

FOMEBEST™

Fomepizole Injection 1.5 g/1.5 ml

For slow IV infusion only

Must be diluted before use

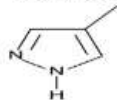
Description

Fomebest™ (Fomepizole injection)

is a competitive inhibitor of alcohol dehydrogenase.

The chemical name of Fomepizole is 4-methylpyrazole. It has the molecular formula $C_4H_6N_2$ and a molecular weight of 82.1

The structural formula is:



It is a clear to yellow liquid at room temperature. Its melting point is 25° C (77° F) and it may present as solid at room temperature.

Composition:

Each ml contains:

Fomepizole IP 1 g

CLINICAL PHARMACOLOGY

Pharmacodynamic

Mechanism of Action

Fomebest™ (fomepizole injection) is a competitive inhibitor of alcohol dehydrogenase. Alcohol dehydrogenase catalyzes the oxidation of ethanol to acetaldehyde. Alcohol dehydrogenase also catalyzes the initial steps in the metabolism of ethylene glycol and methanol to their toxic metabolites. Ethylene glycol, the main component of most antifreezes and coolants, is metabolized to glycoaldehyde, which undergoes subsequent sequential oxidations to yield glycolate, glyoxylate, and oxalate. Glycolate and oxalate are the metabolic byproducts primarily responsible for the metabolic acidosis and renal damage seen in ethylene glycol toxicosis. The lethal dose of ethylene glycol in humans is approximately 1.4 mL/kg. Methanol, the main component of windshield wiper fluid, is slowly metabolized via alcohol dehydrogenase to formaldehyde with subsequent oxidation via formaldehyde dehydrogenase to yield formic acid. Formic acid is primarily responsible for the metabolic acidosis and visual disturbances (e.g., decreased visual acuity and potential blindness) associated with methanol poisoning. A lethal dose of methanol in humans is approximately 1-2 mL/kg. Fomepizole has been shown in vitro 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 μ mol/L. In a study of dogs given a lethal dose of ethylene glycol, three animals each were administered fomepizole, ethanol, or left untreated (control group). The three animals in the untreated group became progressively obtunded, moribund, and died. At necropsy, all three dogs had severe renal tubular damage. Fomepizole or ethanol, given 3 hours after ethylene glycol ingestion, attenuated the metabolic acidosis and prevented the renal tubular damage associated with ethylene glycol intoxication.

Fomepizole Dosing in Patients Requiring Hemodialysis

DOSE AT THE BEGINNING OF HEMODIALYSIS	
If < 6 hours since last Antizol® dose	If ≥6 hours since last Antizol® dose
Do not administer dose	Administer next scheduled dose

DOSING DURING HEMODIALYSIS
Dose every 4 hours

DOSING AT THE TIME HEMODIALYSIS IS COMPLETED	
Time between last dose and the end of hemodialysis	
<1 hour	Do not administer dose at the end of hemodialysis
1–3 hours	Administer 1/2 of next scheduled dose
>3 hours	Administer next scheduled dose

MAINTENANCE DOSING OFF HEMODIALYSIS
Give next scheduled dose 12 hours from last dose administered

Administration

Fomebest™ (Fomepizole injection) solidifies at temperatures less than 25° C (77° F). If the **Fomebest™** (Fomepizole injection) solution has become solid in the vial, the solution should be liquefied by running the vial under warm water or by holding in the hand. Solidification does not affect the efficacy, safety, or stability of Fomebest™ (Fomepizole injection). Using sterile technique, the appropriate dose of Fomebest™ (Fomepizole injection) should be drawn from the vial with a **non-polycarbonate containing** syringe and injected into **at least 100 mL of sterile 0.9% sodium chloride injection or dextrose 5% injection**. Mix well. The entire contents of the resulting solution should be infused over 30 minutes. Fomebest™, like all parenteral products, should be inspected visually for particulate matter prior to administration.

Stability

Fomebest™ (Fomepizole injection) diluted in 100 ml of 0.9% sodium chloride injection or dextrose 5% injection remains stable and sterile for at least 24 hours when stored refrigerated or at room temperature. Fomebest™ (Fomepizole injection) does not contain preservatives. Therefore, maintain sterile conditions, and after dilution do not use beyond 24 hours. Solutions showing haziness, particulate matter, precipitate, discoloration, or leakage should not be used.

Contraindications

Fomebest™ (Fomepizole injection) should not be administered to patients with a documented serious hypersensitivity reaction to Fomebest™ (Fomepizole injection) or other pyrazoles

Pharmacokinetics

The plasma half-life of **Fomebest™** (Fomepizole injection) varies with dose, even in patients with normal renal function, and has not been calculated.

Distribution: After intravenous infusion, **Fomebest™** (Fomepizole injection) rapidly distributes to total body water. The volume of distribution is between 0.6 L/kg and 1.02 L/kg.

Metabolism: In healthy volunteers, only 1-3.5% of the administered dose of **Fomebest™** (Fomepizole) (7-20 mg/kg oral and IV) was excreted unchanged in the urine, indicating that metabolism is the major route of elimination. In humans, the primary metabolite of **Fomebest™** (Fomepizole injection) is 4-carboxypyrazole (approximately 80-85% of administered dose), which is excreted in the urine. Other metabolites of **Fomebest™** (Fomepizole) observed in the urine are 4-hydroxymethylpyrazole and the N-glucuronide conjugates of 4-carboxypyrazole and 4-hydroxymethylpyrazole.

Excretion: The elimination of **Fomebest™** (Fomepizole injection) is best characterized by Michaelis-Menten kinetics after acute doses, with saturable elimination occurring at therapeutic blood concentrations [100-300 µmol/L, 8.2-24.6 mg/L].

With multiple doses, **Fomebest™** (Fomepizole injection) rapidly induces its own metabolism via the cytochrome P450 mixed-function oxidase system, which produces a significant increase in the elimination rate after about 30-40 hours. After enzyme induction, elimination follows first-order kinetics.

Special Populations

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

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

Gender: **Fomebest™** (Fomepizole injection) has not been studied sufficiently to determine whether the pharmacokinetics differ between the genders.

Renal Insufficiency: The metabolites of **Fomebest™** (Fomepizole injection) are excreted renally. Definitive pharmacokinetic studies have not been done to assess pharmacokinetics in patients with renal impairment.

Hepatic Insufficiency: **Fomebest™** (Fomepizole injection) is metabolized through the liver, but no definitive pharmacokinetic studies have been done in subjects with hepatic disease.

Warnings and precautions

Fomebest™ (Fomepizole injection) **should not be given undiluted or by bolus injection.** Venous irritation and phlebosclerosis were noted in two of six normal volunteers given bolus injections (over 5 minutes) of **Fomebest™** (Fomepizole injection) at a concentration of 25 mg/mL.

Do not use polycarbonate syringes or polycarbonate-containing needles (including polycarbonate filter needles) when diluting or administering Fomebest™ (Fomepizole injection). Fomepizole can interact with polycarbonate, compromising the integrity of the syringe and/or needle component containing polycarbonate.

Minor allergic reactions (mild rash, eosinophilia) have been reported in a few patients receiving **Fomebest™** (Fomepizole injection). Therefore, patients should be monitored for signs of allergic reactions.

Pregnancy and Lactation

Pregnancy Category C: Animal reproduction studies have not been conducted with Fomepizole. (Fomepizole injection) **Fomebest™** (Fomepizole injection) 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 **Fomebest™** (Fomepizole injection) 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.

Drug interactions and incompatibility

Oral doses of **Fomebest™** (Fomepizole injection) (10-20 mg/kg), via alcohol dehydrogenase inhibition, significantly reduced the rate of elimination of ethanol (by approximately 40%) given to healthy volunteers in moderate doses. Similarly, ethanol decreased the rate of elimination of **Fomebest™** (Fomepizole) (by approximately 50%) by the same mechanism.

Reciprocal interactions may occur with concomitant use of **Fomebest™** (Fomepizole injection) and drugs that increase or inhibit the cytochrome P450 system (e.g., phenytoin, carbamazepine, cimetidine, ketoconazole), though this has not been studied.

Indications

Fomebest™ is indicated as an antidote for ethylene glycol (such as antifreeze) or methanol poisoning, or for use in suspected ethylene glycol or methanol ingestion, either alone or in combination with hemodialysis

Dosage and administration

Do not use polycarbonate syringes or polycarbonate-containing needles (including polycarbonate filter needles) when diluting or administering Fomebest™. (Fomepizole injection) can interact with polycarbonate, compromising the integrity of the syringe and/or needle component containing polycarbonate.

Treatment Guidelines

If ethylene glycol or methanol poisoning is left untreated, the natural progression of the poisoning leads to accumulation of toxic metabolites, including glycolic and oxalic acids (ethylene glycol intoxication) and formic acid (methanol intoxication). These metabolites can induce metabolic acidosis, nausea/vomiting, seizures, stupor, coma, calcium oxaluria, acute tubular necrosis, blindness, and death. The diagnosis of these poisonings may be difficult because ethylene glycol and methanol concentrations diminish in the blood as they are metabolized to their respective metabolites. Hence, both ethylene glycol and methanol concentrations and acid base balance, as determined by serum electrolyte (anion gap) and/or arterial blood gas analysis, should be frequently monitored and used to guide treatment.

Treatment consists of blocking the formation of toxic metabolites using inhibitors of alcohol dehydrogenase, such as **Fomebest™** (Fomepizole injection) and correction of metabolic abnormalities. In patients with high ethylene glycol or methanol concentrations (≥ 50 mg/dL), significant metabolic acidosis, or renal failure, hemodialysis should be considered to remove ethylene glycol or methanol and the respective toxic metabolites of these alcohols.

Treatment with Fomebest™

Begin **Fomebest™** (Fomepizole injection) treatment immediately upon suspicion of ethylene glycol or methanol ingestion based on patient history and/or anion gap metabolic acidosis, increased osmolar gap, visual disturbances, or oxalate crystals in the urine, OR a documented serum ethylene glycol or methanol concentration greater than 20 mg/dL.

Hemodialysis

Hemodialysis should be considered in addition to **Fomebest™** (Fomepizole injection) in the case of renal failure, significant or worsening metabolic acidosis, or a measured ethylene glycol or methanol concentration of greater than or equal to 50 mg/dL. Patients should be dialyzed to correct metabolic abnormalities and to lower the ethylene glycol concentrations below 50 mg/dL.

Discontinuation Of Fomebest™ Treatment

Treatment with **Fomebest™** (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 Fomebest™ (Fomepizole injection)

A loading dose of 15 mg/kg should be administered, followed by doses of 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours thereafter until ethylene glycol or methanol concentrations are undetectable or have been reduced below 20 mg/dL, and the patient is asymptomatic with normal pH. All doses should be administered as a slow intravenous infusion over 30 minutes (see **Administration**).

Dosage with Renal Dialysis

Fomebest™ (Fomepizole injection) is dialyzable and the frequency of dosing should be increased to every 4 hours during hemodialysis

Side effects

The most frequent adverse events reported as drug-related or unknown relationship to study drug in the 78 patients and 63 normal volunteers who received **Fomebest™** (Fomepizole injection) were headache (14%), nausea (11%), and dizziness, increased drowsiness, and bad taste/metallic taste (6% each). All other adverse events in this population were reported in approximately 3% or fewer of those receiving **Fomebest™** (Fomepizole injection) and were as follows:

Body as a Whole: Abdominal pain, fever, multiorgan system failure, pain during Fomebest™ (Fomepizole injection), inflammation at injection site, lumbalgia/backache, hangover

Cardiovascular: Sinus bradycardia/bradycardia, phlebosclerosis, tachycardia, phlebitis, shock, hypotension

Gastrointestinal: Vomiting, diarrhea, dyspepsia, heartburn, decreased appetite, transient transaminitis

Hemic/Lymphatic: Eosinophilia/hypereosinophilia, lymphangitis, disseminated intravascular coagulation, anemia

Nervous: Lightheadedness, seizure, agitation, feeling drunk, facial flush, vertigo, nystagmus, anxiety, "felt strange", decreased environmental awareness

Respiratory: Hiccups, pharyngitis

Skin/Appendages: Application site reaction, rash

Special Senses: Abnormal smell, speech/visual disturbances, transient blurred vision, roar in ear

Urogenital: Anuria

Overdose and treatment of over dosage

Nausea, dizziness, and vertigo were noted in healthy volunteers receiving 50 and 100 mg/kg doses of **Fomebest™** (Fomepizole injection) (at plasma concentrations of 290-520 μ mol/L, 23.8-42.6 mg/L). These doses are 3-6 times the recommended dose. This dose-dependent CNS effect was short-lived in most subjects and lasted up to 30 hours in one subject.

Fomebest™ (Fomepizole injection) is dialyzable, and hemodialysis may be useful in treating cases of overdosage.

Presentation

Fomebest™ (Fomepizole injection) is supplied as a sterile, preservative-free solution for intravenous use. One vial of 1.5 mL.

Storage: Store at controlled room temperature 20° to 25°C.

Keep out of reach of children

Discard unused portion



Marketed by:

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