

## **Product Monograph**

**Antizol<sup>®</sup>  
(fomepizole) Injection**

**1.5 mL (1 g/mL)**

**Synthetic Alcohol Dehydrogenase Inhibitor**

Paladin Labs Inc.  
Montreal, Quebec  
H4P 2T4

Date of Preparation: November 20, 2006

Control No. 109893

ANTIZOL<sup>®</sup> is a registered trademark of Jazz Pharmaceuticals, Inc.

### **PRODUCT NAME**

**Antizol<sup>®</sup> (fomepizole) Injection**

**1.5 mL (1 g/mL)**

### **THERAPEUTIC CLASSIFICATION**

Synthetic Alcohol Dehydrogenase Inhibitor

### **ACTION AND CLINICAL PHARMACOLOGY**

#### **Mechanism of Action:**

Antizol (fomepizole) 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 by-products primarily responsible for the metabolic acidosis and renal damage seen in ethylene glycol toxicosis which presents with the following morbidities: nausea/vomiting, seizures, cardiac arrhythmias, stupor, coma, calcium oxaluria, acute tubular necrosis and death, depending on the amount of ethylene glycol ingested

and the time elapsing from ingestion. 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* and *in vivo* to block alcohol dehydrogenase enzyme activity in dog, monkey, and human liver. The relative affinity of fomepizole for human ADH is 80,000 times greater than that of methanol and ethylene glycol, and 8,000 times greater than that of ethanol (3, 18, 30). The concentration of fomepizole at which alcohol dehydrogenase is inhibited by 50% *in vitro* is approximately 0.1  $\mu\text{mol/L}$ . The plasma concentrations achieved in humans with the proposed dosage regimen are well above this, with peak concentrations of fomepizole between 100-300  $\mu\text{mol/L}$  (8.6-24.6 mg/L). These levels are achieved with oral or i.v. fomepizole doses of 10-20 mg/kg. Fomepizole is most effective when given in close proximity to the ethylene glycol or methanol ingestion before significant target organ damage occurs.

### **Pharmacokinetics:**

The plasma half-life of fomepizole 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 0.6 L/kg and 1.02 L/kg.

### Metabolism

In healthy volunteers, only 1-3.5% of the administered dose of 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 fomepizole is 4-carboxypyrazole (approximately 80-85% of administered dose), which is excreted in the urine. Other metabolites of fomepizole observed in the urine are 4-hydroxymethylpyrazole and the N-glucuronide conjugates of 4-carboxypyrazole and 4-hydroxymethylpyrazole.

### Excretion

After a single dose, the elimination of fomepizole is best characterized by Michaelis-Menten kinetics with saturable elimination occurring at plasma concentrations of 100-300  $\mu\text{mol/L}$ , 8.2-24.6 mg/L.

With multiple doses, fomepizole 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

No special pharmacokinetic studies have been performed with respect to pediatric, geriatric, hepatically-impaired, or renally-impaired patients. Possible gender differences to recommend dose adjustments for patient subgroups were not investigated.

### INDICATIONS AND CLINICAL USE

Antizol<sup>®</sup> (fomepizole) Injection is indicated as an antidote for ethylene glycol (such as antifreeze) or methanol poisoning (such as windshield washer fluid), or for use in suspected ethylene glycol or methanol ingestion, either alone or in combination with hemodialysis (see **DOSAGE AND ADMINISTRATION**).

### CONTRAINDICATIONS

Antizol<sup>®</sup> (fomepizole) Injection should not be administered to patients with a documented serious hypersensitivity reaction to Antizol or other pyrazoles.

### PRECAUTIONS

#### **General:**

**Antizol<sup>®</sup> (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 Antizol at a concentration of 25 mg/mL.

Minor allergic reactions (mild rash, eosinophilia) have been reported in a few patients receiving Antizol (see **ADVERSE REACTIONS**). Therefore, patients should be monitored for signs of allergic reactions.

**Drug Interactions:**

Oral doses of Antizol (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 Antizol (by approximately 50%) by the same mechanism.

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

**Pregnancy:**

Animal reproduction studies have not been conducted with fomepizole. It is also not known whether Antizol can cause fetal harm when administered to pregnant women or can affect reproduction capacity. Antizol 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, nursing should be discontinued when Antizol is administered to nursing women.

**Pediatric Use:**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use:**

Fomepizole is metabolized by the liver and excreted by the kidney. The functions of both organs are generally lower in elderly patients; therefore, care should be taken when selecting the dose of fomepizole for elderly patients.

**ADVERSE REACTIONS**

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 Antizol<sup>®</sup> (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 Antizol and were as follows :

*Body as a Whole:* Abdominal pain, fever, pain during Antizol

injection, inflammation at injection site, lumbalgia/backache, hangover

*Cardiovascular:* Phlebosclerosis, phlebitis, hypotension

*Gastrointestinal:* Vomiting, diarrhea, dyspepsia, heartburn, decreased appetite, transient increase in liver function tests

*Hemic/Lymphatic:* Eosinophilia/hypereosinophilia, lymphangitis, anemia

*Nervous:* Lightheadedness, 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

### **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

Nausea, dizziness, and vertigo were noted in healthy volunteers receiving 50 and 100 mg/kg doses of Antizol<sup>®</sup> (fomepizole) Injection (at plasma concentrations of 290-520  $\mu\text{mol/L}$ , 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.

Antizol is dialyzable, and hemodialysis may be useful in treating cases of overdose.

### **DOSAGE AND ADMINISTRATION**

#### **Treatment Guidelines:**

Treatment of ethylene glycol and methanol poisonings consist of blocking the formation of toxic metabolites using inhibitors of alcohol dehydrogenase, such as Antizol<sup>®</sup> (fomepizole) Injection, and correction of metabolic abnormalities. In patients with high ethylene glycol or methanol concentrations ( $\geq 50$  mg/dL), significant metabolic acidosis, or renal failure, hemodialysis should

be considered in addition to treatment with Antizol to remove ethylene glycol or methanol and the respective toxic metabolites of these alcohols.

**Treatment with Antizol:**

Begin Antizol 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.

In addition to specific antidote treatment with Antizol, patients intoxicated with ethylene glycol or methanol should be managed as appropriate for metabolic acidosis, acute renal failure (ethylene glycol), adult respiratory distress syndrome, visual disturbances (methanol) and hypocalcemia. At frequent intervals throughout the treatment, patients poisoned with ethylene glycol should be monitored for ethylene glycol concentrations in serum and urine, and the presence of urinary oxalate crystals. Similarly, serum methanol concentrations should be monitored in patients poisoned with methanol. Hepatic enzymes and white blood cell counts should be monitored during treatment, as transient increases in serum transaminase concentrations and eosinophilia have been noted with repeated Antizol dosing.

**Dosing of Antizol:**

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 **Preparation for Intravenous Administration**, below).

### **Dosage with Hemodialysis:**

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

The following guidelines for administering Antizol during hemodialysis should be used:

Before dialysis: Administer next scheduled dose if >6 hours since the last dose

During dialysis: Administer doses every 4 hours

Post-dialysis: If time since last dose is < 1 hour, then give the next scheduled dose 12 hours from the last dose administered, and then follow the normal dosing schedule (see **Dosing of Antizol**).

If time since last dose is  $\geq 1$  hour but < 3 hours, then immediately administer 50% of the next scheduled dose, and then follow the normal dosing schedule.

If time since last dose is  $\geq 3$  hours, then immediately administer 100% of the next scheduled dose, and then follow the normal dosing schedule.

### **Discontinuation of Antizol Treatment:**

Treatment with Antizol 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.

**Preparation for Intravenous Administration:**

When preparing Antizol solution avoid ocular, dermal, or inhalation exposures. In case of eye or skin exposure, flush immediately with copious amounts of water. Seek medical attention if irritation persists. Prepare solution in well-ventilated area. If accidental inhalation occurs, move to fresh air.

Antizol solidifies at temperatures less than 25°C (77°F). If the Antizol 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 Antizol. Using sterile technique, the appropriate dose of Antizol should be drawn from the vial with a 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. Antizol, like all parenteral products, should be inspected visually for particulate matter prior to administration.

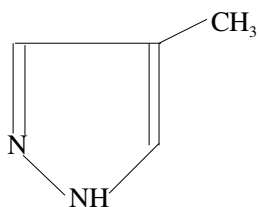
**PHARMACEUTICAL INFORMATION**

**Drug Substance:**

*Common name:* fomepizole

*Chemical name:* 4-methylpyrazole

*Structural formula:*



*Molecular Formula:*  $\text{C}_4\text{H}_6\text{N}_2$

*Molecular weight:* 82.1

*Description:* Fomepizole is a clear to yellow liquid at room temperature. Its melting point is 25°C (77°F) and it may present in a solid form at room temperature. Solidification does not affect the efficacy, safety or stability of fomepizole. Fomepizole is soluble in water and very soluble in ethanol, diethyl ether, and chloroform.

**Composition:**

The drug product is 100% bulk fomepizole (1 g/mL) (wt/vol) with no excipients or preservatives.

**Stability and Storage Recommendations:**

Store at controlled room temperature (20° to 25°C).

Antizol vials are for single use only. Any unused portion should be discarded.

For stability information, please refer to **Parenteral Products, Stability**, below.

**Parenteral Products:**

*Stability:* Antizol diluted in 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. Antizol does not contain preservatives. Therefore, maintain sterile conditions, and after dilution do not use beyond 24 hours. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

**AVAILABILITY OF DOSAGE FORMS**

Antizol<sup>®</sup> (fomepizole) Injection is supplied as a sterile, preservative-free solution for intravenous use. Each package contains four vials, each vial containing 1.5 mL (1 g/mL) of Antizol<sup>®</sup> (fomepizole) Injection.

## PHARMACOLOGY

### **Animal Studies:**

Fomepizole has been shown *in vitro* and *in vivo* to block alcohol dehydrogenase enzyme activity in dog, monkey, and human liver. The relative affinity of fomepizole for human ADH is 80,000 times greater than that of methanol and ethylene glycol, and 8,000 times greater than that of ethanol (3, 18, 30).

Fomepizole has been shown to inhibit ethylene glycol toxicity in rats (8), dogs (11, 17, 13), monkeys (9), and cats (12). Fomepizole has been shown to inhibit methanol toxicity in monkeys (4, 5, 24, 25, 26). Fomepizole is most effective when given in close proximity to the exposure of ethylene glycol or methanol, before significant renal damage or visual disturbance has occurred. When used in sufficient doses, fomepizole inhibits the metabolism of ethylene glycol or methanol to their toxic metabolites and ameliorates metabolic acidosis before significant target organ damage develops in relevant animal models.

Animal and *in vitro* studies indicate that the main metabolite, 4-carboxypyrazole, is not active pharmacologically nor are any of the minor metabolites active at concentrations found following therapeutic doses of fomepizole.

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.

Several studies have demonstrated that fomepizole plasma concentrations of approximately 10  $\mu\text{mol/L}$  (0.82 mg/L) in monkeys are sufficient to inhibit methanol metabolism to formate, which is also mediated by alcohol dehydrogenase. Based on these results, peak plasma concentrations of fomepizole in humans in the range of 100 to 300  $\mu\text{mol/L}$  (8.6-24.6 mg/L) have been targeted to assure adequate plasma concentrations for the effective inhibition of alcohol dehydrogenase.

#### **Clinical Studies:**

Clinical studies demonstrate that fomepizole is rapidly and widely distributed to the total body water after IV infusion and undergoes non-linear Michealis-Menten elimination kinetics after a single dose. Following 36 h of chronic treatment consisting of repeated supplemental doses at 12 h intervals, fomepizole can induce its own metabolism and larger supplemental doses are needed to maintain blood levels in the therapeutic range. After metabolism is induced, the elimination approximates a first order kinetic model. Fomepizole is readily dialyzed, and dosing recommendations must provide for increased dosing during dialysis.

The main metabolite, 4-carboxypyrazole, is formed from fomepizole at the same rate regardless of the size of the dose of fomepizole, suggesting that saturation kinetics arise in the pathway leading to the formation of 4-carboxypyrazole.

Fomepizole can inhibit the metabolism of ethanol and ethylene glycol, and these substances in turn inhibit the elimination of fomepizole. All three substances are substrate inhibitors of alcohol dehydrogenase. One may expect drug interactions with other alcohol dehydrogenase inhibitors, and induction of the elimination of fomepizole by other enzyme inducers that affect the cytochrome P450 enzyme system.

The efficacy of Antizol in the treatment of ethylene glycol and methanol intoxication was studied in two prospective, U.S. clinical trials without concomitant control groups. In these trials, 14/16 patients in the ethylene glycol trial and 7/11 patients in the methanol trial underwent hemodialysis in combination with Antizol therapy. (See **DOSAGE AND ADMINISTRATION**). All patients received Antizol shortly after admission.

The results of these two studies provide evidence that Antizol blocks ethylene glycol and methanol metabolism mediated by alcohol dehydrogenase in the clinical setting. In both studies, plasma concentrations of toxic metabolites of ethylene glycol and methanol (glycolate and formate, respectively) failed to rise. Even though the relationship to fomepizole therapy was confounded by treatment with hemodialysis and significant blood ethanol concentrations, in post-dialysis periods, when ethanol concentrations were insignificant (<100 mg/dL) and the concentrations of ethylene glycol or methanol ranged between 26 to 60 mg/dL administration of Antizol alone prevented any rise in glycolate or formate concentrations.

In a separate French trial, 5 patients presented with ethylene glycol concentrations ranging from 46.5 to 345 mg/dL, insignificant ethanol blood concentrations, and normal renal function. These patients were treated with fomepizole alone without hemodialysis, and none developed signs of renal injury.

Ethanol (intravenous and oral) has been used as an alcohol dehydrogenase inhibitor to treat ethylene glycol poisoning. However, the amount given must be carefully controlled, since ethanol itself is a hepatotoxin and CNS depressant. In contrast, fomepizole exhibits a slow and reproducible rate of elimination and has minimal CNS depressant effects.

## TOXICOLOGY

### **Acute Toxicity:**

An acute toxicology study has been conducted in the mouse and rat over the dose range of 0.75 to 2.00 g/kg. The oral LD<sub>50</sub> of fomepizole in the mouse and rat was 1.3 g/kg and 1.4 g/kg, respectively. The most pronounced toxic symptoms were hypnosis in high doses and sedation in low doses. Death occurred between 2 and 24 hours. One rat in the 1.75 g/kg dose group died between 24 and 48 hours post-dose.

However, in another study the oral LD<sub>50</sub>'s of fomepizole were reported as 0.54 and 0.64 g/kg in the mouse and rat, respectively. The intravenous LD<sub>50</sub> was reported to be 0.32 g/kg in both the mouse and the rat. These dose levels represent significant margins over those proposed in the human therapeutic dose regimen.

### **Subacute Toxicity:**

Based on a dose ranging study, fomepizole was evaluated for systemic toxicity in dogs following 14-days intravenous infusion at doses of 10, 20 and 30 mg/kg/day for 30 minutes every 12 hours. This infusion regimen is generally consistent with the planned label indication, but the duration of this study (14 days) exceeds the maximum therapeutic use in humans.

The results of this study indicated that such a regimen in dogs produces no signs of systemic toxicity or local vascular irritation at a dose of 10 mg/kg (no effect level) twice daily for 14 days. At 20 mg/kg, which is above the maximum planned clinical dose, effects were minimal and were

limited to a decrease in serum triglycerides, an increase in serum sodium (males only), an increase in bicarbonate, and an increase in urine output (increased volume and decreased specific gravity). This dose of 20 mg/kg was considered a no-toxic-effect level in the dog. A dose of 30 mg/kg was a clear effect level, with the liver identified as the primary target organ (increased alkaline phosphatase and ALT, decreased triglycerides and increased liver weights). Also noted at this dose were decreased food consumption, decreased potassium, increased sodium and bicarbonate, and increased urine output. Even at this dose level, none of the effects were life threatening, and most (all except alkaline phosphatase and ALT) were reversible following a 28 day recovery period.

Plasma concentrations determined in this study indicate that, at the no effect level of 10 mg/kg, drug levels observed during the infusion were similar to those seen in humans.

The results of this study indicate that, under the planned conditions of clinical use and considering the short term use and life-saving potential of the drug, fomepizole is safe for the intended indication and does not represent a significant risk to the patient.

### **Chronic Toxicity:**

A series of experiments were conducted to evaluate the chronic toxicity in young male Cynomolgus monkeys. The objective of the first series of experiments was to assess the toxicity of fomepizole after dosing for six weeks in 12 monkeys. Toxicity assessments included clinical signs, hematology, and blood chemistry, and gross and microscopic pathology were evaluated.

Additionally, ophthalmoscopy with assessment of the fundus structures and recordings of the electroretinogram (ERG) were performed. The objective of the second series of experiments was to identify any direct effect of fomepizole on the eye of the monkey as assessed by ERG.

Except for one monkey who died during anesthesia, the administration of fomepizole induced no clinical toxic reactions, regardless of the dose administered and no visual disturbances were observed. The results of these experiments supported that an initial loading dose of fomepizole administered at a dose of 15-20 mg/kg inhibited methanol oxidation in the monkey model. Furthermore, it was concluded that the results of these experiments clearly indicated that fomepizole would be an attractive substitute for ethanol in the treatment of methanol poisoning.

#### **Carcinogenesis:**

There have been no long-term studies performed in animals to evaluate carcinogenic potential.

#### **Mutagenesis:**

There was a positive Ames test result in the *Escherichia coli* tester strain WP2uvrA and the *Salmonella typhimurium* tester strain TA102 in the absence of metabolic activation using fomepizole concentrations of 100, 333, 1000, 3330, and 5000 µg/plate.

In addition, the mutagenicity of fomepizole was tested in the *in vivo* mouse micronucleus assay. In the 35 animals tested, dosed at 75, 150, and 300 mg/kg, the bone marrow showed that fomepizole did not induce a significant increase in the frequency of micronucleated

polychromatic erythrocytes; thus, this test did not indicate bone marrow cytotoxicity. The mutagenicity of fomepizole is considered to be negative in this assay.

**Impairment of Fertility:**

In rats, fomepizole (110 mg/kg) administered orally for 40 to 42 days resulted in decreased testicular mass (approximately 8% reduction). This dose is approximately 0.6 times the human maximum daily exposure based on surface area ( $\text{mg}/\text{m}^2$ ). This reduction was similar for rats treated with either ethanol or fomepizole alone. When fomepizole was given in combination with ethanol, the decrease in testicular mass was significantly greater (approximately 30% reduction) compared to those rats treated exclusively with fomepizole or ethanol.

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