded to other available antiarrhythmic treatments or when alternative agents could not be tolerated. Phenytoin has not been shown to enhance survival in patients with ventricular arrhythmias.

4.2 Posology and method of administration

General

Phenytoin capsules and solution for injection are formulated with the sodium salt of phenytoin. The free acid form of phenytoin is used in the phenytoin tablets. Because there is approximately an 8% increase in drug content with the free acid form over that of the sodium salt, dosage adjustments and serum level monitoring may be necessary when switching from a product formulated with the free acid to a product formulated with the sodium salt and *vice versa*.

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

Optimum control without clinical signs of toxicity occurs most often with serum levels between 10 mcg/mL and 20 mcg/mL.

Parenteral phenytoin may be administered as a slow intravenous (IV) bolus or it may be administered via an IV infusion. Rapid infusion may be associated with adverse cardiovascular events (see Section 4.4 Special warnings and precautions for use – General).

Because of the risks of cardiac and local toxicity associated with intravenous phenytoin, oral phenytoin should be used whenever possible.

If administered in diluted form, parenteral phenytoin should be diluted with normal saline.

Parenteral phenytoin should not be added to dextrose or dextrose-containing solutions due to the potential for precipitation.

Because of the risk of local toxicity, IV phenytoin should be administered directly into a large peripheral or central vein through a large-gauge catheter. Prior to the administration, the patency of the IV catheter should be tested with a flush of sterile saline. Each injection of parenteral phenytoin should then be followed by a flush of sterile saline through the same catheter to avoid local venous irritation due to the alkalinity of the solution (see Section 4.4 Special warnings and precautions for use - Local Toxicity [including Purple Glove Syndrome]).

Bolus Administration

A bolus of parenteral phenytoin should be injected slowly, not exceeding 50 mg/min in adults, into a large vein through a large-gauge needle or IV catheter. Each injection of IV phenytoin should be preceded by a saline flush and followed by an injection of sterile saline through the same needle or catheter to avoid local venous irritation due to the alkalinity of the solution.

Infusion Administration

For administration by infusion, parenteral phenytoin should be diluted in 50 mL to 100 mL of normal saline with the final concentration of phenytoin in the solution not exceeding 10 mg/mL. Administration should commence immediately after the mixture has been prepared and must be completed within 1 hour (the infusion mixture should not be refrigerated). An in-line filter (0.22-0.50 microns) should be used. Each injection of IV phenytoin should be preceded by a saline flush and followed by an injection of sterile saline through the same needle or IV catheter to help reduce local venous irritation due to the alkalinity of the solution.

Dosage is not to exceed 50 mg/minute, intravenously in adults, and not to exceed 1-3 mg/kg/minute in neonates and children or 50 mg/minute, whichever is slower. There is a relatively small margin between full therapeutic effect and minimally toxic doses of this drug (see Section 4.4 Special warnings and precautions for use – General).

On occasions when intramuscular (IM) administration may be required (i.e., postoperatively in comatose patients), a sufficient dose must be administered intramuscularly to maintain the serum level within the therapeutic range. Where oral dosage is resumed following IM usage, the oral dosage should be adjusted to compensate for the slow, continuing IM absorption to avoid toxic symptoms. To avoid drug accumulation due to absorption from the muscle depots, it is

recommended that for the first week back on oral phenytoin, the oral dose be reduced to one-half of the original dose (one-third of the IM dose).

Status Epilepticus

In adults, a loading dose of 10 mg/kg to 15 mg/kg should be administered slowly intravenously, at a rate not exceeding 50 mg/minute (this will require approximately 20 minutes in a 70 kg patient). The loading dose should be followed by a maintenance dose of 100 mg orally or intravenously every 6 to 8 hours.

Absorption of phenytoin in neonates and children may be unreliable after oral administration. A loading dose of 15 mg/kg to 20 mg/kg of phenytoin intravenously will usually produce serum concentrations of phenytoin within the generally accepted therapeutic range (10-20 mcg/mL). The drug should be injected slowly intravenously at a rate not exceeding 1 to 3 mg/kg/minute or 50 mg/minute, whichever is slower.

Continuous monitoring of the electrocardiogram and blood pressure is essential. The patient should be observed for signs of respiratory depression. Determination of phenytoin serum levels is advised when using phenytoin in the management of status epilepticus and in the subsequent establishment of maintenance dosage.

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

For the treatment of status epilepticus, intravenous administration of drug is necessary for rapid control of seizure. Because of the required slow rate of administration of phenytoin, the intravenous administration of a rapid onset anticonvulsant, such as diazepam or rapid onset barbiturate will usually be necessary prior to the intravenous administration of phenytoin.

If administration of parenteral phenytoin does not terminate seizures, the use of other anticonvulsants, IV barbiturates, general anesthesia, or other appropriate measures should be considered.

Intramuscular administration should not be used in the treatment of status epilepticus because the attainment of peak serum levels may require up to 24 hours (see Section 4.4 Special warnings

and precautions for use – General).

Neurosurgery

Prophylactic dosage - 100 mg to 200 mg (2 mL to 4 mL) administered intramuscularly at approximately 4-hour intervals during surgery and continued during the postoperative period. When IM administration is required for a patient previously stabilized orally, compensating dosage adjustments are necessary to maintain therapeutic serum levels. When IM administration is used, the drug should be given by deep IM injection. An IM dose 50% greater than the oral dose is necessary to maintain these levels. When the patient is returned to oral administration, the dose should be reduced by 50% of the original oral dose for 1 week to prevent excessive serum levels due to sustained release form IM tissue sites.

If the patient requires more than a week of IM phenytoin, alternative routes should be explored, such as gastric intubation. For time periods less than 1 week, the patient shifted back from IM administration should receive one-half the original oral dose for the same period of time the patient received IM phenytoin. Monitoring serum levels would help prevent a fall into the sub-therapeutic range. Serum drug level determinations are especially helpful when possible drug interactions are suspected.

Cardiac Arrhythmia

Dosage is 3.5 mg/kg to 5.0 mg/kg bodyweight, repeated once if necessary. Usually, a total daily dosage of 700 mg to 1000 mg is sufficient. If there is no beneficial reaction at plasma levels of 20 mcg/mL, it is unlikely that higher levels will have any effect. Slow administration of 30 mg/min to 50 mg/min is preferred.

Dosing in Special Populations

Patients with Renal or Hepatic Disease: see Section 4.4 Special warnings and precautions for use.

Elderly Patients: Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required (see Section 5.2 Pharmacokinetic properties –Special Populations – Age).

4.3 Contraindications

Phenytoin is contraindicated in patients who are hypersensitive to phenytoin, or its inactive ingredients, or other hydantoins.

Because of its effect on ventricular automaticity, phenytoin is contraindicated in sinus bradycardia, sinoatrial block, second- and third-degree atrioventricular (AV) block, and in patients with Adams-Stokes syndrome.

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

4.4 Special warnings and precautions for use

General

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

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

The most notable signs of toxicity associated with the IV use of this drug are cardiovascular collapse and/or central nervous system depression. Hypotension does occur when the drug is administered rapidly by the IV route. The rate of administration is very important; it should not exceed 50 mg/minute in adults, and 1 to 3 mg/kg/minute or 50 mg/minute (whichever is slower), in neonates and children. At this rate, toxicity should be minimized.

Hypotension usually occurs when the drug is administered by the IV route.

The IM route is not recommended for the treatment of status epilepticus since serum levels of phenytoin in the therapeutic range cannot be readily achieved with doses and methods of administration ordinarily used. In the treatment of status epilepticus, the IV route is preferred because of the delay in absorption of phenytoin when administered intramuscularly.

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

an antiepileptic drug not belonging to the hydantoin chemical class.

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

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

Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution. Unbound concentration of phenytoin may be elevated in patients with hyperbilirubinemia. Unbound phenytoin concentrations may be more useful in these patient populations.

Suicide

Suicidal ideation and behavior have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomized placebo-controlled trials of antiepileptic drugs has also shown a small increased risk of suicidal ideation and behavior. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for phenytoin.

Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms

Hypersensitivity syndrome (HSS) or drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients taking anticonvulsant drugs, including phenytoin. Some of these events have been fatal or life threatening.

HSS/DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leukocytosis, and eosinophilia. The interval between the first drug exposure and symptoms is usually 2 to 4 weeks, but has been reported in individuals receiving anticonvulsants for 3 or more months. If such signs and symptoms occur, the patient should be evaluated immediately. Phenytoin should be discontinued if an alternative etiology for the signs and symptoms cannot be

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

Cardiovascular Effects

Hypotension may occur. Severe cardiotoxic reactions and fatalities have been reported with arrhythmias including bradycardia, atrial and ventricular depression, and ventricular fibrillation. In some cases cardiac arrhythmias have resulted in asystole/cardiac arrest and death. Severe complications are most commonly encountered in elderly or gravely ill patients. Cardiac adverse events have also been reported in adults and children without underlying cardiac disease or comorbidities and at recommended doses and infusion rates. Therefore, careful cardiac (including respiratory) monitoring is needed when administering IV loading doses of phenytoin. Reduction in rate of administration or discontinuation of dosing may be needed. Phenytoin should be used with caution in patients with hypotension and/or severe myocardial insufficiency.

Central Nervous System Effect

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as “delirium,” “psychosis,” or “encephalopathy,” or rarely irreversible cerebellar dysfunction and/or cerebellar atrophy. Accordingly, at the first sign of acute toxicity, serum drug level determinations are recommended. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination of therapy with phenytoin is recommended.

Hematopoietic System

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

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin’s disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without signs and symptoms resembling HSS/DRESS (see Section 4.4 Special Warnings and Precautions for Use – Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and

Systemic Symptoms). In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative anticonvulsant drugs.

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

Hepatic Injury

The liver is the chief site of biotransformation of phenytoin.

Toxic hepatitis and liver damage have been reported and may, in rare cases, be fatal.

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents usually occur within the first 2 months of treatment and may be associated with HSS/DRESS (see Section 4.4 Special Warnings and Precautions for Use – Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms). Patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, phenytoin should be immediately discontinued and not re-administered.

The risk of hepatotoxicity and other hypersensitivity reactions to phenytoin may be higher in black patients.

Local Toxicity (Including Purple Glove Syndrome)

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

Edema, discoloration and pain distal to the site of injection (described as “purple glove syndrome”) have been reported following peripheral IV phenytoin injection. Soft tissue irritation may vary from slight tenderness to extensive necrosis and sloughing of the skin. The syndrome may not develop for several days after injection. Although resolution of symptoms may be spontaneous, skin

necrosis and limb ischemia have occurred and required interventions, such as fasciotomies, skin grafting, and, in rare cases, amputation.

Improper administration including subcutaneous or perivascular injection should be avoided.

Intramuscular phenytoin administration may cause pain, necrosis, and abscess formation at the injection site (see Section 4.2 Posology and Method of Administration).

Serious Dermatologic Reactions

Phenytoin can cause rare, severe cutaneous adverse reactions (SCARs) such as acute generalized exanthematous pustulosis (AGEP) (see Section 4.8 Undesirable Effects – Dermatologic System), exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS, which can be fatal. Although serious skin reactions may occur without warning, patients should be alert for the occurrence of rash and other symptoms of HSS/DRESS (see Section 4.4 Special Warnings and Precautions for Use – Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms) and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. The physician should advise the patient to discontinue treatment if the rash appears. If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated. The risk of serious skin reactions and other hypersensitivity reactions to phenytoin may be higher in black patients.

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

Literature reports suggest that the combination of phenytoin, cranial irradiation, and the gradual reduction of corticosteroids may be associated with the development of erythema multiforme and/or SJS and/or TEN.

Angioedema

Angioedema has been reported in patients treated with phenytoin. Phenytoin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur (see Section 4.8 Undesirable Effects – Immunologic).

Metabolic Effect

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

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

Women of Childbearing Potential

Phenytoin may cause fetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse development outcomes (see Section 4.6 Fertility, Pregnancy and Lactation).

Excipients with Known Effect

Phenytoin sodium IV solution contains the excipient propylene glycol (see Section 6.1 List of Excipients). Prolonged use of >24 hours could result in propylene glycol toxicity (including hemolysis, Central Nervous System (CNS) depression, hyperosmolality, lactic acidosis, and renal insufficiency), especially in patients with pre-existing renal and/or hepatic dysfunction or when co-administered with any other propylene glycol-containing product or substrate of alcohol dehydrogenase. Patients should be monitored for propylene glycol toxicity, including measurement of the anion-gap.

Information for the Patient

Patients should be cautioned on the use of other drugs or alcoholic beverages without first seeking their physician's advice.

Patients should be instructed to call their physician if skin rash develops.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions

Phenytoin is extensively bound to serum plasma proteins and is prone to competitive

displacement. Phenytoin is metabolized by hepatic cytochrome (CYP) P450 enzymes CYP2C9 and CYP2C19, and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity.

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

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

The most commonly occurring drug interactions are listed below.

Drugs that may increase phenytoin serum levels

Table 1 summarizes the drug classes that may potentially increase phenytoin serum levels.

Table 1 Drugs That May Increase Phenytoin Serum Levels

DRUG CLASSES	DRUGS IN EACH CLASS (SUCH AS[a])
Alcohol (acute intake)	
Analgesic/anti-inflammatory agents	Azapropazone Phenylbutazone Salicylates
Anesthetics	Halothane
Antibacterial agents	Chloramphenicol Erythromycin Isoniazid Sulfadiazine Sulfamethizole Sulfamethoxazole-trimethoprim Sulfaphenazole Sulfisoxazole Sulfonamides
Anticonvulsants	Felbamate

DRUG CLASSES	DRUGS IN EACH CLASS (SUCH AS[a])
	Oxcarbazepine Sodium valproate Succinimides Topiramate
Antifungal agents	Amphotericin B Fluconazole Itraconazole Ketoconazole Miconazole Voriconazole
Antineoplastic agents	Fluorouracil Capecitabine
Benzodiazepines/psychotropic agents	Chlordiazepoxide Diazepam Disulfiram Methylphenidate Trazodone Viloxazine
Calcium channel blockers/cardiovascular agents	Amiodarone Dicumarol Diltiazem Nifedipine Ticlopidine
H_2-antagonists	Cimetidine
HMG-CoA reductase inhibitors	Fluvastatin
Hormones	Estrogens
Immunosuppressant drugs	Tacrolimus
Oral hypoglycemic agents	Tolbutamide
Proton pump inhibitors	Omeprazole
Serotonin re-uptake inhibitors	Fluoxetine Fluvoxamine Sertraline

[a]This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted.

Drugs that may decrease phenytoin serum levels

Table 2 summarizes the drug classes that may potentially decrease phenytoin serum levels.

Table 2 Drugs That May Decrease Phenytoin Serum Levels

DRUG CLASSES	DRUGS IN EACH CLASS (SUCH AS[a])
Alcohol (chronic intake)	
Antibacterial agents	Rifampin Ciprofloxacin
Anticonvulsants	Vigabatrin
Antineoplastic agents	Bleomycin Carboplatin Cisplatin Doxorubicin Methotrexate
Antiretrovirals	Fosamprenavir Nelfinavir Ritonavir
Bronchodilators	Theophylline
Cardiovascular agents	Reserpine
Folic acid	Folic acid
Hyperglycemic agents	Diazoxide
St. John's Wort	St. John's Wort

[a]This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted.

Molindone hydrochloride contains calcium ions, which interfere with the absorption of phenytoin. Ingestion times of phenytoin and calcium preparations, including antacid preparations containing calcium, should be staggered to prevent absorption problems.

Drugs that may increase or decrease phenytoin serum levels

Table 3 summarizes the drug classes that may either increase or decrease phenytoin serum levels.

Table 3 Drugs That May Increase or Decrease Phenytoin Serum Levels

DRUG CLASSES	DRUGS IN EACH CLASS (SUCH AS[a])
Antibacterial agents	Ciprofloxacin
Anticonvulsants	Carbamazepine Phenobarbital Sodium valproate[b] Valproic acid[b]
Antineoplastic agents	
Psychotropic agents	Chlordiazepoxide Diazepam Phenothiazines

[a]This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted.

[b] Sodium valproate and valproic acid are similar medications. The term valproate has been used to represent these medications.

Drugs whose serum levels and/or effects may be altered by phenytoin

Table 4 summarizes the drug classes whose serum levels and/or effects may be altered by phenytoin.

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

DRUG CLASSES	DRUGS IN EACH CLASS (SUCH AS[a])
Antibacterial agents	Doxycycline Rifampin Tetracycline
Anticoagulants	Warfarin Apixaban Dabigatran Edoxaban Rivaroxaban
Anticonvulsants	Carbamazepine Lamotrigine Phenobarbital Sodium valproate[b] Valproic acid[b]

DRUG CLASSES	DRUGS IN EACH CLASS (SUCH AS[a])
	Lacosamide
Antifungal agents	Azoles Posaconazole Voriconazole
Anthelmintics	Albendazole Praziquantel
Antineoplastic agents	Teniposide
Antiplatelets	Ticagrelor
Antiretrovirals	Delavirdine Efavirenz Fosamprenavir Indinavir Lopinavir/ritonavir Nelfinavir Ritonavir Saquinavir
Bronchodilators	Theophylline
Calcium channel blockers/Cardiovascular agents	Digitoxin Digoxin Disopyramide Mexiletine Nicardipine Nimodipine Nisoldipine Quinidine Verapamil
Corticosteroids	
Cyclosporine	
Diuretics	Furosemide
HMG-CoA reductase inhibitors	Atorvastatin Fluvastatin Simvastatin
Hormones	Estrogens

DRUG CLASSES	DRUGS IN EACH CLASS (SUCH AS[a])
	Oral contraceptives (see Sections 4.4 and 4.6)
Hyperglycemic agents	Diazoxide
Neuromuscular blocking agents	Alcuronium Cisatracurium Pancuronium Rocuronium Vecuronium
Opioid analgesics	Methadone
Oral hypoglycemic agents	Chlorpropamide Glyburide Tolbutamide
Psychotropic agents/Antidepressants	Clozapine Paroxetine Quetiapine Sertraline
Vitamin D	Vitamin D
Folic acid	Folic acid

[a]This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted.

[b] Sodium valproate and valproic acid are similar medications. The term valproate has been used to represent these medications.

Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

Hyperammonemia with Concomitant Use of Valproate

Concomitant administration of phenytoin and valproate has been associated with an increased risk of valproate-associated hyperammonemia. Patients treated concomitantly with these two drugs should be monitored for signs and symptoms of hyperammonemia.

Drug-Laboratory Test Interactions

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

(GGT). Phenytoin may affect blood calcium and blood sugar metabolism tests.

4.6 Fertility, pregnancy and lactation

Fertility

In animal studies, phenytoin had no direct effect on fertility.

Usage in pregnancy

Phenytoin crosses the placenta in humans.

A number of reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans. Genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of child-bearing potential.

In addition to the reports of increased incidence of congenital malformations, such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other anticonvulsant drugs, there have been reports of a fetal hydantoin syndrome. This consists of prenatal dysmorphic facial features, nail and digit hypoplasia, growth deficiency (including microcephaly), and mental deficiency in children born to mothers who have received phenytoin.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

Phenytoin should only be used in women of childbearing potential and pregnant women if the potential benefit outweighs the risk. When appropriate, counsel pregnant women and women of childbearing potential about alternative therapeutic options.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

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

Women of childbearing potential who are not planning a pregnancy should be advised regarding the use of effective contraception during treatment. Phenytoin may result in a failure of the therapeutic effect of hormonal contraceptives (see Section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction).

Phenytoin is teratogenic in rats, mice and rabbits.

Usage in Nursing Mothers

Breast-feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk. Phenytoin concentration in breast milk is approximately one-third of the corresponding maternal plasma concentration.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive a car or operate potentially dangerous machinery until it is known that this medication does not affect their ability to engage in these activities.

4.8 Undesirable effects

The following adverse reactions have been reported with phenytoin (frequency unknown – cannot be estimated from available data):

Body as a Whole: Anaphylactoid reaction and anaphylaxis.

Cardiovascular System: Asystole/cardiac arrest, bradycardia, and hypotension have been observed (see Section 4.4 Special Warnings and Precautions for Use – General and Cardiovascular Effects).

Central Nervous System: Adverse reactions in this body system are common and are usually dose related. Reactions include nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion. Cerebellar atrophy has been reported and appears more likely in settings of elevated phenytoin levels and/or long-term phenytoin use (see Section 4.4 Special Warnings and Precautions for Use – Central Nervous System Effect).

Dizziness, vertigo, insomnia, transient nervousness, motor twitchings, headache, paresthesia, and somnolence have also been observed.

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

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

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis, and Peyronie’s disease.

Gastrointestinal System: Acute hepatic failure, toxic hepatitis, liver damage, vomiting, nausea, and constipation (see Section 4.4 Special Warnings and Precautions for Use – Hepatic Injury).

Hematopoietic System: Hematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. Macrocytosis and megaloblastic anemia have also occurred. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease have been reported (see Section 4.4 Special Warnings and Precautions for Use – Hematopoietic System). Pure red cell aplasia has also been reported.

Immunologic: HSS/DRESS (see Section 4.4 Special Warnings and Precautions for Use - Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms), systemic lupus erythematosus, periarteritis nodosa, and immunoglobulin abnormalities. Angioedema has been reported (see Section 4.4 Special Warnings and Precautions for Use – Angioedema).

Injection Site: Local irritation, inflammation, tenderness, necrosis, and sloughing of skin have been reported with or without extravasation of IV phenytoin. Edema, discoloration and pain distal to the site of injection (described as “purple glove syndrome”) have also been reported (see Section 4.4 Special Warnings and Precautions for Use – Local Toxicity [Including Purple Glove Syndrome]).

Investigations: Thyroid function test abnormal.

Dermatologic System: Dermatological manifestations, sometimes accompanied by fever, have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms that may be fatal have included bullous, exfoliative, or purpuric dermatitis, lupus erythematosus, AGEP, SJS, and TEN (see Section 4.4 Special Warnings and Precautions for Use –Serious Dermatologic Reactions). Urticaria has been reported.

Special Senses: Taste perversion

4.9 Overdose

The lethal dose in pediatric patients is not known. The lethal dose in adults is estimated to be 2 g to 5 g. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor,

hyperreflexia, somnolence, drowsiness, lethargy, slurred speech, blurred vision, nausea, and vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

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

Treatment

Treatment is non-specific since there is no known antidote.

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

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

5. Pharmacological Properties

5.1 Pharmacodynamic properties

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

5.2 Pharmacokinetic properties

Phenytoin is a weak acid and has limited hydrosolubility, even in the intestine. The compound undergoes a slow and somewhat variable absorption after oral administration. After IM administration, the absorption of phenytoin is slower than after oral administration, due to poor hydrosolubility of the compound and the possibility of its precipitation at the site of injection.

The plasma half-life of phenytoin in man averages 22 hours, with a range of 7 to 42 hours. Phenytoin has an apparent volume of distribution of 0.6 L/kg and is highly bound (90%) to plasma proteins, mainly albumin. Free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal. Phenytoin is distributed into the cerebrospinal fluid (CSF), saliva, semen, gastrointestinal fluid, bile, and breast milk. The concentration of phenytoin in the CSF, brain, and saliva approximates the level of free phenytoin in plasma.

Phenytoin is biotransformed in the liver by oxidative metabolism. The major pathway involves 4-hydroxylation, which accounts for 80% of all metabolites. CYP2C9 plays the major role in the metabolism of phenytoin (90% of net intrinsic clearance), while CYP2C19 has a minor involvement in this process (10% of net intrinsic clearance). This relative contribution of CYP2C19 to phenytoin metabolism may, however, increase at higher phenytoin concentrations.

Because the cytochrome systems involved in phenytoin hydroxylation in the liver are saturable at high serum concentrations, small incremental doses of phenytoin may increase the half-life and produce very substantial increases in serum levels when these are in or above the upper therapeutic range. The clearance of phenytoin has been shown to be impaired by CYP2C9 inhibitors, such as phenylbutazone and sulfaphenazole. Impaired clearance has also been shown to occur in patients administered CYP2C19 inhibitors, such as ticlopidine.

Most of the drug is excreted in the bile as inactive metabolites, which are then reabsorbed from the intestinal tract and eliminated in the urine partly through glomerular filtration, but more importantly via tubular secretion. Less than 5% of phenytoin is excreted as the parent compound.

A fall in phenytoin serum levels may occur when patients are switched from oral to IM administration. The drop is caused by slower absorption, as compared to oral administration, due to the poor hydrosolubility of phenytoin and the possibility of its precipitation at the site of injection. Intravenous administration is the preferred route for producing rapid therapeutic serum levels.

Special Populations

Patients with Renal or Hepatic Disease: see Section 4.4 Special Warnings and Precautions for Use - General.

Age: Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20-30 years of age). Phenytoin dosing requirements are highly variable and must be individualized (see Section 4.2 Posology and Method of Administration - Dosing in Special Populations – Elderly Patients).

5.3 Preclinical safety data

Carcinogenesis

In a transplacental and adult carcinogenicity study, phenytoin was administered in diet at 30 to 600 ppm to mice and 240 to 2400 ppm to rats. Hepatocellular tumors were increased at the higher doses in mice and rats. In additional studies, mice received 10 mg/kg, 25 mg/kg, or 45 mg/kg and rats were given 25 mg/kg, 50 mg/kg, or 100 mg/kg in the diet for 2 years. Hepatocellular tumors in mice increased at 45 mg/kg. No increases in tumor incidence were observed in rats. These rodent tumors are of uncertain clinical significance.

Genetic toxicity studies showed that phenytoin was not mutagenic in bacteria or in mammalian cells *in vitro*. It is clastogenic *in vitro* but not *in vivo*.

6. Pharmaceutical Particulars

6.1 List of Excipients

Sterile solution vehicle contains 40% propylene glycol and 10% alcohol in water for injection, adjusted to pH 12 with sodium hydroxide.

6.2 Incompatibilities

Parenteral phenytoin should not be added to dextrose or dextrose-containing solutions due to the potential for precipitation.

6.3 Shelf life

Please see details on carton.

This product is for single use only. From a microbiological point of view, the aseptically prepared

product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at room temperature 15°C-30°C, unless prepared product has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 30°C.

Protect from light.

6.5 Nature and contents of container

Phenytoin sodium solution containing 50 mg phenytoin sodium per mL is supplied in 5 mL sterivials

6.6 Special precautions for disposal and other handling

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

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

Both the undiluted form and the infusion mixture are suitable for use as long as they remain free of haziness and precipitate.

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

7. Marketing Authorization Holder

Viatris (Thailand) Limited

8. Marketing Authorization Numbers

1C 15053/64

9. Date of Authorization

March 19, 2021

10. Date of Revision of the Text

May 19, 2022

Warning (based on the Ministry of Public Health's Announcement)

1. The drug may cause drowsiness, do not drive a car or operate machinery, or drink alcohol beverages while taking the drug.
2. The drug may cause hematologic disorder.
3. Do not use the drug while pregnant because it may cause teratogenesis.
4. Use the drug with caution in patients with liver and kidney disease.
5. If there is erythema multiforme or flu-like symptom after use, stop using this drug and consult the physician immediately.
6. Is contraindicated in patients who have ever been hypersensitive to this drug.
7. If the following symptoms occur during using this drug, e.g., fever, erythema multiforme, vesicle, skin lesions and other lesions appear in the mucous membranes (such as in the mouth cavity, throat, nasal cavity, sexual organs) and conjunctivitis, stop using this drug and consult the physician immediately as this may be Stevens-Johnson syndrome.

คำเตือน (ตามประกาศกระทรวงสาธารณสุข)

1. ยานี้อาจทำให้ง่วงซึม จึงไม่ควรขับขี่ยานยนต์ หรือทำงานเกี่ยวกับเครื่องจักร และไม่ควรดื่มสุรา หรือสิ่งที่มีแอลกอฮอล์ผสมอยู่ ขณะใช้ยานี้
2. ยานี้อาจทำให้เกิดความผิดปกติของเม็ดเลือด
3. ห้ามใช้ยานี้ในสตรีมีครรภ์เพราะอาจทำให้ทารกพิการได้
4. ควรระมัดระวังการใช้ยานี้ในผู้ป่วยโรคตับโรคไต
5. หากใช้ยานี้แล้วมีอาการผื่นแดง หรือมีอาการคล้ายเป็นหวัด ให้หยุดยาและรีบปรึกษาแพทย์ทันที
6. ห้ามใช้ในผู้ที่เคยแพ้ยานี้
7. เมื่อใช้ยานี้หากมีอาการดังต่อไปนี้ เช่น ไข้ ผื่นแดง ตุ่มน้ำพอง มีการหลุดลอกของผิวหนัง และบริเวณเยื่อบุต่างๆ เช่น ในช่องปาก ลำคอ จมูก อวัยวะสืบพันธุ์ และเยื่อบุตาอักเสบ ให้หยุดยาและปรึกษา

แพทย์เพราะอาจเป็น Stevens-Johnson syndrome

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