

FREEDOM OF INFORMATION SUMMARY

1. General Information

New Animal Drug Application Number: NADA 141-075

Sponsor: Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 475
Minnetonka, MN 55305

Generic Name: Fomepizole

Trade Name: Antizol-Vet™ (fomepizole) for injection

Marketing Status: Rx (prescription)

2. Indications for Use

Antizol-Vet™ is indicated as an antidote for ethylene glycol (antifreeze) poisoning in dogs who have ingested or are suspected of having ingested ethylene glycol.

3. Dosage Form

Antizol-Vet™ (1.5 mL) is formulated as a sterile injectable liquid for dilution with a 30 mL vial of 0.9% sodium chloride injection, USP. Both drugs are packaged together in an antidote kit.

Route of Administration

Antizol-Vet™ is administered intravenously as soon as practical upon suspicion of ethylene glycol poisoning.

Recommended Dosages

The recommended intravenous dosing schedule of a 5% solution (50 mg/mL) of Antizol-Vet™ for treatment of ethylene glycol poisoning in dogs is described below. The drug will be administered following dilution in 0.9% sodium chloride injection, USP.

Initial dose:	20 mg/kg IV
Dose 2 (12 hours after initial dose):	15 mg/kg IV
Dose 3 (24 hours after initial dose):	15 mg/kg IV
Dose 4 (36 hours after initial dose):	5 mg/kg IV

If the animal has not recovered following this regimen and there is a suspicion or documentation of remaining ethylene glycol in the bloodstream of the affected animal, the practitioner should continue to dose the animal with 5 mg/kg every 12 hours until the ethylene glycol does not remain in the bloodstream or the animal has visibly recovered.

4. Effectiveness

The currently recommended Antizol-Vet™ dosing regimen used to treat dogs poisoned with ethylene glycol has been published in all editions of Kirk's, Current Veterinary Therapy: Small Animal Practice since 1986 (ninth edition) and is widely used in clinical practice.

A. Dose Confirmation

Antizol-Vet™ has been shown to be efficacious in treating ethylene glycol poisoning in two experimental laboratory studies and in one clinical field trial. The results of these studies are summarized below.

1. Grauer GF, Thrall MA, Henre BA, Hjelle JJ., Comparison of the effects of ethanol and 4-methylpyrazole on the pharmacokinetics and toxicity of ethylene glycol in the dog. Toxicology Letters 1987; 35:307-14.

Grauer, et al. (1987) studied the comparative efficacy of ethanol and fomepizole in the treatment of ethylene glycol toxicity in the dog. Nine healthy, mixed-breed dogs of both sexes, with an average weight of 21.8 kg, were randomly assigned to one of three groups (3 dogs/group); ethylene glycol alone (Group 1), ethylene glycol plus ethanol (Group 2), or ethylene glycol plus fomepizole (Group 3). Each animal was given an ethylene glycol dose of 10.6 g/kg (twice the lethal ethylene glycol dose) mixed with wet dog food. Group 1 animals received no antidotal therapy. Dogs in Group 2 were treated with 1584 mg/kg ethanol (20% in water) IV at 3, 7, 14, and 24 hours after ingestion of ethylene glycol. Dogs in Group 3 were treated with fomepizole IV at doses of 20, 15, and 5 mg/kg at 3, 24, and 36 hours after ingestion of ethylene glycol, respectively.

All of the dogs exhibited progressive central nervous system depression, ataxia, and polydipsia within 3 hours of ethylene glycol ingestion. The three dogs in Group 1 became progressively depressed, and then moribund. They were euthanized at 12, 80 and 120 hours, respectively, after ethylene glycol ingestion. At necropsy, histopathology results revealed renal proximal tubular degeneration and necrosis with intraluminal calcium oxalate crystal deposition in the renal tissue of all Group 1 animals. Tubular necrosis was more severe in the dogs euthanized at 80 and 120

hours. Treatment with either fomepizole or ethanol yielded similar efficacy in terms of preventing the metabolic acidosis and renal tubular damage associated with ethylene glycol intoxication.

There was a difference in the safety of the two products. The dogs treated with fomepizole were clinically normal within 24 hours. The ethanol treated dogs, remained either recumbent or severely ataxic for 36 hours and were depressed for 72 hours. The central nervous system depression, along with the decreased water consumption, and the ethylene glycol-induced diuresis caused severe dehydration and complicated the management of dogs treated with ethanol. When these animals stopped drinking water, intravenous fluid therapy was initiated at a rate of 5.0 ml/kg/hr. for 18 hours starting at 6 hours after ingestion to correct dehydration. The amount of ethylene glycol excreted unchanged in the urine between 3 and 72 hours was 48%, 51%, and 71% in Groups 1, 2, and 3 respectively. Group 3 exhibited the greatest increase in ethylene glycol excreted unchanged in the urine. Fomepizole was a better antidote than ethanol because it was less toxic and it increased the amount of ethylene glycol excreted unchanged in the urine. No adverse experiences for fomepizole were reported by the authors.

2. Dial SM, Thrall MAH, Hamar DW, Efficacy of 4-methylpyrazole for treatment of ethylene glycol intoxication in dogs, Am J Vet Res 1994; 55(12):1762-1770.

Dial, et al. (1994) studied the effectiveness of fomepizole in ethylene glycol poisoned dogs when treatment was delayed until 5 or 8 hours after ingestion. Eleven mature mixed breed dogs of either sex with a mean body weight of 25.7 kg were given ethylene glycol at a dose of 10.6 g/kg (twice the lethal dose). A 95% ethylene glycol antifreeze solution was mixed with canned dog food and offered to each dog after food was withheld for 24 hours. In two dogs, one from each treatment group, 10.6 grams of reagent grade ethylene glycol/kg was administered in place of the antifreeze solution. Animals were assigned to two treatment groups: Group 1 (5) dogs were treated with fomepizole at 5 hours after ethylene glycol ingestion while Group 2 (6) dogs were treated with fomepizole 8 hours after ethylene glycol ingestion. Fomepizole was administered intravenously in a polyethylene glycol-400 vehicle at a concentration of 50 mg/ml. A loading dose of 20 mg/kg fomepizole was given IV to each group of dogs followed by fomepizole maintenance doses of 15, 10, and 5 mg/kg at 12, 24, and 36 hours after the loading dose.

All dogs became ataxic and depressed by three hours after ethylene glycol ingestion. One dog (Group 2) vomited at five hours following ethylene glycol ingestion. By 12 hours, all dogs in Group 1 (5) and 4 of 6 dogs in Group 2 were clinically normal. The five dogs in Group 1 recovered without morphologic, biochemical, or clinical evidence of renal impairment. Two of the six dogs in Group 2 developed acute renal

failure. One of the dogs in Group 2 remained isosthenuric for two months but did not show any other signs of renal impairment. The remaining three dogs in Group 2 recovered without morphologic, biochemical, or clinical evidence of renal impairment.

The two animals that developed acute renal failure were admitted to the intensive care unit of the teaching hospital at 48 hours with azotemia and peritoneal dialysis was performed. By 96 hours post ingestion, anuria and subsequent acute oliguric renal failure developed. One animal died during replacement of an occluded catheter and the other was euthanized after eight weeks of dialysis without improvement of renal function.

The study demonstrated that fomepizole administration is effective in preventing renal failure, even when treatment is delayed as late as 5 to 8 hours after ethylene glycol ingestion, as long as unmetabolized ethylene glycol is present in serum and the dog is not azotemic. No adverse experiences for fomepizole were reported by the authors.

3. Dial SM, Thrall MA, Hamar DW, 4-Methylpyrazole as treatment for naturally acquired ethylene glycol intoxication in dogs, JAVMA 1989; 195(1):73-6.

Fomepizole was successfully used as a clinical antidote in the treatment of ethylene glycol poisoned dogs in an open-label study conducted by Dial, et al. (1989). Twenty-four dogs were admitted to the Colorado State University Veterinary Teaching Hospital (CSVTH) from 1980 to 1985 and evaluated for placement into the prospective study. Of the 24 dogs, 15 had high serum and urine ethylene glycol concentrations (greater than 50 mg/dl). Seven of the 15 dogs were azotemic upon admission and were excluded from the trial. Eight dogs had high serum and urine ethylene glycol concentrations without azotemia and were the basis of this study. A diagnosis of ethylene glycol poisoning was made if serum and urine ethylene glycol concentrations were greater than 50 mg/dl. Fomepizole was administered intravenously in a polyethylene glycol-400 vehicle at a concentration of 50 mg/mL at doses of 20 mg/kg upon presentation, 15 mg/kg, 17 hours later, and 5 mg/kg at 25 hours after presentation. In 2 of the 8 dogs, an additional dose of 5 mg/kg was administered at 36 hours after admission. Dogs were monitored in the intensive care unit during treatment.

By 24 hours, all dogs had clinical improvement (increased appetite, alleviation of central nervous system and gastrointestinal signs and increased responsiveness). Duration of hospitalization ranged from 3 to 7 days. Of the eight dogs, six were released from clinical care within three days of admission, and the remaining two

were released by day seven after admission. By 36 hours after admission, 7 of 8 dogs were maintaining hydration by oral fluid intake and fluid therapy was discontinued. One animal remained polyuric and the administration of IV fluids was maintained for 5 days. When fluids were discontinued, the animal's hydration status was maintained, but isosthenuria remained. Sixteen days after admission, this dog had regained the ability to concentrate urine, an indication of return to normal tubular function. All four dogs that returned for subsequent evaluation at one week after discharge had normal laboratory findings at that time. This study demonstrated that fomepizole is an effective antidote in treating dogs poisoned with ethylene glycol. No adverse experiences for fomepizole were reported by the authors.

B. Clinical Field Study

A retrospective open-label study was conducted at Colorado State University Veterinary Teaching Hospital, Colorado State University, Fort Collins, Colorado, to assess the efficacy of fomepizole as a treatment for ethylene glycol poisoning in dogs. The principal investigator was Dr. Mary Anna Thrall. One-hundred five (54 males, 51 females) mixed breed and purebred dogs, ranging from 3 months to 15 years of age were admitted to the CSVTH from September 1983 through April 1995 for treatment of suspected or confirmed ethylene glycol toxicity. Of 38 confirmed cases, 14 dogs were confirmed by a commercial test kit, 10 by measurement of ethylene glycol serum concentrations, and the remaining by a combination of history, suggestive clinical and/or laboratory findings. A commercial test kit is available for measuring blood ethylene glycol concentrations greater than 50 mg/dl (EGT Test Kit, PRN Pharmacal, Inc., 5830 McAllister Ave., Pensacola, FL). Fomepizole was administered intravenously in a polyethylene glycol-400 vehicle at a concentration of 50 mg/mL. Dogs were treated with one of the two following dosing regimens:

Dose Regimen 1

Loading Dose	20 mg/kg IV
17 hours after initial dose	15 mg/kg IV
25 hours after initial dose	5 mg/kg IV
36 hours after initial dose	5 mg/kg IV

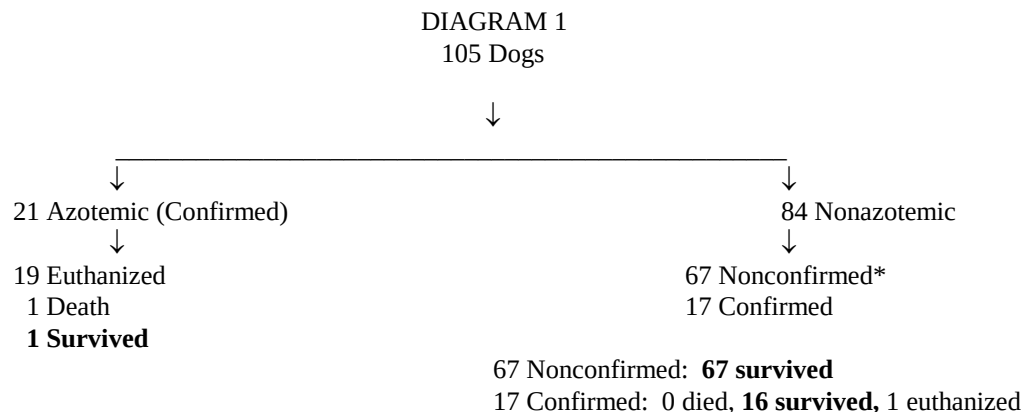
Dose Regimen 2 (Antizol-Vet™)

Loading Dose	20 mg/kg IV
12 hours after initial dose	15 mg/kg IV
24 hours after initial dose	15 mg/kg IV
36 hours after initial dose	5 mg/kg IV

Sixty-nine of the dogs were treated with dose regimen 1 and five were treated with dose regimen 2. The remaining 31 dogs were treated with slight variations of these dosing regimens. Dogs were monitored in the intensive care unit during treatment.

Fluid therapy and other supportive treatment for dehydration and to promote fluid diuresis was initiated as needed. Clinical laboratory data (chemistry profile, CBC, urinalysis, blood gases) were collected.

Eighty-four (80%) animals survived, 20 (19%) were euthanized and 1 (1%) died (See diagram 1). The dogs which survived spent an average of 1.9 ± 1.8 days in the veterinary hospital. Of the 20 euthanized animals, 17 were diagnosed azotemic at the time of admission, two were azotemic at 18 hours post admission, and one was semicomatose and anuric upon admission. Of the two diagnosed azotemic animals at 18 hours post admission, one animal was administered the entire fomepizole dose regimen 1; however, this animal's condition progressed to acute renal failure, and the owner opted for euthanasia. The other animal was administered two doses of fomepizole (regimen 1) before euthanasia. The other animal that was euthanized was presented at admission in a semicomatose and anuric state. It received a loading dose of fomepizole (20 mg/kg) prior to its deterioration. Ethylene glycol poisoning was confirmed in all of the euthanized animals.



* Under actual conditions of use in a veterinary practice ethylene glycol (EG) poisoning may be diagnosed without using the commercial test kit or measurement of serum levels. While test kit results can be read in 30 minutes the steps involved can be labor intensive. It is impractical to wait for test results (from a diagnostic laboratory) thereby delaying treatment for this life threatening emergency. History, clinical signs, etc. are practical ways of diagnosing suspected EG poisoning.

Clinical signs present upon admission included ataxia, central nervous system depression, vomiting, disorientation, dehydration, nystagmus, polyuria and polydipsia. Sixty-three of the 105 animals had no clinical signs present. Of the 38 total confirmed cases, 32 had a combination of these clinical signs present. Abnormal clinical laboratory findings included increased serum osmolality, metabolic acidosis, hyperglycemia, calcium oxalate crystalluria, increased BUN and creatinine.

One animal experienced an anaphylactic type reaction following the second dose of fomepizole. Clinical signs included tachypnea, gagging, excessive salivation and trembling. Dosing with fomepizole was discontinued and the dog survived.

Azotemia is a reliable indicator that significant renal dysfunction is present, and in this study, its presence had a significant impact on the outcome of those cases (38) confirmed with ethylene glycol poisoning. Of the 21 animals confirmed with azotemia, only 1 (5%) survived. Dogs which are azotemic usually have metabolized most of the ingested ethylene glycol. Azotemia is also a reliable indicator that more toxic metabolites have been formed and fomepizole is expected to be less effective as an antidote in these dogs. If an animal presents azotemic, prognosis is usually poor.

Conclusion: These results confirm that fomepizole is a safe and effective antidote for treating ethylene glycol poisoning in dogs. However, in order to prevent renal failure, it must be given before sufficient quantities of ethylene glycol have been metabolized.

5. Animal Safety

A. Overdosing Study

Dennis J. Naas, B.S.
WIL Research Laboratories, Inc.
1407 George Road
Ashland, Ohio 44805-9281

A Dose Range-Finding Toxicity Study with Intravenous 4-Methylpyrazole in Dogs

This study, composed of two phases, utilized ten outbred male Beagle dogs approximately six weeks of age. The objective of the study was to select doses for the subacute toxicity study based upon an evaluation of the toxic effects of the test article, fomepizole, when administered IV (twice daily for fourteen days). Dose levels of 150 and 75 (phase I) and 25 and 50 (phase II) mg/kg of Antizol-Vet™ were administered intravenously twice per day in 0.9% sodium chloride injection.

Antizol-Vet™ administered at 25 mg/kg resulted in decreased food consumption, body weight loss, and breaths with sweet odors. At 50 mg/kg or greater, Antizol-Vet™ administration resulted in adverse clinical signs (ataxia, hypoactivity, hypothermia, tremors and/or prostration, injected sclera, ptosis, decreased defecation, and protruding tongues), elevated clinical chemistries [ALP (231-400 U/L), ALT (422-6622 U/L), AST (335-5003 U/L), CPK (626-2215 U/L), BUN (61.8 MG/DL), total bilirubin (0.7 mg/dl), creatinine (1.6 mg/dl)] and increased levels for RBCs (8.67 mil/uL), hemoglobin (20 g/dl) and hematocrit (61.7%).

B. Subacute Toxicity

Dennis J. Naas, B.S.
WIL Research Laboratories, Inc.
1407 George Road
Ashland, Ohio 44805-9281

An Intravenous Toxicity Study with 4-Methylpyrazole in Dogs

This study was designed to evaluate the potential toxicity of fomepizole when administered intravenously to dogs two times a day for fourteen days. Thirty-two outbred beagle dogs were used in this study. Dogs were all approximately 5 months in age and weighed 6.9 - 9.0 kg for the males, and 7.5 - 8.9 kg for the females. Starting six days prior to initiation of dosing, the dogs were acclimatized to jackets which would contain an infusion pump. Three days prior to the initiation of the study, an indwelling catheter was surgically placed in the jugular vein and connected to the infusion pump.

Dogs were randomly separated into four groups of 4 males and 4 females each (8 dogs/group). Dosage levels of 10 (Group 2), 20 (Group 3), and 30 (Group 4) mg/kg fomepizole were selected for the study based on the results from the overdosing toxicity study. A concurrent control group (Group 1) received only the vehicle, 0.9% sodium chloride. Control and fomepizole formulations were administered intravenously at a constant rate of 4 ml/kg/hour for thirty minutes twice daily for 14 days. After the thirty minute infusion of the control or fomepizole, all animals received a continuous infusion of 0.9% sodium chloride at a rate of 0.4 ml/kg/hr until the next 30 minute infusion of control or fomepizole.

The animals were observed twice daily for mortality and morbidity. Body weights were recorded weekly during the pretest period, daily during the dosing period and twice weekly during the recovery period. Individual food consumption was recorded daily. Individual rectal temperatures were recorded twice during the pretest period, and weekly throughout the study. Blood samples for clinical pathologic evaluations were collected from each dog once prior to initiation of dosing and from all dogs on day 14 and 42 of the study. Urine for urinalysis was collected from all dogs using metabolism cages once prior to initiation of dosing and on study days 13 and 42. Ocular examinations were conducted on all animals prior to the initiation of dosing and on study days 12 and 40.

All animals survived the 14 day dosing period. After 14 days, the cannulae and associated equipment were removed. Six animals from each group (3/sex) were selected for necropsy after 14 days of dosing. The remaining study animals (8) were

observed for an additional 28 days post-dosing to evaluate recovery and necropsies for these animals were conducted on day 42. Complete necropsies were performed on all 32 dogs and tissues were preserved for histological examination. Selected tissues were examined microscopically from all animals.

Hypoactivity was observed in a single female animal in the high-dose group and was considered treatment-related. Vomiting, diarrhea and injected sclera were seen in treated males and females throughout the dosing period. This finding was also seen in the vehicle control (group 1).

Food consumption was not affected during the dosing period. There were no alterations in body weight or body temperatures.

Mean bicarbonate values were elevated and mean potassium values were decreased in the 30 mg/kg group at day 14, but returned to normal by day 42. Males and females in Groups 3 (20 mg/kg) and 4 (30 mg/kg) exhibited increases in urine volume means and associated decreases in the urine specific gravity means when compared to the control group values. An increase in urine volume is not necessarily an abnormal finding in this study and may be associated with the continuous administration of 0.9% sodium chloride and/or increased water consumption. The ocular examinations revealed no abnormalities related to administration of fomepizole.

At necropsy on day 14, two males and two females in the 30 mg/kg group had pale livers and one 30 mg/kg male had a swollen liver. The mean liver weight for the 30 mg/kg group males was greater than all groups at day 14. No treatment effects were seen on necropsy of the remaining animals at day 42.

Intravenous infusion of fomepizole to dogs for 14 days resulted in injected sclera, vomiting and diarrhea in the vehicle control and the 10, 20, and 30 mg/kg groups. A single occurrence of hypoactivity and an increase in the mean liver weights was observed in the 30 mg/kg group animals.

Pharmacokinetics Results from this twice daily 14 day intravenous study evaluating doses of 10, 20, and 30 mg/kg in dogs showed a dose proportional increase in plasma levels of fomepizole after a single (first) dose. However, the terminal elimination half life appears to increase (nonlinear kinetics) with dose following multiple administrations. This nonlinearity was particularly evident in the 30 mg/kg dose group and appeared to occur in four of the eight animals tested in the 20 mg/kg dose group. Accordingly, after the fourteen day dosing regimen in these animals, plasma fomepizole concentrations accumulated in a greater than dose proportional manner. This apparent nonlinear plasma accumulation of fomepizole is assumed to be a result of a saturable elimination process. In contrast, linear pharmacokinetics and an

absence of plasma fomepizole accumulation was observed following the fourteen days of dosing in the 10 mg/kg dose group.

Conclusion: The study demonstrates that fomepizole is safe when administered intravenously at doses up to 20 mg/kg.

6. Human Safety

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is to be labeled for use in dogs, which are non-food animals.

A user handler safety section is included on the label. The label includes the following section: "Not for use in humans. Keep out of reach of children. Irritant. 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. Use product only in a well ventilated area. If accidental inhalation occurs, move to fresh air. The material safety data sheet (MSDS) contains additional information regarding the safe use of this product. For emergency medical assistance, to report adverse effects in users and/or to obtain a copy of the MSDS, call 1-888-867-7426 (888-8ORPHAN)."

7. Agency Conclusions

The data submitted in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that Antizol-Vet™ when used under labeled conditions of use is safe and effective.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to 1) diagnose ethylene glycol poisoning, 2) administer Antizol-Vet™ intravenously, and 3) recognize and treat, if necessary adverse reactions to the drug.

Under Section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(c)(2)(F)(i), this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt thereof) of the drug has been previously approved in any other application filed under section 512(b)(1) of the Act.

8. Labeling (attached)

1. Vial label
2. Diluent label
3. Carton label
4. Package Insert