PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**PHENYTOIN SODIUM**

Extended Phenytoin Sodium Capsules

capsules, 100 mg, oral

House Standard

Anticonvulsant

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RECENT MAJOR LABEL CHANGES

None at the time of most recent authorization.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PHENYTOIN SODIUM (extended phenytoin sodium) capsules are indicated for:

- the control of generalized tonic-clonic and psychomotor (grand mal and temporal lobe) seizures; and
- the prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin is not effective for absence (petit mal) seizures, and not indicated for seizures due to hypoglycemic or other metabolic causes.

1.1 Pediatrics

Pediatrics (< 18 years of age): See 4.2 Recommended Dose and Dosage Adjustments, Pediatrics.

1.2 Geriatrics

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 4.2 Recommended Dose and Dosage Adjustments, Geriatrics.

2 CONTRAINDICATIONS

Phenytoin is contraindicated in:

- Patients who are hypersensitive to phenytoin, other hydantoins, or any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING; and 7 WARNINGS AND PRECAUTIONS, Hypersensitivity; and Skin).

- Patients being treated with delavirdine (a non-nucleoside reverse transcriptase inhibitor). See 9.4 Drug-Drug Interactions.

- Patients who currently suffer from sick sinus syndrome, sinus bradycardia, sinoatrial block, second- and third-degree atrioventricular (A-V) block, QT interval prolongation, Adams-Stokes syndrome, or other heart rhythm disorders. This is due to the effect of phenytoin on ventricular automaticity. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular; and 5 OVERDOSAGE.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Dosage should be individualized to provide maximum benefit. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages.

Phenytoin is highly bound to plasma protein and is subject to saturable metabolism. Consequently:

- small dose increases may substantially raise serum phenytoin concentration (and risk of toxicity), when levels are already in or above the upper therapeutic range; and
- phenytoin is subject to many drug interactions, which may increase serum concentrations.

See 10.3 Pharmacokinetics; and 9 DRUG INTERACTIONS.

Serum blood level determinations may be necessary for optimal dosage adjustments. The clinically effective serum level is usually 40 to 80 micromol/L (10 to 20 mcg/mL). Serum blood level determinations are especially helpful when:

- drug or other interactions are suspected;
- treating geriatric patients;
- patients have renal or hepatic impairment, or hypoalbuminemia, or hyperbilirubinemia (in which case unbound phenytoin levels should be monitored). See 4.2 Renal or Hepatic Disease

Switch carefully between sodium salt and free acid phenytoin products. Because there is approximately an 8% increase in drug content with the free acid form over that of the sodium salt, dosage adjustments may be necessary and serum phenytoin concentrations should be monitored when switching between free acid and sodium salt formulations.

- The sodium salt of phenytoin is used in PHENYTOIN SODIUM extended capsules.

Phenytoin should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus. See 7 WARNINGS AND PRECAUTIONS, General, Withdrawal Precipitated Seizures.

Discoloured capsules should not be used.

4.2 Recommended Dose and Dosage Adjustment

With recommended dosage, a period of 7 to 10 days may be required to achieve therapeutic blood levels with PHENYTOIN SODIUM and changes in dosage (increase or decrease) should not be carried out at intervals shorter than 7 to 10 days.

- **Adults**

Patients who have received no previous treatment may be started on one 100 mg extended phenytoin sodium capsule three times daily, and the dose then adjusted to suit individual requirements. For most adults, the satisfactory maintenance dosage will be three to four capsules (300 to 400 mg) daily. An increase to six capsules daily may be made, if necessary.

- **Pediatrics (< 18 years of age)**

PHENYTOIN SODIUM is intended for use in children over 6 years old, weighing at least 40 kg and who are able to swallow capsules.

PHENYTOIN SODIUM **is not** available in any pediatric dosage forms i.e. a 30 mg capsule strength, a 50 mg chewable tablet, or an oral suspension of 30 mg in each 5 mL.

Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. Given that PHENYTOIN SODIUM is available only as a 100 mg capsule, the child must weigh at least 40 kg in order to initiate therapy with this product. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years old may require the minimum adult dose (300 mg/day).

- **Geriatrics (> 65 years of age)**

Phenytoin clearance is decreased slightly in elderly patients. Lower doses than the doses recommended for adults may be required when initiating treatment. Phenytoin dosing requirements are highly variable and must be individualized (see 10.3 Pharmacokinetics, Geriatrics).

- **Renal or Hepatic Disease**

In patients with renal or hepatic impairment or in those with hypoalbuminemia, plasma levels of unbound phenytoin are elevated. **Unbound** phenytoin concentrations may be more useful in these patient populations. This finding should be considered during therapeutic monitoring and following phenytoin serum level determinations, which may be necessary for optimal dosage adjustment (see 4.1 Dosing Considerations; and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and Renal).

- **Alternative Dose**

Once-a-day dosage for adults with 300 mg of extended phenytoin sodium capsules may be considered if seizure control is established with divided doses of three 100 mg extended phenytoin sodium capsules daily. Studies comparing divided doses of 300 mg with a single daily dose of this quantity indicated that absorption, peak plasma levels, biologic half-life, difference between peak and minimum values, and urinary recovery were equivalent. Once-a-day dosage offers a convenience to the individual patient or to nursing personnel for institutionalized patients, and is intended only to be used for patients requiring this amount of drug daily. A major problem in motivating noncompliant patients may also be lessened when the patient can take all of his medication once-a-day. However, patients should be cautioned not to inadvertently miss a dose. Only extended phenytoin sodium capsules are recommended for once-a-day dosing.

4.5 Missed Dose

The patient/caregiver should be advised that if a dose is missed, the missed dose should be taken as soon it is remembered. If it is almost time for the next dose the missed dose should not be taken. Instead, take the next scheduled dose. The patient/caregiver should be advised to not make up for a missed dose by taking a double dose next time.

5 OVERDOSAGE

The lethal dose of phenytoin in pediatric patients is not known. The lethal dose of phenytoin in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, somnolence, drowsiness, lethargy, slurred speech, blurred vision, nausea, vomiting. The patient may become comatose and hypotensive. Bradycardia and asystole/cardiac arrest have been reported (see 7 WARNINGS AND PRECAUTIONS, Cardiac effects). Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus on lateral gaze, usually appears at 80 micromol/L (20 mcg/mL), ataxia at 119 micromol/L (30 mcg/mL). Dysarthria and lethargy appear when the serum concentration is > 159 micromol/L (40 mcg/mL), but a concentration as high as 198 micromol/L (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 > 396 micromol/L (100 mcg/mL) with complete recovery. Irreversible cerebellar dysfunction and atrophy have been reported.

Treatment and Management

Treatment is nonspecific since there is no known antidote.

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

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Extended capsules 100 mg	Colloidal silicon dioxide, hydroxypropyl methylcellulose, and magnesium stearate. Capsule shells: D&C Red No. 28, D&C Yellow No. 10, FD&C Red No. 40, gelatin, and titanium dioxide. Pharmaceutical ink: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, iron oxide black, propylene glycol, and shellac.

PHENYTOIN SODIUM Capsules: Extended phenytoin sodium capsule is available in dosage strength of 100 mg capsules.

100 mg: Hard gelatin capsule with white opaque body and orange opaque cap. Imprinted "APO P100" in black ink. Filled with white to off-white, round biconvex tablets. Available in bottles of 100 and 1000 capsules.

7 WARNINGS AND PRECAUTIONS

General

Withdrawal Precipitated Seizure: PHENYTOIN SODIUM extended capsules 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 anticonvulsant medication arises, this should be

done gradually. However, in the event of an allergic hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an anticonvulsant drug which does not belong to the hydantoin chemical class.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

Phenytoin is **not indicated for**:

- Seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

- Absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Slow metabolizers: A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Information for Patients and Caregivers

Patients and caregivers should be advised to read the Patient Medication Information for PHENYTOIN SODIUM prior to use. Patients receiving PHENYTOIN SODIUM, and caregivers, should be given the following instructions by the physician and pharmacist:

1. Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing their physician of any clinical condition in which it is not possible to take the drug orally as prescribed, e.g., surgery, etc.

2. Patients should be advised of the early toxic signs and symptoms of potential hematologic, dermatologic, hypersensitivity, or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, the patient should be advised that these signs and symptoms should be reported even if mild or when occurring after extended use. Patients should be advised that a history of hypersensitivity reactions with other antiepileptic drugs may be a risk for developing reactions with phenytoin (see 7 WARNINGS AND PRECAUTIONS, Hematologic; 7 WARNINGS AND PRECAUTIONS, Immune; 7 WARNINGS AND PRECAUTIONS, Skin; and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

3. Patients should be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice (see 9 DRUG INTERACTIONS).

4. Patients should be instructed to call their physician if skin rash develops.

5. The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

6. Patients, their caregivers, and families should be counseled that antiepileptic drugs, including PHENYTOIN SODIUM, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers (see 7 WARNINGS AND PRECAUTIONS, Psychiatric).

7. Women of child-bearing potential should be warned to consult their physician regarding the discontinuation of the drug due to the potential hazards to themselves and to the fetus if they are pregnant or intend to become pregnant (see 7.1.1 Pregnant Women and 7.1.2 Breast-feeding).

8. Patients who become pregnant should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients themselves must call the toll free number 1-888-233-2334. Registry information can also be obtained from the Internet at www.aedpregnancyregistry.org/ (see 7.1.1 Pregnant Women and 7.1.2 Breast-feeding).

Carcinogenesis and Mutagenesis

See 7 WARNINGS AND PRECAUTIONS, Hematopoietic; 7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women.

Cardiovascular

Cardiac Effects

Cardiac-related adverse events have been reported in association with therapeutic and supratherapeutic levels of phenytoin in patients with or without history of cardiac disease or comorbidities and with or without other medications present. These reactions occurred in all age groups and included bradycardia, ventricular tachycardia, cardiac arrest, and death. In a number of cases, patients recovered following phenytoin dose reduction or discontinuation. Patients with any underlying cardiac conditions should be evaluated on an individual basis, and potential benefits of phenytoin treatment should be assessed against its potential risks (see 2 CONTRAINDICATIONS, 5 OVERDOSAGE).

Driving and Operating Machinery

Patients should be advised not to drive or operate complex machinery or engage in other hazardous activities until they have gained sufficient experience on phenytoin to gauge whether or not it affects their mental and/or motor performance adversely.

Endocrine and Metabolism

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.

Hyperglycemia

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

Hematologic

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.

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 (see 7 WARNINGS AND PRECAUTIONS, Skin). In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative anticonvulsant drugs.

While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. If folic acid is added to phenytoin therapy, a decrease in seizure control may occur.

Hepatic/Biliary/Pancreatic

In patients with hepatic impairment or in those with hypoalbuminemia, there is increased

plasma levels of unbound phenytoin. In patients with hyperbilirubinemia, plasma levels of unbound phenytoin may also be elevated. It may be more useful to monitor unbound phenytoin concentrations in these patient populations, for optimal dosage adjustments (see 4.2 Recommended Dose and Dosage Adjustment, Renal or Hepatic Disease).

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. In some cases, these incidents have been associated with a hypersensitivity syndrome characterized by fever, skin eruptions, and lymphadenopathy, and usually occur within the first 2 months of treatment (see 7 WARNINGS AND PRECAUTIONS, Skin). Other common manifestations include arthralgias, rash, jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, phenytoin should be immediately discontinued and not re-administered.

The liver is the chief site of biotransformation of phenytoin. Patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity (see 5 OVERDOSAGE).

Toxic hepatitis, liver damage, and hypersensitivity syndrome have been reported and may, in rare cases be fatal (see 8 ADVERSE REACTIONS).

Immune

Hypersensitivity

Phenytoin and other hydantoins (e.g. fosphenytoin) are contraindicated in patients who have experienced phenytoin hypersensitivity (see 2 CONTRAINDICATIONS). If there is a history of hypersensitivity reactions to structurally similar drugs, such as carboxamides (e.g., carbamazepine), barbiturates, succinimides, and oxazolidinediones (e.g., trimethadione) in these patients or immediate family members, other alternatives should be considered. See also 7 WARNINGS AND PRECAUTIONS, Skin.

Angioedema

Angioedema has been reported in patients treated with phenytoin. Phenytoin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

Monitoring and Laboratory Tests

Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments. See also 9.7 Drug-Laboratory Test Interactions.

Musculoskeletal

Chronic use of phenytoin by patients with epilepsy has been associated with decreased bone mineral density (osteopenia, osteoporosis, osteomalacia) and bone fractures (see 8.5 Post-Market Adverse Reactions).

Phenytoin and other anticonvulsants that have been shown to induce the CYP450 enzyme are thought to affect bone mineral metabolism indirectly by increasing the metabolism of Vitamin D3. This may lead to Vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcemia, and hypophosphatemia in chronically treated epileptic patients. Consideration should be given to monitoring with bone-related laboratory and radiological tests and initiating treatment plans, as appropriate.

Neurologic

Central Nervous System

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 and/or cerebellar atrophy. Accordingly, at the first sign of acute toxicity, serum drug level determinations are recommended. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination of phenytoin therapy is recommended (see 10.3 Pharmacokinetics, Absorption; 7 WARNINGS AND PRECAUTIONS, General).

Psychiatric

Suicidal ideation and behaviour

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

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.

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.

Renal

In patients with renal impairment, plasma levels of unbound phenytoin are elevated. It may be useful to monitor unbound phenytoin concentrations in these patient populations, for optimal dosage adjustments (see 4.2 Recommended Dose and Dosage Adjustment, Renal or Hepatic Disease).

Reproductive Health: Female and Male Potential

- **Teratogenic Risk**

See 7.1.1 Pregnant Women, Risks to Fetus.

Skin

Serious Dermatological Reactions

Phenytoin can cause rare, severe cutaneous adverse reactions (SCARs) such as acute generalized exanthematous pustulosis (AGEP), exfoliative dermatitis, Steven-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be fatal. Although serious skin reactions may occur without warning, patients should be alert for the occurrence of rash and other symptoms of hypersensitivity syndrome (HSS)/DRESS.

Hypersensitivity Syndrome / Drug Reaction with Eosinophilia and Systemic Symptoms

Hypersensitivity Syndrome (HSS) or Drug rash with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking anticonvulsant drugs, including phenytoin. Some of these events have been fatal or life threatening.

HSS/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, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leukocytosis, and eosinophilia. The interval between first drug exposure and symptoms is usually 2 to 4 weeks but has been reported in individuals receiving anticonvulsants for 3 or more months. If such signs and symptoms occur, the patient should be evaluated immediately. Phenytoin should be discontinued (under clinical supervision) if an alternative aetiology for the signs and symptoms cannot be established.

Patients at higher risk for developing HSS/DRESS include Black patients, patients who have experienced HSS/DRESS in the past (with phenytoin or other anticonvulsant drugs), those with a family history of HSS/DRESS, and immune-suppressed patients. The syndrome is more severe in previously sensitized individuals.

Stevens-Johnson Syndrome, Acute Generalized Exanthematous Pustulosis and Toxic Epidermal Necrolysis

Serious and sometimes fatal dermatologic reactions, including Toxic Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP) and Stevens-Johnson Syndrome (SJS), have been reported with phenytoin. Although serious skin reactions may occur without warning, patients should be alert for the occurrence of rash and other symptoms of DRESS (see 7 WARNINGS AND PRECAUTIONS, Skin). In countries with mainly Caucasian populations, these reactions are estimated to occur in 1 to 6 per 10,000 new users, but in some Asian countries (e.g., Taiwan, Malaysia and the Philippines) the risk is estimated to be much higher (see 7 WARNINGS AND PRECAUTIONS, Asian Ancestry and Allelic Variation in the HLA-B Genotyping).

Literature reports suggest that the combination of phenytoin, cranial irradiation and the gradual reduction of corticosteroids may be associated with the development of erythema multiforme, and/or SJS, and/or TEN. In any of the above instances, caution should be exercised if using structurally similar compounds (e.g., barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Treatment recommendations for dermatological reactions

Phenytoin should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus or SJS or TEN is suspected, use of this drug should not be resumed and alternative therapy should be considered (see 8 ADVERSE REACTIONS). If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated. The use of other anti-epileptic drugs associated with SJS/TEN should be avoided in patients who have shown severe dermatological reactions during phenytoin treatment. If a rash occurs and SJS or TEN is not suspected, the patient should be evaluated for signs and symptoms of DRESS (see 7 WARNINGS AND PRECAUTIONS, Skin).

Asian Ancestry and Allelic Variation in the HLA-B Genotyping

HLA-B*1502

In studies that included small samples of patients of Asian ancestry a strong association was found between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. The HLA-B*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia[1]. Results of these studies suggest that the presence of the HLA-B*1502 allele may be one of the risk factors for phenytoin-associated SJS/TEN in patients with Asian ancestry.

Therefore, physicians should consider HLA-B*1502 genotyping as a screening tool in these patients. Until further information is available, the use of phenytoin and other anti-epileptic drugs associated with SJS/TEN should also be avoided in patients who test positive for the HLA-B*1502 allele.

Important Limitations of HLA-B*1502 Genotyping

HLA-B*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B*1502-positive Asian patients treated with phenytoin will not develop SJS/TEN, and these reactions can still occur infrequently in HLA-B*1502-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

In addition, it should be kept in mind that the majority of phenytoin treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration when deciding whether to screen genetically at-risk patients currently on phenytoin.

Should signs and symptoms suggest a severe skin reaction such as SJS or TEN, phenytoin should be withdrawn at once, under clinical supervision.

7.1 Special Populations

[1] The following rates provide a rough estimate of the prevalence of HLA-B*1502 in various populations. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-B*1502, averaging 2 to 4%, but this may be higher in some groups. HLA-B*1502 is present in <1% of the population in Japan and Korea. HLA-B*1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans). The estimated prevalence rates have limitations due to the wide variability in rates that exist within ethnic groups, the difficulties in ascertaining ethnic ancestry and the likelihood of mixed ancestry.

7.1.1 Pregnant Women

Women of child-bearing potential

Women of childbearing potential who are not planning a pregnancy should be advised regarding the use of effective contraception during treatment. Phenytoin may result in a failure of the therapeutic effect of hormonal contraceptives (see 9.4 Drug-Drug Interactions, Table 4).

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating and counseling epileptic women of childbearing potential.

Pregnant Women

Risks to mother: An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage (see 10.3 Pharmacokinetics, Absorption). However, postpartum restoration of the original dosage will probably be indicated.

Risks to fetus: Phenytoin crosses the placental barrier and may cause fetal harm when administered to a pregnant woman. 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), and abnormalities characteristic of fetal hydantoin syndrome, including dysmorphic skull and facial features, nail and digit hypoplasia, growth abnormalities (including microcephaly), and cognitive deficits, have been reported among children born to women with epilepsy who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy.

Risk to newborn: 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.

There have been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

Therefore, PHENYTOIN SODIUM should be used during pregnancy only if the potential benefit outweighs the potential risks. 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 from exposure to phenytoin.

Counsel pregnant women and women of childbearing potential about alternative therapeutic options.

7.1.2 Breast-feeding

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.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Phenytoin clearance is decreased slightly in elderly patients, and dosing requirements are highly variable (see 4.2 Recommended Dose and Dosage Adjustment, Geriatrics; and 10.3 Pharmacokinetics, Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions are nervous system reactions, including nystagmus, ataxia, slurred speech, decreased coordination, somnolence, and mental confusion.

8.5 Post-Market Adverse Reactions

The following listing of adverse events is based on adverse events reported in clinical trials and/or spontaneous adverse event reports from post-marketing experience. All events are listed under Post-Market Adverse Reactions as the clinical trial data on which it was originally authorized is no longer available. Where a frequency cannot be estimated from the available data it is classified as 'not known'.

Body as a whole: Anaphylactic reaction and anaphylaxis

Central Nervous System: The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion. Cerebellar atrophy has been reported and appears more likely in settings of elevated phenytoin levels and/or long term phenytoin use (see 7 WARNINGS AND PRECAUTIONS, Neurologic). Dizziness, vertigo, insomnia, transient nervousness, motor twitchings, headaches, paresthesia and somnolence 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.

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, and Peyronie's Disease.

Gastrointestinal System: Acute hepatic failure, toxic hepatitis, liver damage, vomiting, nausea, constipation. (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Hematopoietic System: Hematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. Pure red cell aplasia has also been reported. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy, including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease has been reported (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

Immunologic: Drug rash with eosinophilia and systemic symptoms (DRESS) (which may include, but is not limited to symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, periarteritis nodosa, and immunoglobulin abnormalities. Angioedema has been reported. Several individual case reports have suggested that there may be an increased, although still rare, incidence of hypersensitivity reactions, including skin rash and hepatotoxicity, in Black patients (see 7 WARNINGS AND PRECAUTIONS, Skin).

Investigations: Thyroid function test abnormal

Musculoskeletal System: Bone fractures and osteomalacia have been associated with chronic use of phenytoin by patients with epilepsy. Osteoporosis and other disorders of bone metabolism such as hypocalcemia, hypophosphatemia and decreased levels of Vitamin D metabolites have also been reported (see 7 WARNINGS AND PRECAUTIONS, Musculoskeletal).

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. Urticaria has been reported. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome and toxic epidermal necrolysis (see 7 WARNINGS AND PRECAUTIONS, Skin). There have also been reports of hypertrichosis.

Special Senses: Taste perversion

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• Multiple drug interactions can occur due to extensive plasma protein binding, saturable metabolism and potent induction of hepatic enzymes. Monitor total and/or unbound serum phenytoin concentrations as appropriate to establish/maintain efficacy and safety. • Delavirdine. See 9.4 Drug-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 (CYP) 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. See 5 OVERDOSAGE.

Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes and may reduce the levels of drugs metabolized by these enzymes.

There are many drugs which may increase or decrease phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected.

9.3 Drug-Behavioural Interactions

Alcohol: Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

The most commonly occurring drug interactions are listed below.

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

Table 1. Drugs Which May Increase Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as)
Alcohol (acute intake)	
Analgesic/anti-inflammatory agents	azapropazone phenylbutazone salicylates
Anesthetics	halothane
Antibacterial agents	chloramphenicol erythromycin isoniazid sulfadiazine sulfamethizole sulfamethoxazole-trimethoprim sulfaphenazole sulfisoxazole sulfonamides
Anticonvulsants	felbamate oxcarbazepine sodium valproate succinimides (e.g. ethosuximide) valproate sodium topiramate[a]
Antifungal agents	amphotericin B fluconazole itraconazole ketoconazole miconazole voriconazole
Antineoplastic agents	capecitabine fluorouracil
Benzodiazepines/psychotropic	chlordiazepoxide

Drug Classes	Drugs in each Class (such as)
agents	diazepam disulfiram methylphenidate trazodone phenothiazine viloxazine
Calcium channel blockers/ Cardiovascular agents	amiodarone dicumarol diltiazem nifedipine ticlopidine
H_2-antagonists	cimetidine
HMG-CoA reductase inhibitors	fluvastatin
Hormones	estrogens
Immunosuppressant drugs	tacrolimus
Oral hypoglycemic agents	tolbutamide
Proton pump inhibitors	omeprazole
Serotonin re-uptake inhibitors	fluoxetine fluvoxamine sertraline

[a] Coadministration 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.

Table 2 summarizes drugs which may decrease phenytoin serum levels.

Table 2. Drugs Which May Decrease Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as)
Alcohol (chronic intake)	
Antibacterial agents/Fluoroquinolones	ciprofloxacin rifampin
Anticonvulsants	carbamazepine vigabatrin[b]

Drug Classes	Drugs in each Class (such as)
Antineoplastic agent	bleomycin carboplatin cisplatin doxorubicin methotrexate
Antiretrovirals	fosamprenavir nelfinavir ritonavir
Antiulcer agents	sucralfate
Bronchodilators	theophylline
Calcium preparation	molindone hydrochloride
Cardiovascular agents	reserpine
Folic acid	folic acid
Hyperglycemic agents	diazoxide
Protease inhibitors	nelfinavir
St. John's Wort	St. John's Wort

[b] Coadministration with vigabatrin reduces serum phenytoin levels by 20 to 30%. This may be clinically significant in some patients and may require dosage adjustment.

Molidone hydrochloride

Molindone hydrochloride contains calcium ions which interfere with the absorption of phenytoin.

Calcium Preparations

Ingestion times of phenytoin and antacid calcium preparations, including antacid preparations containing calcium should be staggered to prevent absorption problems.

Nelfinavir

A pharmacokinetic interaction study between nelfinavir (1,250 mg twice a day) and phenytoin (300 mg once a day) administered orally showed that nelfinavir reduced AUC values of phenytoin (total) and free phenytoin by 29% and 28% (n = 12), respectively. The plasma concentration of nelfinavir was not changed (n = 15). Phenytoin concentration should be monitored during coadministration with nelfinavir, as nelfinavir may reduce phenytoin plasma concentration.

Table 3 summarizes drugs which may either increase or decrease phenytoin serum levels.

Table 3. Drugs Which May Either Decrease or Increase Phenytoin Serum Levels

Drug Classes	Drugs in each class (such as)
Antibacterial agents	ciprofloxacin
Anticonvulsants	carbamazepine phenobarbital sodium valproate[a] valproic acid[a]
Antineoplastic agents	
Psychotropic agents	chlordiazepoxide diazepam phenothiazines

[a] Sodium valproate and valproic acid are similar medications. Elsewhere, the term valproate has been used to represent both these medications.

Similarly, the effect of phenytoin on carbamazepine, phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.

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

Table 4 summarizes drugs whose blood serum levels and/or effects may be altered by phenytoin.

Table 4. Drugs Whose Blood Serum Levels and/or Effects May be Altered by Phenytoin

Drug Classes	Drugs in each Class (such as)
Antibacterial agents	doxycycline rifampin tetracycline
Anticoagulants	warfarin apixaban dabigatran edoxaban rivaroxaban
Anticonvulsants	carbamazepine

Drug Classes	Drugs in each Class (such as)
	lamotrigine[a] phenobarbital sodium valproate[c] topiramate[b] valproic acid [c] lacosamide
Antifungal agents	azoles posaconazole voriconazole
Anthelmintics	albendazole praziquantel
Antineoplastic agents	teniposide
Antiplatelets	ticagrelor
Antiretrovirals	delavirdine efavirenz fosamprenavir indinavir lopinavir/ritonavir nelfinavir ritonavir saquinavir
Bronchodilators	theophylline
Calcium channel blockers / Cardiovascular agents	digitoxin digoxin disopyramide mexiletine nicardipine nimodipine nisoldipine quinidine verapamil
Corticosteroids	
Cyclosporine	

Drug Classes	Drugs in each Class (such as)
Diuretics	furosemide
HMG-CoA reductase inhibitors	atorvastatin fluvastatin simvastatin
Hormones	estrogens oral contraceptives
Hyperglycemic agents	diazoxide
Immunosuppressant	cyclosporine
Neuromuscular blocking agents	alcuronium cisatracurium pancuronium rocuronium vecuronium
Opioid analgesics	methadone
Oral hypoglycemic agents	chlorpropamide glyburide tolbutamide
Psychotropic agents/Antidepressants	clozapine paroxetine quetiapine sertraline
Vitamins	vitamin D
Folic acid	folic acid

[a] Coadministration 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.

[b] Coadministration 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.**

[c] Sodium valproate and valproic acid are similar medications. Elsewhere, the term valproate has been used to represent both these medications.

Delavirdine

Coadministration of phenytoin with delavirdine is contraindicated due to potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.

Hyperammonemia with Concomitant Use of Valproate

Concomitant administration of phenytoin and valproate has been associated with an increased risk of valproate-associated hyperammonemia. Patients treated concomitantly with these two drugs should be monitored for signs and symptoms of hyperammonemia.

9.5 Drug-Food Interactions

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.

9.6 Drug-Herb Interactions

St. John's Wort may decrease phenytoin serum levels.

9.7 Drug-Laboratory Test Interactions

Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT). Phenytoin may affect blood calcium and blood sugar metabolism tests.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

PHENYTOIN SODIUM is an anticonvulsant drug which can be useful in the treatment of epilepsy. The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at synapses. Loss of post-tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of tonic-clonic (grand mal) seizures.

10.3 Pharmacokinetics

Absorption

Phenytoin is a weak acid and has limited hydrosolubility, even in the intestine. The compound undergoes a slow and somewhat variable absorption after oral administration.

The plasma half-life of phenytoin in man after oral administration of phenytoin oral suspension averages 22 hours, with a range of 7 to 42 hours. Steady-state therapeutic levels are achieved at least 7 to 10 days after initiation of therapy with recommended doses of 300 mg/day.

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, congenital enzyme deficiency or drug interactions which result in metabolic interference. The patient with large variations in phenytoin serum levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

When serum level determinations are necessary, they should be obtained at least 7 to 10 days after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that equilibrium or steady-state will have been achieved. Trough levels obtained just prior to the patient's next scheduled dose provide information about clinically effective serum level range and confirm patient compliance. Peak drug levels, obtained at the time of expected peak concentration, indicate an individual's threshold for emergence of dose-related side effects. For extended phenytoin sodium capsules, peak serum levels occur 4 to 12 hours after administration.

Distribution

Phenytoin is distributed into cerebrospinal fluid, saliva, semen, gastrointestinal fluids, bile, and breast milk. The concentration of phenytoin in cerebrospinal fluid approximates the level of free phenytoin in plasma.

Metabolism

Phenytoin is biotransformed in the liver by oxidative metabolism. The major pathway involves 4-hydroxylation, which accounts for 80% of all metabolites. Experiments in human liver microsomes have demonstrated that CYP2C9 plays the major role in the metabolism of phenytoin (90% of net intrinsic clearance), while CYP2C19 has a minor involvement in this process (10% of the net intrinsic clearance). In experiments with human liver microsomes, the relative contribution of CYP2C19 to phenytoin metabolism increased with increasing phenytoin concentrations, above

the concentrations considered to be in the therapeutic range (see 4.1 Dosing Considerations).

Pharmacokinetic data on six patients (age range: 22 to 64 years) receiving phenytoin monotherapy showed that ticlopidine (a CYP2C19 inhibitor), administered for two weeks, decreased plasma clearance of phenytoin.

In a human liver microsome study, phenylbutazone (a CYP2C9 inhibitor) decreased clearance of phenytoin (see 9 DRUG INTERACTIONS).

Elimination

Most of the drug is eliminated in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine partly with glomerular filtration but more importantly by tubular secretion. Less than 5% of phenytoin is excreted as the parent compound. Because phenytoin is hydroxylated in the liver by a cytochrome system which is saturable at high serum levels, small incremental doses may increase the half-life and produce very substantial increases in serum levels when these are in or above the upper therapeutic range. The steady state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

Special Populations and Conditions

Geriatrics (> 65 years of age)

Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20 to 30 years of age). Phenytoin dosing requirements are highly variable and must be individualized (see 4.2 Recommended Dose and Dosage Adjustment, Geriatrics).

11 STORAGE, STABILITY AND DISPOSAL

PHENYTOIN SODIUM Capsules: Store at controlled room temperature 15°C to 30°C. Protect from light and moisture.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling requirements for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

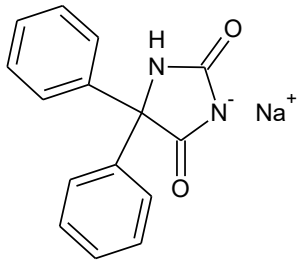
Drug Substance

Proper name: phenytoin sodium

Chemical name: 5,5-Diphenylhydantoin sodium salt

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

Structural formula:



Physicochemical properties: phenytoin sodium is a white powder. It is known to be freely soluble in water; soluble in alcohol; practically insoluble in ether and in chloroform.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

14.3 Comparative Bioavailability Studies

A randomized, double-blinded, single dose, standard 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy adult male volunteers. The results obtained from 31 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of phenytoin was measured and compared following a single oral dose (3 x 100 mg capsule) of PHENYTOIN SODIUM (phenytoin sodium) 100 mg capsule (AA Pharma Inc.) and Dilantin® (phenytoin sodium) 100 mg capsule (Warner Lambert Company LLC, Pfizer Canada Inc.).

Phenytoin (3 x 100 mg) From Measured Data Geometric Mean# Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_t (ng•h/mL)	165822.75 170329.9 (22)	160715.94 165519.8 (25)	103.2	96.6 – 110.2
AUC_{inf} (ng•h/mL)	180451.10 187167.3 (27)	175797.84 182909.0 (29)	102.6	96.0-109.8
C_{max} (ng/mL)	4691.19 4769.7 (19)	4306.37 4384.7 (19)	108.9	103.3 – 114.9
T_{max}§ (h)	5.29 (109)	7.78 (100)		
T_{half}§ (h)	17.32 (25)	17.53 (26)		

*Phenytoin Sodium (phenytoin sodium) 100 mg capsules (AA Pharma Inc.).

†Dilantin® (phenytoin sodium) 100 mg capsules (Warner Lambert Company LLC, Pfizer Canada Inc.) were purchased in Canada.

#For balanced treatment sequence, results are based on Geometric means. For unbalanced treatment sequence, results are based on Least Squares Means (LSM).

§ Expressed as the arithmetic mean (CV %) only

A randomized, double-blinded, single dose, standard 2-way crossover comparative bioavailability study, conducted under fed conditions, was performed on healthy adult male volunteers. The results obtained from 36 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of phenytoin was measured and compared following a single oral dose (3 x 100 mg capsule) of PHENYTOIN SODIUM (phenytoin sodium) 100 mg capsule (AA Pharma Inc.) and Dilantin® (phenytoin sodium) 100 mg capsule (Warner Lambert Company LLC, Pfizer Canada Inc.).

Phenytoin (3 x 100 mg) From Measured Data Geometric Mean# Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	- Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_t (ng•h/mL)	190402.49 197949.0 (29)	203351.83 210883.3 (28)	93.6	90.4 – 97.0
AUC_{inf} (ng•h/mL)	213244.99 227473.5 (39)	229814.91 246218.9 (42)	92.8	89.2 – 96.5
C_{max} (ng/mL)	5910.16 6038.9 (22)	6175.03 6322.1 (21)	95.7	92.1 – 99.4
T_{max}§ (h)	9.34 (41)	10.11 (40)		
T_{half}§ (h)	19.26 (43)	19.88 (45)		

*Phenytoin Sodium (phenytoin sodium) 100 mg capsules (AA Pharma Inc.).

†Dilantin® (phenytoin sodium) 100 mg capsules (Warner Lambert Company LLC, Pfizer Canada Inc.) were purchased in Canada.

#For balanced treatment sequence, results are based on Geometric means. For unbalanced treatment sequence, results are based on Least Squares Means (LSM).

§ Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether phenytoin sodium affects fertility in males or females.

17 SUPPORTING PRODUCT MONOGRAPHS

1. DILANTIN® (30 mg Extended Phenytoin Sodium Capsules, Manufacturer Standard) (100 mg Extended Phenytoin Sodium Capsules USP), Control No: 256632, Product Monograph, Pfizer Canada Inc. March 31, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]PHENYTOIN SODIUM

Extended Phenytoin Sodium Capsules

Read this carefully before you start taking **PHENYTOIN SODIUM** 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 medical condition and treatment and ask if there is any new information about **PHENYTOIN SODIUM**.

What is PHENYTOIN SODIUM used for?

PHENYTOIN SODIUM is used to help:

- control certain types of seizures, called tonic-clonic (grand mal) seizures, and psychomotor (temporal lobe) seizures.
- prevent and treat seizures that may occur during or after surgery to the brain.

How does PHENYTOIN SODIUM work?

PHENYTOIN SODIUM belongs to a group of medicines called anti-seizure medicines. It works by slowing down electrical impulses in the brain that cause seizures.

What are the ingredients in PHENYTOIN SODIUM?

Medicinal ingredients: Phenytoin sodium.

Non-medicinal ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, and magnesium stearate.

Capsule shells: D&C Red No. 28, D&C Yellow No. 10, FD&C Red No. 40, gelatin, and titanium dioxide.

Pharmaceutical ink: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, iron oxide black, propylene glycol, and shellac.

PHENYTOIN SODIUM comes in the following dosage forms:

Capsules: 100 mg.

Do not use PHENYTOIN SODIUM if you/your child:

- are allergic to phenytoin or any other ingredients in PHENYTOIN SODIUM or its container.

- are allergic to other medicines of the hydantoin family, including fosphenytoin.
- take delavirdine (used to treat HIV infection).
- have a heart rhythm condition, such as slow heart rate (bradycardia), heart block, or certain other heart conditions.

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

- are taking any other medications, supplements or other special treatments.
  - they may interact with PHENYTOIN SODIUM, and this can change how well they or PHENYTOIN SODIUM works.
  - they include prescription or non-prescription medications, dietary supplements (e.g., vitamins), herbal supplements, nutritional drinks, and enteral feeding preparations.
- have ever had an allergic rash while taking phenytoin or any other anti-seizure medicine.
- have a personal or family history of severe allergic reaction to phenytoin or any other anti-seizure medicines.
  - symptoms can include fever, rash, swollen lymph gland, and liver problems (seen as yellowing of skin and the whites of the eyes).
- drink alcohol occasionally or regularly.
- are 65 years of age or older.
- are female and:
  - are breastfeeding or plan to breastfeed.
  - are pregnant or plan to become pregnant.
  - are using hormonal birth control, such as the birth control pill.
- are of Asian and/or Black descent. You or your child may be at higher risk of developing serious skin reactions during treatment with PHENYTOIN SODIUM.
- have or have had any of the following diseases or conditions:
  - depression, mood problems, or suicidal thoughts or behaviours.
  - diabetes.
  - heart problems, including slow or fast heart rate, or past heart attack.
  - liver or kidney problems.
  - low levels of albumin or high levels of bilirubin in the blood.
  - porphyria (a condition that affects the nervous system and skin). PHENYTOIN SODIUM can worsen your condition.
  - immune system problems, such as immune suppression or compromise.
  - are having radiation therapy for the brain and take corticosteroids (medicines used to treat inflammation).
  - a medical condition (such as surgery) that prevents you from taking PHENYTOIN SODIUM orally.

Other warnings you should know about:

Do not stop your treatment with PHENYTOIN SODIUM without first checking with your healthcare professional. This could lead to a sudden worsening of your seizures.

Pregnancy, birth control and breastfeeding:

- Avoid becoming pregnant while you are on PHENYTOIN SODIUM. If you become pregnant while taking PHENYTOIN SODIUM, your seizures may become worse. Your healthcare professional may change your dose of PHENYTOIN SODIUM.
- If you take PHENYTOIN SODIUM during pregnancy, your baby is at risk for serious birth defects, and cognitive disabilities. Your baby is also at risk for bleeding problems right after birth.

- If you are pregnant or able to get pregnant, talk to your healthcare professional about using other treatments instead of PHENYTOIN SODIUM. If the decision is made to use PHENYTOIN SODIUM, you should use effective birth control (contraception) during your treatment. If you are using hormonal birth control, it might not work with PHENYTOIN SODIUM. Talk to your healthcare professional about the best kind of birth control to use while you are taking PHENYTOIN SODIUM.
- Tell your healthcare professional right away if you become pregnant or think you are pregnant during treatment with PHENYTOIN SODIUM. You and your healthcare professional should decide if you will continue to take PHENYTOIN SODIUM while you are pregnant.
- **Pregnancy Registry:** If you become pregnant while taking PHENYTOIN SODIUM, 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 passes into breast milk and may harm your baby. Do not breastfeed during treatment with PHENYTOIN SODIUM. Talk to your healthcare professional about the best way to feed your baby during this time.

Driving or using machines: PHENYTOIN SODIUM may make you feel dizzy, drowsy and affect your coordination. Avoid driving, using machinery, or doing activities that requires you to be alert until you know how PHENYTOIN SODIUM affects you.

Alcohol: Do not drink alcohol while taking PHENYTOIN SODIUM, without first talking to your healthcare professional. Drinking alcohol while taking PHENYTOIN SODIUM may change your blood levels of phenytoin, which can cause serious side effects.

Check-ups and testing:

- Your healthcare professional may ask you to do a genetic test before you take PHENYTOIN SODIUM. This test will determine if you have a high risk of experiencing serious skin reactions if you are given PHENYTOIN SODIUM.
- You will have regular visits with your healthcare professional while you are taking PHENYTOIN SODIUM to monitor your health. They will:
  - do blood tests to monitor the amount of phenytoin in the body.
  - do scans to check your bone health.
  - talk to you about how you are feeling, and if you have suicidal thoughts and behaviours.
- PHENYTOIN SODIUM can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

PHENYTOIN SODIUM can cause serious side effects, including:

- **Suicidal thoughts and behaviour changes:** This medicine may cause some people to be agitated, irritable, or display other unusual behaviours. It may also cause some people to have suicidal thoughts and tendencies or to become more depressed. You may find it helpful to tell a relative or close friend you are taking PHENYTOIN SODIUM. Ask them to read this leaflet. You might ask them to tell you if they:
  - think your depression is getting worse, or
  - are worried about changes in your behaviour.

  If you have thoughts of harming or killing yourself or others at any time, tell your healthcare professional or go to a hospital right away. Close observation by a healthcare professional is necessary in this situation.

- **Serious skin reactions:** Serious allergic reactions can be caused by anti-seizure medicines, often involving a skin reaction. These may occur shortly after starting treatment, or several months later. Get help **right away** if you/your child 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.

- **Bone problems (including osteoporosis, osteopenia, osteomalacia):** If you have taken anti-seizure medicines for a long time, it can lead to bone problems. This includes painful and weakened or brittle bones, and possibly 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. It is very important that you care for your mouth properly to decrease the risk of gum damage.

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

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

Serious Drug Interactions

PHENYTOIN SODIUM may interact with a number of other medicines. Your healthcare professional will monitor you while you are taking PHENYTOIN SODIUM to ensure you are taking the dose that is right for you.

PHENYTOIN SODIUM must not be taken with delavirdine, used to treat HIV infection.

The following may interact with PHENYTOIN SODIUM:

- medicines used to treat or prevent:
  - seizures or epilepsy (other than PHENYTOIN SODIUM)
  - bacterial, fungal and parasitic infections
  - HIV infection
  - cancer
  - high blood pressure or certain heart conditions
  - high blood cholesterol
  - high blood sugar
  - blood clots (anticoagulants)
  - depression and other psychological conditions
  - anxiety or alcohol withdrawal
  - pain and inflammation
  - excess stomach acid or ulcers,
  - medicines used to suppress your immune system, and
  - medicines used as a muscle relaxant for intubation or surgery

- these medicines:
  - birth control pills and other birth control methods that use hormones
  - theophylline, used to treat asthma or other breathing problems
  - furosemide, used to lower extra fluid levels
  - halothane, used for general anesthesia
  - methadone, used to treat pain and opioid dependence
  - corticosteroids, used to treat inflammation
  - diazoxide, used to treat low blood sugar

- other supplements:
  - St. John's Wort, a herbal remedy
  - vitamin D, vitamin B9 (folic acid)
  - tube feeding preparations and related nutritional drinks or supplements

- alcohol.

This is not a complete list.

How to take PHENYTOIN SODIUM:

- Always take PHENYTOIN SODIUM exactly as your healthcare professional has told you to. They will decide on the dose that is right for you/your child. Never increase or decrease your dose without talking to your healthcare professional.
- Do not stop taking PHENYTOIN SODIUM without talking to your healthcare professional. Stopping PHENYTOIN SODIUM suddenly can cause serious problems, including seizures that will not stop. Your healthcare professional will tell you if and when you/your child can stop taking this medicine.
- Do not take capsules that are discoloured.
- Tell your healthcare professional if you/your child have difficulty swallowing the capsules. They may prescribe you the oral suspension or chewable tablets instead.

Usual dose:

Adults:

- **Usual initial dose:** 300 mg total a day, divided into 3 doses (one 100 mg capsule, three times a day). Your PHENYTOIN SODIUM dose may be adjusted according to the effect it has, and to the level of medicine in your blood.

- **Usual dose:** 300 to 400 mg total a day, in divided doses. Your healthcare professional may adjust your dose if necessary. In some cases they may recommend that you take 300 mg once a day (3 capsules of 100 mg, taken together once a day). Follow your healthcare professional's instructions carefully.

Children (below 18 years of age):

- Your child's healthcare professional will determine the right dose based on your child's weight. Follow their instructions carefully.
- **PHENYTOIN SODIUM is intended for use in children over 6 years old, weighing at least 40 kg and who are able to swallow capsules**.
- PHENYTOIN SODIUM **is not** available in any pediatric dosage forms i.e. a 30 mg capsule strength, a 50 mg chewable tablet, or an oral suspension of 30 mg in each 5 mL.
- **Usual initial dose:** A total of 5 mg/kg/day (5 mg per day for every kg they weigh), to be

divided and given in 2 or 3 doses. Your child's PHENYOTIN SODIUM dose may be adjusted according to the effect it has, and to the level of medicine in their blood. The maximum dose is 300 mg (total) a day. Given that PHENYTOIN SODIUM is available only as a 100 mg capsule, the child must weigh at least 40 kg in order to initiate therapy with this product.

- **Usual dose:** 4 to 8 mg/kg/day, in divided doses. Children over 6 years old may require the minimum adult dose (300 mg/day).

Overdose:

Signs of an overdose with PHENYTOIN SODIUM 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, slow heart rate, poor blood circulation, heart suddenly stops beating (cardiac arrest),
- feeling sleepy or tired, 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 taken too much PHENYTOIN SODIUM, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you/your child miss a dose, take it as soon as you remember. However, if it is almost time for the next dose, skip the missed dose and take your next dose as scheduled. Do not take a double dose to make up for the missed dose.

What are possible side effects from using PHENYTOIN SODIUM?

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

Side effects may include:

- high blood sugar. If you have diabetes, closely monitor your blood sugar while taking PHENYTOIN SODIUM.
- spinning or dizziness (vertigo)
- trouble falling asleep, or feeling sleepy
- nausea or vomiting, constipation

- nervousness
- headache
- burning or prickling sensation on the skin (sometimes called "pins and needles")
- changes in facial features
- additional body and facial hair
- change in tastes

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Nervous system problems: may include unusual eye movements, slurred speech, decreased coordination, feeling confused.		✓	
Gingival hyperplasia (overgrowth of gum tissue around the teeth): tender gums, inflammation, pain, bad breath, plaque buildup on teeth, gums covering the teeth		✓	
UNCOMMON			
Skin reactions (rashes, eruptions, skin blistering)			✓
Serious skin reactions: any combination of fever, severe rash, swollen lymph glands. May involve 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, swelling of face and/or legs. May also involve problems related to the liver, kidneys, heart, lungs or other organs.			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Angioedema and severe allergic reactions: symptoms may include swelling of the face, eyes, lips or tongue, difficulty swallowing, wheezing, hives and generalized itching, rash, fever, abdominal cramps, chest discomfort or tightness, difficulty breathing, unconsciousness.			✓
Anemias (problems with the blood and immune system): bruising, fever, looking pale, severe sore throat, tiredness, lack of energy, decreased exercise tolerance		✓	
Seizures (fits): uncontrollable shaking		✓	
Suicidal thoughts or behaviour changes: unusual behaviours, depression, worsening of depression, leading to thoughts of self-harm or suicide			✓
Mental changes: feeling confused or disoriented (delirium), seeing, hearing or believing things that aren't real (psychosis)		✓	
Liver problems (including hepatitis, liver failure or damage): yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness, loss of appetite (anorexia)			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN FREQUENCY			
Bone problems (including osteoporosis, osteopenia, osteomalacia): bone pain, muscle weakness, difficulty walking, bone fractures		✓	
Heart problems: unusual heart rate (slow, fast or irregular), dizziness, tiredness, shortness of breath, chest pain			✓

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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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 at controlled room temperature 15°C to 30°C. Protect from light and moisture.
- Keep out of reach and sight of children.

If you want more information about PHENYTOIN SODIUM:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

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