1. NAME OF MEDICINAL PRODUCT

Dilantin Oral Suspension 125 mg/5 mL.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL of suspension contains 125 mg phenytoin, USP.

3. PHARMACEUTICAL FORM

Phenytoin Oral Suspension 125 mg/5 mL will be provided as an opaque orange suspension with an orange–vanilla-banana odor. The drug product is packaged in a round amber glass bottle or round amber polyethylene terephthalate (PET) bottle, having a polypropylene cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Phenytoin is indicated for the control of tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures.

4.2 Posology and Method of Administration

FOR ORAL ADMINISTRATION ONLY; NOT FOR PARENTERAL USE.
A calibrated measuring device is recommended to measure and deliver the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device.

Adult Dosage:
The recommended starting dosage for adult patients who have received no previous treatment is 5 mL (125 mg/5 mL), or one teaspoonful, by mouth three times daily. Adjust the dosage to suit individual requirements, up to a maximum of 25 mL daily (See **Dosage Adjustments**).

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

Dosage Adjustments:
Dosage should be individualized to provide maximum benefit. In some cases, serum blood level determinations may be necessary for optimal dosage adjustments. Trough levels provide information about clinically effective serum level range and confirm patient compliance, and are obtained just prior to the patient's next scheduled dose. Peak levels indicate an individual's threshold for emergence of dose-related side effects and are obtained at the time of expected peak concentration. Therapeutic effect without clinical signs of toxicity occurs more often with serum total concentrations between 10 and 20 mcg/mL (unbound phenytoin concentrations of 1 to 2 mcg/mL), although some mild cases of tonic-clonic (grand mal) epilepsy may be controlled with lower serum levels of phenytoin. In patients with renal or hepatic disease, or in those with hypoalbuminemia, the monitoring of unbound phenytoin concentrations may be more relevant (See **Dosing in Patients with Renal or Hepatic Impairment or Hypoalbuminemia**).

With recommended dosages, a period of seven to ten days may be required to achieve steady-state blood levels with phenytoin and changes in dosage (increase or decrease) should not be carried out at intervals shorter than seven to ten days.

Switching Between Phenytoin Formulations:
The free acid form of phenytoin is used in Dilantin-125 Suspension and Dilantin Infatabs. Dilantin extended capsules are formulated with the sodium salt of phenytoin. 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*.

Dosing in Patients with Renal or Hepatic Impairment or Hypoalbuminemia:
Because the fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the monitoring of phenytoin serum levels should be based on the unbound fraction in those patients (see Sections **4.4 Special Warnings and Precautions for Use** and **4.6 Fertility, Pregnancy and Lactation**).

Geriatric Dosage:
Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required (see Section **5.2 Pharmacokinetic Properties**).

4.3 Contraindications

Phenytoin is contraindicated in those patients with:

- A history of hypersensitivity to phenytoin, its inactive ingredients or other hydantoins (see Section **4.4 Special Warnings and Precautions for Use**). Reactions have included angioedema.
- A history of prior acute hepatotoxicity attributable to phenytoin (see Section **4.4 Special Warnings and Precautions for Use**).
- Co-administration with delavirdine because of 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

Withdrawal Precipitated Seizure, Status Epilepticus
Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When in the judgment of the clinician the need for dosage reduction, discontinuation, or substitution of alternative anticonvulsant medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, more rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an anticonvulsant not belonging to the hydantoin chemical class.

Suicidal Behavior and Ideation
Antiepileptic drugs (AEDs), including phenytoin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice

the risk (adjusted Relative Risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing phenytoin or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Serious Dermatologic Reactions
Dilantin can cause severe cutaneous adverse reactions (SCARs), which may be fatal. Reported reactions in phenytoin-treated patients have included toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see Section **4.4 Special Warnings and Precautions for Use**). The onset of symptoms is usually within 28 days, but can occur later. Dilantin should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest a severe cutaneous adverse reaction, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of SCARs.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. In addition, retrospective, case-control, genome-wide association studies in patients of southeast Asian ancestry have also identified an increased risk of SCARs in carriers of the decreased function CYP2C9*3 variant, which has also been associated with decreased clearance of phenytoin. Consider avoiding phenytoin as an alternative to carbamazepine in patients who are positive for HLA-B*1502 or in CYP2C9*3 carriers (see Sections **4.4 Special Warnings and Precautions for Use** and **5.2 Pharmacokinetic Properties**).

The use of HLA-B*1502 or CYP2C9 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including Dilantin. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Dilantin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Hypersensitivity
Dilantin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity (see Sections **4.3 Contraindications and 4.4 Special Warnings and Precautions for Use**). Additionally, consider alternatives to structurally similar drugs, such as carboxamides (e.g., carbamazepine), barbiturates, succinimides, and oxazolidinediones (e.g., trimethadione) in these same patients. Similarly, if there is a history of hypersensitivity reactions to these structurally similar drugs in the patient or immediate family members, consider alternatives to Dilantin.

Cardiac Effects
Cases of bradycardia and cardiac arrest have been reported in DILANTIN-treated patients, both at recommended phenytoin doses and levels, and in association with phenytoin toxicity (see Section **4.9 Overdose**). Most of the reports of cardiac arrest occurred in patients with underlying cardiac disease.

Angioedema
Angioedema has been reported in patients treated with DILANTIN in the postmarketing setting. DILANTIN should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur. DILANTIN should be discontinued permanently if a clear alternative etiology for the reaction cannot be established.

Hepatic Injury
Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with Dilantin. These events may be part of the spectrum of DRESS or may occur in isolation (see Section **4.4 Special Warnings and Precautions for Use**). Other common manifestations include jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, Dilantin should be immediately discontinued and not re-administered.

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

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

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

Effects on Vitamin D and Bone
The chronic use of phenytoin in patients with epilepsy has been associated with decreased bone mineral density (osteopenia, osteoporosis, and osteomalacia) and bone fractures. Phenytoin induces hepatic metabolizing enzymes. This may enhance the metabolism of vitamin D and decrease vitamin D levels, which may lead to vitamin D deficiency, hypocalcemia, and hypophosphatemia. Consideration should be given to screening with bone-related laboratory and radiological tests as appropriate and initiating treatment plans according to established guidelines.

Renal or Hepatic Impairment, or Hypoalbuminemia
Because the fraction of unbound phenytoin is increased in patients with renal or hepatic disease, or in those with hypoalbuminemia, the monitoring of phenytoin serum levels should be based on the unbound fraction in those patients.

Use in Patients with Decreased CYP2C9 Function
Patients who are intermediate or poor metabolizers of CYP2C9 substrates (e.g., *1/*3, *2/*2, *3/*3) may exhibit increased phenytoin serum concentrations compared to patients who are normal metabolizers (e.g., *1/*1). Thus, patients who are known to be intermediate or poor metabolizers may ultimately require lower doses of phenytoin to maintain similar steady-state concentrations compared to normal metabolizers. If early signs of dose-related central nervous system (CNS) toxicity develop, serum concentrations should be checked immediately (see Section **5.2 Pharmacokinetic Properties**).

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

Teratogenicity and Other Harm to the Newborn
DILANTIN may cause fetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes (see Section **4.6 Fertility, Pregnancy and Lactation**).

Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), and abnormalities characteristic of fetal hydantoin syndrome, including dysmorphic skull and facial features, nail and digit hypoplasia, growth abnormalities (including microcephaly), and cognitive deficits, have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have been several reported cases of malignancies, including neuroblastoma.

A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin *in utero*. This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

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

Serum Phenytoin Levels above Therapeutic Range
Serum levels of phenytoin sustained above the therapeutic 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 levels should be immediately checked. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination is recommended.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Drug Interactions
Phenytoin is extensively bound to plasma proteins and is prone to competitive displacement. Phenytoin is primarily metabolized by the hepatic cytochrome P450 enzyme CYP2C9 and to a lesser extent by 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. Monitoring of phenytoin serum levels is recommended when a drug interaction is suspected.

Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes.

Drugs that Affect Phenytoin Concentrations
Table 2 includes commonly occurring drug interactions that affect phenytoin concentrations. However, this list is not intended to be inclusive or comprehensive. Individual prescribing information from relevant drugs should be consulted.

The addition or withdrawal of these agents in patients on phenytoin therapy may require an adjustment of the phenytoin dose to achieve optimal clinical outcome.

Table 2: Drugs That Affect Phenytoin Concentrations

Interacting Agent	Examples
Drugs that may increase phenytoin serum levels	
Antiepileptic drugs	Ethosuximide, felbamate, oxcarbazepine, methsuximide, topiramate
Azoles	Fluconazole, ketoconazole, itraconazole, miconazole, voriconazole
Antineoplastic agents	Capecitabine, fluorouracil
Antidepressants	Fluoxetine, fluvoxamine, sertraline
Gastric acid reducing agents	H_2 antagonists (cimetidine), omeprazole
Sulfonamides	Sulfamethizole, sulfaphenazole, sulfadiazine, sulfamethoxazole-trimethoprim
Other	Acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, disulfiram, estrogen, fluvastatin, isoniazid, methylphenidate, phenothiazines, salicylates, ticlopidine, tolbutamide, trazodone, warfarin
Drugs that may decrease phenytoin serum levels	
Antacids[a]	Calcium carbonate, aluminum hydroxide, magnesium hydroxide *Prevention or Management:* Phenytoin and antacids should not be taken at the same time of day
Antineoplastic agents (usually in combination)	Bleomycin, carboplatin, cisplatin, doxorubicin, methotrexate
Antiviral agents	Fosamprenavir, nelfinavir, ritonavir
Antiepileptic drugs	Carbamazepine, vigabatrin
Other	Chronic alcohol abuse, diazepam, diazoxide, folic acid, reserpine, rifampin, St. John's Wort[b], sucralfate, theophylline
Drugs that may either increase or decrease phenytoin serum levels	
Antiepileptic drugs	Phenobarbital, valproate sodium, valproic acid

[a] Antacids may affect absorption of phenytoin.
[b] The induction potency of St. John's Wort may vary widely based on preparation.

Drugs Affected by Phenytoin
Table 3 includes commonly occurring drug interactions affected by phenytoin. However, this list is not intended to be inclusive or comprehensive. Individual drug package inserts should be consulted.

The addition or withdrawal of phenytoin during concomitant therapy with these agents may require adjustment of the dose of these agents to achieve optimal clinical outcome.

Table 3: Drugs Affected by Phenytoin

Interacting Agent	Examples
Drugs whose efficacy is impaired by phenytoin	
Azoles	Fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole
Antineoplastic agents	Irinotecan, paclitaxel, teniposide
Delavirdine	Phenytoin can substantially reduce the concentrations of delavirdine. This can lead to loss of virologic response and possible resistance (see Section **4.3 Contraindications**).
Neuromuscular blocking agents	Cisatracurium, pancuronium, rocuronium and vecuronium: resistance to the neuromuscular blocking action of the nondepolarizing neuromuscular blocking agents has occurred in patients chronically administered phenytoin. Whether or not phenytoin has the same effect on other non-depolarizing agents is unknown. *Prevention or Management:* Patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected, and infusion rate requirements may be higher.
Warfarin	Increased and decreased PT/INR responses have been reported when phenytoin is coadministered with warfarin
Other	Corticosteroids, doxycycline, estrogens, furosemide, oral contraceptives, paroxetine, quinidine, rifampin, sertraline, theophylline, and vitamin D
Drugs whose level is decreased by phenytoin	
Antiepileptic drugs[a]	Carbamazepine, felbamate, lamotrigine, topiramate, oxcarbazepine
Antilipidemic agents	Atorvastatin, fluvastatin, simvastatin
Antiviral agents	Efavirenz, lopinavir/ritonavir, indinavir, nelfinavir, ritonavir, saquinavir Fosamprenavir: phenytoin when given with fosamprenavir alone may decrease the concentration of amprenavir, the active metabolite. Phenytoin when given with the combination of fosamprenavir and ritonavir may increase the concentration of amprenavir
Calcium channel blockers	Nifedipine, nimodipine, nisoldipine, verapamil
Other	Albendazole (decreases active metabolite), chlorpropamide, clozapine, cyclosporine, digoxin, disopyramide, folic acid, methadone, mexiletine, praziquantel, quetiapine

[a] The effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.

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 serum 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
Care should be taken when using immunoanalytical methods to measure plasma phenytoin concentrations.

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 methodologic 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, post-partum 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 serious adverse reactions are described elsewhere in the labeling:

- Withdrawal Precipitated Seizure, Status Epilepticus (see Section **4.4 Special Warnings and Precautions for Use**).
- Suicidal Behavior and Ideation (see Section **4.4 Special Warnings and Precautions for Use**).
- Serious Dermatologic Reactions (see Section **4.4 Special Warnings and Precautions for Use**).
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity (see Section **4.4 Special Warnings and Precautions for Use**).
- Hypersensitivity (see Section **4.4 Special Warnings and Precautions for Use**).
- Cardiac Effects (see Section **4.4 Special Warnings and Precautions for Use**).
- Angioedema (see Section **4.4 Special Warnings and Precautions for Use**).
- Hepatic Injury (see Section **4.4 Special Warnings and Precautions for Use**).
- Hematopoietic Complications (see Section **4.4 Special Warnings and Precautions for Use**).
- Effects on Vitamin D and Bone (see Section **4.4 Special Warnings and Precautions for Use**).
- Exacerbation of Porphyria (see Section **4.4 Special Warnings and Precautions for Use**).
- Teratogenicity and Other Harm to the Newborn (see Section **4.4 Special Warnings and Precautions for Use**).
- Hyperglycemia (see Section **4.4 Special Warnings and Precautions for Use**).

The following adverse reactions associated with the use of DILANTIN were identified in clinical studies or postmarketing reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Allergic reactions in the form of rash and rarely more serious forms and DRESS (see Section **4.4 Special Warnings and Precautions for Use**) have been observed, as has angioedema. Anaphylaxis has also been reported.

There have also been reports of coarsening of facial features, systemic lupus erythematosus, periarteritis nodosa, and immunoglobulin abnormalities.

Digestive System: Acute hepatic failure, toxic hepatitis, liver damage, nausea, vomiting, constipation, enlargement of the lips, and gingival hyperplasia.

Hematologic and Lymphatic 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. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease have been reported (see Section **4.4 Special Warnings and Precautions for Use**).

Laboratory Test Abnormality: Phenytoin may decrease serum concentrations of thyroid hormone (T4 and T3), sometimes with an accompanying increase in thyroid-stimulating hormone (TSH), but usually in the absence of clinical hypothyroidism. Phenytoin may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose (see Section **4.4 Special Warnings and Precautions for Use**), alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Nervous System: The most common adverse reactions encountered with phenytoin therapy are nervous system reactions and are usually dose-related. Reactions include nystagmus, ataxia, slurred speech, decreased coordination, somnolence, and mental confusion. Dizziness, vertigo, insomnia, transient nervousness, motor twitchings, paresthesias, and headaches 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. 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**).

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

Skin and Appendages: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see Section **4.4 Special Warnings and Precautions for Use**). There have also been reports of hypertrichosis and urticaria.

Special Senses: Altered taste sensation including metallic taste.

Urogenital: Peyronie's disease.

4.9 Overdose

The lethal dose in pediatric patients is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, blurred vision, nausea, and vomiting. The patient may become comatose and hypotensive. Bradycardia and cardiac arrest have been reported (see Section **4.4 Special Warnings and Precautions for Use**). Death is caused by 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, ataxia at 30 mcg/mL; dysarthria and lethargy appear when the serum concentration is over 40 mcg/mL, but

as high a concentration 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 over 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 other CNS depressants, including alcohol, should be borne in mind.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action
The precise mechanism by which phenytoin exerts its therapeutic effect has not been established but is thought to involve the voltage-dependent blockade of membrane sodium channels resulting in a reduction in sustained high-frequency neuronal discharges.

5.2 Pharmacokinetic Properties

Absorption
For phenytoin, peak levels occur 1½–3 hours after administration. Steady-state therapeutic levels are achieved at least 7 to 10 days (5–7 half-lives) after initiation of therapy with recommended doses of 300 mg/day. When serum level determinations are necessary, they should be obtained at least 5 to 7 half-lives after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that equilibrium or steady-state will have been achieved.

Distribution
Phenytoin is extensively bound to serum plasma proteins.

Elimination
The plasma half-life in man after oral administration of phenytoin averages 22 hours, with a range of 7 to 42 hours.

Metabolism
Phenytoin is primarily metabolized by the hepatic cytochrome P450 enzyme CYP2C9 and to a lesser extent by CYP2C19. Because phenytoin is hydroxylated in the liver by an enzyme system which is saturable at high serum levels, small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be non-compliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, variant CYP2C9 and CYP2C19 alleles, or drug interactions

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

Excretion
Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine. Urinary excretion of phenytoin and its metabolites occurs partly with glomerular filtration but, more importantly, by tubular secretion.

Special Populations

Age: Geriatric Population:
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). Since phenytoin clearance is decreased slightly in elderly patients, lower or less frequent dosing may be required (see section **4.2 Posology and Method of Administration**).

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

Renal or Hepatic Impairment:
Increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia have been reported.

Pregnancy:
It has been reported in the literature that the plasma clearance of phenytoin generally increased during pregnancy, reached a peak in the third trimester and returned to the level of pre-pregnancy after few weeks or months of delivery.

Drug Interaction Studies:
Phenytoin is primarily metabolized by the hepatic cytochrome P450 enzyme CYP2C9 and to a lesser extent by CYP2C19.

Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes (see Section **4.5. Interaction With Other Medicinal Products and Other Forms of Interaction**).

Pharmacogenomics

CYP2C9 activity is decreased in individuals with genetic variants such as the CYP2C9*2 and CYP2C9*3 alleles. Carriers of variant alleles, resulting in intermediate (e.g., *1/*3, *2/*2) or poor metabolism (e.g., *2/*3, *3/*3) have decreased clearance of phenytoin. Other decreased or nonfunctional CYP2C9 alleles may also result in decreased clearance of phenytoin (e.g., *5, *6, *8, *11).

The prevalence of the CYP2C9 poor metabolizer phenotype is approximately 2-3% in the White population, 0.5-4% in the Asian population, and <1% in the African American population. The CYP2C9 intermediate phenotype prevalence is approximately 35% in the White population, 24% in the African American population, and 15-36% in the Asian population (see Section **4.4 Special Warnings and Precautions for Use)**

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

Magnesium aluminum silicate, Sodium benzoate, Citric acid anhydrous, Carboxymethylcellulose sodium, Glycerin, Sucrose, Polysorbate 40, Alcohol, Vanillin, Banana flavor, Orange oil concentrate, FD & C yellow No. 6 and Purified water.

6.2 Incompatibilities

None

6.3 Shelf-life

Observe “Expiry date” (month/year) imprint on outer pack.

6.4 Special Precautions for Storage

Store below 30°C.

6.5 Dosage Forms and Packaging Available

125 mg phenytoin/5 mL packed in a round amber glass bottle or round amber polyethylene terephthalate (PET) bottle, having a polypropylene cap.
8 oz or 237 mL per bottle.

6.6 Instructions for Use/Handling

None

7. MANUFACTURER

Pharmacia and Upjohn Company LLC,
7000 Portage Road
Kalamazoo, Michigan (MI) 49001
United States (USA)

Date of Revision: 18 MAR 2024