PRESCRIBING INFORMATION

[Pr]Phenytoin Sodium Injection USP

50 mg/mL
Sterile Solution

Anticonvulsant agent

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Date of Revision:
September 19, 2018

Submission Control No.: 219349

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50 mg/mL

Sterile Solution

THERAPEUTIC CLASSIFICATION:

Anticonvulsant agent

INDICATIONS

1. Phenytoin Sodium Injection USP is an anticonvulsant used to control tonic-clonic (grand mal) and psychomotor or partial (focal) seizures.

2. Phenytoin Sodium Injection USP may be used for the prevention and treatment of seizures occurring during neurosurgery.

CONTRAINDICATIONS

Hypersensitivity to Phenytoin or to other hydantoins.

Sinus bradycardia, sino-atrial block, second and third degree A.V. block, and Adams-Stokes syndrome.

WARNINGS

a) Intravenous injection should be administered **SLOWLY** in order to avoid extravasation; the injection rate should not exceed 50 mg per minute.

b) Edema, discolouration, and pain of the distal limb (described as "purple glove syndrome") have been reported following peripheral intravenous phenytoin sodium injection. This may or may not be associated with extravasation. Although resolution of symptoms may be spontaneous, skin necrosis and limb ischemia have occurred and required such interventions as fasciotomies, skin grafting and amputation. See **DOSAGE AND ADMINISTRATION** for suggested IV administration of Phenytoin Sodium Injection USP.

c) Abrupt withdrawal of Phenytoin may precipitate status epilepticus. If the dosage has to be reduced or if Phenytoin has to be discontinued or substituted by another antiepileptic drug, the change should be done gradually (except in case of hypersensitivity or allergy).

d) Phenytoin is NOT recommended for seizures with hypoglycaemic or other imbalances of metabolic origin.

e) Phenytoin should be used with caution in patients with hypotension or severe myocardial insufficiency.

f) The intramuscular route is not recommended for the treatment of status epilepticus (See **DOSAGE AND ADMINISTRATION**).

g) Acute alcohol intoxication may increase Phenytoin serum levels while chronic alcoholism may decrease it.

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 43892 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.

PRECAUTIONS:

1. **Pregnancy and the neonate:**

   Risks due to antiepileptic drugs: Considering all antiepileptic drugs, it has been shown that among newborns delivered by women under antiepileptic treatment, the proportion of child defects is two to three times (about 3%) more elevated than among the general population. However, the relationship between antiepileptic treatment and the occurrence of these abnormalities is not clearly established.

   The child defects mostly reported are cleft lip and palate and heart malformations. With the use of Phenytoin or other hydantoins, microcephaly, prenatal growth deficiency and mental deficiency, have also been encountered. These features are often associated with retarded intrauterine growth due to other causes. Animal experimentations did not report any drug related teratogen effect.

   However, the great majority of mothers on antiepileptic medications deliver normal babies and it is up to the prescribing physician to appreciate these considerations in treating or counselling epileptic women of childbearing potential. But when the drug is administered to prevent major seizures the treatment should not be discontinued because of the strong possibility of precipitating status epilepticus. When the severity and the frequency of the seizures are less important, discontinuation of the medication may be considered prior to and during pregnancy although one has to keep in mind that even minor seizures may be hazardous to the developing embryo or foetus.

   In pregnant women, altered Phenytoin absorption and metabolism have been detected resulting in increased seizure frequency. Dosage adjustments should be considered in pregnant, Phenytoin-treated women.

   Coagulation defects have been reported within the first 24 hours in the neonates born from epileptic mothers receiving phenobarbital and/or Phenytoin. Resulting bleeding stopped soon after administration of vitamin K_1. Treatment of the mother, during pregnancy, with vitamin K_1 is the best form of prophylaxis.

2. Lactation: Not recommended because of the secretion of Phenytoin into the mother's milk.

3. In patients on long term Phenytoin therapy, vitamin D and folic acid are given to prevent side effects respectively affecting bones and hematopoiesis.

4. As the liver is the main site of biotransformation of Phenytoin, the drug should be given with precaution to patients with hepatic impairment.

5. In case of appearance of skin rash, Phenytoin should be discontinued. If the rash is of milder type (measles like) therapy may be resumed after the rash has completely disappeared. If the rash is of a more severe type, treatment must be discontinued, and alternate therapy considered. The patient must be warned to call his physician in case of skin rash.

6. A Poor metabolism of Phenytoin in patients might be due to genetic abnormalities such as limited enzyme availability.

7. Lymphadenopathy, including pseudolymphoma, lymphoma and Hodgkin's disease have been reported in relation to Phenytoin administration.

8. Poly-therapy is necessary in patients suffering from both tonic-clonic and absence seizures.

9. Plasma level determinations are recommended to adjust dosage (see **ADVERSE EFFECTS** and **ADMINISTRATION**).

10. Blood count (including platelets) and hemogram should be checked before and during treatment.

11. Alcohol should be avoided during treatment.

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

DRUG INTERACTIONS

Drugs increasing Phenytoin serum levels (risk of overdosage and toxicity):

Chloramphenicol, dicoumarol, disulfiram, tolbutamide, phenothiazines, phenylbutazone, acute alcohol intake, salicylates, chlordiazepoxide, diazepam, estrogens, halothane, methylphenidate, isoniazid, sulfonamides, cimetidine, trazodone, ethosuximide.

Drugs decreasing Phenytoin serum levels (seizures not controlled):

Carbamezapine, chronic alcohol abuse, reserpine. Antiacid preparations containing calcium.

The effects on Phenytoin serum levels of phenobarbital, valproic acid and sodium valproate are unpredictable.

Conversely, effects of Phenytoin on these drugs are not well established.

Drugs whose efficacy is impaired by Phenytoin:

Coumarin anticoagulants, corticosteroids, oral contraceptives, quinidine, vitamin D, digitoxin, doxycycline, rifampin, estrogens, furosemide.

ADVERSE EFFECTS

Reporting Suspected Side Effects

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

The most important signs of toxicity associated with the IV use of Phenytoin sodium are cardiovascular collapse and/or CNS depression (coma and respiratory depression have been observed); hypotension occurs if the drug is administered too rapidly by the IV route.

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.

Central Nervous System:

Progressive neurological deterioration in patients receiving long term Phenytoin therapy: ataxia, impaired speech, diplopia, nystagmus, mental confusion, headache, dizziness, transient nervousness and insomnia, bizarre behaviour, EEG changes. Some of these effects are dose-related and may disappear with reduced dosage. Phenytoin may cause asterixis, orofacial dyskinesia, limb chorea and dystonia in patients given excessive doses (these dyskinesias may be related to the dopamine antagonist properties of Phenytoin). Mild peripheral neuropathy (essentially sensorial) may appear in patients receiving long term therapy.

Conjunctive and Bone tissues:

Rickets; osteomalacia; polyarthropathy. Thickening of the skull, facial changes or gingival hyperplasia.

Skin:

Dermatological manifestations are sometimes accompanied by fever; skin rashes are common, particularly in children, and may resemble measles; Lupus erythematosus; erythema multiform; occurrence of bullous, exfoliative or purpuric rash. Lymphadenopathy may occasionally occur.

Gastrointestinal:

Nausea, vomiting, constipation.

Hematopoiesis:

Leucopenia, thrombocytopenia, pancytopenia, agranulocytosis, granulocytopenia. Megaloblastic anaemia, following prolonged use, usually responds to treatment with folic acid.

Other effects:

Hirsutism (more noticeable in young females), hepatitis, hyperglycemia (resulting from Phenytoin's inhibitory effect on insulin release), liver damage (correlated to the hepatic metabolism of the drug), lymphoma, myasthenia gravis. Anticonvulsants 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).

OVERDOSAGE

Early symptoms of overdosage are slurred speech, digestive disturbances (nausea, vomiting), tremor, hyperreflexia and lethargy. Other signs are nystagmus, ataxia and dysarthria. Most patients experience blurred vision and nystagmus at serum Phenytoin concentrations of 20µg per mL, ataxia and unsteady gait at 30µg per mL and lethargy at more than 40µg per mL. The lethal dose in children is unknown. In adults it is estimated to be in the order of 2 to 5g.

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.

For management of a suspected drug overdose, contact your Regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

***IV route:**

1. Intravenous administration should be used with caution in patients with hypotension and severe myocardial or respiratory insufficiencies.

2. Electrocardiographic monitoring is recommended during intravenous therapy.

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 with cardiac diseases.**

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, although it may be used to maintain or establish plasma concentrations of Phenytoin in patients who are unconscious or otherwise unable to take Phenytoin by mouth.

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 µg/mL).

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 per square meter 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.

STABILITY AND STORAGE RECOMMENDATIONS

1. Store at a controlled room temperature (between 15°C -25°C).

2. Freezing should be avoided.

3. Slight yellowish discoloration of the injection does not affect potency or efficacy, but the injection should not be used if the solution is not clear or if a precipitate is present.

Precipitation of free Phenytoin occurs at a pH of 11.5 or less.

SUPPLIED

- Ampoules of 2 mL (Phenytoin 100 mg/ampoule), packages of 10

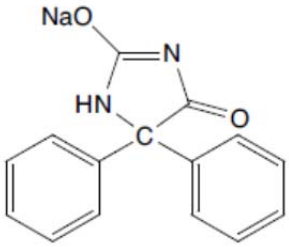
- Ampoules of 5 mL (Phenytoin 250 mg/ampoule), packages of 5

Each ampoule contains:

Phenytoin sodium USP 50 mg/ml with propylene glycol USP 40% and alcohol USP 10% in Water for Injection USP. pH adjusted to 12 approximately with sodium hydroxide.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Phenytoin Sodium
Chemical name:	sodium 5,5-diphenyl-2,4-imidazolidinedione
Molecular formula and molecular mass:	$C_{15}H_{11}N_2NaO_2$ 274.25 g/mol
Structural formula:	

Physicochemical properties

Physical Form:	White to off white powder
Odour:	Bitter, soapy taste
Solubility:	Very soluble in water; soluble in ethyl alcohol; and practically insoluble in chloroform and diethyl ether.
pKa and pH values:	8.33 for Phenytoin
Polymorphism:	Two different polymorphic forms: anhydrous and monohydrate.
Melting Point:	295°C – 298°C for Phenytoin
Hygroscopicity:	Slightly hygroscopic on exposure to air and carbon dioxide

REFERENCES

1. Prescribing Information: Tremytoine®, Omega Laboratories, LTD. Control Number: 161703, Date of Revision: February 12, 2013

Last revised: July 31, 2018

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