PRODUCT MONOGRAPH®

PrCEREBYX*

(Fosphenytoin Sodium Injection)

75 mg/mL

Equivalent to 50 mg/ml Phenytoin Sodium

Manufacturer Standard

ANTIEPILEPTIC AGENT

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Date of Preparation:
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NAME OF DRUG

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Equivalent to 50 mg/ml Phenytoin Sodium

PHARMACOLOGIC CLASSIFICATION

ANTIEPILEPTIC AGENT

IMPORTANT NOTE: Throughout all CEREBYX® products labelling, the amount and concentration of fosphenytoin is expressed in terms of phenytoin sodium equivalents (PE). 1.5 mg of fosphenytoin sodium is equivalent to 1 mg phenytoin sodium, and is referred to as 1 mg phenytoin sodium equivalents (PE). Fosphenytoin's weight is expressed as phenytoin sodium equivalents to avoid the need to perform molecular weight-based adjustments when converting between fosphenytoin and phenytoin sodium doses. CEREBYX should always be prescribed and dispensed in phenytoin sodium equivalent units (PE) (see DOSAGE AND ADMINISTRATION)

ACTIONS AND CLINICAL PHARMACOLOGY

Introduction

Following parenteral administration of CEREBYX (Fosphenytoin Sodium Injection), fosphenytoin is converted to the anticonvulsant phenytoin. For every mmol of fosphenytoin administered, one mmol of phenytoin is produced. The pharmacological and toxicological effects of fosphenytoin include those of phenytoin. However, the hydrolysis of fosphenytoin to phenytoin yields two metabolites, phosphate and formaldehyde. Formaldehyde is subsequently converted to formate, which is in turn metabolized via a folate dependent

mechanism. Although phosphate and formaldehyde (formate) have potentially important biological effects, these effects typically occur at concentrations considerably in excess of those obtained when CEREBYX is administered under conditions of use recommended in this labelling.

Mechanism of Action

Fosphenytoin is a prodrug of phenytoin and accordingly, its anticonvulsant effects are attributable to phenytoin.

After IV administration to mice, fosphenytoin blocked the tonic phase of maximal electroshock seizures at doses equivalent to those effective for phenytoin. In addition to its ability to suppress maximal electroshock seizures in mice and rats, phenytoin exhibits anticonvulsant activity against kindled seizures in rats, audiogenic seizures in mice, and seizures produced by electrical stimulation of the brainstem in rats. The cellular mechanisms of phenytoin thought to be responsible for its anticonvulsant actions include modulation of voltage-dependent sodium channels of neurons, inhibition of calcium flux across neuronal membranes, modulation of voltage-dependent calcium channels of neurons, and enhancement of the sodium-potassium ATPase activity of neurons and glial cells. The modulation of sodium channels may be a primary anticonvulsant mechanism because this property is shared with several other anticonvulsants in addition to phenytoin.

Pharmacokinetics and Drug Metabolism

Fosphenytoin

Absorption/Bioavailability:

Intravenous: When CEREBYX is administered by IV infusion, maximum plasma fosphenytoin concentrations are achieved at the end of the infusion. Fosphenytoin has a half-life of approximately 15 minutes.

Intramuscular: Fosphenytoin is completely bioavailable following IM administration of CEREBYX. Peak concentrations occur at approximately 30 minutes postdose. Plasma fosphenytoin concentrations following IM administration are lower but more sustained than those following IV administration due to the time required for absorption of fosphenytoin from the injection site.

Distribution: Fosphenytoin is extensively bound (95% to 99%) to human plasma proteins, primarily albumin. Binding to plasma proteins is saturable with the result that the percent bound decreases as total fosphenytoin concentrations increase. Fosphenytoin displaces phenytoin from protein binding sites. The volume of distribution of fosphenytoin increases with CEREBYX dose and rate, and ranges from 4.3 to 10.8 litres.

Metabolism and Elimination: The conversion half-life of fosphenytoin to phenytoin is approximately 15 minutes. The mechanism of fosphenytoin conversion has not been determined, but phosphatases probably play a major role. Fosphenytoin is not excreted in urine. Each mmol of fosphenytoin is metabolized to 1 mmol of phenytoin, phosphate, and formate (see CLINICAL PHARMACOLOGY, Introduction and PRECAUTIONS, Phosphate Load for Renally Impaired Patients).

Phenytoin (after CEREBYX Administration)

In general, IM administration of CEREBYX generates systemic phenytoin concentrations that are similar enough to oral phenytoin sodium to allow essentially interchangeable use.

The pharmacokinetics of fosphenytoin following IV administration of CEREBYX, however, are complex, and when used in an emergency setting (e.g., status epilepticus), differences in rate of

availability of phenytoin could be critical. Studies have therefore empirically determined an infusion rate for CEREBYX that gives a rate and extent of phenytoin systemic availability similar to that of a 50 mg/min phenytoin sodium infusion.

A dose of 15 to 20 mg PE/kg of CEREBYX infused at 100 to 150 mg PE/min yields plasma free phenytoin concentrations over time that approximate those achieved when an equivalent dose of phenytoin sodium (e.g., parenteral phenytoin sodium) is administered at 50 mg/min (See DOSAGE AND ADMINISTRATION, WARNINGS).

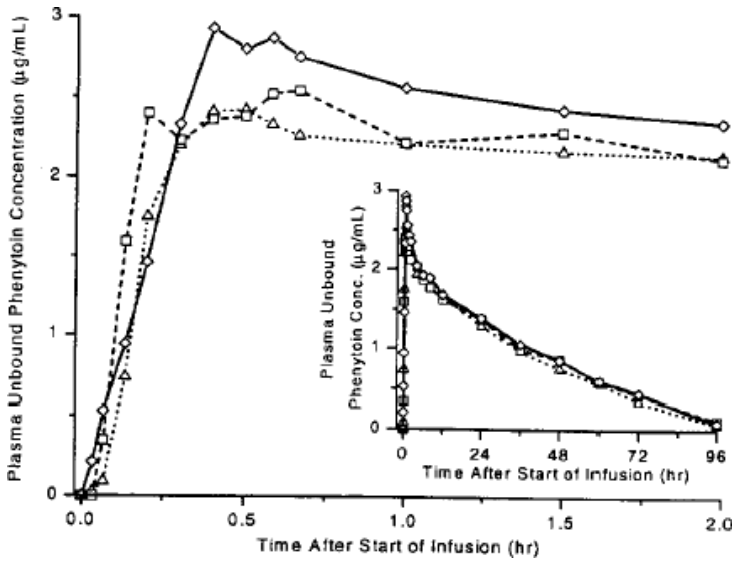

FIGURE 1. Mean plasma unbound phenytoin concentrations following IV administration of 1200 mg PE of CEREBYX infused at 100 mg PE/min (triangles) or 150 mg PE/min (squares) and 1200 mg parenteral phenytoin infused at 50 mg/min (diamonds) to healthy subjects (N = 12). Inset shows time course for the entire 96-hour sampling period.

Following administration of single IV CEREBYX doses of 400 to 1200 mg PE, mean maximum total phenytoin concentrations increase in proportion to dose, but do not change appreciably with changes in infusion rate. In contrast, mean maximum unbound phenytoin concentrations increase with both dose and rate.

Absorption/Bioavailability: Fosphenytoin is completely converted to phenytoin following IV administration, with a half-life of approximately 15 minutes. Fosphenytoin is also completely converted to phenytoin following IM administration and plasma total phenytoin concentrations peak in approximately 3 hours.

Distribution: Phenytoin has an apparent volume of distribution of 0.6L/kg and is highly bound (90%) to plasma proteins, primarily albumin. Free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal. In the absence of fosphenytoin, approximately 12% of total plasma phenytoin is unbound over the clinically relevant concentration range. However, fosphenytoin displaces phenytoin from plasma protein binding sites. This increases the fraction of phenytoin unbound (up to 30% unbound) during the period required for conversion of fosphenytoin to phenytoin (approximately 0.5 to 1 hour postinfusion). Following administration of single IV fosphenytoin doses of 400 to 1200 mg PE, total and unbound phenytoin AUC values increase disproportionately with dose. Mean total phenytoin half-life values (12.0 to 28.9 hr) following fosphenytoin administration at these doses are similar to those after equal doses of parenteral phenytoin and tend to be greater at higher plasma phenytoin concentrations. The concentration of phenytoin in cerebrospinal fluid, brain, and saliva approximates the level of free phenytoin in plasma.

Metabolism and Elimination: Phenytoin is biotransformed in the liver by oxidative metabolism. The major pathway involves 4-hydroxylation, which accounts for 80% of all metabolites. 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 net intrinsic clearance). This relative contribution of CYP2C19 to phenytoin metabolism may however increase at higher phenytoin concentrations.

Because the cytochrome systems involved in phenytoin hydroxylation in the liver are saturable at high serum concentrations, small incremental doses of phenytoin may increase the half-life and produce very substantial increases in serum levels when these are in or above the upper therapeutic range. The clearance of phenytoin has been shown to be impaired by CYP2C9

inhibitors such as phenylbutazone and sulphaphenazole. Impaired clearance has also been shown to occur in patients administered CYP2C19 inhibitors such as ticlopidine.

Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestival tract and eliminated in the urine partly through glomerular filtration but, more importantly via tubular secretion. Less than 5% of the dose is excreted as unchanged phenytoin.

Special Populations

***Patients with Renal or Hepatic Disease*:** Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution (see DOSAGE AND ADMINISTRATION). Unbound phenytoin concentrations may be more useful in these patient populations. After IV administration of fosphenytoin to patients with renal and/or hepatic disease, or in those with hypoalbuminemia, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance. This has the potential to increase the frequency and severity of adverse events (see PRECAUTIONS).

***Age*:** The effect of age was evaluated in patients 5 to 98 years of age, however, no systematic studies in geriatric patients have been conducted. Patient age had no significant impact on fosphenytoin pharmacokinetics. Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20-30 years of age). Phenytoin dosing requirements vary between patients and must be individualized (see DOSAGE AND ADMINISTRATION).

***Gender and Race*:** Gender and race have no significant impact on fosphenytoin or phenytoin pharmacokinetics.

Clinical Studies

Infusion tolerance was evaluated in clinical studies. One double-blind study assessed infusion-site tolerance of equivalent loading doses (15-20 mg PE/kg) of CEREBYX infused at 150 mg PE/min or phenytoin infused at 50 mg/min. The study demonstrated better local tolerance (pain and burning at the infusion site), fewer disruptions of the infusion, and a shorter infusion period for CEREBYX-treated patients (Table 1).

TABLE 1. Infusion Tolerance of Equivalent Loading Doses of IV CEREBYX and IV Phenytoin

	IV CEREBYX N = 90	IV Phenytoin N = 22
Local Intolerance	9%[a]	90%
Infusion Disrupted	21%	67%
Average Infusion Time	13 min	44 min

[a] Percent of patients.

CEREBYX-treated patients, however, experienced more systemic sensory disturbances (see PRECAUTIONS, Sensory Disturbances). Infusion disruptions in CEREBYX-treated patients were primarily due to systemic burning; pruritus, and/or paraesthesia while those in phenytoin-treated patients were primarily due to pain and burning at the infusion site (see Table 1).

In a double-blind study investigating temporary substitution of CEREBYX for oral phenytoin, IM CEREBYX was as well-tolerated as IM placebo. IM CEREBYX resulted in a slight increase in transient, mild to moderate local itching (23% of patients versus 11% of IM placebo-treated patients at any time during the study). This study also demonstrated that equimolar doses of IM CEREBYX may be substituted for oral phenytoin sodium with no dosage adjustments needed when initiating IM or returning to oral therapy. In contrast, switching between IM and oral phenytoin requires dosage adjustments because of slow and erratic phenytoin absorption from muscle.

INDICATIONS AND CLINICAL USE

CEREBYX (Fosphenytoin Sodium Injection) is indicated for short-term parenteral administration when other means of phenytoin administration are unavailable, inappropriate or deemed less advantageous. The safety and effectiveness of CEREBYX in this use has not been systematically evaluated for more than 5 days. CEREBYX should be used only when oral phenytoin administration is not possible. CEREBYX must not be given orally.

CEREBYX can be used for the control of generalized convulsive status epilepticus and prevention and treatment of seizures occurring during neurosurgery. It can also be substituted, short-term, for oral phenytoin.

CONTRAINDICATIONS

CEREBYX (Fosphenytoin Sodium Injection) is contraindicated in patients who have demonstrated hypersensitivity to CEREBYX or its ingredients, or phenytoin or other hydantoins.

Because of the effect of parenteral phenytoin on ventricular automaticity, CEREBYX is contraindicated in patients with sinus bradycardia, sino-atrial block, second- and third-degree A-V block, and Adams-Stokes syndrome.

Coadministration of CEREBYX 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.

WARNINGS

IN THIS MONOGRAPH DOSES OF CEREBYX (FOSPHENYTOIN SODIUM INJECTION (MAUNUFACTURER STANDARD)) ARE ALWAYS EXPRESSED IN TERMS OF MILLIGRAMS OF PHENYTOIN SODIUM EQUIVALENTS (mg PE) 1 MG PE IS EQUIVALENT TO 1 MG PHENYTOIN SODIUM.

DO NOT, THEREFORE, MAKE ANY ADJUSTMENT IN THE RECOMMENDED DOSES WHEN SUBSTITUTING CEREBYX FOR PHENYTOIN SODIUM OR VICE VERSA. FOR EXAMPLE, IF A PATIENT IS RECEIVING 1000 MG PE OF CEREBYX, THAT IS EQUIVALENT TO 1000 MG OF PHENYTOIN SODIUM.

The following warnings are based on experience with CEREBYX or phenytoin.

CARDIOVASCULAR RISK ASSOCIATED WITH RAPID INFUSION RATES

The rate of intravenous CEREBYX administration should not exceed 150 mg phenytoin sodium equivalents (PE) per minute because of the risk of severe hypotension and cardiac arrhythmias. Careful cardiac monitoring is needed during and after administering intravenous CEREBYX. Although the risk of cardiovascular toxicity increases with infusion rates above the recommended infusion rate, these events have also been reported at or below the recommended infusion rate. Reduction in rate of administration or discontinuation of dosing may be needed (see WARNINGS and DOSAGE AND ADMINISTRATION).

As non-emergency therapy, intravenous CEREBYX should be administered more slowly. Because of the risks of cardiac and local toxicity associated with IV CEREBYX, oral phenytoin should be used whenever possible.

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

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

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

Dosing Errors

Do not confuse the amount of drug to be given in PE with the concentration of the drug in the vial.

Medication errors associated with CEREBYX have resulted in patients receiving the wrong dose of fosphenytoin. CEREBYX is marketed in 2 mL vials containing a total of 100 mg PE and 10 mL vials containing a total of 500 mg PE. The concentration of each vial is 50 mg PE/ mL. Errors have occurred when the concentration of the vial (50 mg PE/mL) was misinterpreted to mean that the total content of the vial was 50 mg PE. These errors have resulted in two- or tenfold overdoses of CEREBYX since each vial actually contains a total of 100 mg PE or 500 mg PE. In some cases, ten-fold overdoses were associated with fatal outcomes. To help minimize confusion, the prescribed dose of CEREBYX should always be expressed in milligrams of phenytoin equivalents (mg PE) (see DOSAGE AND ADMINISTRATION). Additionally, when ordering and storing CEREBYX, consider displaying the total drug content (i.e., 100 mg PE/ 2 mL or 500 mg PE/ 10 mL) instead of concentration in computer systems, pre-printed orders, and automated dispensing cabinet databases to help ensure that total drug content can be clearly identified. Care should be taken to ensure the appropriate volume of CEREBYX is withdrawn from the vial **when preparing the drug for administration.** Attention to these details may prevent some CEREBYX medication errors from occurring.

<u>Status Epilepticus Dosing Regimen</u>

Because of the increased risk of adverse cardiovascular reactions associated with rapid administration, do not administer CEREBYX at a rate greater than 150 mg PE/min.

The dose of IV CEREBYX (15 to 20 mg PE/kg) that is used to treat status epilepticus is administered at a maximum rate of 150 mg PE/min. The typical CEREBYX infusion administered to a 50 kg patient would take between 5 and 7 minutes. Note that the delivery of an identical molar dose of phenytoin using phenytoin sodium injection cannot be accomplished in less than 15 to 20 minutes because of the untoward cardiovascular effects that accompany the direct intravenous administration of phenytoin at rates greater than 50 mg/min.

If rapid phenytoin loading is a primary goal, IV administration of CEREBYX is preferred because the time to achieve therapeutic plasma phenytoin concentrations is greater following IM than that following IV administration (see DOSAGE AND ADMINISTRATION).

Withdrawal Precipitated Seizure, Status Epilepticus

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus. When, in the judgement of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

Metabolic

Phenytoin has been infrequently associated with the exacerbation of *porphyria*. Caution should be exercised when CEREBYX is used in patients with this disease.

Serious Dermatologic Reactions Serious and sometimes fatal dermatologic reactions, including Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), have been reported with **CEREBYX** *. 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. The onset of symptoms is usually

within 28 days, but can occur later. CEREBYX * should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. The use of other anti-epileptic drugs associated with SJS/TEN should be avoided in patients who have shown severe dermatological reactions during CEREBYX* If a rash occurs, the patient should be evaluated for signs and symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms (see **DRESS/Multiorgan hypersensitivity** below). If the rash is exfoliative, purpuric, or bullous, or if lupus erythematosus, Stevens-Johnson Syndrome (SJS), or Toxic Epidermal Necrolysis (TEN) is suspected, use of this drug should not be resumed and alternative therapy should be considered. 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 CEREBYX or phenytoin administration is contraindicated.

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 Stevens-Johnson syndrome, and/or toxic epidermal necrolysis. In any of the above circumstances, caution should be exercised if using structurally similar compounds (eg, barbiturates, succinimides, oxazolidinediones, and other related compounds) in these same patients (see CONTRAINDICATIONS; PRECAUTIONS, Dermatologic). Published literature has suggested that there may be an increased, although still rare, risk of hypersensitivity reactions, including skin rash, SJS, TEN, hepatotoxicity, and DRESS in black patients.

Asian Ancestry and Allelic Variation in the HLA-B Gene

- 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†. Results of these studies suggest that the presence of the HLA-B *1502 allele

† 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

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 CEREBYX* and other anti- epileptic drugs associated with SJS/TEN should also be avoided in patients who test positive for the HLA-B*1502 allele (see WARNINGS-Important Limitations of HLA-B Genotyping).

Important Limitations of HLA-B 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 CEREBYX* 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 CEREBYX* 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 CEREBYX*.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan Hypersensitivity, has been reported in patients taking antiepileptic drugs, including phenytoin. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection.

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ethnic ancestry and the likelihood of mixed ancestry.

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.

The mechanism is unknown. The interval between first drug exposure and symptoms is usually 2-4 weeks but has been reported in individuals receiving anticonvulsants for 3 or more months.

CEREBYX should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Patients at higher risk for developing DRESS include black patients, patients who have a family history of or who have experienced this syndrome in the past, and immuno-suppressed patients. The syndrome is more severe in previously sensitized individuals. If a patient is diagnosed with DRESS, discontinue the fosphenytoin and provide appropriate supportive measures.

Hypersensitivity

CEREBYX and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity (see CONTRAINDICATIONS). 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 CEREBYX.

Hepatic

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. 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. Other common manifestations include jaundice, hepatomegaly, elevated serum transaminase levels, leucocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In patients with acute hepatotoxicity, CEREBYX should be immediately discontinued and not readministered.

Hemopoietic

Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression.

There have been a number of reports that have suggested 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 otFher types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling DRESS. In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Local toxicity (Purple Glove Syndrome)

Edema, discoloration, and pain distal to the site of injection (described as “purple glove syndrome”) have also been reported following peripheral intravenous CEREBYX injection. This may or may not be associated with extravasation. The syndrome may not develop for several days after injection. Although resolution of symptoms may be spontaneous, skin necrosis and limb ischemia have occurred and required such interventions as fasciotomies, skin grafting, and in rare cases, amputation.

Alcohol Use

Acute alcohol intake may increase plasma phenytoin concentrations while chronic alcohol use may decrease plasma concentrations.

Use in Pregnancy

Clinical:

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

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

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), minor anomalies (dysmorphic facial features, nail and digit hypoplasia), growth abnormalities (including microcephaly), and mental deficiency have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have also been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. The overall incidence of malformations for children of epileptic women treated with antiepileptic drugs (phenytoin and/or others) during pregnancy is about 10%, or two- to three-fold that in the general population. However, the relative contribution of antiepileptic drugs and other factors associated with epilepsy to this increased risk are uncertain and in most cases it has not

been possible to attribute specific developmental abnormalities to particular antiepileptic drugs.

Patients should consult with their physicians to weigh the risks and benefits of phenytoin during pregnancy and to select the regimen which would provide the least risk to mother and fetus.

Pregnancy Registry

To provide information regarding the effects of *in utero* exposure to CEREBYX, physicians are advised to recommend that pregnant patients who have received CEREBYX during their pregnancy enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

Postpartum Period: A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin *in utero*. This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

Pre-clinical: Increased frequencies of malformations (brain, cardiovascular, digit, and skeletal anomalies), death, growth retardation, and functional impairment (chromodacryorrhea, hyperactivity, circling) were observed among the offspring of rats receiving fosphenytoin during pregnancy. Most of the adverse effects on embryo-fetal development occurred at doses of 33 mg PE/kg or higher (approximately 30% of the maximum human loading dose or higher on a mg/m^2 basis), which produced peak maternal plasma phenytoin concentrations of approximately 20 µg/mL or greater. Maternal toxicity was often associated with these doses and plasma concentrations, however, there is no evidence to suggest that the developmental effects were secondary to the maternal effects. The single occurrence of a rare brain malformation at a non•maternotoxic dose of 17 mg PE/kg (approximately 10% of the maximum human loading dose on a mg/m^2 basis) was also considered drug-induced. The

developmental effects of fosphenytoin in rats were similar to those which have been reported following administration of phenytoin to pregnant rats. No effects on embryo-fetal development were observed when rabbits were given up to 33 mg PE/kg of fosphenytoin (approximately 50% of the maximum human loading dose on a mg/m^2 basis) during pregnancy. Increased resorption and malformation rates have been reported following administration of phenytoin doses of 75 mg/kg or higher (approximately 120% of the maximum human loading dose or higher on a mg/m^2 basis) to pregnant rabbits.

PRECAUTIONS

General: (CEREBYX Specific)

Sensory Disturbances

Severe burning, itching, and/or paraesthesia were reported by 7 of 16 normal volunteers administered IV CEREBYX (Fosphenytoin Sodium Injection) at a dose of 1200 mg PE at the maximum rate of administration (150 mg PE/min). The severe sensory disturbance lasted from 3 to 50 minutes in 6 of these subjects and for 14 hours in the seventh subject. In some cases, milder sensory disturbances persisted for as long as 24 hours. The location of the discomfort varied among subjects with the groin mentioned most frequently as an area of discomfort. In a separate cohort of 16 normal volunteers (taken from 2 other studies) who were administered IV CEREBYX at a dose of 1200 mg PE at the maximum rate of administration (150 mg PE/min), none experienced severe disturbances, but most experienced mild to moderate itching or tingling.

Patients administered CEREBYX at doses of 20 mg PE/kg at 150 mg PE/min are expected to experience discomfort of some degree. The occurrence and intensity of the discomfort can be lessened by slowing or temporarily stopping the infusion.

The effect of continuing infusion unaltered in the presence of these sensations is unknown. No permanent sequelae have been reported thus far. The pharmacologic basis for these positive sensory phenomena is unknown, but other phosphate ester drugs, which deliver smaller phosphate loads, have been associated with burning, itching, and/or tingling predominantly in the groin area.

Phosphate Load

The phosphate load provided by CEREBYX (0.0037 mmol phosphate/mg PE CEREBYX) should be considered when treating patients who require phosphate restriction, such as those with severe renal impairment.

IV Loading in Renal and/or Hepatic Disease or in Those With Hypoalbuminemia

After IV administration to patients with renal and/or hepatic disease, or in those with hypoalbuminemia, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance. This has the potential to increase the frequency and severity of adverse events (see CLINICAL PHARMACOLOGY: Special Populations, and DOSAGE AND ADMINISTRATION: Dosing in Special Populations).

General: (Phenytoin Associated)

CEREBYX is *not* indicated for the treatment of *absence seizures*. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

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

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.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity

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

Phenytoin has the potential to lower serum folate levels.

Musculoskeletal

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 (see ADVERSE REACTIONS, Post-marketing Experience). In patients on long term phenytoin therapy, vitamin D is given to prevent side effects affecting bones.

Neurologic

Plasma concentrations of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely, irreversible cerebellar dysfunction. Accordingly, at the first sign of *acute toxicity*, determination of plasma phenytoin concentrations is recommended (see PRECAUTIONS: Laboratory Tests). CEREBYX dose reduction is indicated if phenytoin concentrations are excessive; if symptoms persist, administration of CEREBYX should be discontinued.

Hepatic

The liver is the primary site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

Psychiatric

Suicidal ideation and behaviour

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

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

An FDA meta-analysis of randomized placebo controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

There were 43892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drug). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and

behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

Laboratory Tests

Phenytoin doses are usually selected to attain therapeutic plasma total phenytoin concentrations of 40 to 80 μmol/L [10 to 20 μg/mL], (unbound phenytoin concentrations of 4 to 8 μmol/L [1 to 2 μg/mL]). Following CEREBYX administration, it is recommended that phenytoin concentrations not be monitored until conversion to phenytoin is essentially complete. This occurs within approximately 2 hours after the end of IV infusion and 4 hours after IM injection.

Prior to complete conversion, commonly used immunoanalytical techniques, such as TDx/TDxFLx (fluorescence polarization) and Emit 2000 (enzyme multiplied), may significantly overestimate plasma phenytoin concentrations because of cross-reactivity with fosphenytoin. The TDx/TDxFLx assay is not recommended while unconverted fosphenytoin is present in plasma, due to an unacceptable margin of error (overestimation) in the phenytoin measurement. The difference between predicted and actual phenytoin concentrations at 4 hours postdose is ≤20 μmol/L [≤5 μg/mL] The error is dependent on plasma phenytoin and fosphenytoin concentration (influenced by CEREBYX dose, route and rate of administration, and time of sampling relative to dosing), and analytical method. Chromatographic assay methods accurately quantitate phenytoin concentrations in biological fluids in the presence of fosphenytoin. Prior to complete conversion, blood samples for phenytoin monitoring should be collected in tubes containing EDTA as an anticoagulant to minimize *ex vivo* conversion of fosphenytoin to phenytoin. However, even with specific assay methods, phenytoin concentrations measured before conversion of fosphenytoin is complete will not reflect phenytoin concentrations ultimately achieved.

Drug Interactions

No drugs are known to interfere with the conversion of fosphenytoin to phenytoin. Conversion could be affected by alterations in the level of phosphatase activity, but given the abundance and wide distribution of phosphatases in the body it is unlikely that drugs would affect this activity enough to affect conversion of fosphenytoin to phenytoin. Drugs highly bound to albumin could increase the unbound fraction of fosphenytoin. Although, it is unknown whether this could result in clinically significant effects, caution is advised when administering CEREBYX with other drugs that significantly bind to serum albumin.

The most significant drug interactions following administration of CEREBYX are expected to occur with drugs that interact with phenytoin. Phenytoin is extensively bound to plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome P450 enzymes and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity. Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes.

The most commonly occurring drug interactions are listed below:

Drugs which may increase phenytoin serum levels

Various drugs which may increase phenytoin serum levels either by decreasing its rate of metabolism by the hepatic CYP450 2C9 and 2C19 enzymatic systems (e.g., omeprazole, ticlopidine), by competing for protein binding sites (e.g. salicylates, sulfisoxazole, tolbutamide), or by a combination of both processes (e.g. phenylbutazone, valproate sodium). The following drug classes are also included.

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

Table 1	
DRUG CLASSES OR DRUG	**DRUGS IN EACH CLASS (SUCH AS)**
Alcohol (acute intake)	
Analgesic / Anti-inflammatory agents	Phenylbutazone Salicylates
Anesthetics	Halothane
Antibacterial agents	Chloramphenicol erythromycin isoniazid sulfonamides
Anticonvulsants	felbamate, succinimides, ethosuximide, methsuximide, oxcarbazepine, topiramate[1]
Antifungal agents	amphotericin B fluconazole ketoconazole miconazole itraconazole
Anticancer drugs	Capecitabine, fluorouracil
Benzodiazepines / Psychotropic agents	Chlordiazepoxide diazepam methylphenidate trazodone
Calcium channel blockers / Cardiovascular agents	Amiodarone diltiazem nifedipine ticlopidine
Disulfiram	
Fluvastatin	
H_2-antagonists	Cimetidine
Hormones	Estrogens
Oral hypoglycemic agents	Tolbutamide
Proton pump inhibitors	Omeprazole

Phenothiazines	
Serotonin re-uptake inhibitors	Fluoxetine fluvoxamine sertraline
Warfarin	

[1] 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.

Drugs which may decrease phenytoin plasma levels

Table 2 summarizes the drug classes which may potentially decrease phenytoin plasma levels:

Table 2	
Alcohol (chronic intake)	
Antibacterial agents	Rifampin Ciprofloxacin
Anticancer agents	Bleomycin Carboplatin cisplatin doxorubicin methotrexate
Anticonvulsants	Vigabatrin[i]
Antiulcer agents	Sucralfate
Antiretroviral	Fosamprenavir Nelfinavir Ritonavir
Bronchodilators	Theophylline
Cardiovascular agents	Reserpine
Folic acid	
Oral hypoglycemic agents	Diazoxide
St John's Wort	

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

Molindone Hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations, including antacid preparations containing calcium should be staggered to prevent absorption problems.

Drugs which may either increase or decrease phenytoin serum levels

Table 3 summarizes the drug classes which may either increase or decrease phenytoin serum levels:

Table 3	
DRUG CLASSES	**DRUGS IN EACH CLASS (SUCH AS)**
Anticonvulsants	Carbamazepine phenobarbital sodium valproate valproic acid
Antineoplastic agents	Teniposide
Psychotropic agents	Chlordiazepoxide diazepam

Similarly, the effects of phenytoin on carbamazepine, phenobarbital, valproic acid and sodium plasma valproate concentrations are unpredictable.

Drugs which blood levels and/or effects may be altered by phenytoin

Table 4 summarizes the drug classes which blood levels and/or effects may be altered by phenytoin:

Table 4	
DRUG CLASSES	**DRUGS IN EACH CLASS (SUCH AS)**
Antibacterial agents	doxycycline praziquantel rifampin tetracycline
Anticonvulsants	Lamotrigine[i], topiramate[ii], carbamazepine, felbamate, lamotrigine, topiramate, oxcarbazepine, quetiapine

Antifungal agents	Azoles (fluconazole, ketoconazole, itraconazole, miconazole, voriconazole, posaconazole)
Antineoplastic agents	Teniposide
Antiretroviral	Delavirdine efavirenz lopinavir/ritonavir indinavir nelfinavir ritonavir saquinavir
Bronchodilators	theophylline
Calcium channel blockers / Cardiovascular agents	Digitoxin Digoxin Nicardipine Nifedipine nimodipine nisoldipine quinidine verapamil
Corticosteroids	
Coumarin anticoagulants	
Cyclosporine	
Diuretics	furosemide
Folic Acid	
Hormones	estrogens oral contraceptives
Hyperglycemic agents	diazoxide
Mexiletine	
Neuromuscular blocking agents	pancuronium vecuronium
Opioid analgesics	methadone
Oral hypoglycemic agents	chlorpropamide glyburide tolbutamide

Psychotropic agents / Antidepressants	clozapine paroxetine sertraline
Praziquantel	
Statins	Atorvastatin Fluvastatin Simvastatin
Vitamin D	
Warfarin	

[i] Coadministration with lamotrigine doubles the plasma clearance and reduces the elimination half life of lamotrigine by 50%. This clinically important interaction requires dosage adjustment.
[ii] 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.

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

Monitoring of plasma phenytoin concentrations may be helpful when possible drug interactions are suspected (see Laboratory Tests).

Drug/Laboratory Test Interactions

Phenytoin may decrease serum concentrations of T_4. It may also produce artifactually low results in dexamethasone or metyrapone tests. Phenytoin may cause increased serum concentrations of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT). Phenytoin may affect blood calcium and blood sugar metabolism tests.

Care should be taken when using immunoanalytical methods to measure plasma phenytoin concentrations following CEREBYX administration (see Laboratory Tests).

Use in Nursing Mothers

It is not known whether fosphenytoin is excreted in human milk.

Following administration of Dilantin, phenytoin appears to be excreted in low concentrations in human milk. Therefore, breast-feeding is not recommended for women receiving CEREBYX.

Use in Children

The safety of CEREBYX in pediatric patients has not been established. Only limited pharmacokinetic data are available in children (N=8; age 5 to 10 years). In these patients with status epilepticus who received loading doses of CEREBYX, the plasma fosphenytoin, total phenytoin, and unbound phenytoin concentration-time profiles did not signal any major differences from those in adult patients with status epilepticus receiving comparable doses.

Use in the Elderly

No systematic studies in geriatric patients have been conducted. Phenytoin clearance tends to decrease with increasing age (see ACTIONS AND CLINICAL PHARMACOLOGY: Special Populations).

Effects on Ability to Drive and Operate Machines

Patients should be advised not to drive a car or operate potentially dangerous machinery until it is known that this medication does not affect their ability to engage in these activities.

ADVERSE REACTIONS

The more important adverse clinical events caused by the IV use of CEREBYX (Fosphenytoin Sodium Injection) or phenytoin are cardiovascular collapse and/or central nervous system depression. Hypotension can occur when either drug is administered rapidly by the IV route. The rate of administration is very important; for CEREBYX, it should not exceed 150 mg PE/min.

The adverse clinical events most commonly observed with the use of CEREBYX in clinical trials were nystagmus, dizziness, pruritus, paraesthesia, headache, somnolence, and ataxia. With two exceptions, these events are commonly associated with the administration of IV phenytoin. Paraesthesia and pruritus, however, were seen much more often following CEREBYX administration and occurred more often with IV CEREBYX administration than with IM CEREBYX administration. These events were dose and rate related; most alert patients (41 of 64; 64%) administered doses of $\geq$15 mg PE/kg at 150 mg PE/min experienced discomfort of some degree. These sensations, generally described as itching, burning, or tingling, were usually not at the infusion site. The location of the discomfort varied with the groin mentioned most frequently as a site of involvement. The paraesthesia and pruritus were transient events that occurred within several minutes of the start of infusion and generally resolved within 10 minutes after completion of CEREBYX infusion. Some patients experienced symptoms for hours. These events did not increase in severity with repeated administration. Concurrent adverse events or clinical laboratory change suggesting an allergic process were not seen (see PRECAUTIONS, Sensory Disturbances).

Approximately 2% of the 859 individuals who received CEREBYX in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were pruritus (0.5%), hypotension (0.3%), and bradycardia (0.2%).

***Dose and Rate Dependency of Adverse Events Following IV CEREBYX*:** The incidence of adverse events tended to increase as both dose and infusion rate increased. In particular, at doses of ≥15 mg PE/kg and rates ≥150 mg PE/min, transient pruritus, tinnitus, nystagmus, somnolence, and ataxia occurred 2 to 3 times more often than at lower doses or rates.

Incidence in Controlled Clinical Trials

All adverse events were recorded during the trials by the clinical investigators using terminology of their own choosing. Similar types of events were grouped into standardized categories using modified COSTART dictionary terminology. These categories are used in the tables and listings below with the frequencies representing the proportion of individuals exposed to CEREBYX or comparative therapy. The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

***Incidence in Controlled Clinical Trials - IV Administration To Patients With Epilepsy or Neurosurgical Patients*:** Table 2 lists treatment-emergent adverse events that occurred in at least 2% of patients treated with IV CEREBYX at the maximum dose and rate in a randomized, double-blind, controlled clinical trial where the rates for phenytoin and CEREBYX administration would have resulted in equivalent systemic exposure to phenytoin.

TABLE 2. Treatment-Emergent Adverse Event Incidence Following IV Administration at the Maximum Dose and Rate to Patients With Epilepsy or Neurosurgical Patients

(Events in at Least 2% of CEREBYX-Treated Patients)

BODY SYSTEM Adverse Event	IV CEREBYX N = 90	IV Phenytoin N = 22
BODY AS A WHOLE		
Pelvic Pain	4.4	0.0
Asthenia	2.2	0.0
Back Pain	2.2	0.0
Headache	2.2	4.5
CARDIOVASCULAR		
Hypotension	7.7	9.1
Vasodilatation	5.6	4.5
Tachycardia	2.2	0.0
DIGESTIVE		
Nausea	8.9	13.6
Tongue Disorder	4.4	0.0
Dry Mouth	4.4	4.5
Vomiting	2.2	9.1
NERVOUS		
Nystagmus	44.4	59.1
Dizziness	31.1	27.3
Somnolence	20.0	27.3
Ataxia	11.1	18.2
Stupor	7.7	4.5
Incoordination	4.4	4.5
Paraesthesia	4.4	0.0
Extrapyramidal Syndrome	4.4	0.0
Tremor	3.3	9.1
Agitation	3.3	0.0
Hypaesthesia	2.2	9.1
Dysarthria	2.2	0.0
Vertigo	2.2	0.0
Brain Edema	2.2	4.5
SKIN AND APPENDAGES		
Pruritus	48.9	4.5
SPECIAL SENSES		
Tinnitus	8.9	9.1
Diplopia	3.3	0.0
Taste Perversion	3.3	0.0
Amblyopia	2.2	9.1
Deafness	2.2	0.0

***Incidence in Controlled Trials - IM Administration to Patients With Epilepsy*:** Table 3 lists treatment-emergent adverse events that occurred in at least 2% of CEREBYX-treated patients in a double-blind, randomized, controlled clinical trial of adult epilepsy patients receiving either IM CEREBYX substituted for oral Dilantin or continuing oral Dilantin. Both treatments were administered for 5 days.

TABLE 3. Treatment-Emergent Adverse Event Incidence Following Substitution of IM CEREBYX for Oral Dilantin in Patients With Epilepsy

(Events in at Least 2% of CEREBYX-Treated Patients)

BODY SYSTEM Adverse Event	IM CEREBYX N = 179	Oral Dilantin N = 61
BODY AS A WHOLE		
Headache	8.9	4.9
Asthenia	3.9	3.3
Accidental Injury	3.4	6.6
DIGESTIVE		
Nausea	4.5	0.0
Vomiting	2.8	0.0
HEMATOLOGIC AND LYMPHATIC		
Ecchymosis	7.3	4.9
NERVOUS		
Nystagmus	15.1	8.2
Tremor	9.5	13.1
Ataxia	8.4	8.2
Incoordination	7.8	4.9
Somnolence	6.7	9.8
Dizziness	5.0	3.3
Paraesthesia	3.9	3.3
Reflexes Decreased	2.8	4.9
SKIN AND APPENDAGES		
Pruritus	2.8	0.0

Adverse Events During All Clinical Trials

CEREBYX has been administered to 859 individuals during all clinical trials. All adverse events seen at least twice are listed in the following, except those already included in previous tables and listings. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 individuals; infrequent adverse events are those occurring in 1/100 to 1/1000 individuals.

Body As a Whole: *Frequent:* fever, injection-site reaction, infection, chills, face edema, injection-site pain; *Infrequent:* sepsis, injection-site inflammation, injection-site edema, injection-site hemorrhage, flu syndrome, malaise, generalized edema, shock, photosensitivity reaction, cachexia, cryptococcosis.

Cardiovascular: *Frequent*: hypertension; *Infrequent*: cardiac arrest, migraine, syncope, cerebral hemorrhage, palpitation, sinus bradycardia, atrial flutter, bundle branch block, cardiomegaly, cerebral infarct, postural hypotension, pulmonary embolus, QT interval prolongation, thrombophlebitis, ventricular extrasystoles, congestive heart failure.

Digestive: *Frequent:* constipation; *Infrequent:* dyspepsia, diarrhea, anorexia, gastrointestinal hemorrhage, increased salivation, liver function tests abnormal, tenesmus, tongue edema, dysphagia, flatulence, gastritis, ileus.

Endocrine: *Infrequent:* diabetes insipidus.

Hematologic and Lymphatic: *Infrequent:* thrombocytopenia, anemia, leucocytosis, cyanosis, hypochromic anemia, leucopenia, lymphadenopathy (see WARNINGS, Hematologic), petechia.

Metabolic and Nutritional: *Frequent:* hypokalemia; *Infrequent*: hyperglycemia, hypophosphatemia, alkalosis, acidosis, dehydration, hyperkalemia, ketosis.

Musculoskeletal: *Frequent:* myasthenia; *Infrequent:* myopathy, leg cramps, arthralgia, myalgia.

Nervous: *Frequent:* reflexes increased, speech disorder, dysarthria, intracranial hypertension, thinking abnormal, nervousness, hypaesthesia; *Infrequent:* confusion, twitching, Babinski sign positive, circumoral paraesthesia, hemiplegia, hypotonia, convulsion, extrapyramidal syndrome, insomnia, meningitis, depersonalization, CNS depression, depression, hypokinesia, hyperkinesia, brain edema, paralysis, psychosis, aphasia, emotional lability, coma, hyperesthesia, myoclonus, personality disorder, acute brain syndrome, encephalitis, subdural hematoma, encephalopathy, hostility, akathisia, amnesia, neurosis.

Respiratory: *Frequent:* pneumonia; *Infrequent:* pharyngitis, sinusitis, hyperventilation, rhinitis, apnea, aspiration pneumonia, asthma, dyspnea, atelectasis, cough increased, sputum increased, epistaxis, hypoxia, pneumothorax, hemoptysis, bronchitis.

Skin and Appendages: *Frequent*: rash; *Infrequent:* maculopapular rash, urticaria, sweating, skin discolouration, contact dermatitis, pustular rash, skin nodule.

Special Senses: *Frequent:* taste perversion, *Infrequent:* deafness, visual field defect, eye pain, conjunctivitis, photophobia, hyperacusis, mydriasis, parosmia, ear pain, taste loss.

Urogenital: *Infrequent:* urinary retention, oliguria, dysuria, vaginitis, albuminuria, genital edema, kidney failure, polyuria, urethral pain, urinary incontinence, vaginal moniliasis.

Post-Marketing Experience

There have been post-marketing reports of anaphylactoid reaction, anaphylaxis, confusion, and dyskinesia. Bone fractures and osteomalacia have been associated with long-term (>10 years) use of phenytoin by patients with chronic epilepsy. Osteoporosis and other disorders of bone metabolism such as hypocalcemia, hypophosphatemia and decreased levels of Vitamin D metabolites have also been reported (see PRECAUTIONS, Musculoskeletal). Reports of Purple

Glove Syndrome (PGS) with fosphenytoin therapy have been identified.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The median lethal dose of fosphenytoin given intravenously in mice and rats was 156 mg PE/kg and approximately 250 mg PE/kg, or about 0.6 and 2 times, respectively, the maximum human loading dose on a mg/m^2 basis. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, and hypoactivity.

Symptoms: Because CEREBYX (Fosphenytoin Sodium Injection) is a prodrug of phenytoin, the following information may be helpful. Initial symptoms of acute phenytoin toxicity are nystagmus, ataxia, and dysarthria. Other signs include tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting, coma, and hypotension. Depression of respiratory and circulatory systems leads to death. There are marked variations among individuals with respect to plasma phenytoin concentrations where toxicity occurs. Lateral gaze nystagmus usually appears at 80 µmol/L [20 µg/mL], ataxia at 120 µmol/L [30 µg/mL], and dysarthria and lethargy appear when the plasma concentration is over 160 µmol/L [40 µg/mL]. However, phenytoin concentrations as high as 200 µmol/L [50 µg/mL] have been reported without evidence of toxicity. As much as 25 times the therapeutic phenytoin dose has been taken, resulting in plasma phenytoin concentrations over 400 µmol/L [100 µg/mL], with complete recovery.

Nausea, vomiting, lethargy, tachycardia, bradycardia, asystole, cardiac arrest, hypotension, syncope, hypocalcemia, metabolic acidosis and death have been reported in cases of overdosage with CEREBYX.

Treatment:

For up-to-date information on the management of a suspected drug overdose, contact the regional Poison Control Center.

Treatment is nonspecific since there is no known antidote to CEREBYX or phenytoin overdosage. 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 children. In acute overdosage the possibility of other CNS depressants, including alcohol, should be borne in mind.

Formate and phosphate are metabolites of fosphenytoin and therefore may contribute to signs of toxicity following overdosage. Signs of formate toxicity are similar to those of methanol toxicity and are associated with severe anion-gap metabolic acidosis. Large amounts of phosphate, delivered rapidly, could potentially cause hypocalcemia with paraesthesia, muscle spasms, and seizures. Ionized free calcium levels can be measured and, if low, used to guide treatment.

DOSAGE AND ADMINISTRATION

The dose, concentration in dosing solutions, and infusion rate of IV CEREBYX (Fosphenytoin Sodium Injection) is expressed as phenytoin sodium equivalents (PE) to avoid the need to perform molecular weight-based adjustments when converting between fosphenytoin and phenytoin sodium doses. CEREBYX should always be prescribed and dispensed in phenytoin sodium equivalent units (PE). 1.5 mg of fosphenytoin sodium is equivalent to 1 mg phenytoin sodium, and is referred to as 1 mg PE. The amount and concentration of fosphenytoin is always expressed in terms of mg of phenytoin sodium equivalents (mg PE). For example, if a patient is receiving 1000 mg PE of CEREBYX, that is equivalent to 1000 mg of phenytoin sodium. CEREBYX has important differences in administration from those for parenteral phenytoin sodium (see below).

Phenytoin doses are usually selected to attain therapeutic plasma total phenytoin concentrations of 40-80 µmol/L [10 to 20 µg/mL], (unbound phenytoin concentrations of 4- 8 µmol/L [1 to 2 µg/mL]. Following CEREBYX administration, it is recommended that phenytoin

concentrations not be monitored until conversion to phenytoin is essentially complete. This occurs within approximately 2 hours after the end of IV infusion and 4 hours after IM injection.

Prior to complete conversion, commonly used immunoanalytical techniques, such as TDx/TDxFLx (fluorescence polarization) and Emit 2000 (enzyme multiplied), may significantly overestimate plasma phenytoin concentrations because of cross-reactivity with fosphenytoin. The TDx/TDxFLx assay is not recommended due to an unacceptable margin of error. The difference between predicted and actual phenytoin concentrations at 4 hours postdose is
≤20 µmol/L [5 µg/mL]. The error is dependent on plasma phenytoin and fosphenytoin concentration (influenced by CEREBYX dose, route and rate of administration, and time of sampling relative to dosing), and analytical method. Chromatographic assay methods accurately quantitate phenytoin concentrations in biological fluids in the presence of fosphenytoin. Prior to complete conversion, blood samples for phenytoin monitoring should be collected in tubes containing EDTA as an anticoagulant to minimize *ex vivo* conversion of fosphenytoin to phenytoin. However, even with specific assay methods, phenytoin concentrations measured before conversion of fosphenytoin is complete will not reflect phenytoin concentrations ultimately achieved.

- Prior to IV infusion, dilute CEREBYX in 5% dextrose or 0.9% saline solution for injection to a concentration ranging from 1.5 to 25 mg PE/mL. Products with particulate matter or discolouration should not be used.

Do not confuse the concentration of CEREBYX with the total amount of drug in the vial.

Status Epilepticus

- The loading dose of CEREBYX is 15 to 20 mg PE/kg administered at 100 to 150 mg PE/min.
- **Because of the risk of hypotension, fosphenytoin should be administered no faster than 150 mg PE/min.** Continuous monitoring of the electrocardiogram, blood pressure, and respiratory function is essential and the patient should be observed throughout the period

where maximal serum phenytoin concentrations occur, approximately 10 to 20 minutes after the end of CEREBYX infusions.

- Because the full antiepileptic effect of phenytoin, whether given as CEREBYX or parenteral phenytoin, is not immediate, other measures, including concomitant administration of an IV benzodiazepine, will usually be necessary for the control of status epilepticus.
- The loading dose should be followed by maintenance doses of CEREBYX, or phenytoin, either orally or parenterally.

If administration of CEREBYX does not terminate seizures, the use of other anticonvulsants and other appropriate measures should be considered.

IM CEREBYX should not be used in the treatment of status epilepticus because therapeutic phenytoin concentrations may not be reached as quickly as with IV administration. If IV access is impossible, loading doses of CEREBYX have been given by the IM route for other indications.

Non-emergent Loading and Maintenance Dosing

The loading dose of CEREBYX is 10 - 20 mg PE/kg given IV or IM. The rate of administration for IV CEREBYX should be no greater than 150 mg PE/min. Continuous monitoring of the electrocardiogram, blood pressure, and respiratory function is essential and the patient should be observed throughout the period where maximal serum phenytoin concentrations occur, approximately 10 to 20 minutes after the end of CEREBYX infusions.

The initial daily maintenance dose of CEREBYX is 4 - 6 mg PE/kg/day in divided doses.

IM or IV Substitution For Oral Phenytoin Therapy

When treatment with oral phenytoin is not possible, CEREBYX can be substituted for oral phenytoin sodium therapy at the same total daily dose.

Dilantin capsules are approximately 90% bioavailable by the oral route. Phenytoin, supplied as CEREBYX, is 100% bioavailable by both the IM and IV routes. For this reason, plasma phenytoin concentrations may increase modestly when IM or IV CEREBYX is substituted for oral phenytoin sodium therapy.

The rate of administration for IV CEREBYX should be no greater than 150 mg PE/min.

In controlled trials, IM CEREBYX was administered as a single daily dose utilizing either 1 or 2 injection sites. Some patients may require more frequent dosing.

Dosing in Special Populations

Patients with Renal or Hepatic Disease: Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution (see CLINICAL PHARMACOLOGY: Special Populations). Unbound phenytoin concentrations may be more useful in these patient populations. After IV CEREBYX administration to patients with renal and/or hepatic disease, or in those with hypoalbuminemia, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance. This has the potential to increase the frequency and severity of adverse events (see PRECAUTIONS).

***Elderly Patients*:** Age does not have a significant impact on the pharmacokinetics of fosphenytoin following CEREBYX administration. Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required.

***Pediatric*:** The safety of CEREBYX in pediatric patients has not been established.

PHARMACEUTICAL INFORMATION

Drug Substance

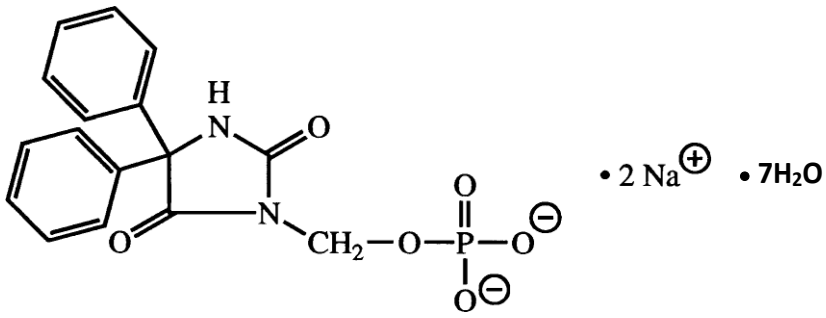
Proper Name: Fosphenytoin Sodium, Heptahydrate

Chemical Name: 5,5-diphenyl-3-[(phosphonooxy)methyl]-2-4-imidazolidinedione disodium heptahydrate salt

Molecular formula: $C_{16}H_{13}N_2O_6PNa_2 \cdot 7H_2O$

Molecular weight: 532.35

Molecular structure:



Description: White to pale yellow solid. Freely soluble in buffer over a pH range of 5.0 to 9.0.

Dissociation Constants: $pK_a = 6.2$

Composition

Each CEREBYX (Fosphenytoin Sodium Injection) vial contains 75 mg/mL fosphenytoin sodium as heptahydrate, equivalent to 50 mg/mL phenytoin sodium after administration. Each vial also contains Water for Injection and tromethamine buffer (12 mg/mL) adjusted to pH 8.6 to 9.0 with either hydrochloric acid or sodium hydroxide.

Stability and Storage Recommendations

Store under refrigeration at 2° to 8°C. The product should not be stored at room temperature for more than 48 hours. Vials that develop particulate matter should be discarded.

Compatibility

CEREBYX added to 5% dextrose or 0.9% saline solution for injection in a concentration range from 2.5 to 40 mg/mL is stable for 8 hours at room temperature or 24 hours when stored under refrigeration (2° to 8°C).

CEREBYX is for parenteral use only. As with all parenteral formulations, CEREBYX vials should be inspected visually for particulate matter and discolouration before administration whenever solution and container permit. Products with particulate matter or discolouration should be discarded.

AVAILABILITY OF DOSAGE FORMS

CEREBYX (Fosphenytoin Sodium Injection, 75 mg/mL) is supplied in 2 mL or 10 mL single-dose vials:

2 mL Vials: Packages of 5 vials (equivalent to **100 mg phenytoin sodium per 2 mL vial**, or 50 mg/mL)

10 mL Vials: Packages of 1 vial (equivalent to **500 mg phenytoin sodium per 10 mL vial**, or 50 mg/mL).

PHARMACOLOGY

Animal Pharmacology

- In the maximal electroshock test with rodents, fosphenytoin and phenytoin are equipotent anticonvulsants on a molar basis.

- The time course of anticonvulsant actions for fosphenytoin and phenytoin do not differ greatly in mice.

- Fosphenytoin and phenytoin have approximately equipotent antiarrhythmic activity in vivo, but phenytoin is more potent in most in vitro tests.

- These data suggest that the predominant pharmacological actions of fosphenytoin are due to metabolic conversion of fosphenytoin to phenytoin and subsequent action of phenytoin on pharmacologically relevant sites in brain or cardiovascular tissue.

- Both phenytoin and fosphenytoin prevent ischemic brain damage in several models of cerebral stroke.

- Fosphenytoin is highly bound (>91%) to dog and human plasma proteins, predominantely to albumin.

- Absolute bioavailability of IM fosphenytoin is essentially 100% in dog, based on phenytoin AUC data.

- Phenytoin pharmacokinetic parameters are similar in dogs following IV fosphenytoin and phenytoin administration.

- [^{14}C]Fosphenytoin radioequivalents are not retained by rodent tissues.

- IM fosphenytoin does not cause tissue damage to dog hindlimb muscles nor drug precipitation at the injection site.

- Fosphenytoin is rapidly converted in vivo to phenytoin by phosphatases in rat and dog.

- Metabolism and urinary excretion profile of IV fosphenytoin and phenytoin are similar in dog.

- 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) glucuronide is the major metabolite in rat urine; whereas 5-(m-hydroxyphenyl)-5-phenylhydantoin (m-HPPH) glucuronide is the major urinary metabolite in dog.

- Urinary excretion is the major elimination pathway of [^{14}C]fosphenytoin and its metabolites in rat.

- At toxicologically relevant doses, total phenytoin exposure in rats following IM fosphenytoin is reduced slightly relative to an IV dose, while phenytoin exposure in dogs is similar following IM and IV fosphenytoin.

TOXICOLOGY

The results of animal toxicology studies (acute, multiple-dose, reproductive, and genetic toxicity) are summarized in Tables 4-10.

The toxicologic profile of the prodrug fosphenytoin is similar to that of phenytoin. Generally, CNS effects were seen at equimolar doses with both compounds.

Effects on serum hepatic enzymes and liver weights observed in multidose studies in rats and dogs with fosphenytoin are known effects of phenytoin in animals and are consistent with microsomal enzyme induction. Microscopic changes in the liver were attributed to increased cellular glycogen content and secondary to phenytoin-induced hyperglycemia which occurs after fosphenytoin administration.

Malformations seen in rats given fosphenytoin are consistent with those seen in rats given phenytoin.

The clastogenic effects of fosphenytoin in vitro are not linked to mutagenic activity as both the bacterial and mammalian cell mutagenicity assays were negative. Because the clastogenic activity of fosphenytoin was restricted to an in vitro assay at concentrations considerably higher than maximum therapeutic plasma concentrations of 20 μg/mL and clastogenic activity was not detected in vivo at doses which substantially exceed the maximum therapeutic dose, the in vitro clastogenic activity of fosphenytoin was not considered biologically relevant.

Local irritation following IV or IM administration was less severe with fosphenytoin than with phenytoin.

TABLE 4. Fosphenytoin Single-Dose Toxicity Studies in Rodents (Page 1 of 2)

Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Observation Period	Dose (mg/kg) Fosphenytoin[a]	Dose (mg/kg) Phenytoin[b]	Results (mg/kg)
Mouse (CD-1)	IV Infusion[c]	SAL		**Fosphenytoin[a]**
5M + 5F, 120	(20 mL/kg)[d]	VC[e]		NOED = 33.3
6 Weeks	14 Days	33.3	33	MNLD = 63.3
		63.3	63	MLD = 156
		120	120	**Phenytoin**
		230	233	NOED = ND
		433	440	MNLD = 63
				MLD = 192
Rat (SD)	IV Bolus	SAL		**Fosphenytoin[a]**
5M + 5F, 150	(10 mL/kg)[f]	VC[g]	VC	NOED = 50
7 Weeks	14 Days	50	45	MNLD = 153
		73.3	65	MLD = 213
		106.7	95	**Phenytoin**
		153	145	NOED = ND
		233	210	MNLD = 45
		333	300	MLD = 90.4
Rat (SD)	IV Infusion[c]	SAL		**Fosphenytoin[a]**
5M + 5F, 130	(10 mL/kg)[f]	50[g]	45	NOED = ND
7 Weeks	14 Days	73.3	65	MNLD = 153
		107	95	MLD = 242
		153	145	**Phenytoin**
		233	210	NOED = ND
		333	300	MNLD = 210
				MLD = 275[h]
Rat (SD)	IV Infusion[c]	SAL		**Fosphenytoin[a]**
5M + 5F, 120	(10 mL/kg)[i]	VC[e]		NOED = 33.3
4 Weeks	14 Days	33.3	33	MNLD = 120
		63.3	63	MLD = 258
		120	120	**Phenytoin**
		230	233	NOED = 33
		433	440	MNLD = 120
				MLD = 297

IV = Intravenous; SAL = Saline (0.9% NaCl) control; VC = Vehicle control; NOED = No observed effect dose; MNLD = Maximum nonlethal dose; MLD = Combined-sex median lethal dose; SD = Sprague-Dawley.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Duration of infusion = 30 minutes.

[d] Fosphenytoin dosing solution concentrations ranged from 2.50 to 32.5 mg/mL. Phenytoin dosing solution concentrations ranged from 1.65 to 22.0 mg/mL.

[e] Vehicle = l-arginine HCl, pH adjusted to 8.8.

[f] Fosphenytoin dosing solution concentrations ranged from 7.5 to 50 mg/mL. Phenytoin dosing solution concentrations ranged from 4.50 to 30.0 mg/mL.

[g] Vehicle = Tris buffer, pH adjusted to 8.8.

[h] Estimated; value could not be calculated using Moving Average Interpretation or Probit Analyses Method

[i] Fosphenytoin dosing solution concentrations ranged from 5.0 to 65 mg/mL. Phenytoin dosing solution concentrations ranged from 3.3 to 44 mg/mL.

TABLE 4. Fosphenytoin Single-Dose Toxicity Studies in Rodents (Page 2 of 2)

Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Observation Period	Dose (mg/kg) Fosphenytoin[a]	Dose (mg/kg) Phenytoin[b]	Results (mg/kg)
Rat (SD)	IM	SAL		**Fosphenytoin**[a]
3M + 3F, 72	(5 mL/kg)[j,k]	33.3[g]	34	NOED = 33.3
7 weeks	14 Days	77	169	MNLD = 167
		167	250	MLD = 278
		247[l]	337[l]	**Phenytoin**
		333[l]		NOED = 34
				MNLD = 337
				MLD = >337
Rat (SD)	IP	SAL		**Fosphenytoin**[a]
5M + 5F, 160	(10 mL/kg)[m]	VC[e]		NOED = 60
6 Weeks	14 Days	33.3	33	MNLD = 177
		60	60	MLD = 352
		100	102	**Phenytoin**
		177	178	NOED = 60
		300	305	MNLD = 178
		500	500	MLD = 339
		850	860	
Rat (SD)	IP	SAL		**Fosphenytoin**[a]
5M + 5F, 140	(20 mL/kg)[n]	VC[e]		NOED = 100
7 Days	14 Days	33.3	33	MNLD = 100
		60	60	MLD = 181
		100	102	**Phenytoin**
		177	178	NOED = 102
		300	305	MNLD = 102
		500	500	MLD = 224

SD = Sprague-Dawley; IM = Intramuscular; SAL = Saline (0.9% NaCl) control; NOED = No observed effect dose; MNLD = Maximum nonlethal dose; MLD = Combined-sex median lethal dose; IP = Intraperitoneal; VC = Vehicle control.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Duration of infusion = 30 minutes.

[e] Vehicle = l-arginine HCl, pH adjusted to 8.8.

[g] Vehicle = Tris buffer, pH adjusted to 8.8.

[j] Dose volume for 337 mg/kg phenytoin group was 6.74 mL/kg.

[k] Fosphenytoin dosing solution concentrations ranged from 10 to 100 mg/mL. Phenytoin dosing solution concentrations ranged from 6.8 to 50 mg/mL.

[l] N = 5 rats/sex.

[m] Fosphenytoin dosing solution concentrations ranged from 5.0 to 75 mg/mL. Phenytoin dosing solution concentrations ranged from 3.3 to 50 mg/mL.

[n] Fosphenytoin dosing solution concentrations ranged from 2.50 to 37.5 mg/mL. Phenytoin dosing solution concentrations ranged from 1.65 to 25.0 mg/mL.

TABLE 5. Fosphenytoin Escalating-Dose Toxicity Studies in Nonrodents

Species (Strain) Sex/Group, Total Age	Route (Dose Volume)	Day	Dose (mg/kg) Fosphenytoin[a]	Dose (mg/kg) Phenytoin[b]	Results (mg/kg)
Rabbit (NZW)	IV Infusion[c]	1	6.7[d]	6.8	**Fosphenytoin**[a]
6M + 6F, 24	(10 mL/kg)[e]	3	13.3	13.5	NOED = 40
NA		6	20	20.2	MTD = 40
		9	26.7	27	No Deaths
		13	40	40.5	**Phenytoin**
		15[f]	53.3	54	NOED = 27
					MTD = 40.5
					No Deaths
Dog (beagle)	IV Bolus	1	6.7[g]	6	**Fosphenytoin**[a]
2M + 2F, 8	(2 mL/kg)[h]	3	13.3	12	NOED = 13.3
10 months		5	26.7	24	MTD = 26.7
		8[f]	40	36	No Deaths
					Phenytoin
					NOED = 6
					MTD = 24
					No Deaths
Dog (beagle)	IV Infusion[c]	1	6.7[g]	6	**Fosphenytoin**[a]
2M + 2F, 8	(2 mL/kg)[h]	3	13.3	12	NOED = 13.3
10 months		5	26.7	24	MTD = 26.7
		8[f]	40	36	No Deaths
					Phenytoin
					NOED = 12
					MTD = 24
					No Deaths
Dog (beagle)	IM	1	6.7[g]	6.7	**Fosphenytoin**[a]
3M + 3F, 12	(0.13-1.00 mL/kg)[i]	3	16.7	16.9	NOED = 33.3
10 months		7	33.3	33.7	MTD = 33.3
		9[f]	50	50	No Deaths
					Phenytoin
					NOED = 6.7
					MTD = >50
					No Deaths

NZW = New Zealand White; IV = Intravenous; NOED = No observed effect dose; NA = Not available; MTD = Maximum tolerated dose; IM = Intramuscular.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Duration of infusion = 30 minutes.

[d] Vehicle = l-arginine HCl, pH adjusted to 8.8.

[e] Fosphenytoin dosing solution concentrations ranged from 1.0 to 8.0 mg/mL. Phenytoin dosing solution concentrations ranged from 0.68 to 5.40 mg/mL.

[f] Animals observed for 14 days after last dose.

[g] Vehicle = Tris buffer, pH adjusted to 8.8.

[h] Fosphenytoin dosing solution concentrations ranged from 5.0 to 30 mg/mL. Phenytoin dosing solution concentrations ranged from 3.0 to 18 mg/mL.

[i] Fosphenytoin dosing solution concentration = 75 mg/mL. Phenytoin dosing solution concentration = 50 mg/mL.

TABLE 6. Fosphenytoin Multidose Toxicity Studies in Rats

Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Duration	Daily Dose[a] (mg/kg)	Results
Rat (SD) 5M + 5F, 60 6-7 Weeks	IV Bolus (10 mL/kg)[c] 7 Days	VC[b] 20 40 66.7 107 160	Deaths at 107 and 160 mg/kg. Dose-related lethargy, ataxia, and head tremors at ≥66.7 mg/kg. Decreased body weight gain and food consumption, glucosuria, and increased ALT, ALP, and BUN at 107 and 160 mg/kg. No pathologic findings.
Rat (SD) 10M + 10F, 100 8 Weeks	IV Bolus (10 mL/kg)[d] 2 Weeks	SAL VC[b] 13.3 33.3 100	Death, hypoactivity, dyspnea, dilated pupils, prostration, ataxia, hypothermia, decreased body weight gain in males, transient decreases in food consumption, increased urine volumes, and glucosuria in both sexes at 100 mg/kg. No pathologic findings.
Rat (Wistar) 15M + 15F, 144[e] 6-7 Weeks	IV Bolus (2 mL/kg)[f] 4 Weeks[g]	VC[b] 20 40 100	No deaths. Ataxia, hypoactivity, and salivation at 40 and 100 mg/kg. Decreased body weight gain and food consumption in males at 100 mg/kg. Reversible increases in ALT and ALP at 100 mg/kg. Increased liver:body weight in males at 100 mg/kg and females at all doses; reversible at 20 and 40 mg/kg. Reversible dose-related injection-site irritation at ≥20 mg/kg and vacuolation of hepatocytes at 100 mg/kg.
Rat (SD) 5M + 5F, 90[e] 7-9 Weeks	IM (0.7-3.3 mL/kg)[h] 2 Weeks	SAL 33.3 66.7 100 133 167	Deaths at 133 and 167 mg/kg. Dose-related lethargy, prostration, ataxia, and/or tremors at ≥66.7 mg/kg. Decreased body weight gain, transient decreases in food consumption, and increased urine volumes in males at ≥100 mg/kg. Injection-related gross pathologic changes in muscle in 1 animal each at 100 and 167 mg/kg.
Rat (SD) 10M + 10F, 150[i] 7 Weeks	IM (0.4-2.0 mL/kg)[h] 13 Weeks	SAL PHT[j] 20 40 100	Increased liver weights in females at all doses. Deaths, dilated pupils, hypoactivity, excessive salivation, decreased body weight, increased AST, ALT, and ALP, hyperglycemia, glucosuria, and intracytoplasmic hepatocellular vacuolation with fosphenytoin at 100 mg/kg. Similar findings were noted with phenytoin. Local irritation with both compounds.

SD = Sprague-Dawley; IV = Intravenous; VC = Vehicle control; ALT = Alanine aminotransferase; ALP = Alkaline phosphatase; BUN = Blood urea nitrogen; SAL = Saline (0.9% NaCl) control; IM = Intramuscular; PHT = Phenytoin; AST = Aspartate aminotransferase;

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Vehicle = Tris buffer, pH adjusted to 8.8.

[c] Fosphenytoin dosing solution concentrations ranged from 3.0 to 24 mg/mL.

[d] Fosphenytoin dosing solution concentrations ranged from 2.0 to 15 mg/mL.

[e] Three additional animals per sex included in control and/or drug-treated groups and utilized only for determination of drug concentrations.

[f] Fosphenytoin dosing solution concentrations ranged from 15 to 75 mg/mL.

[g] Five animals per sex per group were euthanized after a 4-week withdrawal period (Week 8).

[h] Fosphenytoin dosing solution concentration = 75 mg/mL.

[i] Five additional animals per sex per group utilized only for determination of drug concentrations.

[j] Phenytoin Sodium Injection USP, administered at 100 mg/kg, dosing solution concentration = 50 mg/mL; group terminated at Week 9.

TABLE 7. Fosphenytoin Multidose Toxicity Studies in Dogs

Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Duration	Daily Dose[a] (mg/kg)	Results
Dog (beagle) 2M + 2F, 24 11-12 months	IV Bolus (2.0 mL/kg)[c] 7 Days	VC[b] 6.7 13.3 20 26.7 33.3	No deaths. Dose-related incidence of diarrhea, salivation, and emesis at ≥13.3 mg/kg. In addition, ataxia at 26.7 and 33.3 mg/kg. No significant changes in clinical laboratory parameters. No pathologic findings.
Dog (beagle) 4M + 4F, 40 7-8 months	IV Bolus (2.0 mL/kg)[d] 2 Weeks	SAL VC[b] 10 20 33.3	No deaths. Hypoactivity, emesis, excessive salivation, and ataxia at 20 and 33.3 mg/kg. In addition, tremors at 33.3 mg/kg. No significant changes in clinical laboratory parameters. No pathologic findings.
Dog (beagle) 4M + 4F, 24 10-12 months	IV Bolus (0.67 mL/kg)[e] 4 Weeks[f]	VC[b] 10 20 33.3	No deaths. Dose-related incidence of emesis at ≥10 mg/kg and transient salivation, ataxia, and erythema of gums at ≥20 mg/kg. Tremors and hypoactivity at 33.3 mg/kg. Increased ALP at 33.3 mg/kg at Weeks 4 and 8. Increased salivary gland weights in both sexes at 33.3 mg/kg and females at 20 mg/kg at Week 4. Increased liver:body weight in males at 20 and 33.3 mg/kg; reversible at 20 mg/kg. Hypertrophy of salivary glands in males at 33.3 mg/kg at Weeks 4 and 8.
Dog (beagle) 2M + 2F, 24 9-10 months	IM (0.2-1.0 mL/kg)[g] 2 Weeks	SAL 10 20 33.3 40 50	No deaths. Dose-related incidence of emesis and ataxia at ≥33.3. Sporadic convulsions, diarrhea, and/or tonic stance at 40 and 50 mg/kg. In addition, prostration and excessive salivation at 50 mg/kg. No significant changes in clinical laboratory parameters. No pathologic findings.
Dog (beagle) 4M + 4F, 40 7-9 months	IM (0.2-0.8 mL/kg)[g] 13 Weeks	SAL PHT[h] 10 20 40	No deaths. Emesis and excessive salivation at all doses. In addition, ataxia, hypoactivity, diarrhea, increased ALP, increased liver weights, and intracytoplasmic hepatocellular vacuolation with fosphenytoin at 40 mg/kg. Similar findings were noted with phenytoin. Local irritation with fosphenytoin at 20 and 40 mg/kg and with phenytoin.

IV = Intravenous; VC = Vehicle control; SAL = Saline (0.9% NaCl) control; ALP = Alkaline phosphatase; IM = Intramuscular; PHT = Phenytoin;

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Vehicle Control = Tris buffer, pH adjusted to 8.8.

[c] Fosphenytoin dosing solution concentrations ranged from 5.0 to 25 mg/mL.

[d] Fosphenytoin dosing solution concentrations ranged from 7.5 to 25 mg/mL.

[e] Fosphenytoin dosing solution concentrations ranged from 22.4 to 75.0 mg/mL.

[f] One animal per sex per group was euthanized after a 4-week withdrawal period (Week 8).

[g] Fosphenytoin dosing solution concentration = 75 mg/mL.

[h] Phenytoin Sodium Injection USP, administered at 40 mg/kg, dosing solution concentration = 50 mg/mL.

TABLE 8. Fosphenytoin Special Toxicity Studies (Page 1 of 2)

Species (Strain) Sex/Group, Total	Study Design[a]	Results
Venous and Perivascular Irritation[b]		
Rabbits (NZW) 6 Males, 66	**Dosing**: Single 30-min IV infusion or SC injection FOS (mg/mL):VC[c], 10, 25, 50, 75 PHT[d] (mg/mL):VC, 6.7, 16.9, 33.7, 50 **Observation**: 24 hours **Parameters**: Gross and microscopic examinations	No significant differences in perivascular or venous irritation between fosphenytoin and saline controls. Significant venous and perivascular irritation and high incidence of thrombus formation with phenytoin.
Intramuscular Irritation[b]		
Rabbits (NZW) 12 Males, 12	**Dosing**: Single IM injection FOS (mg/mL):VC[e], 25, 50, 75, 100 PHT[d] (mg/mL):VC, 50 **Observation**: 24 hours **Parameters**: Gross and microscopic examinations	Fosphenytoin less irritating than saline or phenytoin. Trace to mild hemorrhage, acute inflammation and necrosis with saline, phenytoin vehicle, and phenytoin.
Rabbits (NZW) 4 Males, 28	**Dosing**: 5 daily IM injections FOS (mg/mL):VC[e], 50, 75, 100 PHT[d] (mg/mL):VC, 50 **Observation**: 5 days **Parameters**: Serum CPK, gross and microscopic examinations	Hemorrhage in all control and treatment groups. Necrosis with phenytoin; less severe with fosphenytoin at 75 and 100 mg/mL. Increased CPK with phenytoin vehicle, phenytoin, and fosphenytoin.
Glucosuria[f]		
Rats (SD) 10 Males, 30	**Dosing**: Single 30-min IV infusion FOS[e] (mg/kg): 100 PHT[d] (mg/kg): 100 **Dose Volume**: 10 mL/kg[g] **Observation**: 48 hours **Parameters**: Clinical signs, serum and urine glucose concentrations	Similar increases in serum and urinary glucose concentrations with fosphenytoin and phenytoin.

NZW = New Zealand White; IV = Intravenous; SC = Subcutaneous; FOS = Fosphenytoin; VC = Vehicle control; PHT = Phenytoin; IM = Intramuscular; CPK = Creatine phosphokinase; SD = Sprague-Dawley;

[a] All in vivo studies included saline (0.9% NaCl) control group.

[b] Concentrations based on the weight of the sodium salt of fosphenytoin or phenytoin.

[c] Vehicle = l-arginine HCl, pH adjusted to 8.8.

[d] Phenytoin Sodium Injection USP, Vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[e] Vehicle = Tris buffer, pH adjusted to 8.8.

[f] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[g] Fosphenytoin dosing solution concentration = 15 mg/mL. Phenytoin dosing solution concentration = 10 mg/mL.

TABLE 8. Fosphenytoin Special Toxicity Studies (Page 2 of 2)

Species (Strain) Sex/Group, Total	Study Design[a]	Results
CNS Safety Screen[f]		
Mice (CD-1) 6 Males, 90	**Dosing**: Single IP injection FOS (mg/kg): VC[e], 33.3, 66.7, 133, 333, 667 PHT[d] (mg/kg): VC[h], 33, 69, 134, 337, 675 **Dose Volume**: 20 mL/kg[j] **Observation**: Approximately 4 hours **Parameters**: Clinical signs and behavioral changes	Deaths at 333 and 667 mg/kg fosphenytoin, and 337 and 675 mg/kg phenytoin. Similar incidence and severity of CNS effects observed with fosphenytoin and phenytoin.
Cardiovascular Safety Screen[f]		
Dogs (beagle) 4 Females, 20	**Dosing**: Single IV injection FOS (mg/kg): VC[e], 18 PHT[d] (mg/kg): VC, 18 **Dose Volume**: 1 mL/kg[j] **Observation**: 60 minutes **Parameters**: Cardiovascular, blood drug concentrations	No deaths. Gradual decrease in hr, LVdP/dt, and MABP with fosphenytoin and immediate decreases in these parameters with phenytoin. Significant increase in LVEDP with phenytoin. Maximum plasma phenytoin concentrations were 22.1 μg/mL 5 minutes postdose and 49.4 μg/mL 30 seconds postdose following administration of fosphenytoin and phenytoin, respectively.
Human Blood Compatibility[b]		
In vitro	**Concentrations**: FOS (mg/mL): 0.15 to 75 PHT[d] (mg/mL): 0.10 to 50 **Parameters**: Hemolysis, plasma protein flocculation	No hemolysis or plasma protein flocculation with fosphenytoin. Hemolysis at 5.0 to 50 mg/mL and mild plasma protein flocculation with phenytoin at 20 mg/mL.

CNS = central nervous system; IP = intraperitoneal; FOS = fosphenytoin; VC = vehicle control; PHT = phenytoin; IV = intravenous; hr = heart rate; LVdP/dt = left ventricular contractility; MABP = mean arterial blood pressure; LVEDP = left ventricular end diastolic pressure;

[a] All in vivo studies included saline (0.9% NaCl) control group

[b] Concentrations based on the weight of the sodium salt of fosphenytoin or phenytoin.

[d] Phenytoin Sodium Injection USP, Vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[e] Vehicle = Tris buffer, pH adjusted to 8.8.

[f] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[h] Vehicle was tested in 3 groups of animals at 100% or diluted to 66% or 32% with saline (0.9% NaCl).

[i] Fosphenytoin dosing solution concentrations ranged from 2.5 to 50 mg/mL. Phenytoin dosing solution concentrations ranged from 1.65 to 33.75 mg/mL.

[j] Fosphenytoin dosing solution concentration = 27 mg/mL. Phenytoin dosing solution concentration = 18 mg/mL

TABLE 9. Fosphenytoin Reproductive Toxicity Studies (Page 1 of 2)

Species (Strain) Sex/Group, Total Age	Route (Vehicle) [Dose Volume]	Daily Dose[a] (mg/kg)	Treatment Regimen	Results
FERTILITY AND GENERAL REPRODUCTION				
Male				
Rat (SD) 40, 200 12-13 Weeks	IM (Tris Buffer) [2 mL/kg]	UC VC 16.7 50 100	75 days prior to and through mating	Paternal toxicity at 50 and 100 mg/kg. No effects on fertility or reproduction.
Female				
Rat (SD) 40, 200 15 Weeks	IM (Tris Buffer) [2 mL/kg]	UC VC 16.7 50 100	15 Days Prior to Mating through Lactation Day 21	Maternal and reproductive toxicity at 50 and 100 mg/kg. Developmental toxicity at all doses including teratogenicity at 16.7 and 100 mg/kg.
TERATOLOGY				
Exploratory				
Rat (SD) 3F, 9 NA	IV Bolus (Tris Buffer) [2,3,10 mL/kg]	100	10 days	All animals euthanized moribund by Day 4. No trauma at injection site.
Dose Range-Finding				
Rat (SD) 5F, 35 20 Weeks	IV Bolus (Tris Buffer) [2 mL/kg]	VC 6.7 16.7 33.3 50 66.7	Gestation Days 7 through 17	Maternal toxicity at 16.7, 33.3, and 66.7 mg/kg. Developmental toxicity at 50 and 66.7 mg/kg. No adverse effects at 6.7 mg/kg. MTD = 66.7 mg/kg.
Definitive				
Rat (SD) 40F, 200 12-13 Weeks	IV Bolus (Tris Buffer) [2 mL/kg]	UC VC 6.7 33.3 66.7	Gestation Days 7 through 17	Four deaths, decreased maternal body weight gain and food consumption, decreased birth and male offspring weights at Week 13 at 66.7 mg/kg. No teratogenicity or behavioral toxicity.

SD = Sprague-Dawley; IM = Intramuscular; UC = Untreated control; VC = Vehicle control; IV = Intravenous; NA = Not available; MTD = Maximum tolerated dose.

[a] Doses expressed as milligram/kilogram phenytoin equivalents; fosphenytoin dosing solution concentrations ranged from 5 to 75 mg/mL. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

TABLE 9. Fosphenytoin Reproductive Toxicity Studies (Page 2 of 2)

Species (Strain) Sex/Group, Total Age	Route (Vehicle) [Dose Volume]	Daily Dose[a] (mg/kg)	Treatment Regimen	Results
TERATOLOGY (continued)				
Exploratory				
Rabbit (NZW) 3F, 6 NA	IV Bolus (Tris Buffer) [1,2 mL/kg]	33.3	13 Days	No clinical signs or effects on body weight or food consumption. No trauma at injection site.
Dose Range-Finding				
Rabbit (NZW) 5F, 35 7-8 months	IV Bolus (Tris Buffer) [1-2 mL/kg]	VC 3.3 16.7 33.3 50 66.7	Gestation Days 6 through 18	Maternal toxicity at 33.3, 50, and 66.7 mg/kg. Developmental toxicity at 66.7 mg/kg. No adverse effects at 3.3 mg/kg. MTD = 33.3 mg/kg.
Definitive				
Rabbit (NZW) 20F, 100 7-8 months	IV Bolus (Tris Buffer) [1 mL/kg]	UC VC 6.7 16.7 33.3	Gestation Days 6 through 18	No deaths. Decreased body weight gain and food consumption at 16.7 and 33.3 mg/kg. No maternal reproductive or fetal toxicity, and no teratogenicity.
PERINATAL-POSTNATAL TOXICITY				
Rat (SD) 25F, 125 12 Weeks	IV Bolus (Tris Buffer) [2 mL/kg]	UC VC 16.7 33.3 66.7	Gestation Day 15 through Lactation Day 20	Maternal and perinatal-postnatal toxicity at 33.3 and 66.7 mg/kg. Subtle behavioral toxicity at 33.3 and 66.7 mg/kg.

NZW = New Zealand White; IV = Intravenous; NA = Not available; VC = Vehicle control; MTD = Maximum-tolerated dose; UC = Untreated control; SD = Sprague-Dawley.

[a] Doses expressed as milligram/kilogram phenytoin equivalents; fosphenytoin dosing solution concentrations ranged from 5 to 75 mg/mL. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

TABLE 10. Fosphenytoin Genetic Toxicity Studies

Test	Concentration Range or Dose	Results
Mutagenicity		
Mutagenesis in *Salmonella typhimurium*	312.5-5000 μg/plate[a]	Nonmutagenic in the absence or presence of S9.
Point mutation assay in V79 Chinese hamster lung cells	500-4000 μg/mL[a]	No mutation at HGPRT locus in the absence or presence of S9.
Clastogenicity		
Structural chromosome aberration assay in V79 chinese hamster lung cells	500-4000 μg/mL[a](-S9) 125-4000 μg/mL[a](+S9)	Clastogenic at ≥3000 μg/mL only in the presence of S9.
Micronucleus assay	33.3, 66.7, 133 mg/kg[b]	No increase in micronucleus frequency.

HGPRT = Hypoxanthine-quanine phosphoribosyltransferase; S9 = Postmitochondrial supernatant from livers of rats induced by Aroclor 1254.

[a] Concentrations based on the weight of fosphenytoin

[b] Doses expressed as mg phenytoin equivalents; fosphenytoin dosing solution concentrations ranged from 5 to 20 mg/mL; dose volume = 10 mL/kg.

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PART III: PATIENT MEDICATION INFORMATION

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

PrCEREBYX®

Fosphenytoin Sodium Injection
75 mg/ml
Equivalent to 50 mg/ml Phenytoin Sodium

Read this carefully before you start taking **CEREBYX** 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 **CEREBYX.**

Serious Warnings and Precautions

Cardiovascular Risk

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

What is CEREBYX used for?
CEREBYX is used in situations when other means of phenytoin administration are unavailable, inappropriate or deemed less advantageous. It can also be used for the control of generalized convulsive status epilepticus or for the prevention and treatment of seizures occurring during neurosurgery.

How does CEREBYX work?
CEREBYX is converted by the body into phenytoin, which is an anticonvulsant medication. This family of medications stops seizure activity in the brain.

What are the ingredients in CEREBYX?
Medicinal ingredients: 75 mg/mL of fosphenytoin sodium as heptahydrate, equivalent to 50 mg/mL phenytoin sodium after administration.
Non-medicinal ingredients: Water for Injection and tromethamine buffer (12 mg/mL) adjusted to pH 8.6 to 9.0 with either hydrochloric acid or sodium hydroxide.

CEREBYX comes in the following dosage forms:
Liquid: 50 mg/mL

Do not use CEREBYX if you:

- are allergic to the active ingredient fosphenytoin sodium, phenobarbital, or any of the other ingredients.

- have a serious heart condition (such as; sinus bradycardia, sino-atrial block, second and third degree AV block and Adams-Stokes syndrome).
- are taking delavirdine, a drug used to treat HIV.

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

- Have ever had a rash or unusual reaction while taking fosphenytoin sodium or any other antiepileptic drug.
- Have kidney or liver problems. Your healthcare professional may need to adjust the dose.
- Drink alcohol. Drinking alcohol with CEREBYX may make you less alert and may make feelings of anger, confusion or sadness worse.
- Suffer from seizures that spread to the whole brain.
- Are pregnant or planning to become pregnant. You must only take CEREBYX during pregnancy if your healthcare professional tells you to.
  - If you become pregnant while taking CEREBYX, talk to your healthcare professional about registering with the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy. You can enroll in this registry by calling 1-888-233-2334. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.
  - Are nursing or plan to nurse your baby. Nursing while you are taking CEREBYX is not recommended.
- Are taking birth control.
  - CEREBYX may make hormonal birth control such as “the pill” less effective.
  - Use other forms of safe and effective birth control when taking CEREBYX.
  - You need to use other forms of birth control until the end of your menstrual cycle after stopping treatment.
- Have low blood pressure.
- Have heart problems.
- Are diabetic.
- Are of Asian or African descent. You may be at a higher risk of developing serious skin reactions.
- Have a blood disorder (such as; porphyria)
- Have a family history of hypersensitivity to CEREBRYX, phenytoin or other hydantoins.
- Are being treated with irradiation and corticosteroids.
- Have low bone density.

Other warnings you should know about:

- Ask your healthcare professional about signs and symptoms of life threatening skin reactions such as Stevens Johnson Syndrome (SJS; a skin reaction with rash and blisters) and Toxic Epidermal Necrolysis (TEN; a skin rash often with blisters, lesions and lifting skin) that have been reported during CEREBRYX treatment. Closely monitor for skin reactions. Most often, SJS or TEN happen in the first weeks of treatment. If symptoms or signs of SJS or TEN are present, CEREBYX treatment should be stopped. The best results in managing SJS and TEN come from early detection and stopping the drug treatment right away (see table **of Serious Side Effects and What to do About Them**, below).

- Anti-epileptic drugs, including CEREBRYX, should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus.

DURING treatment with CEREBRYX, tell your healthcare professional if you develop:
- Thoughts of suicide or self harm
- Abnormal vision (blurry or double vision)

Driving and using machines:
Before doing tasks that require special attention, wait until you know how you respond to CEREBYX. Being dizzy or drowsy can occur. Be careful to avoid accidental injury or falls.

There are many drugs that may increase or decrease CEREBYX levels. Also, CEREBYX may affect the levels of many drugs. Therefore, tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines as there may be a need to adjust your medication or monitor you more carefully.

The following may interact with CEREBYX:
- Birth control pills.
- Other anti-epileptic drugs (such as; ethosuximide, topiramate, phenobarbital, sodium ~~V~~valproate, carbamazepine, valproic acid, felbamate, succinimides, oxycarbazepine, quetiapine, lamotrigine, methsuximide).~~,~~
- Alcohol.
- Drugs used to treat fungal infections (such as; amphotericin B,fluconazole, ketoconazole, miconazole, itraconazole, voriconazole).
- Drugs used to treat heart problems.
- Drugs used to treat HIV infection (such as; delavirdine, efavirenz, lopinavir/ritonavir, indinavir, nelfinavir, ritonavir, saquinavir).
- Warfarin.
- St. John's Wort
- Folic acid

How to take CEREBYX:
- This medication is an injection~~s~~. It will be given to you by your healthcare professional to stop a seizure.
- **If you are taking this medication to control your seizures, do not stop taking CEREBYX without talking to your healthcare professional.** Stopping a seizure medicine suddenly can cause serious problems, including seizures that will not stop. Your healthcare professional will tell you if and when you can stop taking this medicine.

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

Overdose:

If you think you have been given too much CEREBYX contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Every dose should be administered under the supervision of a healthcare professional, if a dose is missed contact your healthcare professional immediately.

What are possible side effects from using CEREBYX?
These are not all the possible side effects you may feel when taking CEREBYX. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

The most common side effects associated with the use of CEREBYX are:
- Sleepiness/drowsiness, feeling tired/fatigue
- Headache, dizziness along with the feeling of a spinning movement
- Nausea/vomiting, constipation, dry mouth, changes in taste
- Double vision, blurred vision
- Poor coordination (dizzy)
- Shakiness
- Eyes moving involuntarily
- Itching
- Sensation of tingling, tickling, or burning of the skin
- Ringing in the ears

CEREBRYX can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious Side Effects and What to do About Them				
Symptom / effect		**Talk to your Healthcare Professional**		**Get Immediate Medical Help**
		Only if Severe	**In all Cases**	
Common	Low sodium level in blood (symptoms like lack of energy, confusion, muscular twitching or convulsions)		X	
	Nervous system problems (symptoms like dizziness, trouble walking or with coordination, feeling sleepy and tired, trouble concentrating, blurred vision, double vision etc.)		X	

	Allergies (symptoms like fever, rash and swollen lymph nodes, and may be associated with symptoms involving other organs, e.g., liver)		X	
	Swelling, irritation, redness and pain at the site of the injection or in the hand/arm where the injection was given		X	
Uncommon	Liver problems (symptoms like yellowing of your skin or the whites of your eyes, nausea or vomiting, loss of appetite, stomach pain, dark tea-like urine etc.)		X	
	Thoughts of suicide or self harm			X
	Thinning of the bone, bone softening, bone disease, or fractures (In situations where healthy people would not normally break a bone you may have sudden pain in any location and especially in the wrist, spine or hip. This may be a fracture.)		X	
	Altered numbers and types of blood cells (symptoms like unexplained tiredness, weakness, shortness of breath, and sometimes, feeling like you are going to pass out and increased bruising, nosebleeds, sore throats, or infections)		X You should tell your healthcare professional who may want to perform a blood test	
	Low blood pressure (dizziness, fainting, lightheadedness. May occur when you go from lying or sitting to standing up)	X		
	Heart problems (symptoms like irregular heartbeat, shortness of breath, chest pain, etc.)			X

Rare	Severe allergic reactions (symptoms like swelling of face, eyes, lips, or tongue, trouble swallowing or breathing, skin rash)			X
	A rare, serious disorder in which your skin reacts severely to a medication (Stevens Johnson Syndrome; SJS). If symptoms or signs of SJS (e.g. skin rash often with blisters or lesions) are present, CEREBYX treatment should be stopped right away.			X
	Severe skin reaction where the upper surface of your skin detaches like a patient who has suffered burns (Toxic Epidermal Necrolysis [TEN]). If symptoms or signs of TEN (e.g. skin rash often with blisters or mucosal lesions and lifting skin) are present, phenobarbital treatment should be stopped right away.			X
Unknown	Respiratory depression (shallow slow, weak breathing)			X

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

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

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

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

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

Storage:
Store under refrigeration at 2° to 8°C. The product should not be stored at room temperature for more than 48 hours.
Keep out of reach and sight of children.

If you want more information about CEREBYX:

- 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 (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website http://www.searchlightpharma.com; or, by calling 1-647-945-9762.

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