NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ANTIZOL®

Fomepizole 1g/mL concentrate for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1.5 g of fomepizole.

Excipient with known effect: none.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Clear to yellow liquid at room temperature. Its melting point is 25 ºC and it may present as a solid at room temperature.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Antizol® (fomepizole) is indicated for the treatment of ethylene glycol or methanol poisoning.

4.2. Dose and method of administration

CAUTION: MUST BE DILUTED PRIOR TO USE

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.

Antizol® solidifies at temperatures less than 25 °C hence, if the fomepizole solution has become solid in the vial, the solution should be liquefied by running the vial under warm tap water or by holding in the hand. Solidification does not affect the stability of Antizol®.

Using sterile technique, the appropriate dose of fomepizole 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. Fomepizole, like all parenteral products, should be inspected for particulate matter prior to administration.

Treatment with Fomepizole: Begin fomepizole 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 (ethylene glycol 3.22 mmol/L, methanol 6.24 mmol/L).

Dosing of Fomepizole: 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 (ethylene glycol 3.22 mmol/L, methanol 6.24 mmol/L), and the patient is asymptomatic with normal pH. All doses should be administered as a slow intravenous infusion over 30 minutes (*see Treatment Guidelines*).

Discontinuation of Fomepizole Treatment: Treatment with fomepizole may be discontinued when ethylene glycol or methanol concentrations are undetectable or have been reduced below 20 mg/dL (ethylene glycol 3.22 mmol/L, methanol 6.24 mmol/L), and the patient is asymptomatic with normal pH.

Haemodialysis: Haemodialysis should be considered in addition to fomepizole in the case of renal failure (Stage 5 CKD, GFR <15mL/min/1.73m^2), significant or worsening metabolic acidosis, or a measured ethylene glycol or methanol concentration of greater than or equal to 50 mg/dL (ethylene glycol 8.06 mmol/L, methanol 15.61 mmol/L). Patients should be dialyzed to correct metabolic abnormalities and to lower the ethylene glycol concentrations below 50 mg/dL (ethylene glycol 8.06 mmol/L).

Fomepizole Dosing in Patients Requiring Haemodialysis

DOSE AT THE BEGINNING OF HAEMODIALYSIS	
If <6 hours since last dose	**If ≥6 hours since last dose**
Do not administer dose	Administer next scheduled dose

DOSING DURING HAEMODIALYSIS
Dose every 4 hours

DOSING AT THE TIME HAEMODIALYSIS IS COMPLETED	
Time between last dose and the end of haemodialysis	
<1 hour	Do not administer dose at the end of haemodialysis
1-3 hours	Administer ½ of next scheduled dose
>3 hours	Administer next scheduled dose

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

Dosage with Renal Dialysis: Fomepizole injection is dialyzable and the frequency of dosing should be increased to every 4 hours during haemodialysis.

Both ethylene glycol and methanol concentrations, acid base balance [as determined by serum electrolyte (anion gap) and/or blood gas analysis], should be frequently monitored and used to guide treatment.

4.3. Contraindications

Fomepizole should not be administered to patients with a documented serious hypersensitivity reaction to fomepizole or other pyrazoles.

Fomepizole should not be used in patients with ethanol intoxication.

Fomepizole should not be used in patients exposed to poisons other than ethylene glycol or methanol alone or in combination (including diethylene glycol).

4.4. Special warnings and precautions for use

General: Fomepizole 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) fomepizole at a concentration of 25 mg/mL (0.3 mol/L).

Major allergic reactions (anaphylaxis) and minor allergic reactions (mild rash, eosinophilia) have been reported in a few patients receiving fomepizole (*see ADVERSE REACTION*). Therefore, patients should be monitored for signs of allergic reactions.

There is a potential risk of muscle damage resulting from creatine kinase elevation with use of fomepizole.

Paediatric Use

Safety and effectiveness in paediatric patients have not been established.

Genotoxicity

The genotoxic potential of fomepizole has only been partially investigated. Fomepizole was shown to be mutagenic in bacteria. Fomepizole did not appear to cause chromosomal aberrations in mouse micronucleus assay. The available evidence indicates that fomepizole is genotoxic.

Carcinogenicity

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

Patient Management

In addition to specific antidote treatment with fomepizole, patients intoxicated with ethylene glycol or methanol must be managed for metabolic acidosis, acute renal failure (ethylene glycol) –, adult respiratory distress syndrome, visual disturbances (methanol) and hypocalcaemia. Fluid therapy and sodium bicarbonate administration are potential supportive therapies. In addition, potassium and calcium supplementation and oxygen administration are usually necessary. Haemodialysis is necessary in the anuric patient, or in patients with severe metabolic acidosis or azotaemia (*see DOSAGE AND ADMINISTRATION*). Treatment success should be assessed by frequent measurements of blood gases, pH, electrolytes, BUN, creatinine and urinalysis, in addition to other laboratory tests as indicated by individual patient conditions. At frequent intervals throughout the treatment, patients poisoned with ethylene glycol or methanol should be monitored. Electrocardiography should be performed because acidosis and electrolyte imbalances can affect the cardiovascular system. In addition, 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 Antizol® dosing.

Elderly

Fomepizole injection has not been studied sufficiently to determine whether the pharmacokinetics differ for an elderly population.

Gender

Fomepizole has not been studied sufficiently to determine whether the pharmacokinetics differ between the genders.

Renal Insufficiency

The metabolites of fomepizole are excreted renally. Definitive pharmacokinetic studies have not been done to assess pharmacokinetics in patients with renal impairment.

Hepatic Insufficiency

Fomepizole is metabolized through the liver, but no definitive pharmacokinetic studies have been done in subjects with hepatic disease.

Other

Medical professionals are warned of the potential risk of hypoglycaemia and/or seizures with use of fomepizole.

4.5. Interaction with other medicines and other forms of interaction

Oral doses of fomepizole (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 fomepizole (by approximately 50%) by the same mechanism. Fomepizole is ineffective at treating ethanol intoxication, and would conversely prolong ethanol intoxication if administered.

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

Fomepizole has been shown to induce the expression of CYP2E1 and to inhibit its activity. These effects were enhanced in rats that had been exposed to ethanol. Fomepizole may also inhibit other CYP enzymes and therefore may alter the exposure to other drugs that are metabolised by CYP enzymes.

Interactions with disulfiram and medications for psychiatric disorders (anti-depressants, anxiolytics and antipsychotics) have not been established.

4.6. Fertility, pregnancy and lactation

Effects on Fertility

The effects of fomepizole on male and female fertility have not been adequately studied in animals. 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 0.1 times the human maximum daily exposure based on surface area (mg/m^2). Reductions in testicular mass were significantly greater when fomepizole was given in combination with ethanol (approximately 30% reduction).

Use in Pregnancy

PREGNANCY CATEGORY B2

Animal reproduction studies have not been conducted with fomepizole. It is also not known whether fomepizole can cause foetal harm when administered to pregnant women or can affect reproduction capacity. Fomepizole has been shown to cross the placenta in pregnant rats, with the concentration higher in foetal tissues that that observed in maternal serum. Fomepizole should be given to pregnant women only if clearly needed.

Use in Lactation

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 breastfeeding woman.

4.7. Effects on ability to drive and use machines

The effect of fomepizole on the ability to drive and use machinery has not been studied.

4.8. Undesirable effects

A total of 141 patients were exposed to fomepizole during the clinical trial period, including both patients (n=78) and healthy volunteers (n=63).

Adverse Events that occurred in at least 2% of patients treated with fomepizole for either methanol or ethylene glycol poisoning or at least 2% of healthy volunteers in clinical trials

Body System/Adverse Event	**Number (%) of patients with adverse events (n=78)**	**Number (%) of healthy volunteers with adverse events (n = 63)**
Body as a Whole		
Fever	14.1%	
Headache	11.5%	20.6%
Abdominal Pain/Tenderness	6.4%	
Bleeding at Venipuncture Site	2.6%	
Backache/Lumbalgia	2.6%	
Feeling Drunk		3.2%
Urogential System		
Acute renal failure	14.1%	
Worsening/increasing acute renal failure	3.8%	
Anuria	2.6%	
Nervous System		
Agitation	7.7%	
Seizure	3.8%	
Anxiety	3.8%	
Increased Drowsiness	2.6%	11.1%
Toxic Encephalopathy	2.6%	
Dizziness	1.3%	14.3%
Lightheadedness		6.3%

Burning/tingling in vein	2.6%	3.2%
Gastrointestinal System		
Vomiting	7.7%	1.6%
Nausea	2.6%	22.2%
Gastrointestinal Bleeding	2.6%	
Haematemesis	2.6%	
Diarrhoea/Loose stool	1.3%	4.8%
Cardiovascular System		
Hypotension	5.1%	
Bradycardia/sinus bradycardia	3.8%	
Hypertension	2.6%	
Collapse	2.6%	
Facial flush		3.2%
Phlebosclerosis		3.2%
Metabolic and Nutritional Disorders		
Hypocalcaemia	2.6%	
Skin and Appendages		
Rash	3.8%	
Respiratory System		
Pneumonia	2.6%	
Pharyngitis	2.6%	
Sinusitis	2.6%	
Pulmonary Oedema	2.6%	
Rhinorrhea/Rhinitis	2.6%	
Blood and Lymphatic System		
Anaemia	6.4%	
Lymphangitis	3.8%	
Disseminated Intravascular Coagulation	2.6%	
Eosinophilia/hypereosinophilia	2.6%	
Special Senses		
Bad/metallic taste		12.7%
Abnormal smell		4.8%

Table of Adverse Reactions – Possibly, Probably, Definitely or Unknown Relationship to Fomepizole from clinical trials and literature.

Body System	**Very Common ≥ 10%**	**Common ≥1% and < 10%**	**Uncommon ≥0.1% and <1%**
Body as a Whole	Headache	Abdominal pain Bleeding at venipuncture site Fever	Multiorgan system failure* Pain during 4MP injection Inflammation of left arm Lumbalgia/ Backache Hangover
Urogenital System			Anuria*

Body System	Very Common ≥ 10%	Common ≥1% and < 10%	Uncommon ≥0.1% and <1%
Nervous System		Dizziness Increased drowsiness Lightheadedness Seizure* Agitation* Feeling drunk Facial flush Vertigo Burning/tingling in vein	Nystagmus Anxiety* Felt strange Decreased environmental awareness
Gastrointestinal System	Nausea	Vomiting Diarrhoea	Dyspepsia* Heartburn Decreased appetite
Cardiovascular System		Bradycardia/sinus bradycardia Phlebosclerosis Hypertension*	Tachycardia Hypotension* Phlebitis Collapse
Skin and Appendages		Application site reaction Rash	
Respiratory System			Hiccups Pharyngitis
Blood and Lymphatic System		Eosinophilia/ hypereosinophilia Lymphangitis*	Disseminated intravascular coagulation* Anaemia
Special Senses		Bad taste/metallic taste Abnormal smell Speech/visual disturbances Transient blurred vision	Roar in ear

** Unknown relationship to fomepizole*

Post-Marketing Experience

Cyanosis, anaphylactic reaction, brain herniation, drug administration error, decreased platelet count, hypoglycaemia, brain oedema, renal failure, renal necrosis, pharyngeal oedema, respiratory distress and superficial thrombophlebitis have been reported in post-market data.
Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

Nausea, dizziness, and vertigo were noted in healthy volunteers receiving 50 – 100 mg/kg doses of fomepizole (at plasma concentrations of 290 – 520 µmol/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.

Fomepizole is dialyzable, and haemodialysis may be useful in treating cases of overdosage.

Contact the Poisons Information Centre, New Zealand 0800 POISON (0800 764 766) for advice on the management of overdose.

NEW ZEALAND DATA SHEET

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of Action:

Fomepizole is a competitive inhibitor of alcohol dehydrogenase. Alcohol dehydrogenase catalyses the oxidation of ethanol to acetaldehyde. Alcohol dehydrogenase also catalyses 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, and oxalate. Glycolate and oxalate are the metabolic by-products primarily responsible for the metabolic acidosis and renal damage seen 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 yield formic acid. Formic acid is primarily responsible for the metabolic acidosis and visual disturbances (e.g. decreased visual activity and potential blindness) associated with methanol poisoning. A lethal dose of methanol in humans is approximately 1- 2 mL/kg.

Fomepizole in the range of 100 to 300 µmol/L (8.6 – 24.6 mg/L) has been targeted to assure adequate plasma concentrations in humans for the effective inhibition of alcohol dehydrogenase.
In healthy volunteers, oral doses of fomepizole (10 – 20 mg/kg) significantly reduced the rate of elimination of moderate doses of ethanol, which is also metabolized through the action of alcohol dehydrogenase (*see PRECAUTIONS, Interactions with other Medicines*).

5.2. Pharmacokinetic properties

The plasma half-life of fomepizole varies with dose, even in patients with normal renal function (GFR $\geq$ 90mL/min/1.73m^2), 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.

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.

Excretion: The elimination of fomepizole 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]. Fomepizole and its metabolites are renally excreted.

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.

5.3. Preclinical safety data

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 µmol/L. In animal studies, fomepizole has been shown to inhibit the formation of toxic metabolites of ethylene glycol and methanol, to reverse acidosis and to prevent mortality and ethylene-glycol induced renal damage.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Antizol® does not contain any excipients.

6.2. Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3. Shelf life

60 months

6.4. Special precautions for storage

Store below 25 °C. Protect from light.

Solidification does not affect the stability of Antizol®.

Contains no antimicrobial preservative. Product is for single use in one patient only. Discard any residue. Use immediately after reconstitution unless Baxter ViaFlex olefin polymer solution bags are used.

If Baxter ViaFlex olefin polymer bags are used: To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2-8 °C for not more than 24 hours.

6.5. Nature and contents of container

Antizol® (fomepizole 1.5 g/1.5 mL injection) is supplied as a clear to yellow liquid (or solid) sterile, preservative-free solution for intravenous use in type I, 2 mL vials.

Packs of 4 vials.

6.6. Special precautions for disposal and dilution

Disposal:

No special requirements for disposal.

Dilution:
Using sterile technique, the appropriate dose of fomepizole 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.

Fomepizole, like all parenteral products, should be inspected for particulate matter prior to administration.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 19/12/2018

10. DATE OF REVISION OF THE TEXT

August 2020

11. SUMMARY TABLE OF CHANGES

Version	Change	Approval Date
1.0	Shelf-life extension from 48 to 60 months	August 2020