**Fomepizole Injection**

Sterile

Rx only

Caution: Must be diluted prior to use.

**DESCRIPTION**

Fomepizole Injection is a competitive inhibitor of alcohol dehydrogenase.

The chemical name of fomepizole is 4-methylpyrazole. It has the molecular formula C5H7N and molecular weight of 82.1. The structural formula is:

\[
\text{CH}_3\text{C}_5\text{H}_4\text{N} = \text{HNO}_2 \quad \text{molecular weight} = 82.1
\]

It is a colorless to yellow liquid at room temperature. Its melting point is 25°C (77°F) and it may be present in a solid form at room temperature. Fomepizole is soluble in water and very soluble in ethyl alcohol, diethyl ether, and chloroform. Each vial contains 1.5 mL (15 mg/mL) of fomepizole base.

**CLINICAL PHARMACOLOGY**

Clinical studies before Fomepizole Injection is a competitive inhibitor of alcohol dehydrogenase. Alcohol dehydrogenase catalyzes the oxidation of ethanol. The availability of reduced coenzymes also catalyzes the initial steps in the metabolism of ethylene glycol and methanol to their toxic metabolites.

Ethylene glycol, the major component of most antifreezes and coolants, is metabolized to glycolate and oxalate. Glucuronic acid and oxalic acid are the metabolic end-products primarily responsible for the metabolic acidosis and renal damage seen in ethylene glycol poisonings. The initial dose of ethylene glycol in humans is approximately 1.4 mL/kg.

Methanol, the main component of windshield washer fluid, is slowly metabolized via alcohol dehydrogenase to formaldehyde, which is further metabolized by formaldehyde dehydrogenase in yield formic acid. Formic acid is directly toxic to the cardiovascular system. Several metabolic pathways are involved in the metabolism of methanol. These pathways include formaldehyde dehydrogenase (e.g., decreased visual acuity and potential blindness) associated with methanol poisoning. A lethal dose of methanol in humans is approximately 0.5 mL/kg. Fomepizole has been shown in vivo to block alcohol dehydrogenase enzyme activity in dog, monkey, and human liver.

The concentration of fomepizole at which alcohol dehydrogenase is inhibited by 50% in vitro is approximately 0.1 µmol/L.

In a study of dogs given a lethal dose of ethylene glycol, those acute fomepizole treated showed methanol, ethanol, or left untreated (control group). The three animals in the untreated group became progressively obtunded, moribund, and eventually died. Necropsy of the three dogs showed a few tubular dilations, no fomepizole, or ethylene glycol administered hours after ethylene glycol ingestion, attenuated the metabolic acidosis and renal tubular changes associated with ethylene glycol intoxication.

Several articles have demonstrated that fomepizole plasma concentrations of approximately 10 µmol/L (0.82 mg/L) in methanol poisoning were associated with initial methanol half-life (t1/2) and elimination half-life (t1/2e), which is also metabolized through the alcohol dehydrogenase route (see PRECAUTIONS). Drug Interactions. Pharmacokinetics: The plasma half-life of Fomepizole Injection varies with dose, even in patients with normal renal function, and has not been calculated.

**Distribution:** After intravenous infusion, fomepizole rapidly distributes to total body water. The volume of distribution is between 10 and 20 L/kg.

**Metabolism:** In healthy volunteers, only 1 to 3.5% of the administered fomepizole was excreted in urine. The major route of fomepizole elimination is by metabolism and bile. The major metabolite of fomepizole is the glucuronide of 4-carboxypyrazole (55%), which is secreted in the urine. The other metabolites of fomepizole observed in the urine are 4-hydroxymethylpyrazole and the N-glucuronides conjugates of 4-carboxypyrazole and 4-carboxyethylpyrazole.

**Excretion:** The elimination of fomepizole is best characterized by Michaelis-Menten kinetics after acute doses of fomepizole. The fomepizole elimination half-life (t1/2) was 30 to 100 minutes in healthy volunteers. After enzyme induction, elimination follows first-order kinetics.

**Special Populations:**

**Geriatric:** Fomepizole Injection has not been studied sufficiently to determine whether the pharmacokinetics differ for a geriatric population.

**Pediatric:** Fomepizole has not been studied sufficiently to determine whether the pharmacokinetics differ for a pediatric population.

**Renal Insufficiency:** The metabolites of fomepizole are excreted nearly exclusively. Definitive pharmacokinetic studies have not been done in patients with renal impairment.

**Hepatic Insufficiency:** Fomepizole is metabolized through the liver, but no definitive pharmacokinetic studies have been undertaken in subjects with hepatic failure.

**Clinical Studies:** The efficacy of fomepizole in the treatment of ethylene glycol and methanol intoxication was studied in two prospective, U.S. clinical trials without in addition control groups. Fourteen of 16 patients in the ethylene glycol trial and 11 of 21 patients in the methanol trial had severe metabolic acidosis and renal failure. At frequent intervals throughout the treatment, electrolytes, BUN, and urinalysis, in addition to other routine laboratory tests as indicated by individual patient condition. Patients poisoned with ethylene glycol were monitored for ethylene glycol concentrations in serum and urine, and the presence of urinary oxalate crystals. Similar, serum methanol concentrations should be monitored in patients poisoned with methanol. Electrocardiography should be performed at frequent intervals in patients recovering from severe metabolic acidosis and renal impairment. The cardiovascular system. In the comatose patient, the administration of fomepizole and ethanol, given 3 hours after alcohol dehydrogenase to yield formic acid. Formic acid is directly toxic to the cardiovascular system. In the comatose patient, the administration of fomepizole to ethanol is not recommended.
Drug Interactions: Oral doses of fomepizole (10 to 30 mg/kg), via alcohol dehydrogenase inhibition, significantly reduced the elimination of ethanol (by approximately 45%) given to healthy volunteers in moderate doses. Similarly, ethyl alcohol and fomepizole interacted in the rate of elimination of fomepizole (by approximately 5%) by the same mechanism.

Reciprocal interactions may occur with concurrent use of fomepizole and other drugs that increase the elimination of alcohol, such as P450 system (e.g., phenytoin, carbamazepine, cimetidine, ketoconazole), though this has not been studied.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: There are no long-term studies performed in animals to evaluate carcinogenic potential.

There was a positive Ames test result in the Escherichia coli WP2uvrA/pKM101 and the Salmonella typhimurium tester strain TA102 in the absence of metabolic activation. There was no evidence of a clastogenic effect in the in vitro mouse micronucleus assay.

In rats, fomepizole (110 mg/kg) administered orally for 4 to 42 days resulted in decreased testicular mass (approximately 6% reduction). This dose is approximately 0.5 times the human maximum daily exposure based on surface area (mg/m²) and is similar for the average child to adult with either ethanol or fomepizole alone. When fomepizole was given in combination with ethanol, the decrease in testicular mass was significantly greater (approximately 36% reduction) compared to those rats treated exclusively with fomepizole or ethanol.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted. It is not known whether fomepizole can cause fetal harm when administered to pregnant women or if it can affect reproductive capacity. Fomepizole should be given to pregnant women only if clearly needed.

Nursing Mothers: It is not known whether fomepizole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when fomepizole is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Safety and effectiveness in geriatric patients have not been established.

ADVERSE REACTIONS

The most frequent adverse events reported as drug-related or un相关 knowledge to study the drug in the 78 patients and 63 normal volunteers who received Fomepizole Injection were headache (14%), nausea (11%), and dizziness, improved drowsiness, and dizziness (5% each). All other adverse events in this population were reported by ≤ 3% or fewer of those receiving fomepizole. These were as follows:

Body as a Whole: a Whole Abdominal pain, fever, multiorgan system toxicity (See Do not use beyond 24 hours. Solutions showing pH fluctuations and sterility of Fomepizole Injection. Using the same mechanism.

DOSING AND ADMINISTRATION

Treatment Guidelines: If ethylglycol or methanol poisoning is suspected, the natural progression of the poisoning leads to accumulation of toxic metabolites, including glycolic and oxalic acids. Aldehyde (ethylene glycol intoxication) and formic acid (methanol intoxication). These metabolites can induce metabolic acidosis, nausea, vomitting, seizures, stupor, coma, calcium oxalate, acute tubular necrosis, blindness, and death. In these poisoning these poisons may be difficult because ethylglycol and methanol concentrations diminish dramatically as they are metabolized to their respective metabolites. Hence, both ethylglycol and methanol concentrations in acid-base balance, as determined by serum electrolyte (anion gap) and arterial blood gas analysis, should be frequently monitored and used to guide treatment.

Treatment of Discontinuation of Fomepizole Injection Treatment: Discontinuation of Fomepizole Injection treatment should be considered when ethylene glycol or methanol concentrations are undetectable or have been reduced below 20 mg/dL. Patients should be drowsy to continue metabolic abnormalities and to lower the ethylene glycol concentrations below 50 mg/L.

Discontinuation of Fomepizole Injection Treatment: Treatment with Fomepizole Injection may be discontinued when ethylene glycol or methanol concentrations are undetectable or have been reduced below 20 mg/dL, and the patient is asymptomatic with normal pH.

Dosing of Fomepizole Injection: A loading dose of 15 mg/kg should be administered, followed by doses of 10 mg/kg every 12 hours for 4 to 10 hours, then 5 mg/kg every 12 hours until ethylene glycol or methanol concentrations are undetectable or have been reduced below 20 mg/dL. Patients should be drowsy to continue metabolic abnormalities and to lower the ethylene glycol concentrations below 50 mg/L.

Discontinuation of Fomepizole Injection Treatment: Treatment with Fomepizole Injection may be discontinued when ethylene glycol or methanol concentrations are undetectable or have been reduced below 20 mg/dL, and the patient is asymptomatic with normal pH.

Dosing at Renal Dosing: Fomepizole Injection is dialyzable and the frequency of dosing should be increased to every 4 hours during hemodialysis.

Fomepizole Injection Dosing in Patients Requiring Hemodialysis

DOSING AT THE TIME OF HEMODIALYSIS

Time between last dose and the end of hemodialysis:

• <1 hour Do not administer dose at the end of the hemodialysis
• 1-3 hours Administer 1/2 of next scheduled dose
• >3 hours Administer next scheduled dose

Note: Fomepizole Injection should be administered intravenously at the end of dialysis and over 30 minutes. Fomepizole Injection, like all parenteral products, should be inspected visually for particulate matter prior to use.

Stability: Fomepizole Injection diluted in 0.9% sodium chloride injection or dextrose 5% injection remain stable in a refrigerated environment for 30 hours when stored refrigerated or at room temperature. Fomepizole Injection does not contain a preservative, maintain sterility conditions, and after dilution do not use beyond 24 hours. Solutions showing dullness, discoloration, precipitation, discoloration, or leakage should not be used.

HOW SUPPLIED

Fomepizole is supplied as a sterile, preservative-free solution for intravenous use as:

Supplied in single vial cartridges. Each vial contains 1.5 mL (1 g) of fomepizole.

Supplied in 120 mg/mL (2.5 mL).

Stor to 2°C to 8°C (36°F to 46°F) [See USP Controlled Room Temperature].

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