EPANUTIN™ 100 MG

NAME OF THE MEDICINAL PRODUCT

EPANUTIN™ 100 MG

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg of phenytoin sodium
Excipients with known effect:
For the full list of excipients, see section Description (11) in this leaflet.

PHARMACEUTICAL FORM

Capsules

1 THERAPEUTIC INDICATIONS

Phenytoin is indicated for the treatment of epilepsy.

2 DOSAGE AND ADMINISTRATION

General
Phenytoin capsules, are formulated with the sodium salt of phenytoin. The free acid form of phenytoin is used in the phenytoin suspensions (125 mg/5 mL). Because there is approximately an 8% increase in drug content with the free acid form over that of the sodium salt, dosage adjustments and serum level monitoring may be necessary when switching from a product formulated with the free acid to a product formulated with the sodium salt and vice versa.

For all oral formulations, dosage should be individualized to provide maximum benefit. In some cases serum drug level determinations may be necessary for optimal dosage adjustments. Optimum control without clinical signs of toxicity occurs more often with serum levels between 10-20 mcg/mL, although some mild cases of tonic-clonic (grand mal) epilepsy may be controlled with lower serum levels of phenytoin.
With recommended dosage a period of seven to ten days may be required to achieve steady state drug levels with phenytoin, and changes in dosage (increase or decrease) should not be carried out at intervals shorter than seven to ten days.

Adult Dosage
Divided daily dosage:
For oral capsules, patients who have received no previous treatment may be started on 300 mg daily, to be taken in three equally divided doses, and the dosage then adjusted to suit individual requirements. For most adults, the satisfactory maintenance dosage will be 300 mg to 400 mg daily, to be taken in three to four equally divided doses respectively. An increase up to 600mg daily may be made if necessary.

Non-emergency oral loading dose in adult patients
An oral loading dose of phenytoin may be used for non-emergency initiation of therapy in adults who require rapid steady state serum levels, and for whom intravenous administration is not desirable. This dosing regimen should be reserved for patients in a clinic or hospital setting where phenytoin serum levels can be closely monitored.
Patients with a history of renal or liver disease should not receive the oral loading dose regimen.

The recommended oral loading dose is one gram of phenytoin divided into three doses (400 mg, 300 mg, 300 mg) and administered at two-hour intervals. Normal maintenance dosage is then instituted 24 hours after the loading dose, with frequent serum level determinations.

Pediatric Dosage
For oral capsules, initially, 5 mg/kg/day in two or three equally divided doses with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years and adolescents may require the minimum adult dose (300 mg/day). If the daily dosage cannot be divided equally, the larger dose should be given at bedtime.

3 DOSAGE FORMS AND STRENGTHS

Each phenytoin sodium capsule, for oral administration, contains 100 mg phenytoin sodium. The description of the capsule: Orange transparent cap, white opaque body, No. 3 hard gelatin capsule with "Epanutin 100" printed radially in black on both parts and containing a fine white powder.

4 CONTRAINDICATIONS

Epanutin is contraindicated in patients with:

- A history of hypersensitivity to phenytoin, its inactive ingredients listed in section *Description (11)*, or other hydantoins *[see Warnings and Precautions (5.5)]*. Reactions have included angioedema.
- A history of prior acute hepatotoxicity attributable to phenytoin *[see Warnings and Precautions (5.8)]*.
- Coadministration with delavirdine because of the potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.

5 WARNINGS AND PRECAUTIONS

5.1 Withdrawal Precipitated Seizure, Status Epilepticus

Abrupt withdrawal of phenytoin in epileptic patients may precipitate 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 or hypersensitivity reaction, more rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an anticonvulsant drug not belonging to the hydantoin chemical class.

5.2 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including Epanutin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk

1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Epanutin or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and 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.

5.3 Serious Dermatologic Reactions

Epanutin can cause Severe cutaneous adverse reactions (SCARs), which may be fatal. Reported reactions in phenytoin-treated patients have included toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) *[see Warnings and Precautions (5.4)]*. The onset of symptoms is usually within 28 days, but can occur later. Epanutin should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest a severe cutaneous adverse reaction, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of SCARs.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. In addition, retrospective, case-control, genome-wide association studies in patients of southeast Asian ancestry have also identified an increased risk of SCARs in carriers of the decreased function CYP2C9*3 variant, which has also been associated with decreased clearance of phenytoin. Consider avoiding phenytoin as an alternative to carbamazepine in patients who are positive for HLA-B*1502 or in CYP2C9*3 carriers *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.5)]*.

The use of HLA-B*1502 or CYP2C9 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.

5.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including Epanutin. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Epanutin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

5.5 Hypersensitivity

Epanutin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity *[see Contraindications (4) and Warnings and Precautions (5.7)]*. Additionally, consider alternatives to structurally similar drugs such as carboxamides (e.g., carbamazepine), barbiturates, succinimides, and oxazolidinediones (e.g., trimethadione) in these same patients. Similarly, if there is a history of hypersensitivity reactions to these structurally similar drugs in the patient or immediate family members, consider alternatives to Epanutin.

5.6 Cardiac Effects

Cases of bradycardia and cardiac arrest have been reported in Epanutin-treated patients, both at recommended phenytoin doses and levels, and in association with phenytoin toxicity [see Overdosage (10)]. Most of the reports of cardiac arrest occurred in patients with underlying cardiac disease.

5.7 Angioedema

Angioedema has been reported in patients treated with Epanutin in the postmarketing setting. Epanutin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur. Epanutin should be discontinued permanently if a clear alternative etiology for the reaction cannot be established.

5.8 Hepatic Injury

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with Epanutin. These events may be part of the spectrum of DRESS or may occur in isolation *[see Warnings and Precautions (5.4)]*. Other common manifestations include jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, Epanutin should be immediately discontinued and not readministered.

5.9 Hematopoietic Complications

Hematopoietic complications, some fatal, have occasionally been reported in association with administration of Epanutin. 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 of DRESS *[see Warnings and Precautions (5.4)]*.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

5.10 Effects on Vitamin D and Bone

The chronic use of phenytoin in patients with epilepsy has been associated with decreased bone mineral density (osteopenia, osteoporosis, and osteomalacia) and bone fractures. Phenytoin induces hepatic metabolizing enzymes. This may enhance the metabolism of vitamin D and decrease vitamin D levels, which may lead to vitamin D deficiency, hypocalcemia, and hypophosphatemia. Consideration should be given to screening with bone-related laboratory and radiological tests as appropriate and initiating treatment plans according to established guidelines.

5.11 Exacerbation of Porphyria

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

5.12 Teratogenicity and Other Harm to the Newborn

Epanutin may cause fetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes [see Use in Specific Populations (8.1)].

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 epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have been several reported cases of malignancies, including neuroblastoma.

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.

5.14 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.

5.15 Serum Phenytoin Levels above Therapeutic Range

Serum levels of phenytoin sustained above the therapeutic 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 levels should be immediately checked. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination is recommended.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Withdrawal Precipitated Seizure, Status Epilepticus *[see Warnings and Precautions (5.1)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.2)]*
- Serious Dermatologic Reactions *[see Warnings and Precautions (5.3)]*
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity *[see Warnings and Precautions (5.4)]*
- Hypersensitivity *[see Warnings and Precautions (5.5)]*
- Cardiac Effects *[see Warnings and Precautions (5.6)]*
- Angioedema *[see Warnings and Precautions (5.7)]*
- Hepatic Injury *[see Warnings and Precautions (5.8)]*
- Hematopoietic Complications *[see Warnings and Precautions (5.9)]*
- Effects on Vitamin D and Bone *[see Warnings and Precautions (5.10)]*
- Exacerbation of Porphyria *[see Warnings and Precautions (5.11)]*
- Teratogenicity and Other Harm to the Newborn *[see Warnings and Precautions (5.12)]*
- Hyperglycemia *[see Warnings and Precautions (5.14)]*

The following adverse reactions associated with the use of Epanutin were identified in clinical studies or postmarketing reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Allergic reactions in the form of rash and rarely more serious forms and DRESS have been observed, as has angioedema *[see Warnings and Precautions (5.3, 5.4, 5.7)]*. Anaphylaxis has also been reported.
There have also been reports of coarsening of facial features, systemic lupus erythematosus, periarteritis nodosa, and immunoglobulin abnormalities.

Digestive System: Acute hepatic failure, toxic hepatitis, liver damage, nausea, vomiting, constipation, enlargement of the lips, and gingival hyperplasia.

Hematologic and Lymphatic System: Hematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease have been reported *[see Warnings and Precautions (5.9)]*. Pure red cell aplasia has also been reported.
Laboratory Test Abnormality: Phenytoin may decrease serum concentrations of thyroid hormone (T4 and T3), sometimes with an accompanying increase in thyroid-stimulating hormone (TSH), but usually in the absence of clinical hypothyroidism. Phenytoin may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose *[see Warnings and Precautions (5.14)]*, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Nervous System: The most common adverse reactions encountered with phenytoin therapy are nervous system reactions and are usually dose-related. Reactions include nystagmus, ataxia, slurred speech, decreased coordination, somnolence, and mental confusion. Dizziness, vertigo, insomnia, transient nervousness, motor twitchings, paresthesias, and headaches have also been observed. There have also been rare reports of phenytoin-induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. Cerebellar atrophy has been reported, and appears more likely in settings of elevated phenytoin levels and/or long-term phenytoin use *[see Warnings and Precautions (5.15)]*.

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

Skin and Appendages: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, and toxic epidermal necrolysis *[see Warnings and Precautions (5.3)]*. There have also been reports of hypertrichosis and urticaria.

Special Senses: Altered taste sensation including metallic taste.

Urogenital: Peyronie's disease

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

7 DRUG INTERACTIONS

Phenytoin is extensively bound to plasma proteins and is prone to competitive displacement. Phenytoin is primarily metabolized by the hepatic cytochrome P450 enzyme CYP2C9 and to a lesser extent by 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. Monitoring of phenytoin serum levels is recommended when a drug interaction is suspected.

Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes.

7.1 Drugs that Affect Phenytoin Concentrations

Table 2 includes commonly occurring drug interactions that affect phenytoin concentrations. However, this list is not intended to be inclusive or comprehensive. Individual prescribing information from relevant drugs should be consulted.

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

Table 2: Drugs That Affect Phenytoin Concentrations

Interacting Agent	Examples
Drugs that may increase phenytoin serum levels	
Antiepileptic drugs	Ethosuximide, felbamate, oxcarbazepine, methsuximide, topiramate
Azoles	Fluconazole, ketoconazole, itraconazole, miconazole, voriconazole
Antineoplastic agents	Capecitabine, fluorouracil
Antidepressants	Fluoxetine, fluvoxamine, sertraline
Gastric acid reducing agents	H_2 antagonists (cimetidine), omeprazole
Sulfonamides	Sulfamethizole, sulfaphenazole, sulfadiazine, sulfamethoxazole-trimethoprim
Other	Acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, disulfiram, estrogen, fluvastatin, isoniazid, methylphenidate, phenothiazines, salicylates, ticlopidine, tolbutamide, trazodone, warfarin
Drugs that may decrease phenytoin serum levels	
Antacids[a]	Calcium carbonate, aluminum hydroxide, magnesium hydroxide *Prevention or Management:* Phenytoin and antacids should not be taken at the same time of day
Antineoplastic agents usually in combination	Bleomycin, carboplatin, cisplatin, doxorubicin, methotrexate
Antiviral agents	Fosamprenavir, nelfinavir, ritonavir
Antiepileptic drugs	Carbamazepine, vigabatrin
Other	Chronic alcohol abuse, diazepam, diazoxide, folic acid, reserpine, rifampin, St. John's wort[b], sucralfate, theophylline
Drugs that may either increase or decrease phenytoin serum levels	
Antiepileptic drugs	Phenobarbital, valproate sodium, valproic acid

a Antacids may affect absorption of phenytoin.
b The induction potency of St. John's wort may vary widely based on preparation.

[c] Valproate sodium and valproic acid are similar medications. The term valproate has been used to represent these medications.

7.2 Drugs Affected by Phenytoin

Table 3 includes commonly occurring drug interactions affected by phenytoin. However, this list is not intended to be inclusive or comprehensive. Individual drug package inserts should be consulted. The addition or withdrawal of phenytoin during concomitant therapy with these agents may require adjustment of the dose of these agents to achieve optimal clinical outcome.

Table 3: Drugs Affected by Phenytoin

Interacting Agent	Examples
Drugs whose efficacy is impaired by phenytoin	
Azoles	Fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole
Antineoplastic agents	Irinotecan, paclitaxel, teniposide
Delavirdine	Phenytoin can substantially reduce the concentrations of delavirdine. This can lead to loss of virologic response and possible resistance *[see Contraindications (4)]*.
Neuromuscular blocking agents	Cisatracurium, pancuronium, rocuronium and vecuronium: resistance to the neuromuscular blocking action of the nondepolarizing neuromuscular blocking agents has occurred in patients chronically administered phenytoin. Whether or not phenytoin has the same effect on other non-depolarizing agents is unknown. *Prevention or Management:* Patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected, and infusion rate requirements may be higher.
Warfarin	Increased and decreased PT/INR responses have been reported when phenytoin is coadministered with warfarin
Other	Corticosteroids, doxycycline, estrogens, furosemide, oral contraceptives, paroxetine, quinidine, rifampin, sertraline, theophylline, and vitamin D
Drugs whose level is decreased by phenytoin	
Anticoagulants	Apixaban, dabigatran, edoxaban, rivaroxaban
Antiepileptic drugs [a]	Carbamazepine, felbamate, lamotrigine, topiramate, oxcarbazepine, lacosamide
Antilipidemic agents[a]	Atorvastatin, fluvastatin, simvastatin
Antiplatelets	Ticagrelor
Antiviral agents	Efavirenz, lopinavir/ritonavir, indinavir, nelfinavir, ritonavir, saquinavir Fosamprenavir: phenytoin when given with fosamprenavir alone may decrease the concentration of amprenavir, the active metabolite. Phenytoin when given with the combination of fosamprenavir and ritonavir may increase the concentration of amprenavir
Calcium channel blockers	Nifedipine, nimodipine, nisoldipine, verapamil
Other	Albendazole (decreases active metabolite), chlorpropamide, clozapine, cyclosporine, digoxin, disopyramide, folic acid, methadone, mexiletine, praziquantel, quetiapine

[a] The effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable

7.3 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.

7.4 Drug Enteral Feeding/Nutritional Preparations Interaction

Literature reports suggest that patients who have received enteral feeding preparations and/or related nutritional supplements have lower than expected phenytoin serum 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.

7.5 Drug/Laboratory Test Interactions

Care should be taken when using immunoanalytical methods to measure serum phenytoin concentrations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

In humans, prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. Prenatal phenytoin exposure is associated with an increased incidence of major malformations, including orofacial clefts and cardiac defects. In addition, the fetal hydantoin syndrome, a pattern of abnormalities including dysmorphic skull and facial features, nail and digit hypoplasia, growth abnormalities (including microcephaly), and cognitive deficits has been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy *[see Data]*. There have been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

Administration of phenytoin to pregnant animals resulted in an increased incidence of fetal malformations and other manifestations of developmental toxicity (including embryofetal death, growth impairment, and behavioral abnormalities) in multiple species at clinically relevant doses *[see Data]*.

Clinical Considerations

Disease-associated maternal risk

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

Fetal/Neonatal Adverse Reactions

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.

Data

Human Data

Meta-analyses using data from published observational studies and registries have estimated an approximately 2.4-fold increased risk for any major malformation in children with prenatal phenytoin exposure compared to controls. An increased risk of heart defects, facial clefts, and digital hypoplasia has been reported. The fetal hydantoin syndrome is a pattern of congenital anomalies including craniofacial anomalies, nail and digital hypoplasia, prenatal-onset growth deficiency, and neurodevelopmental deficiencies.

Animal Data
Administration of phenytoin to pregnant rats, rabbits, and mice during organogenesis resulted in embryofetal death, fetal malformations, and decreased fetal growth. Malformations (including craniofacial, cardiovascular, neural, limb, and digit abnormalities) were observed in rats, rabbits, and mice at doses as low as 100, 75, and 12.5 mg/kg, respectively.

8.2 Lactation

Risk Summary

Phenytoin is secreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Epanutin and any potential adverse effects on the breastfed infant from Epanutin or from the underlying maternal condition.

8.4 Pediatric Use

Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years and adolescents may require the minimum adult dosage (300 mg/day) *[see Dosage and Administration]*.

8.5 Hepatic Impairment

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.

8.7 Use in Patients with Decreased CYP2C9 Function

Patients who are intermediate or poor metabolizers of CYP2C9 substrates (e.g., *1/*3, *2/*2, *3/*3) may exhibit increased phenytoin serum concentrations compared to patients who are normal metabolizers (e.g., *1/*1). Thus, patients who are known to be intermediate or poor metabolizers may ultimately require lower doses of phenytoin to maintain similar steady-state concentrations compared to normal metabolizers. If early signs of dose-related central nervous system (CNS) toxicity develop, serum concentrations should be checked immediately *[see Clinical Pharmacology (12.5)]*.

10 OVERDOSAGE

The lethal dose in pediatric patients is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, blurred vision, nausea, and vomiting. The patient may become comatose and hypotensive. Bradycardia and cardiac arrest have been reported *[see Warnings and Precautions (5.6)]*. Death is caused by respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin serum levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL; dysarthria and lethargy

appear when the serum concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery. Irreversible cerebellar dysfunction and atrophy have been reported.

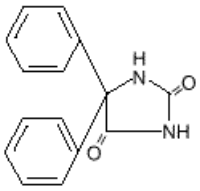
Treatment: Treatment is nonspecific since there is no known antidote.

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

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

11 DESCRIPTION

Epanutin (phenytoin) is related to the barbiturates in chemical structure, but has a five-membered ring. The chemical name is 5,5-diphenyl-2,4 imidazolidinedione, having the following structural formula:



Epanutin capsule, for oral administration contains 100 mg phenytoin sodium.
List of excipient include: lactose monohydrate, magnesium stearate, gelatin, titanium dioxide (E171), erythrosine (E127), quinoline yellow (E104) and black ink (shellac, black iron oxide E172, dehydrated alcohol, propylene glycol, N-butyl alcohol, isopropyl alcohol, industrial methylated spirit, ammonium solution, potassium hydroxide).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which phenytoin exerts its therapeutic effect has not been established but is thought to involve the voltage-dependent blockade of membrane sodium channels resulting in a reduction in sustained high-frequency neuronal discharges.

12.2 Pharmacokinetics

Absorption
For Epanutin capsules, peak serum levels occur 4 to 12 hours after administration. Steady-state therapeutic levels are achieved at least 7 to 10 days (5–7 half-lives) after initiation of therapy with recommended doses of 300 mg/day. When serum level determinations are necessary, they should be obtained at least 5–7 half-lives 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.

Distribution
Phenytoin is extensively bound to serum plasma proteins.

Elimination
The plasma half-life in man after oral administration of phenytoin averages 22 hours, with a range of 7 to 42 hours.

Metabolism
Phenytoin is primarily metabolized by the hepatic cytochrome P450 enzyme CYP2C9 and to a lesser extent by CYP2C19. Because phenytoin is hydroxylated in the liver by an enzyme 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 the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

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, variant CYP2C9 and CYP2C19 alleles, 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.

Excretion
Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine. Urinary excretion of phenytoin and its metabolites occurs partly with glomerular filtration but, more importantly, by tubular secretion.

Specific Populations
Sex/Race:
Gender and race have no significant impact on phenytoin pharmacokinetics.

Drug Interaction Studies
Phenytoin is primarily metabolized by the hepatic cytochrome P450 enzyme CYP2C9 and to a lesser extent by CYP2C19. Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes *[see Drug Interactions (7.1, 7.2)]*.

12.5 Pharmacogenomics

CYP2C9 activity is decreased in individuals with genetic variants such as the CYP2C9*2 and CYP2C9*3 alleles. Carriers of variant alleles, resulting in intermediate (e.g., *1/*3, *2/*2) or poor metabolism (e.g., *2/*3, *3/*3) have decreased clearance of phenytoin. Other decreased or nonfunctional CYP2C9 alleles may also result in decreased clearance of phenytoin (e.g., *5, *6, *8, *11).

The prevalence of the CYP2C9 poor metabolizer phenotype is approximately 2-3% in the White population, 0.5-4% in the Asian population, and <1% in the African American population. The CYP2C9 intermediate phenotype prevalence is approximately 35% in the White population, 24% in the African American population, and 15-36% in the Asian population *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis *[see Warnings and Precautions (5.9)]*
In carcinogenicity studies, phenytoin was administered in the diet to mice (10, 25, or 45 mg/kg/day) and rats (25, 50, or 100 mg/kg/day) for 2 years. The incidences of hepatocellular tumors were increased in male and female mice at the highest dose. No increases in tumor incidence were observed in rats. The highest doses tested in these studies were associated with peak serum phenytoin levels below human therapeutic concentrations.

In carcinogenicity studies reported in the literature, phenytoin was administered in the diet for 2 years at doses up to 600 ppm (approximately160 mg/kg/day) to mice and up to 2400 ppm (approximately 120 mg/kg/day) to rats. The incidences of hepatocellular tumors were increased in female mice at all but the lowest dose tested. No increases in tumor incidence were observed in rats.

Mutagenesis
Phenytoin was negative in the Ames test and in the in vitro clastogenicity assay in Chinese hamster ovary (CHO) cells.

In studies reported in the literature, phenytoin was negative in the in vitro mouse lymphoma assay and the in vivo micronucleus assay in mouse. Phenytoin was clastogenic in the in vitro sister chromatid exchange assay in CHO cells.

Fertility
Phenytoin has not been adequately assessed for effects on male or female fertility.

14 HOW SUPPLIED/STORAGE AND HANDLING

14.1 How Supplied

Each phenytoin sodium capsule, for oral administration, contains 100 mg phenytoin sodium.

Available in HDPE bottles containing 84 or 100 capsules.

Not all pack sizes are marketed.

14.2 Storage and Handling

Store below 25°C.

14.3 Shelf life

The expiry date of the product indicated on the packaging material.

15 MANUFACTURER AND LICENSE HOLDER

Dexcel LTD., 1 Dexcel St., Or Akiva 3060000, Israel.

16 LICENSE NUMBER

104-27-24678

Revised in January 2025 according to MOH guidelines