FOSPHENYTOIN SODIUM

AURANTIN

75 mg/mL Solution for Injection (IM/IV)

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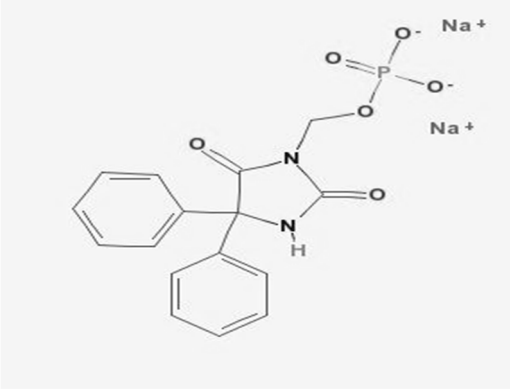
1.0 PHARMACOLOGIC CATEGORY

Antiepileptic (Hydantoin Derivative)

2.0 DESCRIPTION

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



3.0 FORMULATION/ COMPOSITION

Solution for parenteral administration only.
Each fosphenytoin sodium (Aurantin) vial contains 75 mg/mL fosphenytoin sodium (Aurantin) (hereafter referred to as fosphenytoin) equivalent to 50 mg/mL phenytoin sodium after administration.

IMPORTANT NOTE: Throughout all fosphenytoin sodium (Aurantin) product labeling, the amount and concentration of fosphenytoin is expressed in terms of phenytoin sodium equivalents (PE). The weight of fosphenytoin 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 should always be prescribed and dispensed in phenytoin sodium equivalent units (PE). (see **Section 4.2 Dosage and Method of Administration**).

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Fosphenytoin sodium (Aurantin) 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 fosphenytoin sodium (Aurantin) in this use have not been systematically evaluated for more than 5 days.

Fosphenytoin sodium (Aurantin) can be used for the control of generalized convulsive status epilepticus and prevention and treatment of seizures occurring during neurosurgery. Parenterally administered fosphenytoin sodium (Aurantin) can be substituted, short-term, for oral phenytoin.

4.2 Dosage and Method of Administration

The dose, concentration in dosing solutions, and infusion rate of intravenous (IV) fosphenytoin sodium (Aurantin) 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. Fosphenytoin should always be prescribed and dispensed in phenytoin sodium equivalent units (PE). Fosphenytoin sodium (Aurantin) has important differences in administration from those for parenteral phenytoin sodium (see **Section 6.5 Special Precautions for Disposal and Other Handling**).

Adult Dosing

Status Epilepticus

- The loading dose of fosphenytoin sodium (Aurantin) is 15 to 20 mg PE/kg administered at 100 to 150 mg PE/min.

- The rate of intravenous fosphenytoin sodium (Aurantin) administration should not exceed 150 mg phenytoin sodium equivalents (PE) per minute because of the risk of severe hypotension. 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 fosphenytoin sodium (Aurantin) infusions.

- Because the full antiepileptic effect of phenytoin, whether given as fosphenytoin 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 either parenteral fosphenytoin or oral/parenteral phenytoin.

Intramuscular (IM) fosphenytoin sodium (Aurantin) 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 fosphenytoin sodium (Aurantin) have been given by the IM route for other indications.

The typical fosphenytoin sodium (Aurantin) 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 phenytoin 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 IV administration of phenytoin at rates greater than 50 mg/min.

If rapid phenytoin loading is a primary goal, IV administration of fosphenytoin sodium (Aurantin) is preferred because the time to achieve therapeutic plasma phenytoin concentrations is greater following IM administration than that following IV administration.

If administration of fosphenytoin sodium (Aurantin) does not terminate seizures, the use of other anticonvulsants and other appropriate measures should be considered.

Non-emergent Loading and Maintenance Dosing

The loading dose of fosphenytoin sodium (Aurantin) is 10 to 20 mg PE/kg given IV or IM. The rate of administration for IV fosphenytoin sodium (Aurantin) 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 fosphenytoin sodium (Aurantin) infusions.

Following either the loading dose for Status Epilepticus or a Non-Emergent situation, the initial daily maintenance dose of fosphenytoin sodium (Aurantin) is 4 to 6 mg PE/kg/day. After administration of a loading dose, maintenance doses should typically be started at the next identified dosing interval. For example, if the intended dose frequency is every 12 hours then the first maintenance dose of fosphenytoin sodium (Aurantin) should be administered 12 hours after the loading dose.

Maintenance doses should be individualized by monitoring trough plasma phenytoin concentrations to achieve a target therapeutic concentration of phenytoin. Phenytoin equivalent doses are usually selected to attain therapeutic plasma total phenytoin trough concentrations of 10 to 20 mcg/mL, (unbound phenytoin trough concentrations of 1 to 2 mcg/mL).

IM or IV Substitution for Oral Phenytoin Therapy

Parenteral fosphenytoin can be substituted for oral phenytoin sodium therapy at the same total daily phenytoin sodium equivalents (PE) dose.

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

The rate of administration for IV fosphenytoin sodium (Aurantin) should be no greater than 150 mg PE/min.

In controlled trials, IM fosphenytoin sodium (Aurantin) was administered as a single daily dose utilizing either one or two injection sites. Some patients may require more frequent dosing.

Dosing in Special Populations

Patients with Renal or Hepatic Disease:

See **Section 4.4 Special Warnings and Precautions for Use –** General

Elderly Patients

Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required (see **Section 5.2 Pharmacokinetic Properties – Special Populations – *Age***).

Pediatric Patients

Fosphenytoin sodium (Aurantin) may be administered by IV infusion to pediatric patients of all ages. The doses of fosphenytoin sodium (Aurantin) for pediatric patients have been predicted from the known pharmacokinetics of fosphenytoin sodium (Aurantin) and of parenteral phenytoin in adults and pediatric patients (see **Section 5.2 Pharmacokinetic Properties** – **Special Populations** – *Pediatrics*).

Status Epilepticus

The loading dose of fosphenytoin sodium (Aurantin) is 15 mg PE/kg. The recommended infusion rate is 2 mg PE/kg/min. Due to the risk of hypotension, fosphenytoin sodium (Aurantin) 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 fosphenytoin sodium (Aurantin) infusions.

Intramuscular (IM) fosphenytoin sodium (Aurantin) 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 fosphenytoin sodium (Aurantin) have been given by the IM route.

Non-emergent Loading and Maintenance Dosing

The loading dose of fosphenytoin sodium (Aurantin) is 10 to 15 mg PE/kg. The recommended infusion rate is 1 to 2 mg PE/kg/min. Due to the risk of hypotension, fosphenytoin sodium (Aurantin) 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 fosphenytoin sodium (Aurantin) infusions.

Following either the loading dose for Status Epilepticus or a Non Emergent situation, the **initial** maintenance dose of fosphenytoin sodium (Aurantin) is 2 to 4 mg PE/kg which should be given 12 hours after the loading dose and then continued every 12 hours (4 to 8 mg PE/kg/day) at a rate of 1 to 2 mg PE/kg/min (**no faster than 100 mg PE/min**).

Maintenance doses should be individualized by monitoring trough plasma phenytoin concentrations to achieve a target therapeutic concentration of phenytoin. Phenytoin doses are usually selected to attain therapeutic plasma total phenytoin trough concentrations of 10 to 20 mcg/mL, (unbound phenytoin trough concentrations of 1 to 2 mcg/mL).

Laboratory Tests

Phenytoin equivalent doses are usually selected to attain therapeutic plasma total phenytoin concentrations of 10 mcg/mL to 20 mcg/mL (unbound phenytoin concentrations of 1 mcg/mL to 2 mcg/mL). Prior to complete conversion, immunoanalytical techniques may significantly overestimate plasma phenytoin concentrations due to cross-reactivity with fosphenytoin. Chromatographic assay methods (e.g., high performance liquid chromatography [HPLC]) accurately quantitate phenytoin concentrations in biological fluids in the presence of fosphenytoin. Blood samples should be collected in tubes containing ethylenediaminetetraacetic acid (EDTA), not heparin. However, even with specific assay methods, phenytoin concentrations measured before conversion of fosphenytoin is complete will not reflect phenytoin concentrations ultimately achieved.

Therefore, following fosphenytoin sodium (Aurantin) 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.

4.3 Contraindications

Fosphenytoin sodium (Aurantin) is contraindicated in patients who are hypersensitive to fosphenytoin or its inactive ingredients or to phenytoin or other hydantoins.

Because of the effect of phenytoin on ventricular automaticity, fosphenytoin sodium (Aurantin) is contraindicated in patients with sinus bradycardia, sinoatrial block, second and third-degree atrioventricular (AV) block, and Adams-Stokes syndrome.

Co-administration of fosphenytoin sodium (Aurantin) is contraindicated with delavirdine due to the potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.

4.4 Special Warnings and Precautions for Use

Phenytoin sodium equivalents (PE)

Doses of fosphenytoin sodium (Aurantin) are always expressed in terms of milligrams of phenytoin sodium equivalents (mg PE). 1 mg PE is equivalent to 1 mg phenytoin sodium. Do not, therefore, make any adjustment in the recommended doses when substituting fosphenytoin for phenytoin sodium or vice versa. For example, if a patient is receiving 1000 mg PE of fosphenytoin sodium (Aurantin), that is equivalent to 1000 mg of phenytoin sodium.

Dosing Errors

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

Medication errors associated with fosphenytoin sodium (Aurantin) have resulted in patients receiving the wrong dose of fosphenytoin sodium (Aurantin). Fosphenytoin sodium (Aurantin) is marketed in 10 mL vials containing a total of 500 mg PE. The concentration of each vial is 50 mg PE/mL. Errors have occurred when the concentration of the vial (50 mg PE/mL) was misinterpreted to mean that the total content of the vial was 50 mg PE. These errors have resulted in two- or ten-fold overdoses of fosphenytoin sodium (Aurantin) since each vial actually contains a total of 100 mg PE or 500 mg PE. In some cases, ten-fold overdoses were associated with fatal outcomes. To help minimize confusion, the prescribed dose of fosphenytoin sodium (Aurantin) should always be expressed in milligrams of phenytoin

equivalents (mg PE). Additionally, when ordering and storing fosphenytoin sodium (Aurantin), consider displaying the total drug content (i.e., 500 mg PE/10 mL) instead of concentration in computer systems, pre-printed orders, and automated dispensing cabinet databases to help ensure that total drug content can be clearly identified. Care should be taken to ensure the appropriate volume of fosphenytoin sodium (Aurantin) is withdrawn from the vial when preparing the drug for administration. Attention to these details may prevent some fosphenytoin medication errors from occurring.

Maximum Infusion Rate

Because of the increased risk of adverse cardiovascular reactions associated with rapid administration, do not administer fosphenytoin sodium (Aurantin) at a rate greater than 150 mg PE/min (see **Section 4.2 Dosage and Method of Administration**).

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

General

Phenytoin and, consequently, fosphenytoin sodium (Aurantin) are not effective for the treatment of absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

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

Antiepileptic drugs (AEDs) should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus. When, in the judgment 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.

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.

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

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

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. Unbound concentration of phenytoin may be elevated in patients with hyperbilirubinemia. Unbound phenytoin concentrations may be more useful in these patient populations. After IV administration of fosphenytoin sodium (Aurantin) 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.

Phenytoin has the potential to lower serum folate levels.

Suicide

Some AEDs have been associated with an increased risk of suicidal ideation and/or behavior. Based on a meta-analysis of 11 different AEDs, which did not include fosphenytoin/phenytoin, class labeling for all AEDs was instituted by a number of regulatory authorities. The relationship between fosphenytoin/phenytoin and an increased risk of suicidal ideation and/or behavior is unknown. All patients treated with AEDs should be routinely evaluated for depression, anxiety, and suicidality.

Cardiovascular Effect

Hypotension may occur, especially after IV administration at high doses and high rates of administration. Following administration of fosphenytoin or phenytoin, severe cardiovascular reactions have been reported, including atrial and ventricular conduction depression and ventricular fibrillation. In some cases, cardiac arrhythmias have resulted in asystole/cardiac arrest and death. Severe cardiac complications are most commonly encountered in elderly or gravely ill patients. Cardiac adverse events have also been reported in adults and children without underlying cardiac disease or comorbidities and at recommended doses and infusion rates. Therefore, careful cardiac (including respiratory) monitoring is needed when administering IV loading doses of fosphenytoin sodium (Aurantin). Reduction in rate of administration or discontinuation of dosing may be needed.

Fosphenytoin sodium (Aurantin) should be used with caution in patients with hypotension and severe myocardial insufficiency.

Local Toxicity (Including Purple Glove Syndrome)

Edema, discoloration, and pain distal to the site of injection (described as "purple glove syndrome") have also been reported following peripheral IV fosphenytoin sodium (Aurantin) injection. This may or may not be associated with extravasation. The syndrome may not develop for several days after injection.

Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms

Hypersensitivity syndrome (HSS) or drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients taking anticonvulsants, including phenytoin and fosphenytoin. Some of these events have been fatal or life-threatening.

HSS/DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leukocytosis, and eosinophilia. The interval between first drug exposure and symptoms is usually 2 to 4 weeks, but has been reported in individuals receiving anticonvulsants for 3 or more months. If such signs and symptoms occur, the patient should be evaluated immediately. Fosphenytoin sodium (Aurantin) should be discontinued if an alternative etiology for the signs and symptoms cannot be established.

Patients at higher risk for developing HSS/DRESS include black patients, patients who have experienced this syndrome in the past (with phenytoin, fosphenytoin or other

anticonvulsants), patients who have a family history of this syndrome and immunosuppressed patients. The syndrome is more severe in previously sensitized individuals.

Serious Dermatologic Reactions

Phenytoin can cause rare, severe cutaneous adverse reactions (SCARs) such as acute generalized exanthematous pustulosis (AGEP), exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS, which can be fatal. Although serious skin reactions may occur without warning, patients should be alert for the occurrence of rash and other symptoms of HSS/DRESS (see above) and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. The physician should advise the patient to discontinue treatment if the rash appears. 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 fosphenytoin sodium (Aurantin) medication is contraindicated. The risk of serious skin reactions and other hypersensitivity reactions to phenytoin may be higher in black patients.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of Human Leukocyte antigen –B*1502 (HLA-B), an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding use of drugs associated with SJS/TEN, including phenytoin, in HLA-B*1502-positive patients when alternative therapies are otherwise equally available.

Literature reports suggest that the combination of phenytoin, cranial irradiation and the gradual reduction of corticosteroids may be associated with the development of erythema multiforme, and/or SJS, and/or TEN.

Angioedema

Angioedema has been reported in patients treated with phenytoin and fosphenytoin. Fosphenytoin sodium (Aurantin) should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

Hepatic Injury

The liver is the chief site of biotransformation of phenytoin.

Toxic hepatitis and liver damage have been reported with phenytoin and may, in rare cases, be fatal.

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents usually occur within the first 2 months of treatment and may be associated with HSS/DRESS (see **Section 4.4 Special Warnings and Precautions for Use** – Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms). Patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In patients with acute hepatotoxicity, fosphenytoin sodium (Aurantin) should be immediately discontinued and not re-administered.

The risk of hepatotoxicity and other hypersensitivity reactions to phenytoin may be higher in black patients.

Hematopoietic System

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

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 signs and symptoms resembling HSS/DRESS (see **Section 4.4 Special Warnings and Precautions for Use** –Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms). 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 AEDs.

Central Nervous System Effect

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely, irreversible cerebellar dysfunction and/or cerebellar atrophy. Accordingly, at the first sign of acute toxicity, serum drug level determination of phenytoin is recommended (see **Section 4.2 Dosage and Method of Administration** – Laboratory Tests). Fosphenytoin sodium (Aurantin) dose reduction is indicated if phenytoin concentrations are excessive; if symptoms persist, administration of fosphenytoin sodium (Aurantin) should be discontinued.

Metabolic Effect

Phenytoin has been infrequently associated with the exacerbation of porphyria. Caution should be exercised when fosphenytoin sodium (Aurantin) is used in patients with this disease.

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

Women of Childbearing Potential

Phenytoin may cause fetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse development outcomes (see **Section 4.6 Fertility, Pregnancy and Lactation**).

Patient Information

Patients should be cautioned on the use of other drugs or alcoholic beverages without first seeking their physician's advice.

Patients should be instructed to call their physician if skin rash develops.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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 sodium (Aurantin). Although it is unknown whether this could result in clinically significant effects, caution is advised when administering fosphenytoin sodium (Aurantin) 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 fosphenytoin were concurrently administered in single submaximal doses.

The most significant drug interactions following administration of fosphenytoin sodium (Aurantin) are expected to occur with drugs that interact with phenytoin.

Phenytoin is extensively bound to plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome P450 (CYP) enzymes CYP2C9 and CYP2C19, and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity.

Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes and may reduce the levels of drugs metabolized by these enzymes.

There are many drugs that may increase or decrease serum phenytoin levels or that phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected.

The most commonly occurring drug interactions are listed below.

Drugs That May Increase Phenytoin Serum Levels

Table 1 summarizes the drug classes that may potentially increase phenytoin serum levels.

Table 1 Drugs Which May Increase Phenytoin Serum Levels

Drug classes	**Drugs in each class (such as[a])**
Alcohol (acute intake)	
Analgesic/anti-inflammatory agents	Azapropazone Phenylbutazone Salicylates
Anesthetics	Halothane

Table 1 Drugs Which May Increase Phenytoin Serum Levels	
Drug classes	**Drugs in each class (such as[a])**
Antibacterial agents	Chloramphenicol Erythromycin Isoniazid Sulfadiazine Sulfamethizole Sulfamethoxazole-trimethoprim Sulfaphenazole Sulfisoxazole Sulfonamides
Anticonvulsants	Felbamate Oxcarbazepine Sodium valproate Succinimides Topiramate
Antifungal agents	Amphotericin B Fluconazole Itraconazole Ketoconazole Miconazole Voriconazole
Antineoplastic agents	Fluorouracil Capecitabine
Benzodiazepines/psychotropic agents	Chlordiazepoxide Diazepam Disulfiram Methylphenidate Trazodone Viloxazine
Calcium channel blockers/cardiovascular agents	Amiodarone Dicumarol Diltiazem Nifedipine Ticlopidine
H_2-antagonists	Cimetidine
HMG-CoA reductase inhibitors	Fluvastatin
Hormones	Estrogens
Immunosuppressant drugs	Tacrolimus
Oral hypoglycemic agents	Tolbutamide
Proton pump inhibitors	Omeprazole
Serotonin re-uptake inhibitors	Fluoxetine Fluvoxamine Sertraline

[a] This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted.

Drugs That May Decrease Phenytoin Plasma Levels

Table 2 summarizes the drug classes that may potentially decrease phenytoin plasma levels.

Table 2 Drugs That May Decrease Phenytoin Serum Levels	
Drug classes	**Drugs in each class (such as[a])**
Alcohol (chronic intake)	
Antibacterial agents	Rifampin Ciprofloxacin
Anticonvulsants	Vigabatrin
Antineoplastic agents	Bleomycin Carboplatin Cisplatin Doxorubicin Methotrexate
Antiretrovirals	Fosamprenavir Nelfinavir Ritonavir
Bronchodilators	Theophylline
Cardiovascular agents	Reserpine
Folic acid	
Hyperglycemic agents	Diazoxide
St. John's Wort	

[a] This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted.

Drugs That May Increase or Decrease Phenytoin Serum Levels

Table 3 summarizes the drug classes that may either increase or decrease phenytoin serum levels.

Table 3 Drugs That May Increase or Decrease Phenytoin Serum Levels	
Drug classes	**Drugs in each class (such as[a])**
Antibacterial agents	Ciprofloxacin
Anticonvulsants	Carbamazepine Phenobarbital Sodium valproate Valproic acid
Antineoplastic agents	
Psychotropic agents	Chlordiazepoxide Diazepam Phenothiazines

[a] This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted.

Drugs Whose Serum Levels and/or Effects May be Altered by Phenytoin

Table 4 summarizes the drug classes whose serum levels and/or effects may be altered by phenytoin.

Table 4 Drugs Whose Serum Levels and/or Effects May be Altered by Phenytoin	
Drug classes	**Drugs in each class (such as[a])**
Antibacterial agents	Doxycycline Rifampin Tetracycline

Table 4 Drugs Whose Serum Levels and/or Effects May be Altered by Phenytoin	
Drug classes	**Drugs in each class (such as[a])**
Anticonvulsants	Carbamazepine Lamotrigine Phenobarbital Sodium valproate Valproic acid
Antifungal agents	Azoles Posaconazole Voriconazole
Antihelmintics	Albendazole Praziquantel
Antineoplastic agents	Teniposide
Antiretroviral	Delavirdine Efavirenz Fosamprenavir Indinavir Lopinavir/ritonavir Nelfinavir Ritonavir Saquinavir
Bronchodilators	Theophylline
Calcium channel blockers/cardiovascular agents	Digitoxin Digoxin Disopyramide Mexiletine Nicardipine Nimodipine Nisoldipine Quinidine Verapamil
Corticosteroids	
Coumarin anticoagulants	Warfarin
Cyclosporine	
Diuretics	Furosemide
HMG-CoA reductase inhibitors	Atorvastatin Fluvastatin Simvastatin
Hormones	Estrogens Oral contraceptives (see **Sections 4.4 Special Warnings and Precautions for Use and 4.6 Fertility, Pregnancy and Lactation**)
Hyperglycemic agents	Diazoxide
Neuromuscular blocking agents	Alcuronium Cisatracurium Pancuronium Rocuronium Vecuronium
Opioid analgesics	Methadone
Oral hypoglycemic agents	Chlorpropamide Glyburide Tolbutamide

Table 4 Drugs Whose Serum Levels and/or Effects May be Altered by Phenytoin	
Drug classes	**Drugs in each class (such as[a])**
Psychotropic agents/Antidepressants	Clozapine Paroxetine Quetiapine Sertraline
Vitamin D	

[a] This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted.

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

Drug-Laboratory Test Interactions

Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It also may produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT). Phenytoin may affect blood calcium and blood sugar metabolism tests.

Monitoring of plasma phenytoin concentrations may be helpful when possible drug interactions are suspected.

4.6 Fertility, Pregnancy and Lactation

Fertility

In animal studies, fosphenytoin sodium (Aurantin) had no effect on fertility in male rats but decreased fertility in female rats.

Usage in Pregnancy

Phenytoin crosses the placenta in humans.

A number of reports suggest an association between the use of anticonvulsants by women with epilepsy and a higher incidence of birth defects in children born to these women. Less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsants.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans. Genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant drugs deliver normal infants. It is important to note that anticonvulsants should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of child-bearing potential.

In addition to the reports of increased incidence of congenital malformations such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other anticonvulsants, there have been reports of a fetal hydantoin syndrome. This consists of prenatal dysmorphic facial features, nail and digit hypoplasia, growth deficiency (including microcephaly), and mental deficiency in children born to mothers who have received phenytoin.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

Fosphenytoin sodium (Aurantin) should only be used in women of childbearing potential and pregnant women if the potential benefit outweighs the risk. When appropriate, counsel pregnant women and women of childbearing potential about alternative therapeutic options.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

Women of childbearing potential who are not planning a pregnancy should be advised regarding the use of effective contraception during treatment. Fosphenytoin sodium (Aurantin) may result in a failure of the therapeutic effect of hormonal contraceptives (see **Section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Fosphenytoin sodium (Aurantin) was teratogenic in rats and its metabolite, phenytoin, is teratogenic in rats, mice and rabbits.

Usage in Nursing Mothers

Infant breast-feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk. Phenytoin concentration in breast milk is approximately one-third of the corresponding maternal plasma concentration.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

The more important adverse reactions caused by the IV use of fosphenytoin or phenytoin are cardiovascular collapse and/or central nervous system (CNS) depression. Hypotension can occur when either drug is administered rapidly by the IV route.

The adverse reactions (treatment-related adverse clinical events) most commonly observed with the use of fosphenytoin sodium (Aurantin) in clinical trials were nystagmus, dizziness,

pruritus, paresthesia, 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 fosphenytoin sodium (Aurantin) administration and occurred more often with IV fosphenytoin sodium (Aurantin) administration than with IM fosphenytoin sodium (Aurantin) 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. Overall, sensory disturbances occurred in 13% of the patients exposed to fosphenytoin sodium (Aurantin) and were more common after IV administration, higher doses, or faster infusion rates. These sensations, generally described as itching, burning, warmth, 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. In general, these sensory disturbances occurred within several minutes of the start of the IV infusion and resolved spontaneously within 10 minutes after completion of the infusion, although some patients experienced symptoms for several hours. The sensations were not consistent with the signs of an allergic reaction and may be avoided or minimized by using a slower rate of IV infusion or by temporarily stopping the infusion. These events did not increase in severity with repeated administration and were similar to those seen with other phosphate-ester drugs such as dexamethasone phosphate.

Approximately 2% of the 873 individuals who received fosphenytoin sodium (Aurantin) in clinical trials discontinued treatment because of an adverse event. The adverse reactions most commonly associated with withdrawal were pruritus (0.7%), hypotension (0.5%), and bradycardia (0.2%).

Dose and Rate Dependency of Adverse Reactions Following IV Fosphenytoin sodium (Aurantin)

The incidence of adverse reactions 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 of Adverse Reactions in Aggregate Clinical Trials with IV or IM Administration

Table 5 lists the adverse reactions that occurred in at least 2% of patients treated with IV or IM fosphenytoin sodium (Aurantin); incidence in placebo is shown for comparison. Nystagmus (20.6%) and dizziness (15.6%) were the most commonly reported adverse reactions in IM or IV fosphenytoin sodium (Aurantin) patients.

Table 5 Adverse Reactions Following IV or IM Fosphenytoin sodium (Aurantin) Administration (Events in at Least 2% of Fosphenytoin sodium (Aurantin) - treated Patients)

MedDRA System Organ Class Adverse Event	**IM or IV Fosphenytoin sodium (Aurantin) N = 873**	**Placebo N = 47**
Nervous system disorders		
Nystagmus	20.6%	6.4%
Dizziness	15.6%	4.3%
Paresthesia	9.6%	2.1%
Somnolence	6.9%	0%
Ataxia	5.7%	0%
Headache	5.0%	2.1%

Table 5 Adverse Reactions Following IV or IM Fosphenytoin sodium (Aurantin) Administration (Events in at Least 2% of Fosphenytoin sodium (Aurantin) -treated Patients)		
MedDRA System Organ Class Adverse Event	**IM or IV Fosphenytoin sodium (Aurantin) N = 873**	**Placebo N = 47**
Tremor	3.0%	0%
Ear and labyrinth disorders		
Tinnitus	2.1%	5.3%
Ear disorder	2.4%	0%
Gastrointestinal disorders		
Nausea	2.1%	4.0%
Skin and subcutaneous tissue disorders		
Pruritus	12.4%	0%

Incidence of Adverse Reactions in a Controlled Clinical Trial: IV Administration to Adult Patients with Epilepsy or Neurosurgical Patients

Table 6 lists adverse reactions that occurred in at least 2% of adult patients treated with IV fosphenytoin sodium (Aurantin) at the maximum dose and rate in a randomized, double-blind, controlled clinical trial where the rates for phenytoin and fosphenytoin sodium (Aurantin) administration would have resulted in equivalent systemic exposure to phenytoin (Study 982-026).

Table 6 Adverse Reactions Following IV Administration at the Maximum Dose and Rate to Adult Patients with Epilepsy or Neurosurgical Patients in Study 982-026 (Events in at Least 2% of Fosphenytoin sodium (Aurantin) -treated Patients)		
MedDRA System Organ Class Adverse Event	**IV Fosphenytoin sodium (Aurantin) N = 90**	**IV Phenytoin N = 22**
Nervous system disorders		
Nystagmus	43.3%	59.1%
Dizziness	31.1%	27.3%
Somnolence	20.0%	27.3%
Ataxia	10.0%	18.2%
Stupor	7.8%	4.5%
Coordination abnormal	4.4%	4.5%
Paresthesia	4.4%	0%
Extrapyramidal disorder	3.3%	0%
Hypoesthesia	2.2%	9.1%
Dysarthria	2.2%	0%
Dysgeusia	2.2%	0%
Eye disorders		
Diplopia	3.3%	0%
Blurred vision	2.2%	9.1%
Ear and labyrinth disorders		
Vertigo	2.2%	0%
Tinnitus	8.9%	9.1%
Vascular disorders		
Hypotension	7.8%	9.1%
Vasodilation	5.6%	4.5%

Table 6 Adverse Reactions Following IV Administration at the Maximum Dose and Rate to Adult Patients with Epilepsy or Neurosurgical Patients in Study 982-026 (Events in at Least 2% of Fosphenytoin sodium (Aurantin) -treated Patients)		
MedDRA System Organ Class Adverse Event	**IV Fosphenytoin sodium (Aurantin) N = 90**	**IV Phenytoin N = 22**
Gastrointestinal disorders		
Nausea	6.7%	13.6%
Tongue disorder	4.4%	0
Dry mouth	3.3%	4.5%
Vomiting	2.2%	9.1%
Skin and subcutaneous tissue disorders		
Pruritus	47.8%	4.5%
Musculoskeletal and connective tissue disorders		
Back pain	2.2%	0%
Reproductive system and breast disorders		
Pelvic pain	4.4%	0%
General disorders and administrative site conditions		
Asthenia	2.2%	0%

Incidence in Controlled Clinical Trials - IV Administration to Pediatric Patients with Epilepsy or Neurosurgical Patients: The overall incidence of adverse reactions and the types of adverse reactions seen were similar among children and adults treated with fosphenytoin sodium (Aurantin). In an open-label, safety, tolerability, and pharmacokinetic study (982-028) of fosphenytoin sodium (Aurantin) in pediatric subjects (neonates through age 16), the following adverse reactions occurred at a frequency greater than 5% in 96 subjects treated with intravenous fosphenytoin sodium (Aurantin): vomiting (20.8%), nystagmus (17.7%), ataxia (10.4%), fever (8.3%), nervousness (7.3%), pruritus (6.3%), somnolence (6.3%), hypotension (5.2%), and rash (5.2%).

Incidence of Adverse Reactions in a Controlled Clinical Trial: IM Administration to Patients with Epilepsy

Table 7 lists adverse reactions that occurred in at least 2% of fosphenytoin sodium (Aurantin) -treated patients in a double-blind, randomized, controlled clinical trial of adult epileptic patients receiving either IM fosphenytoin sodium (Aurantin) substituted for oral phenytoin or continuing oral phenytoin (Study 982-013). Both treatments were administered for 5 days.

Table 7 Adverse Reactions Following Substitution of IM Fosphenytoin sodium (Aurantin) for Oral Phenytoin in Patients with Epilepsy in Study 982-013 (Events in at Least 2% of Fosphenytoin sodium (Aurantin) -treated Patients)		
MedDRA System Organ Class Adverse Event	**IM Fosphenytoin sodium (Aurantin) N = 179**	**Oral Phenytoin N = 61**
Nervous system disorders		
Nystagmus	8.4%	1.6%
Tremor	6.7%	8.2%
Coordination abnormal	5.6%	1.6%
Somnolence	5.6%	9.8%
Dizziness	4.5%	1.6%
Ataxia	3.4%	0.0%

Table 7	**Adverse Reactions Following Substitution of IM Fosphenytoin sodium (Aurantin) for Oral Phenytoin in Patients with Epilepsy in Study 982-013 (Events in at Least 2% of Fosphenytoin sodium (Aurantin) -treated Patients)**	
Headache	2.8%	1.6%
Gastrointestinal disorders		
Nausea	2.8%	0%
Skin and subcutaneous tissue disorders		
Ecchymosis	6.1%	3.3%
Pruritus	2.2%	0%
General disorders and administration site conditions		
Asthenia	2.8%	1.6%

Incidence of Adverse Reactions in a Controlled Trial: IM Administration to Patients with Epilepsy

In a double-blind study (Study 982-013) investigating temporary substitution of fosphenytoin sodium (Aurantin) for oral phenytoin, IM fosphenytoin sodium (Aurantin) was as well tolerated as IM placebo. IM fosphenytoin sodium (Aurantin) resulted in a slight increase in transient, mild to moderate 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 fosphenytoin sodium (Aurantin) may be substituted for oral phenytoin sodium with no dosage adjustments needed when initiating IM therapy 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.

Tolerability of Infusion

Tolerability of infusion was evaluated in clinical studies. One double-blind study (Study 982-026) assessed infusion-site tolerance of equivalent loading doses (15-20 mg PE/kg) of fosphenytoin sodium (Aurantin) 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 fosphenytoin sodium (Aurantin) -treated patients (see Table 8).

Fosphenytoin sodium (Aurantin) -treated patients, however, experienced more systemic sensory disturbances.

Infusion disruptions in fosphenytoin sodium (Aurantin) -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 8).

Table 8	**Infusion Tolerance of Equivalent Loading Doses of IV Fosphenytoin sodium (Aurantin) and IV Phenytoin in Study 982-026**	
	IV Fosphenytoin sodium (Aurantin) N = 90	**IV Phenytoin N = 22**
Local intolerance	7/81 (9%)	18/20 (90%)
Infusion disrupted	2/81 (2%)	13/20 (65%)
Average infusion time	13 min	44 min
Percentages based on the number of patients with evaluable data.		

Frequency of Adverse Reactions

Adverse reactions in a pooled analysis of clinical trial data are listed in Table 9 by MedDRA system organ class and frequency: Very common (≥10%), common (≥1% - <10%), uncommon (≥0.1% - <1%), rare (≥0.01% - <0.1%), very rare (<0.01%).

Table 9 Adverse Reactions from Clinical Trial Experience	
MedDRA System Organ Class Frequency Classification	**MedDRA Preferred Term**
Cardiac disorders	
Uncommon	Asystole/cardiac arrest
Ear and labyrinth disorders	
Common	Tinnitus, ear disorder, vertigo
Eye disorders	
Common	Visual impairment, vision blurred
Uncommon	Diplopia
Gastrointestinal disorders	
Common	Nausea, dry mouth, vomiting
General disorders and administrative site conditions	
Common	Pain, asthenia, injection site reaction, injection site pain, chills
Uncommon	Edema peripheral
Injury, poisoning and procedural complication	
Uncommon	Injury
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle twitching, muscle spasms
Nervous system disorders	
Very common	Nystagmus, dizziness
Common	Paresthesia, somnolence, ataxia, headache, tremor, coordination abnormal, dysgeusia, stupor, dysarthria
Uncommon	Hypoesthesia, speech disorder, hyporeflexia
Psychiatric disorders	
Common	Euphoric mood
Uncommon	Thinking abnormal, nervousness
Skin and subcutaneous tissue disorders	
Very common	Pruritus
Common	Ecchymosis
Uncommon	Rash
Vascular disorders	
Common	Hypotension, vasodilatation

The following adverse events (frequency unknown-cannot be estimated from available data) were reported during post-marketing surveillance: Anaphylactoid reaction, anaphylaxis, confusion, dyskinesia, Purple Glove Syndrome (see **Section 4.4 Special Warnings and Precautions for Use –** Local Toxicity (including Purple Glove Syndrome), and HSS/DRESS (see **Section 4.4 Special Warnings and Precautions for Use** – Hypersensitivity Syndrome Drug Reaction with Eosinophilia and Systemic Symptoms).

4.9 Overdose and Treatment

Because fosphenytoin is a prodrug of phenytoin, the following information is provided.

The lethal dose of phenytoin in children is not known.

The lethal dose of phenytoin in adults is estimated to be 2 g to 5 g. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, somnolence, drowsiness, lethargy, slurred speech, blurred vision, nausea and vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin serum levels where toxicity may occur. Nystagmus on lateral gaze usually appears at 20 mcg/mL, and ataxia at 30 mcg/mL; dysarthria and lethargy appear when the serum concentration is >40 mcg/mL, but a concentration as high as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration >100 mcg/mL with complete recovery. Irreversible cerebellar dysfunction and atrophy have been reported.

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

Overdosage Treatment

Treatment is nonspecific since there is no known antidote.

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

In acute overdosage, the possibility of the presence 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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Fosphenytoin is a prodrug intended for parenteral administration. Following parenteral administration, fosphenytoin is converted to its active metabolite, the anticonvulsant phenytoin. For every mmol of fosphenytoin sodium (Aurantin) administered, 1 mmol of phenytoin is produced. The pharmacological and toxicological effects of fosphenytoin sodium (Aurantin) 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 fosphenytoin sodium (Aurantin) 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.

5.2 Pharmacokinetic Properties

Pharmacokinetics and Metabolism

Fosphenytoin sodium (Aurantin)

Absorption/Bioavailability: When fosphenytoin sodium (Aurantin) 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. Fosphenytoin is completely bioavailable following IM administration. 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 sodium (Aurantin) 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 (Aurantin) dose and rate, and ranges from 4.3 to 10.8 L.

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 sodium (Aurantin) is not excreted in urine. Each mmol of fosphenytoin is metabolized to 1 mmol of phenytoin, phosphate, and formate (see **Section 4.4 Special Warnings and Precautions for Use** – General).

Phenytoin (After Fosphenytoin sodium (Aurantin) Administration)

In general, IM administration of fosphenytoin sodium (Aurantin) 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 fosphenytoin sodium (Aurantin), however, is complex, and when used in an emergency setting (e.g., status

epilepticus), differences in rate of availability of phenytoin could be critical. Studies have therefore empirically determined an infusion rate for fosphenytoin sodium (Aurantin) 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 fosphenytoin sodium (Aurantin) infused at 100 to 150 mg PE/min yields plasma-free phenytoin concentrations over time that approximate those achieved when an equivalent dose of phenytoin sodium (e.g., parenteral phenytoin) is administered at 50 mg/min (see **Section 4.2 Dosage and Method of Administration**).

Following administration of single IV fosphenytoin sodium (Aurantin) 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.

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

Metabolism and Elimination: Phenytoin is biotransformed in the liver by oxidative metabolism. The major pathway involves 4-hydroxylation, which accounts for 80% of all metabolites. CYP2C9 plays a major role in the metabolism of phenytoin (90% of net intrinsic clearance), while CYP2C19 has a minor involvement in this process (10% of net intrinsic clearance). This relative contribution of CYP2C19 to phenytoin metabolism may however increase at higher phenytoin concentrations.

Because the cytochrome systems involved in phenytoin hydroxylation in the liver are saturable at high serum concentrations, small incremental doses of phenytoin may increase the half-life and produce very substantial increases in serum levels when these are in or above the upper therapeutic range. The clearance of phenytoin has been shown to be impaired by CYP2C9 inhibitors such as phenylbutazone and sulfaphenazole. Impaired clearance has also been shown to occur in patients administered CYP2C19 inhibitors such as ticlopidine.

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

Special Populations

Patients with Renal or Hepatic Disease: See **Section 4.4 Special Warnings and Precautions for Use** – General

Age: The effect of age was evaluated in patients 5 to 98 years of age; however, no systematic studies in geriatric patients have been conducted. Patient age had no significant impact on fosphenytoin sodium (Aurantin) pharmacokinetics. Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20 to 30 years of age). Phenytoin dosing requirements are highly variable and must be individualized (see **Section 4.2 Dosage and Method of Administration** – **Dosing in Special Populations** – Elderly Patients).

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

Pediatrics: Pharmacokinetic data are available in pediatric patients from birth through 16 years of age. In these patients with status epilepticus who received loading doses of fosphenytoin sodium (Aurantin), 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.

Pharmacokinetic Interaction

Co-administration of nelfinavir tablets (1250 mg twice a day) with phenytoin capsule (300 mg once a day) did not change the plasma concentration of nelfinavir. However, co-administration of nelfinavir reduced the AUC values of phenytoin (total) and free phenytoin by 29% and 28%, respectively.

5.3 Preclinical Safety Data

Carcinogenesis

Carcinogenicity studies with fosphenytoin sodium (Aurantin) are unavailable. Since fosphenytoin is a prodrug of phenytoin, the carcinogenicity results with phenytoin can be extrapolated. In a transplacental and adult carcinogenicity study, phenytoin was administered in diet at 30 to 600 ppm to mice (4.5 to 90 mg/kg/day) and 240 to 2400 ppm (12 to 120 mg/kg/day) to rats. Hepatocellular tumors were increased at the higher doses in mice and rats. In additional studies, mice received 10, 25, or 45 mg/kg/day and rats were given 25, 50, or 100 mg/kg/day in the diet for 2 years. Hepatocellular tumors in mice increased at 45 mg/kg/day. No increases in tumor incidence were observed in rats. These rodent tumors are of uncertain clinical significance.

Genetic toxicity studies showed that fosphenytoin sodium (Aurantin) was not mutagenic in bacteria or in mammalian cells *in vitro*. It is clastogenic *in vitro* but not *in vivo*.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

See outer package for the expiry date of the product.

6.2 Storage Condition

Store between 2 and 8°C (under refrigeration). Do not freeze.

6.3 Availability

Fosphenytoin sodium (Aurantin) is supplied in 10-mL Type I, USP/EP, glass vials stoppered with fluorotec butyl compound stopper and sealed with an aqua colored button in an aluminum shell as a ready-mixed, clear, colorless to pale yellow, sterile solution in water for injection and TRIS buffer adjusted to pH 8.6 to 9.

6.4 Special Precautions for Storage

The product should not be stored at room temperature for more than 48 hours. Vials that develop particulate matter should not be used.

6.5 Special Precautions for Disposal and Other Handling

For single-use only. After opening, unused product should be discarded.

Products with particulate matter or discoloration should not be used.

Prior to IV infusion, dilute fosphenytoin in 5% dextrose or 0.9% saline solution for injection to a concentration ranging from 1.5 to 25 mg PE/mL.

7.0 FDA REGISTRATION NUMBER

75 mg/mL Solution for Injection (IM/IV): DR-XY47680

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

75 mg/mL Solution for Injection (IM/IV): 20 January 2022

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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