Product Monograph

Including Patient Medication Information

[Pr] PHENYTOIN SODIUM INJECTION USP

Sterile solution for injection

For Intramuscular and Intravenous use

50 mg / mL of Phenytoin Sodium

USP

Anticonvulsant agent

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Recent Major Label Changes

No recent major label changes.

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Part 1: Healthcare Professional Information

1. Indications

Phenytoin Sodium Injection USP is indicated for the control of generalized tonic-clonic status epilepticus, and for the prevention and treatment of seizures occurring during neurosurgery. Phenytoin Sodium Injection USP should be used only when oral phenytoin administration is not possible.

1.1. Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (age range): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2. Contraindications

Phenytoin is contraindicated:

- In patients who with a history of hypersensitivity to phenytoin or to other hydantoins.
- In patients who have sinus bradycardia, sino-atrial block, second and third degree AV block, and Adams-Stokes syndrome.
- In conjunction with delavirdine due to potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.
- For intra-arterial administration in view of the high pH of the preparation.

3. Serious Warnings and Precautions Box

CARDIOVASCULAR RISK ASSOCIATED WITH RAPID INFUSION

The rate of intravenous phenytoin sodium injection administration should not exceed 50 mg per minute in adults and 1-3 mg/kg/min (or 50 mg per minute, whichever is slower) in pediatric patients because of the risk of severe hypotension and cardiac arrhythmias. In elderly patients, those who are gravely ill, or those with cardiovascular disease, the drug should be administered at a rate not exceeding 25 mg/minute, and if necessary, at a slow rate of 5 to 10 mg/minute. Careful cardiac monitoring is needed during and after administering intravenous phenytoin sodium injection. Although the risk of cardiovascular toxicity increases with infusion rates above the recommended infusion rate, these events have also been reported at or below the recommended infusion rate. Reduction in rate of administration or discontinuation of dosing may be needed (see 7. Warnings and

Precautions and 4. Dosage and Administration).

4. Dosage and Administration

4.1. Dosing Considerations

Because of the increased risk of adverse cardiovascular reactions associated with rapid administration, intravenous administration should not exceed 50 mg per minute in adults. In pediatric patients, the drug should never be administered at a rate exceeding 1-3 mg/kg/min or 50 mg per minute, whichever is slower.

As non-emergency therapy, phenytoin should be administered more slowly as either a loading dose or by intermittent infusion. Because of the risks of cardiac and local toxicity associated with intravenous phenytoin, oral phenytoin should be used whenever possible.

Because adverse cardiovascular reactions have occurred during and after infusions, careful cardiac, blood pressure, and respiratory function monitoring is needed during and after the administration of intravenous phenytoin. Reduction in rate of administration or discontinuation of dosing may be needed.

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.

The addition of parenteral phenytoin to dextrose and dextrose-containing solutions should be avoided due to lack of solubility and resultant precipitation.

Dosing Considerations for Special Populations

Patients with Renal or Hepatic Disease: 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 phenytoin concentrations may be more useful in these patient populations.

Elderly Patients: Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required.

Do not mix with other IV solutions unless it respects the condition mentioned in "incompatibility".

4.2. Recommended Dose and Dosage Adjustment

Usual dosage for parenteral administration:

1. Treatment of status epilepticus: 150 to 250 mg of phenytoin sodium administered by slow intravenous injection. An additional 100 to 250 mg may be given 30 minutes later if necessary. Dosage for children is usually determined according to weight in proportion to the dosage for a 68 kg adult. Pediatric dosage may also be calculated on the basis of 250 mg/m^2 of body surface.

2. Neurosurgery: prophylactic intramuscular administration of 100 to 200 mg of phenytoin every 4 hours during surgery and the post-operative period.

4.4. Administration

***IV route:**

1. Intravenous administration should be used with caution in patients with hypotension and severe myocardial or respiratory insufficiencies.
2. Electrocardiographic and blood pressure monitoring is recommended during intravenous therapy. The patient should be observed for signs of respiratory depression.
3. **In adults, the rate of administration should not exceed 50 mg/minute and should even be slower (50 mg over 2 or 3 minutes) for the elderly, those who are gravely ill, and those with cardiovascular disease.**
4. **In neonates, the rate of administration should not exceed 1 to 3 mg/kg/minute.**
5. The IV injection should be done in a large vein through a large gauge needle or IV catheter. The injection of the drug should be followed by administration of isotonic sodium chloride injection through the same needle or IV catheter to avoid local irritation of the vein caused by the alkalinity of the phenytoin sodium solution.
6. Phenytoin should not be added to IV infusions (due to lack of solubility and risk of precipitation) nor should it be given as a continuous infusion (risk of phlebitis due to the alkaline pH).

***IM route:**

1. Due to slow and erratic absorption of phenytoin, the IM route is not recommended for emergency treatment of status epilepticus because the attainment of peak levels may require up to 24 hours. Intramuscular phenytoin may cause pain, necrosis, and abscess formation at the injection site.
2. Passage from oral to intramuscular administration may cause a drop in phenytoin plasma level due to the poor absorption of phenytoin when administered by intramuscular route. Studies established that the best regimen for the transfer of phenytoin by mouth to the IM route was the following: dosage should be increased by 50% in order to maintain a constant concentration of phenytoin in the plasma. Upon returning patients to phenytoin by oral route, a dose equivalent to 50% of the original oral dose should be administered for the same period as that during which, the IM route was used to allow for continued absorption of phenytoin from the intramuscular site. However, for periods of treatment greater than one week, blood level monitoring is recommended. When patients cannot take phenytoin orally for more than one week, gastric intubation may be considered.
3. The dosage of phenytoin should be adjusted to the needs of each patient to achieve adequate control of seizures and to avoid toxicity (concentrations usually required: 10 to 20 mcg/mL).

IV Substitution for Oral Phenytoin Therapy

When treatment with oral phenytoin is not possible, IV phenytoin can be substituted for oral phenytoin at the same total daily dose. Phenytoin is 100% bioavailable by the IV route, with oral phenytoin

approximately 90% bioavailable. For this reason, plasma phenytoin concentrations may increase modestly when IV phenytoin is substituted for oral 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.

5. Overdosage

Early symptoms of overdosage are slurred speech, digestive disturbances (nausea, vomiting), tremor, hyperflexia and lethargy. Other signs are nystagmus, ataxia, and dysarthria. The patient may become comatose and hypotensive.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Most patients experience blurred vision and nystagmus at serum phenytoin concentrations of 20 mcg/mL, ataxia and unsteady gait at 30 mcg/mL and lethargy at more than 40 mcg/mL. 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.

The lethal dose in children is unknown. In adults it is estimated to be in the order of 2 to 5 g. Death is generally due to respiratory and circulatory depression.

Treatment of Overdosage

There is no known antidote; consequently the treatment is not specific. Respiratory and circulatory functions should be carefully monitored and appropriate supportive measures should be employed. The effectiveness of hemodialysis and peritoneal dialysis has been seriously questioned. As phenytoin's volume of distribution is relatively small, blood transfusion, particularly at high drug concentrations, should contribute significantly to total drug removal. Total exchange transfusion has been used in the treatment of severe intoxication in children.

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

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Intramuscular, Intravenous	sterile solution for injection, 50 mg / mL	ethyl alcohol, propylene glycol, sodium hydroxide, water for injection

Phenytoin Sodium Injection USP is a sterile solution of the drug containing 40% propylene glycol, 10% (v/v) ethyl alcohol in water for injection. Sodium hydroxide is added during manufacture of the injection to adjust the pH to 12.

Phenytoin Sodium Injection USP is a clear, colourless solution contained in an amber ampoule. Each mL of Phenytoin Sodium Injection USP contains 50 mg of phenytoin sodium. Available in 2 mL and 5 mL single use vials, boxes of 10.

7. Warnings and Precautions

See 3. Serious Warnings and Precautions Box.

As non-emergency therapy, phenytoin should be administered more slowly as either a loading dose or by intermittent infusion. Because of the risks of cardiac and local toxicity associated with intravenous phenytoin, oral phenytoin should be used whenever possible.

Because adverse cardiovascular reactions have occurred during and after infusions, careful cardiac monitoring is needed during and after the administration of intravenous phenytoin. Reduction in rate of administration or discontinuation of dosing may be needed.

General

In patients on long term phenytoin therapy, vitamin D and folic acid are given to prevent side effects respectively affecting bones and hematopoiesis. Long-term use of antiepileptics such as phenytoin, phenobarbital, primidone, carbamazepine, lamotrigine and sodium valproate is associated with a risk of decreased bone mineral density that may lead to weakened or brittle bones.

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 genetically determined.

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

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

Phenytoin is not effective for absence seizures. Therefore, if tonic-clonic and absence seizures are both present, combined drug therapy is needed.

Patients should be aware of the importance of a good dental hygiene in order to prevent gingival hyperplasia.

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

Alcohol Use

Acute alcohol intoxication may increase phenytoin serum levels while chronic alcoholism may decrease it. Alcohol should be avoided during treatment with phenytoin

Cardiovascular

Adverse cardiovascular reactions include severe hypotension and cardiac arrhythmias. Cardiac arrhythmias have included bradycardia, heart block, ventricular tachycardia, and ventricular fibrillation which have resulted in asystole, cardiac arrest, and death.

Severe complications are most commonly encountered in critically ill patients, elderly patients, and patients with hypotension and severe myocardial insufficiency. However, cardiac events have also been reported in adults and children without underlying cardiac disease or comorbidities and at recommended doses and infusion rates.

Dependence, Tolerance and/or Abuse Liability

Withdrawal-Precipitated Seizure, Status Epilepticus

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.

Driving and Operating Machinery

Caution is recommended in patients performing skilled tasks (e.g. driving or operating machinery) as treatment with phenytoin may cause central nervous system adverse effects such as dizziness and drowsiness. Phenytoin in appropriate doses may as such impair driving skills but epilepsy itself dictates the practice of driving. Patients affected by drowsiness should not drive or operate machinery.

Hematologic

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.

Hematopoietic

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. Complete blood counts should be carried out before treatment is instituted and periodically thereafter.

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 DRESS. 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.

Hepatic/Biliary/Pancreatic

Hepatic impairment

The liver is the main site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early toxicity. The drug should be given with caution to these patients (see 4.1 Dosing Considerations, Dosing Considerations for Special Populations).

Hepatic Injury

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These events may be part of the spectrum of DRESS or may occur in isolation. 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, phenytoin should be immediately discontinued and not re-administered.

Immune

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 phenytoin. Some of these events have been fatal or life-threatening. 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, 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. Phenytoin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Hypersensitivity

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity (see 2. Contraindications). Additionally, in these patients, consider alternatives for those anti-convulsant drugs that are structurally similar to phenytoin, such as carboxamides (e.g., carbamazepine), barbiturates, succinimides, and oxazolidinediones (e.g., trimethadione). Similarly, if there is a history of hypersensitivity reactions to these structurally similar drugs in the patient or immediate family members, consider alternatives to phenytoin.

Local Toxicity (including Purple Glove Syndrome)

Soft tissue irritation and inflammation has occurred at the site of injection with and without extravasation of intravenous phenytoin (See 4. Dosage and Administration for IV administration of Phenytoin Sodium Injection USP).

Edema, discolouration and pain distal to the site of injection (described as "purple glove syndrome") have also been reported following peripheral intravenous phenytoin injection. Soft tissue irritation may vary from slight tenderness to extensive necrosis, and sloughing. 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.

Subcutaneous or perivascular administration should be avoided because of the highly alkaline nature of the solution.

Intramuscular phenytoin administration may cause pain, necrosis, and abscess formation at the injection site (see 4. Dosage and Administration).

Monitoring and Laboratory Tests

Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments. Phenytoin doses are usually selected to attain therapeutic plasma total phenytoin concentrations of 10 to 20 mcg/mL (unbound phenytoin concentrations of 1 to 2 mcg/mL).

Psychiatric

Suicidal Ideation and Behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications.

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge. An FDA meta-analysis of randomized placebo controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

There were 43,892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of

the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drug). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

Skin

Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with phenytoin treatment. The onset of symptoms is usually within 28 days, but can occur later.

Phenytoin should be discontinued at the first sign of a rash, unless the rash is clearly not drug related.

If signs or symptoms suggest SJS/TEN, 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 symptom ms of Drug Reaction with Eosinophilia and Systemic Symptoms (see 7. Warnings and Precautions, Immune, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity). The patient must be warned to call his/her physician in case of skin rash.

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* l502 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. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502.

The use of HLA-B*1502 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.

7.1. Special Populations

7.1.1. Pregnancy

An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Risks to the Fetus:

If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential harm to the fetus.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse development outcomes. Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), minor anomalies (dysmorphic facial features, nail and digit hypoplasia), growth abnormalities (including microcephaly), and mental deficiency have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have also been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. The overall incidence of malformations for children of epileptic women treated with antiepileptic drugs (phenytoin and/or others) during pregnancy is about 10%, or two to three fold that in the general population.

However, the relative contribution of antiepileptic drugs and other factors associated with epilepsy to this increased risk are uncertain and in most cases it has not been possible to attribute specific developmental abnormalities to particular antiepileptic drugs.

Patients should consult with their physicians to weigh the risks and benefits of phenytoin during pregnancy.

Pregnancy Registry:

Pregnant patients taking phenytoin should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the following website: http://www.aedpregnancyregistry.org/.

Postpartum Period:

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.

7.1.2. Breastfeeding

Infant breast feeding is not recommended for women taking phenytoin. Phenytoin is secreted into human milk. Limited observations in patients suggest that phenytoin concentration in breast milk is approximately one-third of the corresponding maternal plasma concentration.

7.1.3. Geriatrics

Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required.

8. Adverse Reactions

8.5. Post-Market Adverse Reactions

The margin between therapeutic and toxic levels of phenytoin is very narrow. Moreover, there is a considerable variation from patient to patient in relation to blood and tissue concentrations.

Body As a Whole: Allergic reactions in the form of rash and rarely more serious forms (see 8.5 Post-Market Adverse Reactions, Skin below) and DRESS (see 7. Warnings and Precautions) have been observed. Anaphylaxis has also been reported.

There have also been reports of hirsutism (more noticeable in young females), systemic lupus erythematosus, periarteritis nodosa, and immunoglobulin abnormalities.)

Cardiovascular: Severe cardiovascular events and fatalities have been reported with atrial and ventricular conduction depression and ventricular fibrillation. Severe complications are most commonly encountered in elderly or critically ill patients (see 7. Warnings and Precautions).

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, diplopia, decreased coordination, somnolence, and mental confusion. Dizziness, vertigo, insomnia, transient nervousness, motor twitchings, paresthesia, 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.

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

Musculoskeletal and Connective Tissue: Rickets; osteomalacia; polyarthropathy. Thickening of the skull, coarsening of facial features, or gingival hyperplasia.

Respiratory: Rare reports of pulmonary infiltrates or fibrosis, with symptoms including fever, troubled or quick, shallow breathing, unusual tiredness or weakness, loss of appetite and weight, and chest discomfort have also occurred.

Alterations in respiratory function, respiratory arrest, and Pneumonitis.

Skin: 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 7. Warnings and Precautions section). There have also been reports of hypertrichosis.

Local irritation, inflammation, tenderness, necrosis, and sloughing have been reported with or without extravasation of intravenous phenytoin (see 7. Warnings and Precautions).

Gastrointestinal: Nausea, vomiting, constipation, enlargement of the lips.

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 following prolonged use, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease have been reported (see 7. Warnings and Precautions).

Hepatobiliary: Hepatitis, acute hepatotoxicity, acute hepatic failure, hepatomegaly (see 7. Warnings and Precautions, Hepatic/Biliary/Pancreatic, Hepatic Injury).

Phenytoin Sodium Injection USP contains propylene glycol which may cause alcohol-like symptoms.

Phenytoin Sodium Injection USP contains 10% Alcohol USP. This may be harmful for those suffering from alcoholism and should be taken into account in pregnant or breast-feeding women, and high-risk groups such as patients with liver disease.

Special Senses: Altered taste sensation including metallic taste.

Urogenital: Peyronie's disease.

Other effects: Hyperglycemia (resulting from phenytoin's inhibitory effect on insulin release), myasthenia gravis. Anticonvulsants can diminish sexual potency and fertility in young male epileptics. Phlebitis, under IV administration. In some patients high serum triglycerides and cholesterol levels have been reported (due to the effect of phenytoin on lipid metabolism).

9. Drug Interactions

9.2. Drug Interactions Overview

Phenytoin is extensively bound to serum plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome 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. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected.

The most commonly occurring drug interactions are listed below:

Note: The list is not intended to be inclusive or comprehensive. Individual Product Monographs should be consulted.

9.4. Drug-Drug Interactions

Drugs that affect phenytoin concentrations:

Drugs that may increase phenytoin serum levels include: acute alcohol intake, amiodarone, antiepileptic agents (ethosuximide, felbamate, oxcarbazepine, methsuximide, topiramate), azoles (fluconazole, ketoconazole, itraconazole, voriconazole), capecitabine, chloramphenicol, chlordiazepoxide, cimetidine, diazepam, disulfiram, estrogens, fluorouracil, fluoxetine, fluvastatin, fluvoxamine, H2-antagonists (e.g. cimetidine), halothane, isoniazid, methylphenidate, omeprazole, phenothiazines, salicylates, sertraline, succinimides, sulfonamides (e.g., sulfamethizole, sulfaphenazole, sulfadiazine, sulfamethoxazole-trimethoprim), ticlopidine, tolbutamide, trazodone, and warfarin.

Co-administration with topiramate reduces serum topiramate levels by 59%, and has the potential to increase phenytoin levels by 25% in some patients. The addition of topiramate therapy to phenytoin should be guided by clinical outcome.

Drugs that may decrease phenytoin levels include: anticancer drugs usually in combination (e.g., bleomycin, carboplatin, cisplatin, doxorubicin, methotrexate), carbamazepine, chronic alcohol abuse, diazoxide, folic acid, fosamprenavir, nelfinavir, reserpine, ritonavir, St. John's Wort, and vigabatrin.

Drugs that may either increase or decrease phenytoin serum levels include: phenobarbital, sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valproic acid, and sodium valproate serum levels is unpredictable.

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

Drugs affected by phenytoin:

Drugs that should not be co-administered with phenytoin: delavirdine (see 2. Contraindications).

Drugs whose efficacy is impaired by phenytoin include: azoles (fluconazole, ketoconazole, itraconazole, voriconazole, posaconazole), corticosteroids, doxycycline, estrogens, furosemide, irinotecan, oral contraceptives, paclitaxel, paroxetine, quinidine, rifampin, sertraline, tenisposide, theophylline, and Vitamin D.

Increased and decreased prothrombin time (PT)/International Normalized Ratio (INR) responses have been reported when phenytoin is coadministered with warfarin.

Phenytoin decreases plasma concentrations of certain HIV antivirals (efavirenz, lopinavir/ritonavir, indinavir, nelfinavir, ritonavir, saquinavir), anti-epileptic agents (felbamate, topiramate, oxcarbazepine, quetiapine, lamotrigine), atorvastatin, calcium, cyclosporine, digoxin, fluvastatin, folic acid, mexiletine, nifedipine,nisoldipine, praziquantel, simvastatin, and verapamil.

Co-administration with lamotrigine doubles the plasma clearance and reduces the elimination half-life of lamotrigine by 50%. This clinically important interaction requires dosage adjustment for lamotrigine. There is no significant change in phenytoin plasma levels in the presence of lamotrigine.

Co-administration with topiramate reduces serum topiramate levels by 59%, and has the potential to increase phenytoin levels by 25% in some patients. The addition of topiramate therapy to phenytoin should be guided by clinical outcome.

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.

Resistance to the neuromuscular blocking action of the nondepolarizing neuromuscular blocking agents pancuronium, vecuronium, rocuronium, and cisatracurium has occurred in patients chronically administered phenytoin. Whether or not phenytoin has the same effect on other nondepolarizing agents is unknown. Patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected, and infusion rate requirements may be higher.

Use of intravenous phenytoin in patients maintained on dopamine may produce sudden hypotension and bradycardia. This appears to be dose-dependent. If anticonvulsant therapy is necessary during administration of dopamine, an alternative to phenytoin should be considered.

Concurrent use of intravenous phenytoin with lidocaine or beta-blockers may produce additive cardiac depressant effects. Phenytoin may also enhance metabolism of lidocaine.

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

9.5. Drug-Food Interactions

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.

9.7. Drug-Laboratory Test Interactions

Phenytoin may decrease serum concentrations of thyroxine (T4). It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may also cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Care should be taken when using immunoanalytical methods to measure plasma phenytoin concentrations following fosphenytoin administration.

Incompatibility

Phenytoin sodium only remains in solution when the pH is considerably alkaline (about 10 to 12). The mixing of phenytoin sodium injection with other drugs or its addition to infusion solutions is not recommended.

10. Clinical Pharmacology

10.2. Pharmacodynamics

Phenytoin sodium inhibits the spread of seizure activity in the motor cortex. It appears that by promoting sodium efflux from neurons, phenytoin sodium tends to stabilise the threshold against hyperexcitability caused by environmental changes or excessive stimulation capable of reducing membrane sodium gradient. This includes the reduction of post tetanic potentiation

of synapses. Loss of post tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin thereby reduces the over-activity of brain stem centres responsible for the tonic phase of grand mal seizures.

Phenytoin sodium's antiarrhythmic action may be attributed to the normalization of influx of sodium and calcium to cardiac Purkinje fibres. Abnormal ventricular automaticity and membrane responsiveness are decreased. It also shortens the refractory period, and therefore shortens the QT interval and the duration of the action potential.

Hydantoins induce production of liver microsomal enzymes, thereby accelerating the metabolism of concomitantly administered drugs.

10.3. Pharmacokinetics

The onset of action after an intravenous dose is 30 to 60 minutes and the effect persists up to 24 hours. Phenytoin is about 90% protein bound. Protein binding may be lower in neonates and hyperbilirubinemic infants; also altered in patients with hypoalbuminaemia, uraemia or acute trauma, and in pregnancy. Optimum control without clinical signs of toxicity occurs most often with serum levels between 10 and 20 μg/mL. In renal failure or hypoalbuminaemia, 5 to 12 mcg/mL or even less may be therapeutic.

Phenytoin is metabolised in the liver, the major inactive metabolite is 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH). The rate of metabolism is increased in younger children, pregnant women, in women during menses and in patients with acute trauma. The rate decreases with advancing age. Phenytoin may be metabolised slowly in a small number of individuals due to genetic factors, which may cause limited enzyme availability and lack of induction.

The plasma half-life is normally from 10 to 15 hours. Because phenytoin exhibits saturable or dose-dependent pharmacokinetics, the apparent half-life of phenytoin changes with dose and serum concentration. At therapeutic concentrations of the drug, the enzyme system responsible for metabolising phenytoin becomes saturated. Thus a constant amount of drug is metabolised, and small increases in dose may cause disproportionately large increases in serum concentrations and apparent half-life, possibly causing unexpected toxicity.

11. Storage, Stability, and Disposal

Store between 15°C and 30°C; freezing should be avoided. A precipitate may form if the injection is refrigerated or frozen; however, this will dissolve after warming to room temperature.

Protect from light. Slightly yellowish discolouration of the injection will not affect potency or efficacy, but the injection should not be used if the solution is not clear or if a precipitate is present.

Part 2: Scientific Information

13. Pharmaceutical Information

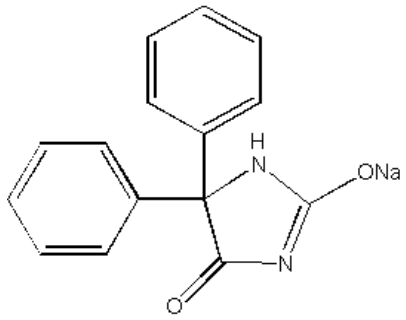
Drug Substance

Non-proprietary name of the drug substance: Phenytoin Sodium

Chemical Name: 5,5 - Diphenyl - 2,4 Imidazolidinedione Monosodium Salt, 5,5 - Diphenylhydantoin sodium salt

Molecular Formula and molecular mass: $C_{15}H_{11}N_2NaO_2$ and 274.25 g/mol

Structural formula:



phenytoin sodium

Description: Phenytoin sodium occurs as a white, odourless, hygroscopic powder and is freely soluble in water, soluble in alcohol, and freely soluble in warm propylene glycol. It is insoluble in ether and chloroform.

17. Supporting Product Monographs

1. Pr TREMYTOINE, phenytoine sodium solution for injection, 50 mg/mL, control 176329 product monograph, Omega Laboratories Ltd. (2015-03-03)

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrPHENYTOIN SODIUM INJECTION USP

This Patient Medication Information is written for the person who will be receiving **PHENYTOIN SODIUM INJECTION USP**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **PHENYTOIN SODIUM INJECTION USP**, talk to a healthcare professional.

Serious warnings and precautions box

Cardiovascular risk: You will receive PHENYTOIN SODIUM INJECTION USP through an injection into the vein or muscle. If your healthcare professional injects this medication into the vein too fast, your blood pressure may drop quickly, and you may experience an irregular heartbeat. This can be serious. Your healthcare professional should monitor you closely while you are receiving PHENYTOIN SODIUM INJECTION USP and after.

What PHENYTOIN SODIUM INJECTION USP is used for:

PHENYTOIN SODIUM INJECTION USP is used to:

- control certain types of seizures (generalized tonic-clonic status epilepticus)
- prevent and treat seizures during surgery of the nervous system (e.g., brain, nerves, spinal cord)

How PHENYTOIN SODIUM INJECTION USP works:

PHENYTOIN SODIUM INJECTION USP belongs to a group of medicines called anticonvulsants. It works by blocking electrical impulses in the brain that cause seizures.

The ingredients in PHENYTOIN SODIUM INJECTION USP are:

Medicinal ingredient: phenytoin sodium

Non-medicinal ingredients: ethyl alcohol, propylene glycol, sodium hydroxide, and water for injection.

PHENYTOIN SODIUM INJECTION USP comes in the following dosage form:

Solution for injection; 50 mg / mL

Do not receive PHENYTOIN SODIUM INJECTION USP if:

- you are allergic to phenytoin sodium or to any of the other ingredients in PHENYTOIN SODIUM INJECTION USP or its container.
- you are allergic to other medicines of the hydantoin family, including fosphenytoin.
- you have a heart rhythm condition such as a slow heart rate (bradycardia), heart block, or certain other heart conditions (e.g., Adams-Stokes syndrome).

- you take delavirdine, used to treat HIV infection.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive PHENYTOIN SODIUM INJECTION USP. Talk about any health conditions or problems you may have, including if you:

- have a personal or family history of rash or unusual reaction while taking phenytoin sodium or any other anti-seizure medicines.
- are currently taking any other medications, supplements or other special treatments:
  - as they may interact with PHENYTOIN SODIUM INJECTION USP, and this can affect how well they or PHENYTOIN SODIUM INJECTION USP work.
  - including prescription or non- prescription medications, dietary supplements (e.g., vitamins), herbal supplements, nutritional drinks, and tube feeding preparations.
  - PHENYTOIN SODIUM INJECTION USP may decrease the effectiveness of medications containing estrogen (e.g., hormonal birth control methods or hormone replacement therapies).
- have kidney or liver problems.
- drink alcohol occasionally or on a regular basis.
- have suicidal thoughts or behaviours.
- are pregnant, think you might be pregnant, or planning to become pregnant.
- are breastfeeding or planning to breastfeed.
- have high blood sugar levels or diabetes. PHENYTOIN SODIUM INJECTION USP may raise your blood sugar (glucose) levels.
- have porphyria (a condition that affects the nervous system and skin). PHENYTOIN SODIUM INJECTION USP can worsen your condition.
- have been told by a healthcare professional that you have low levels of albumin in your blood.
- are of Asian descent. You may be at higher risk of developing serious skin reactions during your treatment with PHENYTOIN SODIUM INJECTION USP.
- have absence seizures (brief, sudden lapse of consciousness) or seizures caused by low blood sugar levels or other conditions associated with your metabolism.
- have heart problems (e.g., heart failure).
- have breathing problems.
- have low blood pressure.
- are 65 years of age or older.
- are severely ill.

Other warnings you should know about:

Stopping your treatment: Do NOT stop taking PHENYTOIN SODIUM INJECTION USP without first talking to your healthcare professional. Suddenly stopping your treatment can cause you to have more seizures. Your healthcare professional will monitor and guide you on how to safely stop taking PHENYTOIN SODIUM INJECTION USP.

Serious side effects with PHENYTOIN SODIUM INJECTION USP can include:

- **Bone problems**: Talk to your healthcare professional if you have taken anti-seizure medications (such as phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine, sodium valproate and/or carbamazepine) for a prolonged period. Long-term use of anti-seizure medications,

including PHENYTOIN SODIUM INJECTION USP, can lead to weakened or brittle bones. This can even lead to bone fractures.

- **Gingival hyperplasia** (overgrowth of gum tissue around the teeth): Talk to your healthcare professional about the best way to care for your teeth, gums, and mouth during your treatment with PHENYTOIN SODIUM INJECTION USP. It is very important that you care for your mouth properly to decrease the risk of gum damage.
- **Suicidal thoughts and behaviour changes:** If you have thoughts of harming or killing yourself at any time, contact a healthcare professional or go to a hospital **right away**. You may find it helpful to tell a relative or close friend how you are feeling and ask them to tell you if they notice any changes in your behaviour.
- **Injection site reactions:** PHENYTOIN SODIUM INJECTION USP may cause irritation and inflammation at the site of injection. It can also be accompanied by leakage into the surrounding tissue. A rare but serious complication called purple glove syndrome can also occur several days after your injection. Tell your healthcare professional **right away** if you experience pain, swelling, and purple-blue discolouration at the extremity of the limb where the injection was given. This can lead to tissue death, which may require surgical intervention.
- **Serious skin reactions:** Serious allergic reactions can be caused by anti-seizure medicines, often involving a skin reaction. These may occur within a month of starting treatment, but can occur later. Get help **right away** if you develop a skin rash, regardless of its severity, either alone or with a combination of the following symptoms:
  - any other serious skin reaction such as blistering or peeling of the mouth, nose, eyes or genitals,
  - fever,
  - swollen glands,
  - flu-like feeling,
  - swelling of the face and/or legs,
  - problems related to the liver, kidneys, heart, lungs or other organs.

See the **Serious side effects and what to do about them** table for more information on these and other serious side effects.

Alcohol: Do not drink alcohol during your treatment with PHENYTOIN SODIUM INJECTION USP without talking to your healthcare professional first. Drinking alcohol during your treatment may change your blood levels of phenytoin sodium, which can cause serious side effects.

Driving and using machines: Patients with uncontrolled epilepsy should not drive or operate machinery. PHENYTOIN SODIUM INJECTION USP may cause you to feel dizzy or drowsy. Avoid doing tasks which require special attention until you know how PHENYTOIN SODIUM INJECTION USP affects you.

Testing and check-ups:

- Your healthcare professional may ask you to do a genetic test before you receive PHENYTOIN SODIUM INJECTION USP. This test will determine if you have a high risk of experiencing serious skin reactions if you are given PHENYTOIN SODIUM INJECTION USP.
- You will have regular visits with your healthcare professional during your treatment with PHENYTOIN SODIUM INJECTION USP to monitor your health. They may:
  - do blood tests to monitor the amount of phenytoin sodium in the body.
  - talk to you about how you are feeling, and if you have suicidal thoughts and behaviours.

- PHENYTOIN SODIUM INJECTION USP can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Pregnancy, birth control and breastfeeding:

- Avoid becoming pregnant during your treatment with PHENYTOIN SODIUM INJECTION USP. If you become pregnant, your seizures may become worse. Your healthcare professional may need to adjust your dose.
- PHENYTOIN SODIUM INJECTION USP is not recommended during pregnancy as it can harm an unborn child. Tell your healthcare professional **right away** if you become pregnant or think you are pregnant during your treatment with PHENYTOIN SODIUM INJECTION USP. Your healthcare professional will discuss the potential risks to your unborn child with you. You and your healthcare professional will then decide if you should continue your treatment with PHENYTOIN SODIUM INJECTION USP or use other treatments while you are pregnant.
- If you are able to get pregnant, you should use an effective birth control method (contraception) during your treatment with PHENYTOIN SODIUM INJECTION USP. If you are using a hormonal birth control method, it might not work. Talk to your healthcare professional about the best non-hormonal birth control methods to use during your treatment with PHENYTOIN SODIUM INJECTION USP.
- **Pregnancy Registry:** If you become pregnant during your treatment with PHENYTOIN SODIUM INJECTION USP, talk to your healthcare professional about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicines during pregnancy. Information about the registry can also be found at the website: http://www.aedpregnancyregistry.org/.
- PHENYTOIN SODIUM INJECTION USP passes into breast milk and may harm your baby. Do not breastfeed during treatment with PHENYTOIN SODIUM INJECTION USP. Talk to your healthcare professional about the best way to feed your baby during this time.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PHENYTOIN SODIUM INJECTION USP:

- Alcohol
- Other medicines used to treat seizures or epilepsy (e.g., ethosuximide, oxcarbazepine, carbamazepine, topiramate, phenobarbital, sodium valproate, valproic acid, quetiapine, lamotrigine, vigabatrin, diazepam)
- Medicines used to treat heart rhythm problems (e.g., amiodarone, mexiletine, verapamil)
- Medicines used to treat cancer (e.g., capecitabine, fluorouracil, bleomycin, carboplatin, cisplatin, doxorubicin, methotrexate, irinotecan, paclitaxel)
- Medicines used to treat bacterial infections (e.g., sulfamethoxazole-trimethoprim, doxycycline)
- Medicines used to treat fungal infections (e.g., fluconazole, ketoconazole, itraconazole, voriconazole, posaconazole)
- Medicines used to treat anxiety and alcoholism (e.g., chlordiazepoxide, diazepam)
- Medicines used to reduce the amount of acid in the stomach (e.g., cimetidine, omeprazole)
- Estrogen containing medications (including birth control methods or hormone replacement therapies)
- Medicines used to treat depression (e.g., fluoxetine, paroxetine, fluvoxamine, sertraline, trazodone)

- Medicines used to treat high blood cholesterol (e.g., fluvastatin, atorvastatin, simvastatin)
- Medicines used to treat tuberculosis (e.g., isoniazid, rifampin)
- Medicines known as phenothiazines, used to treat schizophrenia and other psychotic disorders
- Medicines used for muscle relaxation during surgery (e.g., rocuronium, cisatracurium)
- Medicines used to prevent blood clots (e.g., ticlopidine, warfarin)
- Medicines used to treat HIV infection (e.g., delavirdine, ritonavir, efavirenz, lopinavir)
- Medicines used to treat high blood pressure (e.g., nifedipine, beta blockers)
- Medicines used to treat inflammation (e.g., corticosteroids, acetylsalicylic acid (ASA), magnesium salicylate)
- Halothane, used for general anesthesia
- Methylphenidate, used to treat ADHD
- Tolbutamide, used to treat high blood sugar levels
- Diazoxide, used to treat low blood sugar levels
- Furosemide, used to treat fluid retention
- Praziquantel, used to treat parasitic infections
- Cyclosporine, used to prevent the rejection of organ transplants
- Digoxin, used to treat various heart conditions
- Theophylline, used to treat asthma or other breathing problems
- Dopamine, used to treat severe heart failure and shock.
- Lidocaine, used to prevent pain caused by certain conditions or procedures
- St. John's Wort, a herbal remedy
- Vitamin B9 (folic acid)
- Vitamin D (calciferol)
- Calcium
- Tube feeding preparations and related nutritional drinks or supplements

How PHENYTOIN SODIUM INJECTION USP is given:

- PHENYTOIN SODIUM INJECTION USP will be given to you:
  - by a healthcare professional, and
  - as an injection into a vein or muscle.
- Your healthcare professional may ask you to take supplements during your treatment to prevent side effects. Follow their instructions carefully.

Usual dose:

Your healthcare professional will decide the dose that is right for you.

Overdose:

Signs of an overdose with PHENYTOIN SODIUM INJECTION USP include:

- blurred vision, involuntary eye movements (side-to-side, up and down, circular motion)
- lack of muscle control or coordination, shaking (tremors), overactive reflexes
- low blood pressure
- lack of energy
- slurred or slow speech
- nausea or vomiting
- slow and ineffective breathing

- coma

If you think you, or a person you are caring for, have been given too much PHENYTOIN SODIUM INJECTION USP, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

PHENYTOIN SODIUM INJECTION USP is given by healthcare professionals. They will ensure that you receive your doses on time. If you feel that a dose has been missed, tell your healthcare professional.

Possible side effects from using PHENYTOIN SODIUM INJECTION USP:

These are not all the possible side effects you may have when taking PHENYTOIN SODIUM INJECTION USP. If you experience any side effects not listed here, tell your healthcare professional.

Side effects with PHENYTOIN SODIUM INJECTION USP may include:

- Sleepiness/drowsiness, feeling tired/fatigue
- Headache, dizziness along with the feeling of a spinning movement
- Nausea/vomiting
- Changes in taste (metallic taste)
- Double vision, blurred vision
- Poor coordination (dizzy)
- Shakiness
- Unwanted, male-pattern hair growth in women
- Thickening of the gums

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your Healthcare Professional		Get Immediate medical help
	Only if severe	In all cases	
Common			
Allergies: fever, rash and swollen lymph nodes, and may be associated with symptoms involving other organs, e.g., liver		✓	
Gingival hyperplasia (overgrowth of gum tissue around the teeth): tender gums, inflammation, pain, bad breath, plaque buildup on teeth, gums covering the teeth		✓	

Frequency/Side Effect/Symptom	Talk to your Healthcare Professional		Get Immediate medical help
	Only if severe	In all cases	
Nervous system problems: unusual eye movements, slurred speech, decreased coordination, feeling confused, shaking (tremors), involuntary movements		✓	
Uncommon			
Blood disorders (low white and/or red blood cell or platelet count): feeling tired or weak, pale skin, bruising or bleeding for longer than usual if you hurt yourself, fever, chills		✓	
Bone problems: bone pain, muscle weakness, difficulty walking, bone fractures		✓	
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness, unexplained loss of appetite			✓
Mental changes: feeling confused or disoriented (delirium), seeing, hearing or believing things that aren't real (psychosis).		✓	
Serious skin reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body. Can be accompanied with yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine			✓
Skin rashes or redness			✓
Suicidal thoughts or behaviour changes: unusual behaviours, depression, worsening of depression, leading to thoughts of self-harm or suicide			✓

Frequency/Side Effect/Symptom	Talk to your Healthcare Professional		Get Immediate medical help
	Only if severe	In all cases	
Rare			
Breathing problems			✓
Heart problems: rapid, slow or irregular heartbeat, shortness of breath, feeling tired, chest discomfort, dizziness, fainting			✓
Purple glove syndrome (severe soft-tissue injury): pain, swelling, and purple-blue discolouration in the hand or arm where the injection was given		✓	
Severe allergic reactions: swelling of face, eyes, lips, or tongue, trouble swallowing or breathing, skin rash			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Your healthcare professional will store PHENYTOIN SODIUM INJECTION USP between 15°C and 30°C, protected from light. Freezing should be avoided.
- Keep out of reach and sight of children.

If you want more information about PHENYTOIN SODIUM INJECTION USP:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-

canada/adverse-reaction-reporting.html); the manufacturer's website (www.sandoz.com); or by calling 1-800-361-3062.

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