FOSPHENYTOIN SODIUM INJECTION, USP
100 mg PE/2 mL
(50 mg PE/mL)

(PE = phenytoin sodium equivalents)

For IM or IV use RX only
2 mL Single Use Vials

Sterile.

Each vial contains fosphenytoin sodium 150 mg equivalent to 100 mg phenytoin sodium, tromethamine (TRIS) as a buffer, hydrochloric acid or sodium hydroxide to adjust the pH to 8.6 to 9, and sufficient water for injection.

Usual Dosage: See insert.

Note: Administration differs from parenteral phenytoin. See Dosage and Administration.

Vial stoppers do not contain natural rubber latex.

Store under refrigeration at 2°C to 8°C (36°F to 46°F).
FOSPHENYTOIN SODIUM

INJECTION, USP

100 mg PE/2 mL

(50 mg PE/mL)

(PE=Phenytoin sodium equivalents).

For IM or IV use

Usual Dosage: See Insert.

2 mL Single Use Vial

Abraxis
Pharmaceutical Products
Schaumburg, IL 60173

402314

LOT/EXP
FOSPHENYTOIN SODIUM

INJECTION, USP

500 mg PE/10 mL
(50 mg PE/mL)
(PE = phenytoin sodium equivalents)

For IM or IV Use
10 mL Single Use Vial
10 VIALS Rx only

Each vial contains fosphenytoin sodium 750 mg equivalent to 500 mg phenytoin sodium, tromethamine (TRIS) as a buffer, hydrochloric acid, or sodium hydroxide to adjust the pH to 8.6 to 9, and sufficient water for injection.

Usual Dosage: See insert.

Note—Administration differs from parenteral phenytoin. See Dosage and Administration.

Each vial contains fosphenytoin sodium 750 mg equivalent to 500 mg phenytoin sodium, tromethamine (TRIS) as a buffer, hydrochloric acid, or sodium hydroxide to adjust the pH to 8.6 to 9, and sufficient water for injection.

Usual Dosage: See insert.

Note—Administration differs from parenteral phenytoin. See Dosage and Administration.

Store under refrigeration at 2°C to 8°C (36°F to 46°F).

DOSSES OF FOSPHENYTOIN SODIUM INJECTION ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS (PE = phenytoin sodium equivalents) Vial stoppers do not contain natural rubber latex.
Sterile.

Each vial contains fosphenytoin sodium 750 mg equivalent to 500 mg phenytoin sodium.

Usual Dosage: See insert.

Note- Administration differs from parenteral phenytoin. See Dosage and Administration.

Store under refrigeration at 2°C to 8°C (36°F to 46°F).

Vial stoppers do not contain natural rubber latex.

Abraxis Pharmaceutical Products
Schaumburg, IL 60173

402315

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

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

M.W. 406.24.

IMPORTANT NOTE: Throughout all fosphenytoin sodium injection 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. Fosphenytoin sodium injection should always be prescribed and dispensed in phenytoin sodium equivalent units (PE) (see DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY: Introduction

Following parenteral administration of 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 in turn is 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 fosphenytoin sodium injection 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 ionic 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 fosphenytoin sodium 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 fosphenytoin sodium. Peak concentrations occur at approximately 30 minutes post dose. 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 fosphenytoin sodium 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, phosphates, and formaldehyde (formate).

Absorption/Bioavailability:

Intravenous: When fosphenytoin sodium is administered by IV infusion, maximum plasma 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.

Distribution:

Phenytoin is highly bound to plasma proteins, primarily albumin, although to a lesser extent than fosphenytoin. In the absence of phenytoin, approximately 15% 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) for the period required for conversion of fosphenytoin to phenytoin, and leads to increased clearance of phenytoin.

During IV administration of single IV fosphenytoin sodium doses of 400 to 1200 mg PE, mean 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.

Pharmacokinetics and Drug Metabolism

Phenytoin

Absorption/Bioavailability: Intravenous: When fosphenytoin sodium 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 fosphenytoin sodium. Peak concentrations occur at approximately 30 minutes post dose. 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 fosphenytoin sodium 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, phosphates, and formaldehyde (formate).

Absorption/Bioavailability:

Intravenous: When fosphenytoin sodium is administered by IV infusion, maximum plasma 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.

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Pharmacokinetics and Drug Metabolism

Phenytoin

Absorption/Bioavailability: Intravenous: When fosphenytoin sodium 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 fosphenytoin sodium. Peak concentrations occur at approximately 30 minutes post dose. 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 fosphenytoin sodium 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, phosphates, and formaldehyde (formate).
Age: The effect of age was evaluated in patients 5 to 98 years of age. Patient age had no significant impact on serum pharmacokinetics. Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age compared to those 20 to 30 years of age). Phenytoin dosing requirements are highly variable and should be individually titrated (see DOSAGE AND ADMINISTRATION).

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

Pediatrics: Only limited pharmacokinetic data are available in children (N = 8; age 5 to 10 years). In these patients, therapeutic equivalence was demonstrated with IV fosphenytoin for a single loading dose equivalent to the control of generalized convulsive status epilepticus. The study demonstrated better local tolerance (pain and burning at the infusion site). In older children, fosphenytoin concentration-time profiles did not signal any major differences from those in adult patients with similar weight receiving comparable doses.

Clinical Studies
Infusion tolerance was evaluated in clinical studies. Tolerance is similar in patients treated with IV and IV-converted, short-term, for oral phenytoin. The study period for fosphenytoin sodium-treated patients was approximately 10% of the maximum human loading dose (see DOSAGE AND ADMINISTRATION).

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

<table>
<thead>
<tr>
<th>IV Fosphenytoin Sodium</th>
<th>IV Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading Dose (mg)</td>
<td>Loading Dose (mg)</td>
</tr>
<tr>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Average Infusion Time</td>
<td>Average Infusion Time</td>
</tr>
<tr>
<td>13 min</td>
<td>44 min</td>
</tr>
</tbody>
</table>

The single occurrence of a rare brain malformation at a nonmaternal dose of 17 mg PE/kg (approximate 10% of the maximum human loading dose on a mg/m² basis) was also considered drug-induced. The developmental effects of fosphenytoin sodium were observed following administration of phenytoin to pregnant rats. Maternal toxicity was often associated with these drug and plasma concentration. However, there is no evidence to suggest that the developmental effects were reflected in the maternal effects. The single occurrence of a rare brain malformation at a nonmaternal dose of 17 mg PE/kg (approximate 10% of the maximum human loading dose on a mg/m² basis) was also considered drug-induced. The developmental effects of fosphenytoin sodium were observed following administration of phenytoin to pregnant rats. Maternal toxicity was often associated with these drug and plasma concentration. However, there is no evidence to suggest that the developmental effects were reflected in the maternal effects. The single occurrence of a rare brain malformation at a nonmaternal dose of 17 mg PE/kg (approximate 10% of the maximum human loading dose on a mg/m² basis) was also considered drug-induced. The developmental effects of fosphenytoin sodium were observed following administration of phenytoin to pregnant rats. Maternal toxicity was often associated with these drug and plasma concentration. However, there is no evidence to suggest that the developmental effects were reflected in the maternal effects. The single occurrence of a rare brain malformation at a nonmaternal dose of 17 mg PE/kg (approximate 10% of the maximum human loading dose on a mg/m² basis) was also considered drug-induced. The developmental effects of fosphenytoin sodium were observed following administration of phenytoin to pregnant rats. Maternal toxicity was often associated with these drug and plasma concentration. However, there is no evidence to suggest that the developmental effects were reflected in the maternal effects. The single occurrence of a rare brain malformation at a nonmaternal dose of 17 mg PE/kg (approximate 10% of the maximum human loading dose on a mg/m² basis) was also considered drug-induced. The developmental effects of fosphenytoin sodium were observed following administration of phenytoin to pregnant rats. Maternal toxicity was often associated with these drug and plasma concentration. However, there is no evidence to suggest that the developmental effects were reflected in the maternal effects.
Phenobarbital and other inducers of hepatic drug-metabolizing enzymes. Caution should be exercised when fosphenytoin sodium injection is used in patients with this disease. Hypoglycemia, resulting from phenytoin’s inhibitory effect on insulin release, has been reported. Although commonly used, the serum glucose concentrations in diabetic patients. Plasma concentrations of fosphenytoin sustained for the optimal range may produce confusional states referred to as “delirium,” “psychosis,” or “undifferentiated behavior.” Caution should be exercised when using structurally similar (e.g., barbiturate, carbamazepine, oxazepam) and related compounds in these same patients.

Phenyltoin has been infrequently associated with the exacerbation of porphyria. Caution should be exercised when fosphenytoin sodium injection is used in patients with this disease.

Fosphenytoin should not be used in patients with known or suspected allergies to fosphenytoin or phenyltoin. Fosphenytoin should be used with caution in patients with a history of infections, particularly infections of the respiratory tract.

Fosphenytoin may be used in patients with impaired renal function, including patients with end-stage renal disease on hemodialysis or peritoneal dialysis and patients undergoing continuous ambulatory peritoneal dialysis (CAPD).

Fosphenytoin has been studied in patients with hepatic disease, including patients with severe cirrhosis. Fosphenytoin may be used in patients with hepatic disease, including patients with severe cirrhosis. Fosphenytoin may be used in patients with cirrhosis who are taking medications that may decrease the metabolic clearance rate of fosphenytoin.

Fosphenytoin has been studied in patients with renal or hepatic disease, but the results of these studies have not been confirmed in patients with hepatic or renal disease.

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**TABLE 2. Adverse Drug Reaction**

**Incidence Following IV Administration at the Maximum Dose and Rate to Patients with Epilepsy or Neurosurgical Procedures (at Least 90% of Phenytoin Sodium Injection Patients)**

<table>
<thead>
<tr>
<th>Body System</th>
<th>N=90</th>
<th>N=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>Taste</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>Incoordination</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Tremor</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Erythema</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Urtication</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

**Incidence in Controlled Trials - IM Administration to 859 Individuals**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N=90</th>
<th>N=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>22</td>
<td>8</td>
</tr>
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</tr>
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<td>1</td>
</tr>
<tr>
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<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Erythema</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Urtication</td>
<td>10</td>
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</tr>
<tr>
<td>Hypersensitivity</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

**INFORMATION FOR THE PATIENT**

- **Frequent**: Headache, dizziness, taste perversion.
- **Infrequent**: Pruritus.

**Pharmacologic Properties**

- **Pharmacokinetics**: Phenytoin is rapidly absorbed after oral administration. Peak plasma concentrations are achieved within 1 to 3 hours. The extent of absorption is reduced by food intake and by simultaneous administration of other drugs. Phenytoin is extensively metabolized in the liver and the plasma half-life is dose-dependent. The plasma elimination half-life is approximately 20 hours in adults and 4 hours in children. Phenytoin is excreted in the urine as the active metabolites, phenobarbital, and phenylglycinic acid. Approximately 60% of an oral dose is recovered in the urine in 24 hours. Phenytoin and its metabolites are also excreted in the bile.

**Dosage and Administration**

- **Initial Intravenous Dose**: The initial intravenous dose is 15 to 20 mg PE/kg given IV or IM. The rate of injection should be no faster than 100 mg PE/min. If administration of fosphenytoin sodium injection is substituted for oral phenytoin therapy, the initial daily dose of fosphenytoin sodium injection should be no greater than 150 mg PE/min.

**Special Considerations**

- **Elderly Patients**: Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required.

**Precautions**

- **Contraindications**: Phenytoin sodium is contraindicated in patients with a known history of phenytoin allergy. Phenytoin sodium is also contraindicated in patients with a history of aminopenicillin, cephalosporin, or nonpenicillin beta-lactam allergy.

**Adverse Reactions**

- **Frequent**: Headache, dizziness, taste perversion.
- **Infrequent**: Pruritus.

**Pharmacology**

- **Pharmacokinetics**: Phenytoin is extensively metabolized in the liver and the plasma half-life is dose-dependent. The plasma elimination half-life is approximately 20 hours in adults and 4 hours in children. Phenytoin is excreted in the urine as the active metabolites, phenobarbital, and phenylglycinic acid. Approximately 60% of an oral dose is recovered in the urine in 24 hours. Phenytoin and its metabolites are also excreted in the bile.

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