

PRESCRIBING INFORMATION



PHENOBARBITAL SODIUM INJECTION USP

30 mg/ml, 120 mg/ml

Therapeutic Classification

Anticonvulsant, Hypnotic, Sedative

(Barbiturate)

Sandoz Canada Inc.
145 Jules-Léger
Boucherville, QC, Canada
J4B 7K8

Date of Revision: February 26, 2015

Submission Control No: 179559



PHENOBARBITAL SODIUM INJECTION USP

Therapeutic Classification

Anticonvulsant, Hypnotic, Sedative
(Barbiturate)

PHARMACOLOGY

Phenobarbital, like many other barbiturates, is a nonselective central nervous system (CNS) depressant, capable of producing all degrees of depression from mild sedation and hypnosis to general anesthesia, deep coma and death. The extent of CNS depression varies with the route of administration, dose and pharmacokinetic characteristics of the particular barbiturates. Patient specific factors such as age, physical or emotional state and the concomitant use of other drugs will also affect response.

The mechanism of action of phenobarbital is not completely known. Phenobarbital may act by enhancing and/or mimicking the synaptic action of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. The sedative-hypnotic action of phenobarbital may be due to an inhibition of conduction in the reticular formation resulting in a decrease in the number of impulses reaching the cerebral cortex.

Anticonvulsant activity may result from a reduction in CNS synaptic transmission and an increase in the threshold for electrical stimulation of the motor cortex. Phenobarbital is the only barbiturate with anticonvulsant activity at subhypnotic doses.

The therapeutic index of barbiturates, such as phenobarbital, is narrow. Therefore, the use of phenobarbital is almost always accompanied by some degree of impairment of cognitive function. Supratherapeutic doses lead to marked mental and motor impairment. In some patients (especially children and the elderly), drowsiness may be paradoxically preceded by transient euphoria, elation, excitement and confusion.

Pharmacokinetics

The pharmacokinetics of phenobarbital as well as other common barbiturates are shown in Table 1. After oral administration, absorption is usually rapid and relatively complete. The sodium salts undergo rapid dissolution and are absorbed more quickly than their corresponding free acids. The rate of absorption is increased when the barbiturate is formulated as a liquid, when the stomach is empty and when alcohol is ingested concurrently. The onset of action following rectal administration is similar to that following oral administration. After IV administration, the onset of action is immediate for amobarbital and pentobarbital and within 5 minutes for phenobarbital. The onset of action following IM administration is slightly faster than when the drugs are administered orally or rectally.

Once absorbed, phenobarbital is rapidly distributed to all tissues and fluids. High concentrations appear in the brain, liver and kidneys. Secobarbital has the highest degree of lipid solubility and thus the fastest distribution, phenobarbital is the least lipid soluble and has the slowest distribution. Phenobarbital readily cross the placenta and is excreted into breast milk. If administered IV, fetal blood concentrations are approximately equal to maternal serum concentration; if administered orally, fetal concentrations are less than maternal levels.

Barbiturates are slowly metabolized and/or conjugated in the liver and then excreted renally. Amobarbital, pentobarbital and secobarbital are almost completely metabolized. Due to its lower lipid solubility, phenobarbital is not metabolized as extensively and almost 25% is excreted unchanged in the urine. One of the metabolites of primidone is phenobarbital.

Metabolic elimination is influenced by age (being slower in the elderly and infants), chronic liver disease and other drugs.

Table 1: Barbiturates
Pharmacokinetics

Drug	Onset of Action (minutes)	Half-life (hours)	Duration of Action (hours)
Amobarbital ^a	45 to 60	8 to 42	6 to 8
Butalbital ^a	15 to 60	35	4 to 6
Pentobarbital ^a	10 to 15	15 to 48	3 to 4
Phenobarbital ^a	60	80 to 120	10 to 12
Primidone	N/A	10 to 12	10 to 12
Secobarbital ^a	10 to 15	15 to 40	3 to 4
Thiopental ^b	1	8 to 10	10 to 30 minutes

^a. Oral administration.

^b. Intravenous administration.

INDICATIONS

Phenobarbital is indicated for the control of generalized tonic-clonic and complex partial seizures.

The use of barbiturates as sedative/hypnotics has largely been replaced by less toxic agents such as benzodiazepines. Barbiturates have been used parenterally in the management of status epilepticus or acute seizure episodes that are secondary to meningitis or other causes.

CONTRAINDICATIONS

Phenobarbital is contraindicated in:

- patients who are known to be hypersensitive to barbituric acid derivatives, any ingredient in the formulation or component of the container
- patients with porphyria,
- patients with severe respiratory depression or pulmonary insufficiency, renal impairment, hepatic impairment, sleep apnea, suicidal potential, alcoholism, drug dependence or in the presence of uncontrolled pain (paradoxical excitement may be produced). With the exception of phenobarbital, barbiturates should be avoided in older individuals.
- newborns

WARNINGS AND PRECAUTIONS

Administer with caution to pregnant women, myxedema, myasthenia gravis, patients with central nervous system depression, hypotension, severe anemia, hemorrhagic shock, cardiac, hepatic or renal impairment, asthma, diabetes mellitus, hyperkinesis tendencies. Concomitant use of the following drugs should be avoided because of likely occurrence of adverse effects: alcohol, anaesthetics and CNS depressants and to a lesser extent, acetaminophen, oral anticoagulants, carbamazepine, oral contraceptives, estrogens, corticosteroids, digitalis, digitoxin, tricyclic antidepressants, cyclophosphamide, doxycycline, griseofulvin, monoamine oxidase inhibitors, phenytoin, quinidine, sodium valproate, valproic acid and vitamin D.

Phenobarbital should not be discontinued in patients in whom the drug is administered to prevent seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risk to both the mother and the unborn child. With regard to drugs given for minor seizures, the risk of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history. Lower doses are required in elderly and debilitated patients in order to preclude oversedation.

Prolonged use of phenobarbital, even in therapeutic dosages, may result in psychologic and physiologic dependence. Patients may escalate dosage without medical advice. Withdrawal symptoms may occur following abrupt termination of hypnotic doses causing nightmares or insomnia, sweating, irritability, tremor, weight loss, anorexia or after chronic use of large doses, resulting in delirium, seizures, or death. Withdrawal should be cautious and gradual.

Rarely, rickets and osteomalacia have been reported following prolonged usage of phenobarbital due to increased metabolism of vitamin D (see ADVERSE REACTIONS, Bone Disorders).

Phenobarbital should be used with caution in patients with impaired liver function or in patients with a history of drug dependence or abuse. Caution is essential when the drug is administered in the presence of any respiratory difficulty. Special care should be taken when phenobarbital is administered to patients in whom the hypnotic effect may be prolonged or intensified, as in those suffering from shock, hepatic dysfunction, uremia, or after recent administration of other respiratory depressants.

Since phenobarbital is a potent CNS depressant, IV administration should not be attempted without adequate provisions for supporting respiration and circulation. Rapid injection can cause

cardiovascular collapse. Slow administration will usually prevent this occurrence but may cause apnea, laryngospasm, coughing, or other respiratory difficulties. IM injection should not exceed a volume of 5 mL at any one site because of possible tissue damage.

Phenobarbital solutions are highly alkaline. Extreme care should be exercised to avoid extravasation or intra-arterial injection. Extravascular injection may cause local tissue damage with subsequent necrosis. The consequences of intra-arterial injection may vary from transient pain along the course of the artery to gangrene of the limb. Signs of accidental injection by this route include, in addition to pain, delayed onset of hypnosis, pallor and cyanosis of the extremity and patchy discoloration of the skin. Any complaint of pain in the limb warrants stopping the injection.

Hypotension may result from IV administration of the drug, particularly in patients with hypertension. Slow administration will usually prevent this occurrence.

Solutions that appear cloudy or in which a precipitate has formed should not be used.

Bone Disorders

Long-term use of antiepileptics such as carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine and sodium valproate is associated with a risk of decreased bone mineral density that may lead to weakened or brittle bones. Discontinuation of phenobarbital should be considered if evidence of significant bone marrow depression develops (see ADVERSE REACTIONS).

Occupational Hazards

Phenobarbital may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a vehicle or operating machinery. The concomitant use of alcohol or other CNS depressants may have an additive effect. Patients should be warned accordingly. The incidence of fractures due to falls may be increased, particularly in the elderly. Following use of phenobarbital in office procedures, warn patients against operating motor vehicles for the remainder of the day.

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.

Serious Dermatological Reactions

Stevens-Johnson syndrome and Toxic Epidermal Necrolysis

Serious and sometimes fatal dermatologic reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported with phenobarbital. Post-marketing reporting rate is generally accepted to be an underestimate due to under-reporting. Recurrence of serious skin reactions following re-challenge with phenobarbital has also been reported. Therefore, if a patient develops a skin reaction during phenobarbital treatment, consideration should be given to permanent discontinuation and replacement of the drug with alternative treatment (see ADVERSE REACTIONS).

Pregnancy: Phenobarbital readily crosses the placental barrier.

Phenobarbital and Primidone: The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic 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.

In addition to reports of increased incidence of congenital malformations such as cleft lip/palate and heart malformations in children of women receiving phenobarbital and other antiepileptic drugs, there have been reports of fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenobarbital, phenytoin, alcohol or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

If women receiving phenobarbital become pregnant, plan to become pregnant, or if the need to initiate treatment with phenobarbital arises during pregnancy, the drug's potential benefits must carefully be weighed against its hazards, particularly during the first 3 months of pregnancy. The prescribing physician should weigh all these considerations in treating or counseling epileptic women of childbearing potential regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

The serum level of anticonvulsants may decline during pregnancy requiring adjustments in dosage. 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, primidone 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.

Folic acid deficiency is known to occur in pregnancy and can contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Like many other anti-epileptic drugs, primidone may contribute to, or aggravate, folic acid deficiency. Folic acid supplementation is recommended before and during pregnancy.

Phenobarbital withdrawal has occurred in newborns who were exposed to the drug *in utero* and may be characterized by hypotonia, irritability and vomiting.

Lactation: Phenobarbital passes into breast milk. Concentration of barbiturates in breast milk is 35 to 50% that of maternal serum concentrations. Phenobarbital is eliminated slowly in neonates and may accumulate. Therefore, the benefits of breast feeding should be weighed against the possible risks to the infant and a decision should be made whether to discontinue nursing or to discontinue phenobarbital, taking into account the importance of the drug to the mother. Breastfed infants should be observed for excessive drowsiness, dizziness, feeding problems, allergic skin reactions such as rash or other adverse reactions. If any of these occur, breastfeeding should be discontinued. When breastfeeding is discontinued there is a potential for withdrawal symptoms in infants.

DRUG INTERACTIONS

Most drug interactions have been documented with phenobarbital, however they are likely applicable to other barbiturates as well. The barbiturates are inducers of cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19 and CYP3A4, and are capable of increasing the clearance of many hepatically metabolized drugs. This can result in two concerns: i) decrease in or loss of effectiveness of other drug(s) during phenobarbital use; ii) increase in effect or frank toxicity of the other drug(s) on discontinuation of phenobarbital.

When adding or deleting any barbiturate to or from the patient's therapeutic regimen, pharmacotherapy must be monitored closely as dosage adjustment may be necessary.

Anticoagulants, Oral: Metabolism of coumarin anticoagulants may be accelerated, resulting in decreased anticoagulant response. Correspondingly, if phenobarbital is discontinued from a stabilized regimen, the hypoprothrombinemic response may be greatly increased, potentially resulting in hemorrhagic complications. Prothrombin times should be monitored closely when barbiturates are added to or deleted from a regimen that includes oral anticoagulants.

Anticonvulsants: Phenytoin: When phenobarbital is used with phenytoin, concentrations of either or both drugs may be increased, decreased or unchanged. While phenobarbital may induce the metabolism of phenytoin, it may also decrease it because both drugs compete for the same metabolic pathway. Plasma concentrations of both drugs should be monitored when any change in the therapeutic regimen occurs. **Valproic Acid:** Concomitant administration of valproic acid and phenobarbital usually results in increased levels of phenobarbital and resultant oversedation. There have been case reports of progression of CNS depression to coma. Plasma concentrations of both drugs should be monitored when any change in the therapeutic regimen occurs.

Carbamazepine: When phenobarbital and carbamazepine are used together, the metabolism of carbamazepine is usually accelerated and plasma concentrations may be decreased. The clinical significance of this interaction is not known. Plasma concentrations of both drugs should be monitored when any change in the therapeutic regimen occurs.

Antidepressants, MAO Inhibitors: MAO inhibitors may inhibit phenobarbital metabolism, resulting in increased CNS depressant effects. A reduction in phenobarbital dosage may be required.

Antidepressants, Tricyclic: Phenobarbital may increase metabolism of tricyclic antidepressants resulting in lack of effect. Plasma tricyclic concentrations should be monitored if possible, especially if the patient is not responding to standard dosages of antidepressant. The use of both drugs concomitantly may result in additive respiratory depressant effects.

CNS Depressants: Alcohol, benzodiazepines and other CNS depressants used concurrently with phenobarbital may result in excessive CNS depression.

Corticosteroids: Phenobarbital may increase the metabolism of corticosteroids. There have been several reports of exacerbation of asthma and other conditions when phenobarbital was added to regimens containing corticosteroids.

Contraceptives, Oral: Phenobarbital may accelerate the metabolism of both the estrogenic and progestagenic components of the contraceptive, resulting in decreased effectiveness, which may or may not be signalled by breakthrough bleeding. There have been reports of pregnancy resulting from this combination. If phenobarbital is necessary it would be advisable to use some other form of contraception.

Miscellaneous: Phenobarbital has been reported to increase the metabolism and correspondingly reduce the effectiveness of the following: griseofulvin, digitoxin and doxycycline. When ketamine is used for anesthesia following preoperative administration of phenobarbital, profound respiratory depression may result.

ADVERSE REACTIONS

Dizziness, headache, "hangover" confusion especially in the elderly, paradoxical excitation, exacerbation of pre-existing pain, nausea, vomiting, epigastric pain, hypotension, facial edema, skin rash with bullae and vesicles, purpura, erythema multiforme, exfoliative dermatitis (rare), megaloblastic anemia, agranulocytosis and thrombocytopenia.

In children, behavioral disturbances and cognitive impairment may occur.

Central Nervous System (CNS)

Drowsiness is frequent, especially at initiation of therapy. Mild impairment of concentration, judgment, memory, and fine motor skills may occur. Disturbances of sleep, dizziness, vertigo, headache and depression may occur. Patients with uncontrolled pain may experience paradoxical euphoria, elation, excitement and confusion. In children, hyperactivity is not uncommon; behavioural disturbances and cognitive impairment may occur. Geriatric patients may experience excitation, confusion or depression.

Cardiovascular

Hypotension may be observed with IV administration and is generally related to the rate of administration (see WARNINGS AND PRECAUTIONS).

Gastrointestinal

Nausea, vomiting, diarrhea and constipation.

Hematologic

Megaloblastic anemia (responds to folic acid therapy). Agranulocytosis and thrombocytopenia are rare.

Hepatic: Severe allergic reactions may result in jaundice due to degenerative changes in the liver. Toxic hepatitis is rare.

Hypersensitivity: Facial edema, skin rash (1 to 2%) may be purpuric, vesicular or erythematous. Exfoliative dermatitis and erythema multiforme are rare. Hypersensitivity reactions have a greater tendency to occur in patients with a history of asthma, urticaria or angioedema.

Metabolic

Phenobarbital may increase vitamin D requirements, possibly by increasing vitamin D metabolism *via* enzyme induction. Rarely, rickets and osteomalacia have been reported following prolonged use of phenobarbital.

Respiratory

Respiratory depression (see WARNINGS AND PRECAUTIONS).

Miscellaneous: Exacerbation of porphyria, pain at the injection site, withdrawal (see WARNINGS AND PRECAUTIONS).

Post-Market Adverse Drug Reactions

Bone Disorders

There has been post-marketing reports of decreased bone mass, osteomalacia, and osteopenia osteoporosis and fractures in patients receiving long-term anti-epileptic therapy, including phenobarbital. The mechanism by which phenobarbital affects bone metabolism has not been identified. Some studies have indicated that supplemental calcium and vitamin D may be of benefit in these patients (see WARNINGS AND PRECAUTIONS).

Serious Dermatological Reactions

Serious and sometimes fatal post-marketing cases of dermatologic reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported in patients treated with phenobarbital. Post-marketing reporting rate is generally accepted to be an underestimate due to under-reporting. Recurrence of serious skin reactions following re-challenge with phenobarbital has also been reported. Therefore, if a patient develops a skin reaction during phenobarbital treatment, consideration should be given to permanent discontinuation and replacement of the drug with alternative treatment (see WARNINGS AND PRECAUTIONS).

OVERDOSAGE

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

Symptoms

Acute overdose with phenobarbital primarily affects the CNS and the cardiovascular system. Mild overdose resembles alcohol intoxication. Drowsiness, confusion, stupor, respiratory depression, ataxia, sluggish or absent reflexes, early hypothermia, late fever, cardiovascular depression with hypotension, renal failure, cardiac arrhythmias, pulmonary edema, aspiration pneumonia, bullae over pressure points and decreased gastrointestinal motility are all possible symptoms. Severe overdose may progress to shock, coma and death.

Doses that result in toxicity vary widely among patients and depend on co-ingestion of other drugs and the patient's underlying comorbidities. The lethal dose of phenobarbital is believed to be 5 g.

The lowest dose of phenobarbital reported to have led to fatality is 1.41 g.

According to literature, the highest acute dose of phenobarbital that has not resulted in fatality was 27 g, which corresponded to 253 mcg/mL phenobarbital in human plasma.

Chronic ingestion of phenobarbital results in the development of tolerance and large doses can be ingested without overt toxicity. Serious toxicity can result at lower phenobarbital levels if combined with alcohol or other CNS depressant drugs.

Treatment

Patients who have ingested phenobarbital in overdose often require respiratory and hemodynamic support. This may include intubation, ventilation, boluses of isotonic IV fluids, and inotrope infusions. Once a patient's airway is protected, activated charcoal should be administered to minimize absorption of orally administered phenobarbital. Administering multiple doses of activated charcoal enhances the clearance of phenobarbital, though there is no evidence that it actually improves clinical outcomes such as duration of intubation. In patients with normal renal and cardiac function, urinary alkalinization also enhances phenobarbital clearance. Likewise, urinary alkalinization has not actually been shown to improve clinical outcomes.

DOSAGE AND ADMINISTRATION

The general use of phenobarbital as a sedative or hypnotic has for the most part, been supplanted by other less toxic drugs (i.e. benzodiazepines). Decreased dosage is recommended in older individuals and in patients with decreased renal or hepatic function. Phenobarbital can be given by deep IM or slow IV injection.

Doses exceeding 2 g daily are not recommended.

Pentobarbital sodium injection is not for use in newborns (see CONTRAINDICATIONS).

Preoperative

For intramuscular or slow intravenous injection.

Adults (≥18 years):

100 mg to 200 mg 60 to 90 minutes prior to surgery.¹

Children (<18 years):

1 mg to 3 mg/kg 60 to 90 minutes prior to surgery.¹

Anticonvulsant

For intramuscular or slow intravenous injection.

Adults (≥18 years):

100 to 320 mg IV with additional doses if necessary to a maximum daily dose of 600 mg.

Children (<18 years):

Initial Loading Dose: 10-20 mg/day, maximum 125 mg/m² daily.

Maintenance Dose: 1 to 6 mg/kg/day.

Status Epilepticus

For slow intravenous injection.

Adults (≥18 years):

20 mg/kg IV at a rate of 50 mg/min.¹

Children (<18 years):

20 mg/kg IV over 20 minutes.¹

¹ <https://www.e-therapeutics.ca> (Barbiturates)

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each ml of Phenobarbital Sodium Injection USP 30 mg/mL contains phenobarbital sodium 30 mg, propylene glycol 0.6 mL, benzyl alcohol 20 mg (as a preservative), hydrochloric acid to adjust pH, and water for injection.

Phenobarbital Sodium Injection USP 30 mg/mL is supplied in boxes 10 ampoules of 1 mL each.

Each ml of Phenobarbital Sodium Injection USP 120 mg/mL contains phenobarbital sodium 120 mg, propylene glycol 0.6 mL, benzyl alcohol 20 mg (as a preservative), hydrochloric acid to adjust pH, and water for injection.

Phenobarbital Sodium Injection USP 120 mg/mL is supplied in boxes 10 ampoules of 1 mL each.

Do not use if precipitate present. Store between 15°C and 25°C. Protect from freezing. Protect from light.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**



Phenobarbital Sodium Injection USP[®]
Phenobarbital Sodium

Read this carefully before you or your child start taking Phenobarbital Sodium Injection USP and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your or your child's medical condition and treatment and ask if there is any new information about Phenobarbital Sodium Injection USP.

Serious Warnings and Precautions

Cardiovascular Risk

- **You will receive Phenobarbital Sodium Injection USP through injection into the vein or muscle. If your doctor injects this medication into the vein too fast, your blood pressure may drop quickly, and you may experience irregular heartbeat. This can be serious. Therefore, your doctor should observe you closely while you are receiving Phenobarbital Sodium Injection USP and after.**

What is Phenobarbital Sodium Injection USP used for?

- Phenobarbital Sodium Injection USP is used to treat seizures that affect part of the brain or spread to the whole brain (generalized tonic-clonic and complex partial seizures), and to induce sleep.

How does Phenobarbital Sodium Injection USP work?

It is not completely known how phenobarbital works.

What are the ingredients in Phenobarbital Sodium Injection USP?

Medicinal ingredients: phenobarbital sodium

Non-medicinal ingredients: benzyl alcohol (as a preservative), propylene glycol, hydrochloric acid (to adjust pH), water for injection.

Phenobarbital Sodium Injection USP comes in the following dosage forms:

Solution for injection; 30 mg phenobarbital sodium/mL and 120 mg phenobarbital sodium/mL.

Do not use Phenobarbital Sodium Injection USP if you or your child:

- is allergic to the active ingredient, phenobarbital, or any of the other ingredients, or to barbituric acid derivatives
- have the following symptom or problems:
 - Porphyria (a genetic disorder that can cause nervous system, blood, and skin problems).

- Lung problems or severe respiratory depression
- Liver or kidney problem
- Pauses in breathing during sleep
- Suicidal potential
- Alcohol addiction
- Drug addiction
- Uncontrolled pain

Phenobarbital sodium injection USP is not for use in the newborn.

To help avoid side effects and ensure proper use, talk to your healthcare professional about any health conditions or problems you or your child may have BEFORE taking Phenobarbital Sodium Injection USP, including if you or your child:

- Have ever had a rash or unusual reaction while taking phenobarbital sodium or any other antiepileptic drug.
- Have kidney or liver problems. Your doctor may need to adjust the dose.
- Drink alcohol. Drinking alcohol with phenobarbital products may make you less alert and may make feelings of anger, confusion or sadness worse.
- Are pregnant or planning to become pregnant. You must only take Phenobarbital Sodium Injection USP during pregnancy if your doctor tells you to.
 - If you become pregnant while taking Phenobarbital Sodium Injection USP, talk to your healthcare provider about registering with the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy. You can enroll in this registry by calling 1-888-233-2334. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.
- Are nursing or plan to nurse your baby. Nursing while you are taking Phenobarbital Sodium Injection USP is not recommended.
- Are taking birth control.
 - Phenobarbital Sodium Injection USP may make hormonal birth control such as “the pill” less effective.
 - Use other forms of safe and effective birth control when taking Phenobarbital Sodium Injection USP
 - You need to use other forms of birth control until the end of your menstrual cycle after stopping treatment.
- Have used or abused drugs in the past.
- Have any of the following diseases or conditions:
 - suffer from seizures that spread to the whole brain.
 - heart problems
 - have kidney or liver problems. Your doctor may need to adjust the dose
 - hypothyroidism (a condition in which your body has low thyroid hormone)
 - myasthenia Gravis (a chronic disease that causes severe muscle weakness)
 - central nervous system depression
 - low blood pressure
 - severe anemia (low red blood cell count)

- hemorrhagic shock (shock due to bleeding)
- asthma (wheeze or gasp for air due to spasm of the airway)
- diabetes mellitus
- hyperkinesia tendencies (abnormally heightened, sometimes uncontrollable muscle movement)

Other warnings you should know about:

- If you use Phenobarbital Sodium Injection USP regularly for a long time, it may cause mental and physical dependence.
- Sudden removal of this drug may cause unwanted side effects. Your doctor should discontinue your drug slowly and carefully.
- Ask your doctor about signs and symptoms of life threatening skin reactions such as Stevens Johnson Syndrome (SJS; a skin reaction with rash and blisters) and Toxic Epidermal Necrolysis (TEN; a skin rash often with blisters, lesions and lifting skin) that have been reported during phenobarbital treatment. Closely monitor for skin reactions. Most often, SJS or TEN happen in the first weeks of treatment. If symptoms or signs of SJS or TEN are present, phenobarbital treatment should be stopped and you should seek urgent medical help. The best results in managing SJS and TEN come from early detection and stopping the drug treatment right away (see table of Serious Side Effects and What to do About Them, below).

DURING treatment with Phenobarbital Sodium Injection USP, tell your doctor if you or your child develops:

- Thoughts of suicide or self-harm
- Abnormal vision (blurry or double vision)
- Pale, blue or purple coloration of the extremity and patchy discoloration of the skin, any complaint of pain in the limb

Driving and using machines:

Before doing tasks that require special attention, wait until you know how you respond to Phenobarbital Sodium Injection USP. Being dizzy or drowsy can occur. Be careful to avoid accidental injury or falls.

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

The following may interact with Phenobarbital Sodium Injection USP:

- Birth control pills
- Other anti-seizure drugs including phenytoin, valproic acid, carbamazepine
- Oral coumarin anticoagulants
- Antidepressants, MAO Inhibitors (e.g. isocarboxazid, moclobemide, or linezolid etc.)
- Tricyclic antidepressants (e.g. clomipramine, imipramine, or nortriptyline, amitriptyline)
- CNS depressants, including alcohol, benzodiazepines
- Corticosteroids (e.g. beclomethasone, fluticasone furoate etc.)
- Griseofulvin (an antifungal drug)

- Digitoxin
- Doxycycline (an antibiotic)
- Ketamine
- Anesthetics
- To a lesser extent: acetaminophen, estrogens, digitalis, digitoxin, cyclophosphamide, doxycycline, quinidine, and vitamin D.

How to take Phenobarbital Sodium Injection USP:

- This medication is an injection. It should be given to you by your doctor to stop a seizure.
- **If you are taking this medication to control your seizures, do not stop Phenobarbital Sodium Injection USP without talking to your doctor.** Stopping a seizure medicine suddenly can cause serious problems, including seizures that will not stop. Your doctor will tell you if and when you or your child can stop taking this medicine.
- When given for minor seizures, the risk of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.

Pentobarbital sodium injection is not for use in newborns.

Usual dose:

Preoperative

For intramuscular or slow intravenous injection.

Adults (≥18 years):

100 mg to 200 mg 60 to 90 minutes prior to surgery.

Children: (<18 years):

1 mg to 3 mg/kg 60 to 90 minutes prior to surgery.

Anticonvulsant

For intramuscular or slow intravenous injection.

Adults (≥18 years):

100 to 320 mg IV with additional doses if necessary to a maximum daily dose of 600 mg.

Children: (<18 years):

Initial Loading Dose: 10-20 mg/day, maximum 125 mg/m² daily.

Maintenance Dose: 1 to 6 mg/kg/day.

Status Epilepticus

For slow intravenous injection.

Adults (≥18 years):

20 mg/kg IV at a rate of 50 mg/min.

Children: (<18 years):

20 mg/kg IV over 20 minutes.

Overdose:

If you think you have taken too much Phenobarbital Sodium USP, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Your healthcare professional will ensure that this product is administered as it should be and that doses are not missed.

What are possible side effects from using Phenobarbital Sodium Injection USP?

These are not all the possible side effects you may feel when taking Phenobarbital Sodium Injection USP. If you or your child experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

The most common side effects associated with the use of Phenobarbital Sodium Injection USP are:

- Sleepiness/drowsiness, feeling tired/fatigue
- Headache, dizziness along with the feeling of a spinning movement
- Nausea/vomiting
- Broken sleep
- Depression
- Diarrhea, constipation
- Unusual or unexpected feeling of joy, happiness, excitement and confusion
- Hypotension (low blood pressure)
- Hyperactivity in children
- "Hangover" confusion especially in the elderly (drowsiness the day after a dose)

Other possible side effects associated with the use of Phenobarbital sodium injection USP:

- Increased or worsening of pre-existing pain
- Epigastric pain (pain in the upper abdomen)

Serious Side Effects and What to do About Them				
Symptom / effect		Talk to your Healthcare Professional		Get Immediate Medical Help
		Only if Severe	In all Cases	
Common	Low sodium level in blood (symptoms like lack of energy, confusion, muscular twitching or convulsions)		X	

Serious Side Effects and What to do About Them

Symptom / effect	Talk to your Healthcare Professional		Get Immediate Medical Help
	Only if Severe	In all Cases	
Nervous system problems (symptoms like dizziness, trouble walking or with coordination, feeling sleepy and tired, trouble concentrating, blurred vision, double vision, etc.)		X	
Allergies (symptoms like fever, rash and swollen lymph nodes, and may be associated with symptoms involving other organs, e.g., liver)			X
Uncommon Liver problems (symptoms like yellowing of your skin or the whites of your eyes, nausea or vomiting, loss of appetite, stomach pain, dark [brownish] urine etc.)		X	
Thoughts of suicide or self harm			X
Respiratory depression (shallow slow, weak breathing)			X

Serious Side Effects and What to do About Them			
Symptom / effect	Talk to your Healthcare Professional		Get Immediate Medical Help
	Only if Severe	In all Cases	
Thinning of the bone, bone softening, bone disease, or fractures (In situations where healthy people would not normally break a bone you may have sudden pain in any location and especially in the wrist, spine or hip. This may be a fracture.)		X	
Altered numbers and types of blood cells, symptoms like unexplained tiredness, weakness, shortness of breath, and sometimes, feeling like you are going to pass out and increased bruising, nosebleeds, sore throats, or infections)		X You should tell your doctor who may want to perform a blood test	
Rare Severe allergic reactions (symptoms like swelling of face, eyes, lips, or tongue, trouble swallowing or breathing, skin rash)			X

Serious Side Effects and What to do About Them			
Symptom / effect	Talk to your Healthcare Professional		Get Immediate Medical Help
	Only if Severe	In all Cases	
A rare, serious disorder in which your skin reacts severely to a medication (Stevens Johnson Syndrome; SJS). If symptoms or signs of SJS (e.g. skin rash often with blisters or lesions) are present, phenobarbital treatment should be stopped right away.			X
Severe skin reaction where the upper surface of your skin detaches like a patient who has suffered burns (Toxic Epidermal Necrolysis [TEN]). If symptoms or signs of TEN (e.g. skin rash often with blisters or mucosal lesions and lifting skin) are present, phenobarbital treatment should be stopped right away.			X

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

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to: 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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

Storage:

Store between 15°C and 25°C. Protect from freezing. Protect from light. Do not use if precipitate present.

Keep out of reach and sight of children.

If you want more information about Phenobarbital Sodium Injection USP:

- Talk to your healthcare professional
- Find the full Prescribing Information that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<http://hc-sc.gc.ca/index-eng.php>) or, by calling the manufacturer at 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

Last Revised: February 26, 2015