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DILANTIN®

(Extended-release Phenytoin Sodium Capsules, USP)

1. NAME OF THE MEDICINAL PRODUCT

Dilantin® (Capsules 100 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each phenytoin sodium extended-release capsule for oral administration contains 100 mg phenytoin sodium.

3. PHARMACEUTICAL FORM

Extended release capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and Method of Administration

General

Phenytoin extended-release 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*.

For all oral formulations, dosage should be individualized to provide maximum benefit. In

some cases serum drug level determinations may be necessary for optimal dosage adjustments. Optimum control without clinical signs of toxicity occurs more often with serum levels between 10 mcg/mL and 20 mcg/mL, although some mild cases of tonic-clonic (grand mal) epilepsy may be controlled with lower serum levels of phenytoin. With recommended dosage, a period of 7 to 10 days may be required to achieve steady-state serum levels with phenytoin, and changes in dosage (increase or decrease) should not be carried out at intervals shorter than 7 to 10 days.

Adult Dosage

Divided daily dosage

Patients who have received no previous treatment may be started on 300 mg daily, to be taken in three equally divided doses, and the dosage then adjusted to suit individual requirements. For most adults, the satisfactory maintenance dosage will be 300 mg to 400 mg daily, to be taken in three to four equally divided doses, respectively. An increase up to 600 mg daily may be made if necessary.

Once-a-day dosage

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

Only extended phenytoin sodium capsules are recommended for once-a-day dosing. Inherent differences in dissolution characteristics and resultant absorption rates of phenytoin due to different manufacturing procedures and/or dosage forms preclude such recommendation for other phenytoin products. When a change in the dosage form or brand is prescribed, careful monitoring of phenytoin serum levels should be carried out.

Non-emergency oral loading dose in adult patients

An oral loading dose of phenytoin may be used for non-emergency initiation of therapy in adults who require rapid steady-state serum levels, and for whom intravenous administration is not desirable. This dosing regimen should be reserved for patients in a clinic or hospital setting where phenytoin serum levels can be closely monitored. Patients with a history of renal or liver disease should not receive the oral loading dose regimen.

The recommended oral loading dose is 1 g of phenytoin divided into three doses (400 mg, 300 mg, and 300 mg) and administered at 2-hour intervals. Normal maintenance dosage is then instituted 24 hours after the loading dose, with frequent serum level determinations.

Pediatric Dosage

Initially 5 mg/kg/day in two or three equally divided doses with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 mg/kg to 8 mg/kg. Children over 6 years and adolescents may require the minimum adult dose (300 mg/day). If the daily dosage cannot be divided equally, the larger dose should be given at bedtime.

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.

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 hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin 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 anti-epileptic 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 anticonvulsant drug which does not belong 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 anti-epileptic agents in several indications. A meta-analysis of randomized placebo-controlled trials of anti-epileptic 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.

Cardiac Effects

Cases of bradycardia and asystole/cardiac arrest have been reported, most commonly in association with phenytoin toxicity (see Section 4.9 **Overdose**), but also at recommended phenytoin doses and levels.

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.

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, determination of serum drug levels is recommended. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination of phenytoin therapy 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.

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 may also raise serum glucose levels in diabetic patients.

Musculoskeletal Effect

Phenytoin and other anticonvulsants that have been shown to induce the CYP450 enzyme are thought to affect bone mineral metabolism indirectly by increasing the metabolism of Vitamin D_3. This may lead to Vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcemia, and hypophosphatemia in chronically treated epileptic 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**).

Information for the Patient Using an Oral Formulation of Phenytoin

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

Patients should also 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.

The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

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 Potentially 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

Drug Classes	Drugs In Each Class (such as[a])
	Sulfisoxazole Sulfonamides
Anticonvulsants	Felbamate Oxcarbazepine Sodium valproate Succinimides Topiramate
Antifungal agents	Amphotericin B Fluconazole Itraconazole Ketoconazole Miconazole Voriconazole
Antineoplastic agents	Capecitabine Fluorouracil
Benzodiazepines/Psychotropic agents	Chlordiazepoxide Diazepam Disulfiram Methylphenidate Trazodone Viloxazine
Calcium channel blockers/Cardiovascular agents	Amiodarone Dicumarol Diltiazem Nifedipine Ticlodipine
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

Drug Classes	Drugs In Each Class (such as[a])
	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	Ciprofloxacin Rifampin
Anticonvulsants	Vigabatrin
Antineoplastic agents	Bleomycin Carboplatin Cisplatin Doxorubicin Methotrexate
Antiulcer agents	Sucralfate
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 either 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 Either 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

Drug Classes	Drugs In Each Class (such as[a])
Anticonvulsants	Carbamazepine Lamotrigine Phenobarbital Sodium valproate[b] Valproic acid[b] Lacosamide
Antifungal agents	Azoles Posaconazole Voriconazole
Antihelminthics	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	

Drug Classes	Drugs In Each Class (such as[a])
Diuretics	Furosemide
HMG-CoA reductase inhibitors	Atorvastatin Fluvastatin Simvastatin
Hormones	Estrogens Oral contraceptives (see Sections 4.4 and 4.6)
Hyperglycemic agents	Diazoxide
Immunosuppressant drugs	
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-Enteral Feeding/Nutritional Preparations Interaction

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

Drug-Laboratory Test Interactions

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

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.

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 dyskinesias, including chorea, dystonia, tremor, and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients receiving

long-term phenytoin therapy.

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, 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**).

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.

Musculoskeletal System: Bone fractures and osteomalacia have been associated with long-term (>10 years) use of phenytoin by patients with chronic epilepsy. Osteoporosis and other disorders of bone metabolism, such as hypocalcemia, hypophosphatemia and decreased levels of vitamin D metabolites have also been reported.

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, hyper-reflexia, somnolence, drowsiness, lethargy, slurred speech, blurred vision, nausea, and vomiting. The patient may become comatose and hypotensive. Bradycardia and asystole/cardiac arrest have been reported (see Section 4.4 **Special Warnings and Precautions for Use** – **Cardiac Effects**). 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 can be useful in the treatment of epilepsy. The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at 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 absorption is complete, it is rapidly distributed into all tissues.

The plasma half-life of phenytoin in man averages 22 hours, with a range of 7 to 42 hours. Steady-state therapeutic drug levels are achieved at least 7 to 10 days after initiation of therapy with recommended doses of 300 mg/day. For phenytoin extended-release capsule, peak serum levels occur 4-12 hours after administration. 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 fluids, 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 steady-state level may be disproportionately increased with resultant intoxication from an increase in dosage of 10% or more. 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.

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low serum levels may be non-compliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, congenital enzyme deficiency or drug interactions which result in metabolic interference. Patients with large variations in phenytoin serum levels, despite standard doses, present a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. When they are necessary, they should be obtained at least 7 to 10 days after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that equilibrium or steady state will have been achieved. Trough levels, obtained just prior to the patient's next scheduled dose, provide information about clinically effective serum level range and confirm patient compliance. Peak drug levels, obtained at the time of expected peak concentration, indicate an individual's threshold for emergence of dose-related side effects.

Clinical studies show that chewed and unchewed tablets are bioequivalent, yield approximately equivalent serum levels, and are more rapidly absorbed than 100 mg capsules.

Pharmacokinetic Interaction

Co-administration of nelfinavir tablets (1250 mg twice a day) with phenytoin capsule (300 mg once a day) did not change the plasma concentration of nelfinavir. However, co-administration of nelfinavir reduced the AUC values of phenytoin (total) and free phenytoin by 29% and 28%, respectively.

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

Lactose, sucrose, talc, and other ingredients. The capsule shell and band contain colloidal silicon dioxide, FD&C red No. 3, gelatin, glyceryl monooleate, and sodium lauryl sulfate.

6.2 Incompatibilities

None known.

6.3 Shelf-life

Please see details on container.

6.4 Special Precautions for Storage

Store below 30°C (86°F).

Protect from light and moisture.

6.5 Nature and Contents of Container

Dilantin extended-release capsule contains phenytoin sodium 100 mg and are packed in HDPE bottle, pack size 100 and 1000 capsules per bottle.

7. MARKETING AUTHORIZATION HOLDER

Viatris (Thailand) Limited

Manufactured by:
Viatris Pharmaceuticals LLC, Vega Baja, Puerto Rico

8. MARKETING AUTHORIZATION NUMBERS

1C 29/63

9. DATE OF AUTHORIZATION

3 August 2020

10. DATE OF REVISION OF THE TEXT

15 March 2024

NOTE: WARNINGS (based on the Ministry of Public Health 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 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.