PHENYTOIN SODIUM

DILANTIN
50 mg/mL Solution For Injection (IM/IV)

1.0 THERAPEUTIC CATEGORY
Anticonvulsant

2.0 DESCRIPTION
Phenytoin Sodium injection, USP (Dilantin) is a ready-mixed solution of phenytoin sodium in a vehicle containing 40% propylene glycol and 9.5% alcohol in water for injection, adjusted to pH 12 with a sodium hydroxide.

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 represented by the following structural formula

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\text{\includegraphics{structural_formula.png}}
\]

3.0 FORMULATION
Each mL contains 50 mg phenytoin sodium with 40% propylene glycol and 9.5% alcohol in water for injection, adjusted to pH 12 with sodium hydroxide.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications
Phenytoin is indicated for the control of status epilepticus of the tonic-clonic (grand mal) type and prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.

4.2 Dosage 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 suspension (30 mg/5mL (pediatric) and 125 mg/5mL). 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 and 20 mcg/mL.

Parenteral phenytoin may be administered as a slow intravenous (IV) bolus or it may be administered via an IV infusion.

Because of the risk of local toxicity, intravenous 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 Special Precautions for Use – Local Toxicity (including Purple Glove Syndrome)).

**Bolus Administration:** A bolus of parenteral phenytoin should be injected slowly, not exceeding 50 mg per minute in adults, into a large vein through a large-gauge needle or intravenous catheter. Each injection of intravenous 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 50-100 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 one hour (the infusion mixture should not be refrigerated). An in-line filter (0.22-0.50 microns) should be used. Each injection of intravenous phenytoin should be preceded by a saline flush and followed by an injection of sterile saline through the same needle or intravenous 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. There is a relatively small margin between full therapeutic effect and minimally toxic doses of this drug.** (see Section 4.4 Special Warnings and Special Precautions for Use – General)

On those occasions when intramuscular administration may be required (ie. 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 to 15 mg/kg should be administered slowly intravenously, at a rate not exceeding 50 mg per 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 6-8 hours.

Absorption of phenytoin in neonates and children may be unreliable after oral administration. A loading dose of 15-20 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 1-3 mg/kg/minute.

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 intravenous benzodiazepine such as diazepam, or intravenous short-acting barbiturate, will usually be necessary for rapid control of seizures because of the required slow rate of administration of phenytoin.

If administration of parenteral phenytoin does not terminate seizures, the use of other anticonvulsants, intravenous 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 Special Precautions for Use – General)

Neurosurgery: Prophylactic dosage - 100 to 200 mg (2 to 4 mL) intramuscularly at approximately 4 hour intervals during surgery and continued during the postoperative period. When intramuscular administration is required for a patient previously stabilized orally, compensating dosage adjustments are necessary to maintain therapeutic serum levels. When intramuscular administration is used, the drug should be given by deep intramuscular injection. An intramuscular 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 one week to prevent excessive serum levels due to sustained release form intramuscular 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 one 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 subtherapeutic range. Serum drug level determinations are especially helpful when possible drug interactions are suspected.

Cardiac arrhythmia: 3.5 to 5 mg/kg bodyweight, repeated once if necessary. Usually a total daily dosage of 700-1000 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 30-50 mg/min is preferred.

4.3 Contraindications

Phenytoin is contraindicated in those 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, sino-atrial block, second and third degree A-V block, and in patients with Adams-Stokes syndrome.

4.4 Special Warnings and Special 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 intravenous use of this drug are cardiovascular collapse and/or central nervous system depression. Hypotension does occur when the drug is administered rapidly by the intravenous route. The rate of administration is very important; it should not exceed 50 mg per minute in adults, and 1-3 mg/kg/minute in neonates and children. At this rate, toxicity should be minimized.

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

Phenytoin should be used with caution in patients with hypotension and severe myocardial insufficiency.

The intramuscular 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 intravenous 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.

Several individual case reports have suggested that there may be an increased, although still rare, incidence of hypersensitivity reactions, including skin rash and hepatotoxicity, in black patients.

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.

Anticonvulsant Hypersensitivity Syndrome
Anticonvulsant Hypersensitivity Syndrome (AHS) is a rare drug-induced, multiorgan syndrome that is potentially fatal and occurs in some patients taking anticonvulsant medication. It is
characterized by fever, rash, lymphadenopathy, and other multiorgan pathologies, often hepatic. The mechanism is unknown. The interval between first drug exposure and symptoms is usually 2-4 weeks, but has been reported in individuals receiving anticonvulsants for 3 or more months.

Drug rash with eosinophilia and systemic symptoms (DRESS) reflects a serious hypersensitivity reaction to drugs, characterized by skin rash, fever, lymph node enlargement, and internal organ involvement. Cases of DRESS have been noted in patients taking phenytoin.

Patients at higher risk for developing AHS include black patients, patients who have a family history of or who have experienced this syndrome in the past, and immuno-suppressed patients. The syndrome is more severe in previously sensitized individuals. If a patient is diagnosed with AHS, discontinue the phenytoin and provide appropriate supportive measures.

**Cardiovascular Effect**
Severe cardiotoxic reactions and fatalities have been reported with atrial and ventricular depression and ventricular fibrillation. Severe complications are most commonly encountered in elderly or gravely ill patients.

**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. 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 Effect**
There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness - e.g., fever, rash, and liver involvement. 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/Immunologic Effect**
The liver is the chief site of biotransformation of phenytoin. Patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity. 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 have been associated with a hypersensitivity syndrome characterized by fever, skin eruptions, and lymphadenopathy, and usually occur within the first 2 months of treatment. Other common manifestations include arthralgias, rash, jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, phenytoin should be
immediately discontinued and not re-administered.

Local Toxicity (including Purple Glove Syndrome)
Soft tissue irritation and inflammation have occurred at the site of injection with and without extravasation of intravenous phenytoin.

Edema, discoloration and pain distal to the site of injection (described as “purple glove syndrome”) have been reported following peripheral intravenous phenytoin injection. Soft tissue irritation may vary from slight tenderness to extensive necrosis, and sloughing of 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 such interventions 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. Dosage and Method of Administration).

Integumentary Effect
Phenytoin can cause rare, serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, 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 scarlantiform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Published literature has suggested that there may be an increased, although still rare, risk of hypersensitivity reactions, including skin rash, SJS, TEN, hepatotoxicity, and AHS 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 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.

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.

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

There are many drugs which may increase or decrease serum phenytoin levels or which phenytoin may affect. Determinations of serum phenytoin concentrations are especially helpful when possible drug interactions are suspected. The most commonly occurring drug interactions are listed below.

Drugs which may increase phenytoin serum levels

Various drugs may increase phenytoin serum levels either by decreasing its rate of metabolism by the hepatic CYP450 2C9 and 2C19 enzymatic systems (e.g. dicumarol, disulfiram, omeprazole, ticlopidine), by competing for protein binding sites (e.g. salicylates, sulfisoxazole, tolbutamide), or by a combination of both processes (e.g. phenylbutazone, valproate sodium).

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

<table>
<thead>
<tr>
<th>DRUG CLASSES</th>
<th>DRUGS IN EACH CLASS (SUCH AS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (acute intake)</td>
<td></td>
</tr>
<tr>
<td>Analgesic / Anti-inflammatory agents</td>
<td>Azapropazone</td>
</tr>
<tr>
<td></td>
<td>phenylbutazone</td>
</tr>
<tr>
<td></td>
<td>salicylates</td>
</tr>
<tr>
<td>Anesthetics</td>
<td>halothane</td>
</tr>
<tr>
<td>Antibacterial agents</td>
<td>chloramphenicol</td>
</tr>
<tr>
<td></td>
<td>erythromycin</td>
</tr>
<tr>
<td></td>
<td>isoniazid</td>
</tr>
<tr>
<td></td>
<td>sulfonamides</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Felbamate</td>
</tr>
<tr>
<td></td>
<td>succinimides</td>
</tr>
<tr>
<td>Antifungal agents</td>
<td>amphotericin B</td>
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<tr>
<td></td>
<td>fluconazole</td>
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<tr>
<td></td>
<td>ketoconazole</td>
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<tr>
<td></td>
<td>miconazole</td>
</tr>
<tr>
<td></td>
<td>itraconazole</td>
</tr>
<tr>
<td>Antineoplastic agents</td>
<td>Fluorouracil</td>
</tr>
<tr>
<td>Benzodiazepines / Psychotropic agents</td>
<td>chlordiazepoxide</td>
</tr>
<tr>
<td></td>
<td>diazepam</td>
</tr>
<tr>
<td></td>
<td>disulfiram</td>
</tr>
<tr>
<td></td>
<td>methylphenidate</td>
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<tr>
<td></td>
<td>trazodone</td>
</tr>
<tr>
<td></td>
<td>viloxazine</td>
</tr>
<tr>
<td>Calcium channel blockers / Cardiovascular</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>agents</td>
<td>dicumarol</td>
</tr>
<tr>
<td></td>
<td>diltiazem</td>
</tr>
</tbody>
</table>
### Drugs which may decrease phenytoin serum levels

Table 2 summarizes the drug classes which may potentially decrease phenytoin plasma levels:

<table>
<thead>
<tr>
<th>DRUG CLASSES</th>
<th>DRUGS IN EACH CLASS (SUCH AS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (chronic intake)</td>
<td></td>
</tr>
<tr>
<td>Antibacterial agents</td>
<td>Rifampin, Ciprofloxacin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Vigabatrin</td>
</tr>
<tr>
<td>Antiulcer agents</td>
<td>Sucralfate</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Cardiovascular agents</td>
<td>Reserpine</td>
</tr>
<tr>
<td>Hyperglycemic agents</td>
<td>Diazoxide</td>
</tr>
</tbody>
</table>

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.

A pharmacokinetic interaction study between nelfinavir and phenytoin both administered orally showed that nelfinavir reduced AUC values of phenytoin (total) and free phenytoin by 29% and 28%, respectively. Therefore, phenytoin concentration should be monitored during co-administration with nelfinavir, as nelfinavir may reduce phenytoin plasma concentration (see section 5.2 Pharmacokinetic Properties – Pharmacokinetic Interaction).

### Drugs which may either increase or decrease phenytoin serum levels

Table 3 summarizes the drug classes which may either increase or decrease phenytoin serum levels:

<table>
<thead>
<tr>
<th>DRUG CLASSES</th>
<th>DRUGS IN EACH CLASS (SUCH AS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibacterial agents</td>
<td>Ciprofloxacin</td>
</tr>
</tbody>
</table>
Similarly, the effect of phenytoin on carbamazepine, phenobarbital, valproic acid, and sodium valproate serum levels is unpredictable.

**Drugs which blood levels and/or effects may be altered by phenytoin**

Table 4 summarizes the drug classes which blood levels and/or effects may be altered by phenytoin:

<table>
<thead>
<tr>
<th>DRUG CLASSES</th>
<th>DRUGS IN EACH CLASS (SUCH AS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibacterial agents</td>
<td>doxycycline praziquantel rifampin tetracycline</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Antifungal agents</td>
<td>Azoles</td>
</tr>
<tr>
<td>Antineoplastic agents</td>
<td>Teniposide</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Calcium channel blockers / Cardiovascular agents</td>
<td>Digitoxin nicardipine nimodipine quinidine verapamil</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Coumarin anticoagulants</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>Furosemide</td>
</tr>
<tr>
<td>Hormones</td>
<td>Estrogens oral contraceptives</td>
</tr>
<tr>
<td>Hyperglycemic agents</td>
<td>diazoxide</td>
</tr>
<tr>
<td>Neuromuscular blocking agents</td>
<td>Alcuronium Pancuronium Vecuronium</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>Methadone</td>
</tr>
<tr>
<td>Oral hypoglycemic agents</td>
<td>Chlorpropamide glyburide tolbutamide</td>
</tr>
<tr>
<td>Psychotropic agents / Antidepressants</td>
<td>Clozapine Paroxetine Sertraline</td>
</tr>
<tr>
<td>Vitamin D</td>
<td></td>
</tr>
</tbody>
</table>

9
Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

**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 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**

**Usage in Pregnancy**

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. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed anticonvulsant drugs. 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 growth deficiency, microcephaly, and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

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

**Usage in Nursing Mothers**

Infant 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**

**Body as a Whole:** Anaphylactoid reaction, and anaphylaxis.

**Cardiovascular System:** Hypotension has been observed. (see Section 4.4 Special Warnings and Special Precautions for Use – General and Cardiovascular Effect)

**Central Nervous System:** The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion. (See Section 4.4 Special Warnings and Special Precautions for Use – Central Nervous System Effect)

Dizziness, insomnia, transient nervousness, motor twitching, 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:** Nausea, vomiting, constipation, toxic hepatitis, and liver damage. (see Section 4.4 Special Warnings and Special Precautions for Use – Hepatic/Immunologic Effect)

**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 Special Precautions for Use – Hematopoietic Effect)

**Immunologic:** Hypersensitivity syndrome, systemic lupus erythematosus, periarteritis nodosa, and immunoglobulin abnormalities. (see Section 4.4 Special Warnings and Special Precautions for Use – Hepatic/Immunologic Effect). Drug rash with eosinophilia and systemic symptoms (DRESS) (see Special Warnings and Special Precautions for Use - Anticonvulsant Hypersensitivity Syndrome (AHS)).

**Injection Site:** Local irritation, inflammation, tenderness, necrosis, and sloughing of skin have been reported with or without extravasation of intravenous 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 Special Precautions for Use – Local Toxicity (including Purple Glove Syndrome)).

**Integumentary 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 which may be fatal have included bullous, exfoliative, or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis. (see Section 4.4 Special Warnings and Special Precautions for Use – Integumentary Effect)

**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 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, somnolence, drowsiness, lethargy, slurred speech, blurred vision, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin 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.

**Treatment**

Treatment is nonspecific since there is no known antidote.

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

In acute overdosage the possibility of the presence of other CNS depressants, including alcohol, should be 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 intramuscular 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%) plasma proteins, mainly albumin. Free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal. Phenytoin is distributed into cerebrospinal fluid (CSF), saliva, semen, gastrointestinal fluids, bile, and breast milk. The concentration of phenytoin in 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 sulphaphenazole. 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 intramuscular (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.

Pharmacokinetic Interaction
Co-administration of nelfinavir tablets (1,250 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.

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

None known.

6.2 Shelf-Life

Please see outer package for the expiry date of this product.

6.3 Special Precautions for Storage

Store at room temperature not to exceed 25°C.

Protect from light.

6.4 How Supplied

Dilantin Solution for Injection containing 50 mg phenytoin sodium per milliliter is a clear colorless solution free from readily visible particles. Available as 5-mL and 2 mL glass ampoules, packages of tens.

6.5 Instructions for Use/Handling

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.


Manufactured by:

For 5mL Injection:
Actavis Italy S.p.A.
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Milan Italy

For 2mL Injection:
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