Cerebyx®
(Fosphenytoin Sodium Injection)

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 for injection in water for injection, USP, and tromethamine, USP (TRIS), buffered to pH 6.8 to 9.0 with either hydrochloric acid, NF, or sodium hydroxide, NF. Cerebyx is a clear, colorless to pale yellow, sterile solution, considerably in excess of that obtened 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.

CLINICAL PHARMACOLOGY
Introduction
Following parenteral administration of Cerebyx, fosphenytoin is converted to the anticonvulsant phenytoin. For every mole of fosphenytoin administered, one mole of phenytoin is produced. The pharmacologic and toxicologic effects of fosphenytoin include those of phenytoin.

Distribution
Fosphenytoin is rapidly distributed throughout the body. The volume of distribution of fosphenytoin is similar to that of phenytoin, and the protein binding is comparable. The mean apparent volume of distribution is approximately 23 L/kg in patients with normal renal function and 13 L/kg in patients with severe renal impairment.

Pharmacokinetics and Drug Metabolism
Fosphenytoin
Absorption
Fosphenytoin is administered IV as a 4% solution in water for injection or 50% in a 4% solution of tromethamine. It is rapidly absorbed following IV administration. The mean peak plasma fosphenytoin concentrations occur at approximately 30 minutes postdose. Plasma fosphenytoin concentrations are rapidly cleared from the plasma following IV administration.

DISTRIBUTION:
Fosphenytoin is extensively distributed (85% to 99%) to human plasma proteins. Protein binding is not altered by concomitant drug therapy. The apparent volume of distribution of fosphenytoin is similar to that of phenytoin, and the protein binding is comparable. There is a total body clearance of approximately 0.9 L/hr/kg following IV administration.

Metabolism
Fosphenytoin is biologically inactive and is not metabolized by the hepatic microsomal enzymes. The metabolites of fosphenytoin are excreted in the urine and feces. Approximately 25% of the dose is excreted in the urine as unchanged fosphenytoin and approximately 75% is excreted as metabolites.

Elimination
Fosphenytoin is eliminated primarily by renal excretion. The mean apparent terminal elimination half-life of fosphenytoin is approximately 20 hours. The renal clearance of fosphenytoin is similar in patients with normal renal function and in patients with severe renal impairment.

Phenyltoin
Absorption
Phenyltoin is administered as an IV solution in water for injection or 50% in a 4% solution of tromethamine. It is rapidly absorbed following IV administration. The mean peak plasma phenytoin concentrations occur at approximately 30 minutes postdose. Plasma phenytoin concentrations are rapidly cleared from the plasma following IV administration.

DISTRIBUTION:
Phenytoin is extensively distributed (85% to 99%) to human plasma proteins. Protein binding is not altered by concomitant drug therapy. The apparent volume of distribution of phenytoin is similar to that of fosphenytoin, and the protein binding is comparable. There is a total body clearance of approximately 0.9 L/hr/kg following IV administration.

Metabolism
Phenytoin is extensively metabolized by the hepatic microsomal enzymes. The metabolites of phenytoin are excreted in the urine and feces. Approximately 25% of the dose is excreted in the urine as unchanged phenytoin and approximately 75% is excreted as metabolites.

Elimination
Phenytoin is eliminated primarily by renal excretion. The mean apparent terminal elimination half-life of phenytoin is approximately 30 hours. The renal clearance of phenytoin is similar in patients with normal renal function and in patients with severe renal impairment.

Indications
Cerebyx is indicated for the treatment of seizures in adults and children as adjunctive therapy for partial seizures, for primary generalized tonic-clonic seizures, and for myoclonic seizures associated with West syndrome. Cerebyx is also indicated for the treatment of generalized tonic-clonic seizures in patients with epilepsy.

Cerebyx is indicated for the treatment of seizures in adults and children as adjunctive therapy for partial seizures, for primary generalized tonic-clonic seizures, and for myoclonic seizures associated with West syndrome.

CONTRAINDICATIONS
Cerebyx is contraindicated in patients with a history of hypersensitivity to fosphenytoin or any other component of the product. Cerebyx is also contraindicated in patients who have shown a significant allergenic reaction to valproic acid.

WARNING
Cerebyx should be administered slowly over a period of at least 15 minutes. Faster intravenous injection may result in toxicity, including hypotension, bradycardia, and cardiac arrest. Cerebyx should be administered slowly over a period of at least 15 minutes. Faster intravenous injection may result in toxicity, including hypotension, bradycardia, and cardiac arrest.

ADVERSE REACTIONS
Cerebyx is generally well tolerated. The most common adverse reactions associated with Cerebyx use are injection site reactions, including pain, burning, and stinging.

SERIOUS ADVERSE REACTIONS:
Cerebyx has been associated with several serious adverse reactions, including seizures, status epilepticus, hypersensitivity reactions, and anaphylaxis. These reactions are typically managed with supportive care and discontinuation of Cerebyx.

PRECAUTIONS
Cerebyx is not recommended for patients with a history of hypersensitivity to fosphenytoin or any other component of the product. Cerebyx is also not recommended for patients who have shown a significant allergenic reaction to valproic acid.

PREGNANCY
Cerebyx is classified as category B by the US Food and Drug Administration (FDA). However, there is no information available on the use of Cerebyx during pregnancy. The safety and effectiveness of Cerebyx in pregnancy have not been established. It is not known whether Cerebyx crosses the placenta.

Nursing Mothers
It is not known whether fosphenytoin or phenytoin is excreted in human milk. The decision to discontinue breastfeeding when a woman is administered Cerebyx should be made based on the importance of the drug to the mother and the potential for harmful effects to the infant.

Pediatric Use
The safety and effectiveness of Cerebyx in children have not been established. Cerebyx is indicated for the treatment of seizures in children as adjunctive therapy for partial seizures, for primary generalized tonic-clonic seizures, and for myoclonic seizures associated with West syndrome.

UTERINE CONTRACTIONS
Cerebyx has been associated with uterine contractions in pregnant women. These contractions are typically managed with supportive care and discontinuation of Cerebyx.

OVERDOSAGE
Cerebyx overdosage is generally managed by supportive care. Cerebyx is not recommended for patients with a history of hypersensitivity to fosphenytoin or any other component of the product. Cerebyx is also not recommended for patients who have shown a significant allergenic reaction to valproic acid.

REFERENCES
For complete prescribing information, including CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS, please see the full prescribing information for fosphenytoin sodium injection.

FIGURE 1: Mean plasma unbound phenytoin concentrations following IV administration of 1200 mg PE Carbyx infused at 100 mg PE/min (squares) and 1200 mg Diamox injected at 50 mg/min (diamonds) for 60 minutes (N = 12). Each symbol represents mean concentration for subjects (N = 12). Each symbol represents mean concentration for subjects (N = 12).

TABLE 1: IX Tolerance of Equivalent Loading Doses of IV Cerebyx and IV Phenytoin

<table>
<thead>
<tr>
<th>IV Cerebyx</th>
<th>IV Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 80</td>
<td>N = 22</td>
</tr>
<tr>
<td>Local Intolerance</td>
<td></td>
</tr>
<tr>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Intursion Disrupted</td>
<td></td>
</tr>
<tr>
<td>21%</td>
<td>67%</td>
</tr>
<tr>
<td>Average Intusion Time</td>
<td></td>
</tr>
<tr>
<td>13 min</td>
<td>41 min</td>
</tr>
</tbody>
</table>

*Percent of patients.

Cerebyx-treated patients, however, experienced more systemic sensory disturbances (see PRECAUTIONS, Sensory Disturbances). Cerebyx-treated patients were primarily due to systemic burning, pruritus, and motor and sensory paralysia while those in phenytoin-treated patients were primarily due to pain and burning at the injection 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 placebo-treated patients at 1 hour during the study). The study demonstrated that equivalent 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. Cerebyx can be used for the control of generalized convulsive status epilepticus and the treatment of seizures occurring during neurosurgery. Cerebyx can also be substituted, short-term, for oral phenytoin.
basal), 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 these developmental effects were secondary to the maternal effects. The single occurrence of a rare maternal brain malformation and a sporadic dose of 17 mg PE/kg (approximately 10% of the maximum human loading dose on a mg/m² basis) was considered drug-induced. The maternal toxicity data are similar to those which have been reported following administration of phenytoin to pregnant rats.

Neonates on antenatal/neonatal development were observed when rabbits were given up to 33 mg PE/kg of phenytoin (approximately 50% of the maximum human loading dose) and monitored until conception during pregnancy. Increased resorption and malformation rates have been reported following administration of phenytoin doses of 75 mg/m² on a mg/m² basis (approximately 100% of the maximum human loading dose or higher on a mg/mg basis) to pregnant rats.

PRECAUTIONS

General: (General specific)

Sexual Disturbances

Severe burning, itching, and/or parasthesia were reported by 7 of 16 normal volunteers administered IV Cerebyx at a dose of 1000 mg PE at the maximum rate of administration (150 mg PE/min). The severe sensory disturbance lasted from 3 to 5 minutes in 5 of 6 cases 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 18 normal volunteers (taken from other studies) who were administered IV Cerebyx at a dose of 7200 mg PE at the maximum rate of administration (150 mg PE/min), none experienced severe disturbances, but most experienced mild to moderate itching or burning.

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 pharmacologic phenomena such as increased blood phosphatase loads, have been associated with burning, itching, and/or tingling predominantly in the groin area.

Phosphate Load

The phosphate load provided by Cerebyx (0.037 mol of phosphate/PE Cerebyx) should be considered when treating patients who require phosphate restriction, such as those with severe renal impairment.

IV Cerebyx in Renal and/or Hepatic Disease or in Those With Hypophosphatemia

After IV administration to patients with renal and/or hepatic disease, or in those with hypophosphatemia, fosphenytoin clearance to phenytoin may be decreased 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, which is due to limited enzyme activity and lack of induction, is not applicable to the phenomenon.

Phenytin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally caution should be exercised in those with a family history of urticaria or anaphylaxis to these drugs.

Hypophosphatemia

Hypophosphatemia, especially after prolonged use of IV fosphenytoin or IV Cerebyx, has been reported in patients with hypophosphatemia. IV Cerebyx has been shown to increase the frequency of adverse events (see CLINICAL PHARMACOLOGY: Special Populations, and DOSAGE AND ADMINISTRATION: Dosing in Special Populations).

Drug Interactions

No drugs are known to interfere with the conversion of fosphenytoin to phenytoin. Conversion could be affected by alterations in the liver or by the presence of hepatic disease, as well as by the presence of certain substances, such as alcohol, theophylline, or other anticonvulsants. Induction of hepatic enzyme activity may affect the rate of conversion to phenytoin. Phenytoin may interact with a variety of other drugs that may affect the liver, such as alcohol. Such drugs may lower the half-life of phenytoin and increase the risk of toxicity.

Phenytoin has the potential to lower serum folate levels.:

Laboratory Tests

Phenytoin doses are usually selected to attain therapeutic plasma total phenytoin concentrations of 10-20 µg/mL (unbound phenytoin concentrations of 1-2 µg/L). Following Cerebyx administration, it is recommended that phenytoin concentrations be monitored to ensure that 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, conversion can only be monitored by means of plasma total phenytoin concentrations. If the plasma total phenytoin concentration is elevated, repeat blood samples for plasma total phenytoin concentrations should be obtained until the plasma total phenytoin concentration is within the desired range. If the plasma total phenytoin concentration is elevated, repeat blood samples should be obtained until the plasma total phenytoin concentration is within the desired range.

Drug interactions

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Phenytoin has the potential to lower serum folate levels.
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The most commonly occurring drug interactions are listed below:

- Drugs that may increase plasma phenytoin concentrations include: acute alcohol intake, amigdala, ethosuximide, fluoxetine, H2-antagonists, nortriptyline, propranolol, ranitidine, sedatives, sympathomimetics, theophylline, vibaseptic.
- Drugs that may decrease plasma phenytoin concentrations include: carbamazepine, chronic alcohol abuse, desipramine.
- 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 valproate concentrations are unpredictable.
- Although no true drug-drug interaction is known, some anticonvulsants may precipitate seizures in susceptible patients and Cerebyx® dosage may need to be titrated.
- Drugs whose efficacy is impaired by phenytoin include: aripiprazole, citalopram, citalopram, diltiazem, diazepam, diazepam, disulfiram, fluoxetine, fluoxetine, haloperidol, haloperidol, imipramine, imipramine, isoniazid, isoniazid, lorazepam, lorazepam, metoclopramide, metoclopramide, mirtazapine, mirtazapine, nortriptyline, nortriptyline, paroxetine, paroxetine, phenobarbital, phenobarbital, phenelzine, phenelzine, phenytoin, phenytoin, quetiapine, quetiapine, raloxifene, raloxifene, riluzole, riluzole, sulfisoxazole, sulfisoxazole, valproic acid, valproic acid, valproate, valproate, valproate, valproate, valproate.

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 T4. It may also produce unfailingly low results in denervation and adrenocortical dominance (ADT). Care should be taken when using immunocytoclastic methods to measure plasma phenytoin concentrations following Cerebyx® laboratory tests.

Cardiogenesis, Metagenesis, Impairment of Fertility

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

Systemic chromosomal abnormalities 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 bacterial assays (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 (doses of 50 mg PE/kg or higher [approximately 40% of the maximum human body dose or 0.5X of the maximum therapeutic dose]) were noted in two studies in pregnant rats. 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, breastfeeding 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 or exacerbate for Cerebyx; it should not exceed 100 mg PE/kg.

The adverse clinical events most commonly observed with the use of Cerebyx in clinical trials were: rash, pruritus, dermatitis, ecchymosis, hypotension, headache, somnolence, and ataxia. With two Patients the rash, pruritus, dermatitis, and ecchymosis have been described as rashes. These events were dose and rate related; most patients (41 of 64, 64%) admitted doses were generally described as itching, burning, or pruritic. Rash, pruritus, and ecchymosis were usually not at the infusate site. The rash, pruritus, and ecchymoses 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. This event did not occur in severity with allergic reactions were not seen (see PRECAUTIONS, Sensory Disturbances).

Approximately 2% of the 685 individuals who received Cerebyx in premarketing clinical trials did not experience treatment because of an adverse event. The adverse events most commonly associated with withdrawal were pruritus (0.2%), hypotension (0.3%), and cardiodepression (0.2%).

Dose and Rate Dependency of Adverse Events Following IV Cerebyx: The incidence of adverse events PE/kg and rates 250 mg PE/kg transient pruritus, rash, nausea, somnolence, and ataxia occurred 2 to 3 times more often at lower doses than 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 standard categories modified COSTART dictionary terminology. These categories are used in the tables and listings below with the following representations of the proportion of individuals exposed to Cerebyx or placebo. The data for Cerebyx are presented in the tables and listings below with the following representations of the proportion of patients exposed to Cerebyx or placebo.

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 cannot be directly compared with figures obtained from clinical trials. The following tables list adverse events which were reported more frequently in other clinical investigations involving Cerebyx. An inspection of these frequencies, however, does provide the prescriber with an overall impression of the relative contribution of drug and non-drug factors to the adverse event incidence 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 Cerebyx and placebo. The table includes events occurring 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.

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TABLE 2. Treatment-Emergent Adverse Event Incidence Following IV Administration of Cerebyx at the Maximum Dose and Rate to Patients With Epilepsy or Neurosurgical Patients (Events in at Least 2% of Cerebyx-Treated Patients)

<table>
<thead>
<tr>
<th>Event</th>
<th>Cerebyx</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>4.4%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4.4%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4.4%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3.3%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>2.2%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

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 administered for oral Dilantin or for 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)

<table>
<thead>
<tr>
<th>Event</th>
<th>IM Cerebyx</th>
<th>Oral Dilantin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>6.5%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4.5%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

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 administered for oral Dilantin or for oral Dilantin. Both treatments were administered for 5 days.

Adverse Events During All Clinical Trials

Cerebyx has been administered to 850 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 listed more frequently using the following definitions: frequent adverse events are defined as at least 1/1000 individuals, infrequent adverse events are those occurring at greater than 1/1000 individuals, adverse events are those occurring at any frequency. The following table lists adverse events and rates of occurrence in defined groups of patients.

Body as a Whole: The most common adverse events reported in subjects treated with Cerebyx were gastrointestinal disturbances, injection-site reactions, nausea, vomiting, and diarrhea. The incidence of these events was not significantly different from placebo. The incidence of these events was not significantly different from placebo.

Infectious: The incidence of infection did not differ significantly between groups treated with Cerebyx and placebo. The incidence of infection did not differ significantly between groups treated with Cerebyx and placebo.

Hematologic and Lymphatic: The incidence of leukocytosis and neutrophilia did not differ significantly between groups treated with Cerebyx and placebo. The incidence of leukocytosis and neutrophilia did not differ significantly between groups treated with Cerebyx and placebo.

Cardiovascular: The incidence of hypotension did not differ significantly between groups treated with Cerebyx and placebo. The incidence of hypotension did not differ significantly between groups treated with Cerebyx and placebo.

Gastrointestinal: The incidence of nausea and vomiting did not differ significantly between groups treated with Cerebyx and placebo. The incidence of nausea and vomiting did not differ significantly between groups treated with Cerebyx and placebo.

Skin and Appendages: The incidence of pruritus did not differ significantly between groups treated with Cerebyx and placebo. The incidence of pruritus did not differ significantly between groups treated with Cerebyx and placebo.

Endocrine: The incidence of diabetes mellitus did not differ significantly between groups treated with Cerebyx and placebo. The incidence of diabetes mellitus did not differ significantly between groups treated with Cerebyx and placebo.

Metabolic and Nutritional: The incidence of hyperglycemia did not differ significantly between groups treated with Cerebyx and placebo. The incidence of hyperglycemia did not differ significantly between groups treated with Cerebyx and placebo.

Hemato logical and Lymphatic: The incidence of leukocytosis and neutrophilia did not differ significantly between groups treated with Cerebyx and placebo. The incidence of leukocytosis and neutrophilia did not differ significantly between groups treated with Cerebyx and placebo.

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personality disorder, acute brain syndrome, encephalitis, subdural hematoma, mephalopothy, hostility, akathisia, anemia, neuropathy.

Respiratory: frequent pneumonia, hypotension, syncope, hypothalamic, rhinitis, sway, aspiration pneumonia, asthma, dyspnea, edema, cough increased, spasm increased, epigastric, pneumonia, hematemesis, bronchitis.

Skin: Acne, frequent rash, maculopapular rash, urticaria, sweating, pain, disorientation, rash, psoriasis, skin nodules.

Special Senses: frequent taste perversion, frequent deafness, visual field defect, eye pain, conduction deafness, photophobia, hyperesthesia, myalgia, paraesthesia, ear pain, taste loss.

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

OVERDOSE

Nausea, vomiting, lethargy, tachycardia, Bradycardia, laryngitis, cardiac arrest, hypotension, syncope, hypocalcemia, metabolic acidosis, and death have been reported in cases of overdose 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 9.8 and 2 times, respectively, the maximum human loading dose on a mg/kg basis. Signs of acute toxicity in animals included ataxia, labored breathing, piloerection, and hypothermia. Because Cerebyx is a prodrug of phenytoin, the following information may be helpful. In lethal symptoms of acute phenytoin toxicity are myoclonus, 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 and dysarthria usually appear at 20 μg/mL, ataxia at 30 μg/mL, and dysarthria and lethargy appear at the plasma concentrations 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 antitoxin to Cerebyx or phenytoin overdose. 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 overdose the possibility of other CNS depressants including alcohol, should be borne in mind. Fomepizole and sodium are metabolites of fosphenytoin and therefore may contribute to signs of toxicity following overdose. Signs of fomepizole toxicity are similar to those of methanol toxicity and are associated with severe liver function and renal dysfunction. Large amounts of sodium, delivered rapidly, could potentially cause hypocalcemia with pseudohypoparathyroidism, muscle spasm, and convulsions. Corrected 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 0.9% 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.

The loading dose of Cerebyx is 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 to 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.

DOSING IN SEVERAL PEDIATRIC PATIENTS WITH RENAL OR HEPATIC DISEASES

Patients with Renal or Hepatic Disease

DOSING IN SEVERAL PEDIATRIC PATIENTS WITH RENAL OR HEPATIC DISEASES

Women: Cerebyx should be administered as a single daily dose lasting 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 hypocalcemia, the interpretation of total phenytoin plasma concentrations should be made with caution (see CLINICAL PHARMACOLOGY: Special Populations, Special Populations). Unbound phenytoin concentrations may be more useful in these populations. After IV Cerebyx administration to patients with renal and/or hepatic disease, or in those with hypocalcemia, 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

2 mL per vial — Each vial contains fosphenytoin sodium 150 mg equivalent to 100 mg of phenytoin sodium: N-0011-4601-05. Packages of 25. Both sets of vials contain Thrombocrit, 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.


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