CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-450/S-005

FINAL PRINTED LABELING

Cerebyx®
(Fosphenytoin Sodium Injection)

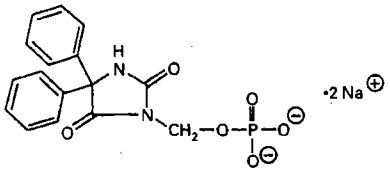
APPROVED

AUG 13 2001

DESCRIPTION

Cerebyx® (fosphenytoin sodium injection) is a prodrug intended for parenteral administration; its active metabolite is phenytoin. Each Cerebyx vial contains 75 mg/mL fosphenytoin sodium (hereafter referred to as fosphenytoin) **equivalent to 50 mg/mL phenytoin sodium** after administration. Cerebyx is supplied in vials as a ready-mixed solution in Water for Injection, USP, and Tromethamine, USP (TRIS), buffer adjusted to pH 8.6 to 9.0 with either Hydrochloric Acid, NF, or Sodium Hydroxide, NF. Cerebyx is a clear, colorless to pale yellow, sterile solution.

The chemical name of fosphenytoin is 5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt. The molecular structure of fosphenytoin is:



The molecular weight of fosphenytoin is 406.24.

IMPORTANT NOTE: Throughout all Cerebyx® product labeling, the amount and concentration of fosphenytoin is expressed in terms of 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).

CLINICAL PHARMACOLOGY

Introduction

Following parenteral administration of Cerebyx, 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 labeling.

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 liters.

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 (eg, 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 (eg, parenteral Dilantin®) is administered at 50 mg/min (see DOSAGE AND ADMINISTRATION, WARNINGS).

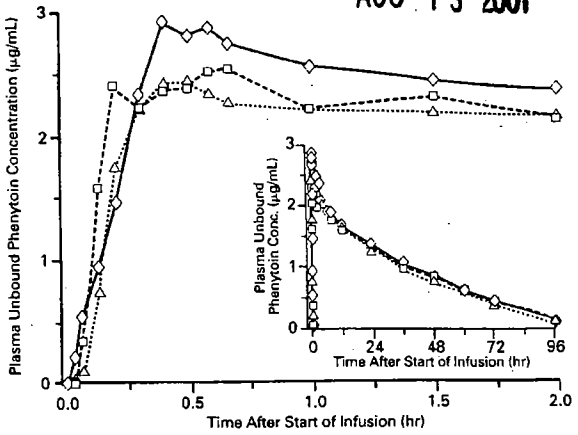


FIGURE 1. Mean plasma unbound phenytoin concentrations following IV administration of 1200 mg PE Cerebyx infused at 100 mg PE/min (triangles) or 150 mg PE/min (squares) and 1200 mg Dilantin infused at 50 mg/min (diamonds) to healthy subjects (N = 12). Inset shows time course for the entire 96-hour sampling 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 is highly bound to plasma proteins, primarily albumin, although to a lesser extent than fosphenytoin. 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).

Metabolism and Elimination: Phenytoin derived from administration of Cerebyx is extensively metabolized in the liver and excreted in urine primarily as 5-(p-hydroxyphenyl)-5-phenylhydantoin and its glucuronide; little unchanged phenytoin (1%-5% of the Cerebyx dose) is recovered in urine. Phenytoin hepatic metabolism is saturable, and following administration of single IV Cerebyx 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 Cerebyx administration at these doses are similar to those after equal doses of parenteral Dilantin and tend to be greater at higher plasma phenytoin concentrations.

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 Cerebyx 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. 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 are highly variable and must be individualized (see DOSAGE AND ADMINISTRATION).

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

Pediatrics: 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.

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 paresthesia 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 vs 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 USAGE

Cerebyx 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 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.

Cerebyx®
(Fosphenytoin Sodium Injection)

CONTRAINDICATIONS

Cerebyx is contraindicated in patients who have demonstrated hypersensitivity to Cerebyx or its ingredients, or to 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.

WARNINGS

DOSES OF CEREBYX ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS IN THIS LABELING (PE=phenytoin sodium equivalent).

DO NOT, THEREFORE, MAKE ANY ADJUSTMENT IN THE RECOMMENDED DOSES WHEN SUBSTITUTING CEREBYX FOR PHENYTOIN SODIUM OR VICE VERSA.

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

Status Epilepticus Dosing Regimen

• 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 parenteral Dilantin or generic 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.

Cardiovascular Depression

Hypotension may occur, especially after IV administration at high doses and high rates of administration. Following administration of phenytoin, severe cardiovascular reactions and fatalities have been reported with atrial and ventricular conduction depression and ventricular fibrillation. Severe complications are most commonly encountered in elderly or gravely ill patients. Therefore, careful cardiac monitoring is needed when administering IV loading doses of Cerebyx. Reduction in rate of administration or discontinuation of dosing may be needed.

Cerebyx should be used with caution in patients with hypotension and severe myocardial insufficiency.

Rash

Cerebyx should be discontinued if a skin rash appears. If the rash is exfoliative, purpuric, or bullous, or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis 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.

Hepatic Injury

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, leukocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, Cerebyx should be immediately discontinued and not readministered.

Hemopoietic System

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

There have been a number of reports 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 other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash, and liver involvement. 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.

Alcohol Use

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

Usage 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.

B. 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 threefold that in the general population. However, the relative contributions 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.

C. 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.

Preclinical: 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/m² 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/m² 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/m² 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/m² basis) to pregnant rabbits.

PRECAUTIONS

General: (Cerebyx specific)

Sensory Disturbances

Severe burning, itching, and/or paresthesia were reported by 7 of 16 normal volunteers administered IV Cerebyx 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.*

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. Additionally, caution should be exercised if using structurally similar (eg, barbiturates, succinimides, oxazolidinediones, and other related compounds) in these same patients.

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

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

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.

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

Phenytoin has the potential to lower serum folate levels.

Laboratory Tests

Phenytoin doses are usually selected to attain therapeutic plasma total phenytoin concentrations of 10 to 20 μg/mL, (unbound phenytoin concentrations of 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 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 pharmacokinetics and protein binding of fosphenytoin, phenytoin, and diazepam were not altered when diazepam and Cerebyx were concurrently administered in single submaximal doses.

The most significant drug interactions following administration of Cerebyx are expected to occur with drugs that interact with phenytoin. Phenytoin is extensively bound to serum 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 that may increase plasma phenytoin concentrations include: acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, cimetidine, diazepam, dicumarol, disulfiram, estrogens, ethosuximide, fluoxetine, H_2-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.
- Drugs that may decrease plasma phenytoin concentrations include: carbamazepine, chronic alcohol abuse, reserpine.
- Drugs that may either increase or decrease plasma phenytoin concentrations include: phenobarbital, valproic acid, and sodium valproate. Similarly, the effects of phenytoin on phenobarbital, valproic acid and sodium plasma valproate concentrations are unpredictable.
- Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and Cerebyx dosage may need to be adjusted.
- Drugs whose efficacy is impaired by phenytoin include: anticoagulants, corticosteroids, coumarin, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, rifampin, quinidine, theophylline, vitamin D.

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 also cause increased serum concentrations of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of fosphenytoin has not been studied. Assessment of the carcinogenic potential of phenytoin in mice and rats is ongoing.

Structural chromosome aberration frequency in cultured V79 Chinese hamster lung cells was increased by exposure to fosphenytoin in the presence of metabolic activation. No evidence of mutagenicity was observed in bacteria (Ames test) or Chinese hamster lung cells *in vitro*, and no evidence for clastogenic activity was observed in an *in vivo* mouse bone marrow micronucleus test.

No effects on fertility were noted in rats of either sex given fosphenytoin. Maternal toxicity and altered estrous cycles, delayed mating, prolonged gestation length, and developmental toxicity were observed following administration of fosphenytoin during mating, gestation, and lactation at doses of 50 mg PE/kg or higher (approximately 40% of the maximum human loading dose or higher on a mg/m² basis).

Pregnancy - Category D: (see WARNINGS)

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.

Pediatric Use

The safety of Cerebyx in pediatric patients has not been established.

Geriatric Use

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

ADVERSE REACTIONS

The more important adverse clinical events caused by the IV use of Cerebyx 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, paresthesia, headache, somnolence, and ataxia. With two exceptions, these events are commonly associated with the administration of IV phenytoin. Paresthesia 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 ≥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 paresthesia 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.

Cerebyx®
(Fosphenytoin Sodium Injection)

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
Paresthesia	4.4	0.0
Extrapyramidal Syndrome	4.4	0.0
Tremor	3.3	9.1
Agitation	3.3	0.0
Hypesthesia	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
Paresthesia	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, leukocytosis, cyanosis, hypochromic anemia, leukopenia, lymphadenopathy, petechia.

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

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 discoloration, 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.

OVERDOSAGE

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

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/m² basis. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, and hypoactivity.

Because Cerebyx 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 20 μg/mL, ataxia at 30 μg/mL, and dysarthria and lethargy appear when the plasma concentration is over 40 μg/mL. However, phenytoin concentrations as high as 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 100 μg/mL, with complete recovery.

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 paresthesia, 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 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). Cerebyx has important differences in administration from those for parenteral phenytoin sodium (see below).

Products with particulate matter or discoloration should not be used. 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.

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.

Nonemergent 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.

IM or IV Substitution For Oral Phenytoin Therapy

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.

HOW SUPPLIED

Cerebyx®
(Fosphenytoin Sodium Injection)

2 mL per vial — Each vial contains fosphenytoin sodium 150 mg equivalent to 100 mg of phenytoin sodium:

N 0071-4007-05. Packages of 25.

Both sizes of vials contain Tromethamine, USP (TRIS), Hydrochloric Acid, NF, or Sodium Hydroxide, NF, and Water for Injection, USP.

Cerebyx should always be prescribed in phenytoin sodium equivalent units (PE) (see DOSAGE AND ADMINISTRATION).

Storage

Store under refrigeration at 2°C to 8°C (36°F to 46°F). The product should not be stored at room temperature for more than 48 hours. Vials that develop particulate matter should not be used.

℞ only

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