



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Fomepizole

Proprietary Product Name: Antizol

Sponsor: AFT Pharmaceuticals

August 2017

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Common abbreviations

| Abbreviation | Meaning |
|------------------|--|
| AACT | American Academy of Clinical Toxicology |
| ADH | aldehyde dehydrogenase |
| AE | Adverse event |
| AUC | Area under curve |
| APACHE II | Acute Physiology and Chronic Health Evaluation II |
| BD | Base deficit |
| BP | Blood pressure |
| bpm | Beats per minute |
| BUN | Blood urea nitrogen |
| C _{max} | Maximum plasma concentration |
| CI | Confidence Interval |
| CVVH | Continuous-venovenous haemofiltration |
| CVVHD/HDF | Continuous veno-venous haemodialysis/ haemodiafiltration |
| DSW | Distilled water |
| EAPCCT | European Association of Poisons Centres and Clinical Toxicologists |
| ECG | Electrocardiogram |
| EEG | Electroencephalogram |
| EG | Ethylene glycol |
| IHD | Intermittent haemodialysis |
| IV | Intravenous |
| IQR | Inter quartile range |
| GCP | Good Clinical Practice |
| 4MP | 4-MethylPyrazole (Fomepizole) |
| Kg | Kilogram |
| L | Litre |
| LLN | Lower limit of normal |

| Abbreviation | Meaning |
|------------------|---|
| mg | Milligram |
| ml | Millilitre |
| NS | Normal Saline |
| NCC-MERP | National Coordinating Council for Medication Error Reporting and Prevention |
| OG | Osmolar Gap |
| PK | Pharmacokinetic |
| PD | Pharmacodynamic |
| SD | Standard deviation |
| SE | Standard error |
| SEM | Standard error of mean |
| ULN | Upper limit of normal |
| μmol | Micromoles |
| mmol | Millimole |
| Vd | Volume of distribution |
| T_{max} | Time to maximum plasma concentration |
| $T_{1/2}$ | Half life |

I. Introduction to product submission

Submission details

| | |
|------------------------------------|--|
| <i>Type of submission:</i> | New chemical entity |
| <i>Decision:</i> | Approved |
| <i>Date of decision:</i> | 25 November 2016 |
| <i>Date of entry onto ARTG</i> | 1 December 2016 |
| <i>Active ingredient(s):</i> | Fomepizole |
| <i>Product name(s):</i> | Antizol |
| <i>Sponsor's name and address:</i> | AFT Pharmaceuticals PO Box 748 North Ryde NSW 1670 |
| <i>Dose form(s):</i> | Concentrated injection |
| <i>Strength(s):</i> | 1.5 g/ 1.5 mL |
| <i>Container(s):</i> | Vials |
| <i>Pack size(s):</i> | 1 and 4s |
| <i>Approved therapeutic use:</i> | <i>Antizol® (fomepizole) is indicated for the treatment of ethylene glycol or methanol poisoning. (see Dosage and Administration).</i> |
| <i>Route(s) of administration:</i> | Intravenous (IV) |
| <i>Dosage:</i> | A loading dose of 15 mg/kg should be administered, followed by doses of 10 mg/kg every 12 h for 4 doses, then 15 mg/kg every 12 h 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). See Attachment 1 (PI) for further details. |
| <i>ARTG number (s):</i> | 263913 |

Product background

This AusPAR describes the application by the sponsor to register fomepizole (as Antizol), a new chemical entity for intravenous infusion in patients with methanol or ethylene glycol poisoning.

The sponsor has proposed the following indications:

Antizol is indicated as an antidote for ethylene glycol (such as antifreeze) or methanol poisoning, either alone or in combination with haemodialysis.

and the following dosing regimen:

A loading dose of 15 mg/kg should be administered, followed by doses of 10 mg/kg every 12 h for 4 doses, then 15 mg/kg every 12 h 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.

Further details on preparation and use renal dialysis are detailed in Attachment 1 (PI).

Fomepizole (or 4-methylpyrazole, 4MP) is a competitive inhibitor of alcohol dehydrogenase. The current treatment for methanol or ethylene glycol (EG) poisoning in Australia is ethanol alone or in combination with haemodialysis.

EG is a toxic alcohol found in radiator coolants and antifreeze, de-icing solutions, solvents and brake fluid. Ingestion of >1 mL/kg is potentially lethal. It causes central nervous system (CNS) effects similar to those of ethanol but the more important toxic effects are due to metabolites rather than the parent compound. Peak plasma concentrations occur 1 to 4 h after oral ingestion. EG is distributed across total body water (volume of distribution (Vd) approximately 0.7 L/kg) and there is rapid central nervous system (CNS) penetration. EG is metabolised sequentially by alcohol dehydrogenase and aldehyde dehydrogenase to glycoaldehyde and glycolic acid, which is in turn converted to glyoxylic acid and oxalic acid. The elimination half-life is 3 h and is via the renal route. Ethylene glycol is dialysable (haemodialysis abbreviated to HD).

A severe anion gap metabolic acidosis develops secondary to accumulation of glycolic acid and lactate (due to increased nicotinamide adenine dinucleotide hydrogen (NADH) and decreased conversion of lactate to pyruvate). Calcium oxalate crystals form in tissues, including renal tubules, myocardium, muscles and brain. Hypocalcaemia follows. Acute oliguric renal failure occur secondary to the nephrotoxic effects of both glycolic acid and calcium oxalate. The clinical picture is initially that of CNS intoxication with euphoria, nystagmus, drowsiness, nausea and vomiting. The features of more severe toxicity emerge in the next 4 to 12 hours. Cranial nerve pathologies have been reported 5 to 20 days after the initial exposure.

Methanol is also a toxic alcohol found in solvents (thinners, varnishes, paints, enamels), model aeroplane fuel and biodiesel production, dyes and stains, wood alcohol and wood spirits, and as a diluent in/contaminant of 'bootleg' alcohol. Small quantities are found in some fruit juices and fruit fermentation can increase the content, distillation of the ferment increases the content further. Ingestion of >0.5 mL/kg is potentially lethal. Peak plasma concentrations occur within 30 to 60 minutes of oral ingestion. It is rapidly distributed and has a volume of distribution of 0.7 L/kg. Methanol is metabolised in the liver by alcohol dehydrogenase to formaldehyde and in turn metabolised by aldehyde dehydrogenase to formic acid. The elimination half-life is 24 h via the renal route. Methanol is dialysable.

Accumulation of formic acid produces a severe anion-gap acidosis and direct cellular toxicity due to the inhibition of cytochrome oxidase. Retinal injury and oedema lead to blindness. Subcortical white matter haemorrhages and putamenal oedema classically occur. Early acidosis is related to formic acid formation. Late elevation of serum lactate occurs due to the uncoupling of cytochrome oxidase by formate. Mitochondrial respiration is impaired and tissue hypoxia results. A consequence of increasing acidosis is the increased formation of the unionised state of formic acid that is more readily taken up into the CNS. Optic nerves are particularly susceptible to the effects of formic acid since they have few mitochondria and are susceptible to histotoxic hypoxia.

The clinical picture is of mild CNS depression similar to ethanol intoxication within the first hour of ingestion, followed by a latent period of 12 to 24 h then symptoms of headache, dizziness, vertigo, dyspnoea, blurred vision and photophobia. Severe intoxication can include tachypnoea, drowsiness and blindness. Papilloedema is characteristic with progressive demyelination and up to one third of patient have irreversible visual complications. Coma and seizures herald the onset of cerebral oedema. Extrapiramidal movement disorders are often a consequence of serious CNS toxicity in those that recover.

As mentioned, the current treatment for methanol or EG poisoning in Australia is ethanol alone or in combination with haemodialysis. The reason for using ethanol as an antidote is that it competitively blocks the formation of toxic metabolites in toxic alcohol ingestions by having a higher affinity (up to 20 times) for alcohol dehydrogenase and blocking the receptor sites. Inhibition is said to be complete with blood ethanol concentrations of around 22 mmol/L (100 mg/dL, 0.1 g%). Metabolism is via alcohol dehydrogenase and aldehyde dehydrogenase. Alcohol dehydrogenase is a saturable enzyme at relatively low concentrations but there is considerable individual variability and therefore variability in the rate of metabolism. Concomitant ingestion of ethanol may accompany deliberate or accidental ingestion of toxic alcohols and may result in later presentation of the toxic effects. Ethanol as a therapy can be administered intravenously (IV) as a 10% solution. Ethanol can be administered orally and there are dosage regimens for commercial ethanol preparations of approximately 43% volume/volume (v/v). The disadvantages of ethanol include local phlebitis from intravenous solutions, the behavioural consequences of prolonged intoxication can make some patients difficult to manage, the kinetics can be difficult to predict and frequent monitoring of ethanol levels is required, and ethanol can cause hypoglycaemia in children and malnourished patients particularly.

The time from ingestion to management is a key factor in positive outcomes from the ingestion of toxic alcohols.

Regulatory status

On 6 January 2015, fomepizole was designated as an orphan product for the indications of treatment of ethylene glycol and methanol poisonings by the TGA. It appears in the WHO Essential Medicines list (18th edition 2013).

Fomepizole is approved in the USA (1997), Canada (2000) and Japan (2014) for the following indications:

- US and Canada:

Fomepizole Injection 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

- In Japan it is approved for the treatment of ethylene glycol and methanol poisoning.

Fomepizole is also approved in Ireland as '*an antidote used in the treatment of acute ethylene glycol poisoning*'.

Product Information

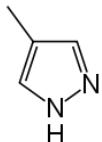
The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

Introduction

Fomepizole has a simple non-chiral pyrazole structure, as shown below.

Figure 1: Fomepizole structure



The product contains no excipients and consists only of neat fomepizole filled into vials. The product must be diluted in at least 100 mL of 0.9% sodium chloride solution or 5% glucose solution before infusion IV.

The maximum daily dose in the proposed in the draft PI is 30 mg/kg, which is equivalent to 3 g for a patient with a body weight of 100 kg, given in two divided doses.

There are no British Pharmacopeia /European Pharmacopeia (Ph. Eur) or US Pharmacopeia (USP) monographs for the drug substance or finished product, however, the BP/Ph. Eur. Parenteral Preparations monograph is applicable.

Drug substance (active ingredient)

Fomepizole appears as a clear, colourless to yellow liquid which solidifies below about 25°C. It is freely soluble in water and very soluble in many organic solvents (such as ethanol, diethyl ether % chloroform). Aqueous solutions of fomepizole have a neutral pH and it has a pKa of 2.9.

The drug substance is produced by chemical synthesis in two steps from ethyl 1-propenyl ether. Final purification is by fractional distillation (boiling point 210°C) resulting in a substance with low levels of impurities. Residual levels of the potentially genotoxic reagents hydrazine and 4-nitrobenzaldehyde are controlled to acceptably low levels.

Pending demonstration of adequate control of residual levels of the synthetic intermediate 1,1,3,3-tetraethoxy-2-methylpropane (TEMP) and the starting material ethyl 1-propenyl ether, specifications applied to the drug substance are considered acceptable.

Drug product

The proposed product contains no solvents or other excipients and consists only of 1.5 g of the sterile-filtered liquid drug substance 'fomepizole' filled into a glass vials.

The density of fomepizole is approximately 1.0 g/mL, so 1.5 g fill of fomepizole occupies 1.5 mL and accordingly the nominal strength of the product is stated as 1.5 g/1.5 mL. An overfill of 0.3 mL is added to ensure that the labelled quantity can be withdrawn from the container. Nitrogen gas is used as a processing aid to minimise oxidation.

The product appears as a 'Clear, colourless to yellow solution', although at cool ambient temperatures it may present as a solid since the drug substance melts at about 25°C. The draft PI includes instructions that the product should be liquefied by running the vial under warm water or by holding in the hand, prior to dilution.

The product must be diluted into at least 100 mL of 0.9% sodium chloride solution or 5% glucose solution before infusion IV. The draft PI and labels include appropriate warnings that the product must be diluted before use.

The product is manufactured by aseptic sterile filtration of the liquid drug substance followed by filling into clear, Type I glass vials with 2 mL capacity. The vials are sealed with Teflon-coated bromobutyl rubber stoppers with an aluminium overseal with white plastic flip-off cap.

The proposed finished product specifications included controls on appearance, fill volume, identity of drug substance, assay of active drug, particulate matter, 5 specified degradation products, endotoxins and sterility. The proposed acceptance criteria were adequately justified and comply with TGA requirements. The revised finished product specifications are considered adequate to ensure the quality of the finished product at release and throughout the shelf-life.

A shelf-life 24 months, stored below 25°C and protected from light is considered appropriate based on the submitted stability data.

Quality summary and conclusions

Some issues remain to be finalised (minor revision of PI and labels as well as the Good Manufacturing Practice (GMP) clearance of an overseas manufacturing site).

Pending demonstration of adequate control of residual levels of two potential impurities in the drug substance (discussed above), all quality issues raised during the initial evaluation of this application have now been satisfactorily resolved.

Microbiological and bacterial endotoxin-related aspects of the submission have been evaluated separately and all issues raised have been resolved.

Pending resolution of the remaining issues, registration of the proposed 'Antizol' fomepizole 1.5 g/1.5 mL concentrated injection in vials, is recommended with respect to chemistry aspects.

As no significant pharmaceutical chemistry issues were identified, the submission was not referred to the Pharmaceutical Subcommittee of the Advisory Committee on Prescription Medicines (ACPM) [now called Advisory Committee on Medicines].

III. Nonclinical findings

Introduction

Fomepizole is the first drug in its pharmacological class.

The sponsor submitted a combined literature based submission with three toxicity studies. Overall, the quality of the nonclinical dossier and the nonclinical components of the sponsor's summaries and overview were very poor. The literature references were not provided in the relevant nonclinical locations. The sponsor's Nonclinical Overview contained full replications of the Pharmacodynamics Written Summary, Pharmacokinetics Written Summary and Toxicity Written Summary without additional interpretation or integration of findings. Tabulated summaries were not included. The written summaries were poorly written, with incorrect citation of the literature as well as a lack of clarity in the citation of literature publications. In addition, some sections were transcribed from the published literature without quotation and in some instances with typographical errors which altered the meaning of the copied statements.

Furthermore, some submitted studies were not considered in the written summaries, while other cited publications were either not submitted, were submitted but incorrectly labelled (wrong year), or were submitted in the clinical part (bacterial mutagenesis study). The quality of reproduction of some publications was also poor, with some text, figures and/or tables illegible. There were also concerns regarding the level of detail reported in some publications, and due to the age of the publications the majority of data provided were not Good Laboratory Practice (GLP) compliant.

Pharmacology

Primary pharmacology

In vitro studies demonstrated that fomepizole inhibited human liver alcohol dehydrogenase (ADH) with inhibitory constant (Ki) values of approximately 0.1 to 0.2 μ M. Similar inhibition was observed in ADH isolated from dogs (Ki 0.1 μ M), but lower efficacy in cat and monkey ADH (Ki values of approximately 1 to 3 and approximately 8 to 9 μ M, respectively). Fomepizole was a competitive inhibitor of 5 of 6 human Class I ADH isozymes, and inhibited these isozymes with Ki values of 0.06 to 1.2 μ M. Only weak inhibition of Class II and IV ADH isozymes was observed, which may be related to the lower efficiency for alcohol oxidation of these isozymes. The predicted C_{max} in humans is approximately 800 μ M¹ indicating that the proposed dosing regimen is sufficient to inhibit alcohol dehydrogenase, particularly given the high distribution of fomepizole to the liver.

The in vivo effects of fomepizole were investigated in animal models of ethylene glycol and methanol poisoning. Clinically, methanol and ethylene glycol poisoning is characterised by a latent period between ingestion and the onset of symptoms and metabolic acidosis. This delay is due to the metabolites of ethylene glycol and methanol being the toxic moieties. The rationale for the use of fomepizole is to inhibit the formation of metabolites and prevent their accumulation. Ethanol treatment works by the same mechanism; the affinity of ethanol for alcohol dehydrogenase is higher than that of methanol or ethylene glycol, thereby making it an effective competitive inhibitor.

Administration of fomepizole prior to, or concomitantly with, ethylene glycol prevented mortality in rats (240 mg/kg), cats (20 mg/kg²), dogs (20 mg/kg³) and monkeys (50 mg/kg). Increased time between exposure to ethylene glycol and fomepizole administration reduced the efficacy of the antidote. In rats, a high dose of fomepizole (490 mg/kg) was ineffective compared to a dose of 240 mg/kg in preventing mortality when given 4 or 6 h after ethylene glycol. The reason for this was unclear but may be due to relatively low numbers of experimental animals. In dogs, fomepizole prevented or attenuated ethylene glycol induced central nervous system (CNS) depression, metabolic acidosis and renal damage and increased the urinary excretion of ethylene glycol. Fomepizole also decreased glycolic acid levels in ethylene glycol poisoned monkeys.

Monkeys were identified as an animal model of methanol poisoning. Fomepizole prevented mortality when given prior to or after a lethal dose of methanol. Initial doses of 15 to 50 mg/kg were effective in protecting against methanol toxicity initially, and administration of lower subsequent doses (2.5 and 7.5 mg/kg) prevented overt toxicity but did not completely inhibit formate accumulation. Limited data were available to

¹ Plasma C_{max} was 389 μ M in patients that received a 7 mg/kg dose in Study S2, giving a dose-adjusted C_{max} of 834 μ M for a 15 mg/kg dose. In another study, the maximum observed plasma value was ~750 μ M in patients received the proposed dosing regimen (Study S8).

² The dosing in cats was a 20 mg/kg loading dose (at 0, 2 or 3 h post-ethylene glycol), followed by 10 mg/kg at 12 and 14 h and 5 mg/kg at 30 h after the initial dose

³ The dosing in dogs was a 20 mg/kg loading dose (3h post-ethylene glycol), followed by 15 mg/kg at 24 h and 5 mg/kg at 36 h after ethylene glycol.

determine the serum concentrations of fomepizole that were effective in inhibiting formate accumulation. The effective concentrations appeared to be in the range of 10 to 35 μ M. Fomepizole prolonged the half-life of methanol by inhibiting its metabolism.

Together, the in vitro and in vivo data demonstrate the ability of fomepizole to inhibit alcohol dehydrogenase and thereby inhibit the formation of toxic metabolites of ethylene glycol and methanol. This supports the proposed clinical indication.

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacology studies were not submitted and it is unclear whether fomepizole has been investigated for interactions with other enzymes, transporters or receptors. The effects of fomepizole on alcohol dehydrogenase have been shown to alter the pharmacokinetics of ethanol (see Pharmacokinetic drug interactions).

Specialised safety pharmacology studies were not submitted, and no specific data on the effects of fomepizole on the cardiovascular, respiratory or renal systems were provided. Two literature publications were submitted that investigated the effects of fomepizole on the central nervous system in rodents. Fomepizole decreased exploratory behaviour in mice at doses of \geq 100 mg/kg intraperitoneal, a dose which depleted brain noradrenaline levels. A single dose of 200 mg/kg intraperitoneal fomepizole caused a transient decrease in body temperature, which preceded a fall in brain noradrenaline. There was no effect on brain noradrenaline levels following repeated dosing with 50 to 200 mg/kg/day in mice and 10 to 50 mg/kg/day in rats for 4 days. However, brain serotonin levels were increased after 4 days dosing in mice that received 200 mg/kg/day intraperitoneal. There was also a marked decrease in body weight in mice after the 4 day treatment period, which appeared likely to be secondary to inhibition of water intake. In a separate study, a single dose of 70 mg/kg intraperitoneal fomepizole modestly impaired motor coordination in mice. In a repeat dose toxicity study, fomepizole-treated dogs had adverse CNS-related clinical signs and a marked increase in urine volume (see Major toxicities).

Pharmacokinetics

The absorption of fomepizole was not thoroughly investigated in animals, which is acceptable given the intended clinical route. Exposure to fomepizole appeared to be approximately dose-proportional in dogs (based on C_{max}) and monkeys (based on 24 h serum levels). Exposure was greater than dose- proportional in dogs based on the area under the concentration versus time curve (AUC), and also showed marked accumulation with repeated dosing, which was exaggerated at higher doses. There was no effect of gender on fomepizole exposure in dogs. Plasma half-life was estimated to be approximately 11 h in rats following a dose of approximately 117 mg/kg, but was substantially shorter at lower doses.

Plasma protein binding was claimed to be low, but no data were submitted. Data on the volume of distribution in animals were not available. In humans, the volume of distribution was claimed to 0.6 to 1.0 L/kg, indicating extensive tissue distribution. In male rats the peak fomepizole level in liver was approximately 6 times the peak serum level. Distribution to the brain and reproductive tissues was not investigated but is considered likely based on the physiochemical properties and observed CNS effects.

The metabolic profile was poorly characterised with minimal data available in animals. The metabolism of fomepizole appeared to be oxidation to an intermediate metabolite, 4-hydroxy- methylpyrazole (4-OH-MP) followed by subsequent oxidation to 4-carboxypyrazole (4-CP). The enzymes responsible were not investigated. In rats and monkeys the predominant circulating species was fomepizole, with 4-OH-MP present at

approximately 10% of the level of fomepizole. The human plasma metabolite profile was not reported in the sponsor's Clinical Overview.

Fomepizole was excreted predominantly via the urine as metabolites. In humans the major urinary metabolite was 4-CP, with low levels of unchanged fomepizole (<3%). In rats, the major urinary metabolites were 4-OH-MP and 4-CP, with unchanged fomepizole present at either very low or undetectable levels in urine. The excretion of fomepizole was altered by co-administration of ethanol, with decreased elimination and increased urinary excretion of unchanged fomepizole.

The restricted characterisation of the pharmacokinetic profile in animals and humans limits interpretation of the suitability of the animal models used to investigate the toxicity profile of fomepizole. The available data indicate a similarity in the metabolic profile between rats, monkeys and humans. Data were not available for the metabolism of fomepizole in dogs, which were used in the pivotal repeat dose toxicity study.

Pharmacokinetic drug interactions

The characterisation of fomepizole interactions with cytochrome P450 (CYP) enzymes was limited, and no transporter interaction studies were submitted. The available data indicate that fomepizole is both an inhibitor and an inducer of CYP enzymes. Fomepizole bound to CYPs and also increased the binding of ethanol and DMSO to CYP enzymes. In addition, microsomes from rats treated with fomepizole had a higher microsomal protein content and an activity profile consistent with induction of CYP2E1. However, fomepizole was also shown to be a mixed type inhibitor of ethanol oxidation in control microsomes, with greater inhibition reported for microsomes with CYPs induced by either fomepizole or ethanol (K_i values of 0.1 to 0.7 mM). Similarly, antipyrine clearance was inhibited by approximately 85% by a single 100 mg/kg intraperitoneal dose of fomepizole in rats, indicating the potential for fomepizole to inhibit other CYP enzymes (including CYP1A2, 2B6, 2C and/or 3A4⁴). Together, these data indicate that inhibition of CYP2E1 is expected in patients based on an estimated clinical C_{max} of approximately 800 μ M¹.

Due to their pharmacological effects and CYP interactions, fomepizole and ethanol alter the pharmacokinetics of each other. When co-administered, the half-life of each is prolonged by reduced elimination, and plasma concentrations of both reach higher levels. There are also exaggerated effects on CYP induction and inhibition and CNS depression, which appear consistent with the greater exposure to both compounds. Clinically, fomepizole can be expected to enhance and prolong the effects of alcohol by altering its pharmacokinetics.

Toxicology

Acute toxicity

The acute toxicity of fomepizole was investigated in mice and rats, with limited details reported. Rodents were monitored for up 7 days after a single IV or oral dose of fomepizole. The 50% lethal dose (LD50) values were 312 mg/kg IV in mice and rats, 640 mg/kg orally in mice and 534 mg/kg orally in rats. This indicates a very high order of

⁴ Engel, G., Hofmann, U., Heidemann, H., Cosme, J., Eichelbaum M. (1996) Antipyrine as a probe for human oxidative drug metabolism: identification of the cytochrome P450 enzymes catalyzing 4-hydroxyantipyrine, 3-hydroxymethylantipyrine, and norantipyrine formation. Clin Pharmacol Ther.: 59; 613-623

acute toxicity, as the LD₅₀ values for the IV dose were 1 to 2 times the maximum recommended human dose based on body surface area.⁵

Repeat-dose toxicity

Repeat-dose toxicity studies were conducted in rats (\leq 38 weeks; oral), dogs (2 weeks; IV, twice a day (bd)) and monkeys (6 weeks, intramuscularly (IM)). The dog studies were the only GLP compliant studies and were also the only studies using the proposed clinical route and frequency of administration. However, the duration of these studies was shorter than that recommended in ICH guideline S4.⁶ The rat and monkey studies did not adhere to the relevant international guidelines in terms of the study design (limited observations) and conduct and were reported in very limited detail in published papers. It is noted that many of these studies were conducted prior to the development of the current international guidelines, and therefore were not intended to address their requirements. The toxicity profile of fomepizole given alone or in combination with ethanol was investigated in three of the four repeat-dose toxicity studies conducted in rats.

Relative exposure

Exposure ratios were predominantly based on body surface area calculations due to the limited availability of pharmacokinetic data. The nonclinical evaluator calculated AUC_{0-12h} values for the pivotal dog study, with the mean male and female AUC_{0-12h} values from study day 14 used to estimate exposure ratios. A number of adjustments were made in order to make appropriate comparisons between the dog and human data. Firstly, the AUC_{0-12h} data in dogs was doubled to account for bd dosing. For the human data, an appropriate AUC value was extrapolated from Study S-2⁷. Human AUC_{0-24h} values derived from volunteers given an IV dose were adjusted for dose level (from 7 to 15 mg/kg), and then the value was doubled to account for the recommended frequency of dosing (maximum recommended human dose (MRHD) of 15 mg/kg bd; see Table 1).

The relative exposures (RE) achieved in the repeat-dose toxicity studies were low or very low. There was a good agreement between the body surface area (BSA) and AUC calculations on Day 1 of the dog study (RE values of 0.2, 0.5 and 0.9 based on AUC). Due to accumulation of fomepizole with repeated dosing, the RE increased by study Day 14 to give a maximum RE of approximately 5. The ER achieved in the rat studies were all \leq 0.1, except for the study shown in Table 1.

Table 1: Relative exposure in repeat-dose toxicity studies

| Species | Study duration; route [Study no.] | Daily dose | | AUC _{0-24h} μmol·h/ L | Exposure ratio | |
|-----------|--|------------------|-------------------|--------------------------------------|------------------|--------------|
| | | mg/kg | mg/m ² | | AUC [#] | BSA |
| Rat SD | 4 weeks; oral [Magnusson <i>et al.</i> , 1972] | 10 | 60 | - | - | 0.06 |
| | | 99 \rightarrow | 594/ | | | 0.6 / 1.2 |
| | | 197 | 1182 | | | |

⁵ The MRHD was assumed to be 30 mg/kg, given as two doses of 15 mg/kg with an assumed body weight of 50 kg.

⁶ In ICH guideline S4, it is recommended that nonclinical studies of one month duration be submitted to support registration of drugs with intended duration of use in humans of \leq 2 weeks.

⁷ McMartin, K.E., Makar, A.B., Martin, A., Palese, M., Tephly, T.R. (1975) Methanol poisoning I. The role of formic acid in the development of metabolic acidosis in the monkey and the reversal by 4-methylpyrazole. Biochemical Medicine, 13: 319 – 333.

| Species | Study | Daily dose | | AUC _{0-24h} | Exposure ratio |
|--------------------------------|---|---------------|---------------|-------------------------|----------------|
| Dog Beagle | 2 weeks; IV [Study WIL-258003] | 50 25 bd | 1000 | - | - |
| | | 100 50 bd | 2000 | - | - |
| | | 150 75 bd | 3000 | - | - |
| | | 300 150 bd | 6000 | - | - |
| | 2 weeks; IV [Pivotal; Study WIL-258004] | 20 10 bd | 400 | 1838 [^] | 0.2 |
| | | 40 20 bd | 800 | 10, 275 [^] | 1.3 |
| | | 60 30 bd | 1200 | 36, 503 [^] | 4.5 |
| | | 20* | 240 | - | - |
| Monkey Cynomolgus | 6 weeks; IM [Blomstrand <i>et al.</i> , 1984] | 100→ 200* | 1200/ 2400 | - | - |
| Human healthy volunteers | Single dose; IV [McMartin <i>et al.</i> , 2012] | 15 bd\$ | 990 | 8079\$ | - |

= animal:human plasma AUC_{0-24h}; ^ = data are for the sexes combined at the last sampling occasion with the AUC_{0-12h} value multiplied by 2 to give AUC_{0-24h}; * = dosing was on 5 of every 7 days; \$ = AUC extrapolated from a single 7 mg/kg IV dose, with the AUC_{0-24h} value doubled to reflect the intended bd dosing.

Major toxicities

The major target organs for fomepizole were the CNS, liver and muscle, with marked effects on electrolyte balance also reported in dogs. At higher doses the gastrointestinal tract also appeared to be a target of fomepizole, but this may have been secondary to effects on Activated Partial Thromboplastin Time (APTT).

Adverse CNS effects were reported in the dose range-finding study in dogs that received ≥50 mg/kg bd (RE 2). Ataxia, hypoactivity, prostration, ptosis and tremors were observed, the severity of which led to discontinuation of dosing. There appeared to be a relatively narrow safety margin, with no adverse CNS signs in dogs that received 30 mg/kg bd for two weeks (RE 4.5).

Similar effects were not observed in rats or monkeys, even at higher doses which in monkeys appeared to give relatively high serum fomepizole levels (up to 1984 µM 24 h

post-dose). However, adverse CNS effects have been reported in healthy human volunteers (including dizziness, vertigo and headache), suggesting clinical relevance.

There was evidence of severe hepatotoxicity in the dose range-finding study in dogs. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were elevated by ≥ 2 fold on day 7 in dogs that received 50 mg/kg bd for 6 days (RE 2). Liver enzymes were further increased on Day 14, indicating liver damage was irreversible and progressive, even after cessation of dosing (ALT by 61 fold and AST by 76 fold). Alkaline phosphatase (ALP) and bilirubin levels were also increased at both time points and coagulation times were prolonged which was considered likely to be secondary to hepatic dysfunction. Similar effects were observed in the limited observations of dogs that received seven doses of 75 mg/kg bd. Serum creatine kinase activity was also increased in dogs that received 50 and 75 mg/kg bd, indicating muscle damage which may have exacerbated the elevations in AST. The effects at 50 mg/kg bd were inconsistent, with marked increase in creatine kinase activity in the premature decedent, with a more moderate but delayed increase in the dog surviving to Day 14. Histopathology was not evaluated in these dogs, making it difficult to distinguish between muscle and liver damage.

Mild hepatic changes were also observed in dogs that received 30 mg/kg bd for 14 days, with small increases in ALT, relative liver weight and a pale or swollen appearance of the liver. There were no clear histological correlates but given the elevation in liver enzymes in the dose range-finding study these changes are considered to be treatment-related. Creatine kinase levels were normal, as was muscle histopathology. There was no clear evidence of hepatotoxicity in rats but the doses used were generally lower and were administered orally and the data reported was not extensive.

Assessment of serum liver enzymes did not indicate hepatotoxicity in monkeys that received up to 100/200 mg/kg IM for 5 of 7 days for 6 weeks. While there is some ambiguity in the data in terms of inconsistency between species and uncertainty in attributing effects to liver or muscle damage, the weight of evidence indicates a potential for clinically relevant hepatotoxicity.

The cause of electrolyte imbalance in dogs was not clear but was associated with large increases in urinary volume. The electrolyte profile was characterised by increased bicarbonate and sodium and decreased potassium. This profile is indicative of metabolic acidosis, and was observed in dogs that received ≥ 20 mg/kg bd, with the severity being dose-dependent (RE approximately 1). The marked decreases in potassium (approximately 30%) may have contributed to some of the adverse CNS effects. While these effects could occur clinically, they may antagonise the metabolic acidosis induced by methanol or ethylene glycol poisoning. Reduction in anion gap and restoration of serum bicarbonate was observed in primary pharmacology studies using animal models of both ethylene glycol and methanol poisoning. Therefore, while the metabolic alkalosis observed in dogs is considered adverse, these effects may actually contribute to the antidote action and be beneficial when used as clinically indicated.

In summary, there were significant deficiencies in the repeat-dose toxicity studies in terms of the study design and duration, in particular the lack of extensive observations in more than one species. Of the identified effects, the potential for hepatotoxicity, muscle and CNS toxicity are considered to be of most clinical relevance.

Genotoxicity

The studies submitted to investigate the potential genotoxicity of fomepizole did not meet the requirements of the relevant guideline.⁸ One validated bacterial mutagenesis study was submitted, with the summary of an in vivo chromosomal aberration study (mouse micronucleus assay) also submitted. To meet the requirements of ICH S2 (R1), either an additional in vitro chromosomal damage study or in vivo assessment of genotoxicity would be required. The mouse micronucleus study was reported to be negative but as the study report was not submitted it is not possible to verify the results or the validity of the assay. The study report for the bacterial mutagenesis study was located by the nonclinical evaluator in the clinical part of the submission. This study demonstrated that fomepizole was genotoxic in two strains (*S. typhimurium* TA102 and *E. coli* WP2 uvrA). Both these strains are sensitive to base-pair substitutions with an AT primary reversion site.

The bacterial mutagenesis assay indicates the potential for genotoxic effects clinically. These effects were not further investigated by the sponsor. In guideline ICH S2 (R1) it is recommended that further investigation of the in vivo mutagenic and carcinogenic potential be investigated when a positive in vitro result is obtained, unless the benefit is considered to outweigh this risk. This may be acceptable given the clinical indication for fomepizole, but requires the consideration of the Delegate.

Carcinogenicity

Carcinogenicity studies were not conducted, which is acceptable for the intended duration of dosing. However, based on the positive genotoxicity result this requires consideration by the Delegate (see above).

Reproductive toxicity

No suitable studies were submitted to assess the reproductive toxicity of fomepizole. Placental transfer of fomepizole was demonstrated in pregnant rats, with the level of fomepizole in fetal tissues approximately 6 times higher than in maternal serum. One published paper on the effects of fomepizole on the development of *Drosophila melanogaster* was submitted which indicated no apparent teratogenicity. However, studies in mammalian species are required for the assessment of reproductive toxicity (ICH S5 (R2)). In male rats, fomepizole decreased testosterone and luteinising hormone levels, as well as testicular mass, which could affect fertility. However, no investigation of spermatogenesis or reproductive function was reported. Overall, the data available are inadequate to assess the potential effects of fomepizole on fertility, embryofetal development or postnatal development. No data were available for excretion into milk.

Pregnancy classification

The sponsor has proposed Pregnancy Category C.⁹ The pharmacological effects of fomepizole are not considered likely to cause fetal harm, and therefore Pregnancy Category C is not considered appropriate. Instead, the lack of animal studies supports the assignment of Pregnancy Category B2¹⁰.

⁸ ICH S2 (R1): Guidance On Genotoxicity Testing And Data Interpretation For Pharmaceuticals Intended For Human Use S2(R1) Current Step

⁹ Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

¹⁰ Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Local tolerance

Local tolerance was investigated in the repeat-dose toxicity study in dogs. There were no clear differences in local reactions in dogs that received fomepizole (5 to 15 mg/mL) or vehicle as 30 minute intravenous infusions bd for 2 weeks. Instructions for dilution of fomepizole were not included in the draft PI document. Therefore, it is unclear whether the concentration of fomepizole given to dogs was comparable to that intended for administration in humans.

Ocular toxicity

Ophthalmological examinations and electroretinograms were performed in monkeys that received single (20 and 100 mg/kg) or repeated (≤ 200 mg/kg/day) doses of fomepizole. There were no adverse effects of fomepizole on ocular morphology or retinal function.

Antioxidant status

Two publications were submitted that investigated the effects of fomepizole alone and in combination with methanol or ethylene glycol on antioxidant status in the brain and liver. Fomepizole alone appeared to modestly deplete total antioxidant capacity in the brain and induced antioxidant enzymes in the liver. The latter is suggestive of a response to increased production of reactive oxygen species. However, fomepizole had little effect on accumulation of hepatic lipid peroxides. There was no clear synergistic effect on antioxidant status of fomepizole in combination with methanol or ethylene glycol in the brain or liver, respectively. In the liver, fomepizole appeared to reduce the formation of lipid peroxides secondary to ethylene glycol. This effect may be associated with acute inhibition of CYP2E1.

Paediatric use

Studies in juvenile animals were not submitted. Fomepizole is not indicated for use in children.

Nonclinical summary and conclusions

- The submitted nonclinical dossier was a hybrid literature based submission with some original study reports. Overall the dossier was of poor quality and did not address all requirements of the relevant International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline for the nonclinical assessment of pharmaceuticals.¹¹ In addition, there was a lack of critical assessment of the literature used to support registration in the sponsor's Nonclinical overview and summaries.
- In vitro, fomepizole inhibited alcohol dehydrogenase with a K_i value of approximately 0.1 to 0.2 μ M which is markedly lower than the predicted clinical fomepizole C_{max} . In vivo, fomepizole antagonised the effects of ethylene glycol poisoning in rats, dogs and monkeys and was also effective in preventing methanol poisoning in monkeys.
- Secondary pharmacology studies were not submitted. In metabolism studies it was shown that fomepizole is also a CYP2E1 inhibitor. It is unknown whether fomepizole interacts with other enzymes, receptors or transporters.

¹¹ ICH M3(R2): Guidance On Nonclinical Safety Studies For The Conduct Of Human Clinical Trials And Marketing Authorization For Pharmaceuticals

- The effects of fomepizole on the cardiovascular, respiratory and renal systems were not investigated. In studies investigating the effects of fomepizole on the CNS it was shown that fomepizole impaired motor coordination in mice at subclinical doses (relative exposure [RE] 0.2 times based on body surface area [BSA]). Fomepizole also caused a transient decrease in body temperature and brain noradrenaline levels in mice (RE 0.6). After 4 days dosing, brain noradrenaline levels were normal but serotonin was increased. In the repeat-dose toxicity study in dogs, clinically relevant doses of fomepizole caused a marked increase in urinary volume.
- The pharmacokinetics of fomepizole was not fully investigated in animals or humans. Therefore, there is uncertainty regarding the suitability of animal models used to investigate the toxicity profile of fomepizole. Fomepizole was excreted predominantly in the urine as metabolites, with the urinary metabolite profile being qualitatively similar between rats and humans.
- Fomepizole inhibited and induced CYP2E1 at clinically relevant concentrations and doses. Antipyrine metabolism was markedly inhibited by fomepizole, indicating inhibition of other CYPs at clinically relevant doses. The interactions with CYP2E1 and with the pharmacological target (alcohol dehydrogenase) have the potential to markedly alter ethanol metabolism, as well as the metabolism of other xenobiotics. In vivo data demonstrate the ability of fomepizole and ethanol to reciprocally inhibit the elimination of each other. The interactions of fomepizole with other transporters were not investigated.
- Fomepizole had a very high order of acute intravenous toxicity in rodents. LD50 values for the IV dose were 1 to 2 times the maximum recommended human dose based on body surface area.
- Repeat-dose toxicity studies by the oral route were conducted in rats (up to 38 weeks), by twice daily IV infusion in dogs (2 weeks) and by IM injection in Cynomolgus monkeys (6 weeks). Maximum exposures (AUC) were generally low or subclinical, but were more acceptable in the dose range-finding study in dogs. Only the dog studies were GLP compliant and reported in sufficient detail to assess the toxicity profile of fomepizole. Even so, these studies were of shorter duration than required by the relevant guidelines (2 weeks instead of 1 month). The target organs for toxicity in dogs were the central nervous system (ataxia, hypoactivity, prostration, ptosis and tremors at RE of 3 to 6), liver (serum liver enzyme elevation at RE ≥ 2 , which was severe and irreversible in some dogs) and muscle (creatine kinase elevation at RE ≥ 2). In addition, fomepizole caused a marked metabolic alkalosis and hypokalaemia in dogs at clinically relevant doses.
- The investigation of the genotoxicity of fomepizole did not address all requirements of ICH guideline S2 (R1). Fomepizole was mutagenic in the bacterial mutation assay. Fomepizole did not cause chromosomal aberrations in vivo in the mouse micronucleus test. The available data demonstrate that fomepizole poses a genotoxic risk. No carcinogenicity studies were submitted, which is appropriate based on the duration of use of fomepizole but inconsistent with the positive genotoxicity findings. The lack of studies may be acceptable for the proposed indication.
- The reproductive toxicity of fomepizole was not studied in mammalian species. Placental transfer of fomepizole was demonstrated in pregnant rats. Fomepizole appeared to decrease testosterone levels and testicular mass in male rats but the consequences of these changes on male fertility were not investigated.

Nonclinical conclusion

- There were significant deficiencies in the nonclinical dossier, in particular the lack of data for:
 - effects on the cardiovascular, respiratory and renal systems
 - the pharmacokinetic profile to assess the suitability of animal models
 - the effects of repeated dosing with fomepizole (lack of high quality data in more than one species for an adequate duration of dosing)
 - the effects of fomepizole on fertility, embryofetal and post-natal development
- The primary pharmacology studies support the proposed indication for fomepizole.
- Fomepizole appeared to have adverse CNS effects in mice and dogs. Fomepizole also appeared to alter renal function in dogs.
- Omepizole is an inhibitor and inducer of CYP2E1 and also appeared to strongly inhibit other CYPs.
- Repeat-dose toxicity studies identified adverse CNS, liver and muscle effects that may be clinically relevant. Liver toxicity is of particular concern as liver damage progressed in dogs during the recovery period indicating irreversible hepatotoxicity. The observed metabolic alkalosis is likely to counter the metabolic acidosis present in methanol and ethylene glycol poisoning and is therefore of less clinical concern.
- Fomepizole poses a genotoxic hazard and the carcinogenicity has not been investigated. The Delegate should consider whether the benefit of fomepizole outweighs the genotoxic risk.
- The sponsor proposed Pregnancy Category C but based on the lack of animal data a Pregnancy Category of B2 is recommended.
- The data provided is insufficient for the nonclinical evaluator to support the registration of fomepizole. The numerous deficiencies in the nonclinical data may potentially be compensated for by the long history of clinical use overseas. Outstanding areas of concern include the carcinogenic risk and effects of fomepizole in pregnant women.
- The draft Product Information should be amended (the details of proposed amendments are beyond the scope of this AusPAR) and the concerns regarding nonclinical statements in the Risk Management Plan must be addressed.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Prior to the availability of specific therapies, approximately two-thirds of EG poisoned patients died, even with supportive therapy. No specific therapies existed until 1965,

when ethanol was used in the successful treatment of two cases of EG poisoning.¹² Ethanol is a better substrate for alcohol dehydrogenase (ADH) than EG and prevents EG from being metabolised to its toxic metabolites while EG itself is being eliminated by the kidneys. Around this time, dialysis also became available. The outcome of a patient with EG poisoning depends on three primary factors: 1) the amount of time between ingestion of the poison and the initiation of treatment, 2) the degree of metabolic acidosis and 3) the serum EG level at presentation. Of these factors, the first two are the most important in determining the patient's outcome. The use of ethanol and haemodialysis has proven relatively effective, particularly for patients being treated by physicians familiar with these poisonings.

Methanol is the primary component of windshield washer fluid. Considering its widespread use, methanol poisoning is relatively rare and these poisonings are a result of accidental or intentional ingestion of methanol. Since ingestion of a small amount of methanol is potentially fatal, immediate effective treatment is essential. Initially, methanol is metabolised by the enzyme ADH to formaldehyde with subsequent rapid oxidation via ADH to its toxic metabolite, formic acid or formate, depending on pH. Formate production is responsible for the severe metabolic acidosis and progressive visual toxicities associated with methanol poisoning. Historically, clinical management of methanol poisoning has focussed on three major areas: sodium bicarbonate therapy for correction of metabolic acidosis, ethanol therapy to limit the conversion of methanol to its toxic metabolites, formate; and haemodialysis for elimination of methanol and/or formate. If left untreated or treatment is delayed, methanol poisoning can be lethal. The lethal dose of methanol is approximately 1.4 mL/kg or about 100 mL for a 70 kg person. Due to its ability to competitively bind with ADH, ethanol has been the antidote treatment of choice for EG and methanol poisonings for many decades.

However, the use of ethanol in the treatment of EG poisoning requires constant monitoring of the patient. If the dose of ethanol is too high, its depressive effects can add dangerously to those of EG and its metabolites. If the dose of ethanol is too low, the enzyme ADH will not be inhibited and toxic metabolites will accumulate. Thus, hourly ethanol plasma level determinations with frequent adjustments to the ethanol infusion are necessary to maintain efficacious ethanol levels. Additionally, ethanol is eliminated rapidly from the blood with considerable inter-individual variability and finally, ethanol is a significant hepatotoxin. Similar limitations apply to the use of ethanol for treatment of methanol poisoning.

4MP is a competitive inhibitor of ADH and offers a substantial improvement over the use of ethanol in the treatment of EG and methanol poisonings.

Contents of the clinical dossier

Scope of the clinical dossier

This product was originally developed and approved in the USA and Canada in the late 1990's and early 2000's, before ICH guidelines came into force. Thus, the clinical studies and nonclinical data that were provided with this dossier are quite old, and therefore case report forms (CRFs) are not available for all clinical studies. To bridge this time gap, the sponsors have conducted systematic literature reviews, the strategies of which have been approved by the TGA.

The search strategy described provides a comprehensive and broad search selecting relevant studies. However most of the available literature is case reports.

¹² Wacker, et al. 'Treatment of ethylene glycol poisoning with ethyl alcohol.' JAMA Dec 13, 1965. Vol. 194, No. 11.

The submission contained the following clinical information:

- 10 clinical studies have been conducted to evaluate the pharmacokinetic parameters of fomepizole in healthy volunteers and in patients with ethylene glycol and methanol poisoning to determine optimum dosing recommendation, interactions with ethanol, and the effects of renal dialysis on fomepizole plasma levels, since dialysis is commonly used as a component of the treatment for both EG and methanol poisonings.
- Three pivotal efficacy/safety studies conducted by the manufacturer: Studies S7 (OMC-4MP-3), S8 (OMC-4MP-1) and S13 (OMC-4MP-2).
- Other efficacy/safety studies: these include many published studies and case reports.
- 272 literature references

Paediatric data

The submission did not include any paediatric clinical studies (conducted by the manufacturer). However, some case reports and case series of use of fomepizole in treatment of EG and methanol poisoning in infants and children were provided.

Good clinical practice (GCP)

The 3 main studies submitted by the manufacturer were conducted according to GCP ICH guidelines. Most of the other published studies were conducted with ethics approval from the investigating centre.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 2 below shows the studies submitted relating to each pharmacokinetic topic.

Table 2: Submitted pharmacokinetic studies

| PK topic | Subtopic | Study ID |
|---------------------------|---------------------------------|---|
| PK in healthy adults | General PK- Single dose | S-2 S-3 Maraffa, 2008 Jacobsen, 1996 |
| | - Multi-dose | McMartin, 2012 |
| | Bioequivalence† - Single dose | S-2 |
| | - Multi-dose | S-3 |
| | Food effect | Not applicable. |
| PK in special populations | Target population - Single dose | S1 S11 |

| PK topic | Subtopic | Study ID |
|---------------------------|--|---|
| | - Multi-dose | S8 (EG poisoning) S13 (methanol poisoning) |
| | Hepatic impairment | None |
| | Renal impairment | S12 Jobard, 1996 |
| | Neonates/infants/children/ Adolescents | None |
| | Elderly | None |
| Genetic/gender-related PK | Males versus females | None |
| PK interactions | Drug interaction study with ethanol | Jacobsen, 1990 (Study S4) Jacobsen, 1996 |
| | Drug interaction study with ethylene glycol | Studies S1 and S11 |
| Population PK analyses | Healthy subjects | None |
| | Target population | None |

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

For a summary of absorption, distribution, metabolism and excretion please see Attachment 2 *Evaluator's conclusions on pharmacokinetics*.

PK data to support proposed dosing recommendations for fomepizole

In Study S3, the rate of elimination of fomepizole was increased markedly (2 to 3 fold) within 3 days of multiple dosing. This increase in the elimination of fomepizole was associated with an enhanced urinary excretion of 4-CP, the primary urinary metabolite of fomepizole, indicating most probably an induction of metabolism of fomepizole. Hence, supplemental doses of fomepizole need to be increased at the time that the enhanced elimination occurs (about 36 to 48 hours) in order to maintain therapeutic fomepizole concentrations. Data from the multiple dose part of study¹³ demonstrated that the 4MP dosing schedule that seems to be the best at maintaining therapeutic levels for up to 5 days was: loading dose of 10 mg/kg, plus 5 mg/kg/12 h up to 36 h and then 10 mg/kg/12 h up to 96 h. The IV dosage of fomepizole proposed in this submission is 15 mg/kg as a loading dose, followed by 10 mg/kg every 12 hours, if indicated, for 4 doses (to 48 hours) and 15 mg/kg thereafter until blood levels of ethylene glycol are <20 mg/L. Oral dosing

¹³Jacobsen D, et al. Effects of 4-Methylpyrazole, Methanol/ Ethylene Glycol Antidote in healthy humans. The Journal of Emergency Medicine, Vol. 8. pp. 455-461, 1990

studies (S-3, S-4, S-6) that included doses of up to 100 mg/kg support the proposed clinical IV dosage.

Drug interactions

Results of Study S6¹⁴ in healthy subjects showed that that socially relevant concentrations of ethanol can inhibit the elimination of 4MP, most likely by inhibiting the metabolism of 4MP to 4-CP. Such an interaction should enhance the effectiveness of 4MP by increasing the duration of inhibition of ADH activity. As methanol has a much lower (1/10) affinity for ADH, such doses of 4MP will most likely cause a marked inhibition of methanol metabolism in humans. Ethylene glycol has an even lower affinity for ADH and the inhibition of its metabolism should be more complete, as has been demonstrated in clinical studies and case reports in this submission. Drug interaction studies were not conducted to evaluate effects of other ADH inhibitors or induction of the elimination of fomepizole by other enzyme inducers that affect the cytochrome P-450 enzyme system.

Limitations of the pharmacokinetic data

- Drug interaction studies were not conducted to evaluate effects of other ADH inhibitors and induction of the elimination of fomepizole by other enzyme inducers that affect the cytochrome P-450 enzyme system.
- No specific PK studies were conducted in patients with renal hepatic impairment or in the paediatric population.

Pharmacodynamics

Studies providing pharmacodynamic data

No specific pharmacodynamics studies were conducted in humans.

Reports of 9 studies that evaluated the safety and/or the pharmacological activity of fomepizole in normal healthy subjects or in patients poisoned with ethylene glycol/ methanol have been discussed above.

Evaluator's conclusions on pharmacodynamics

Fomepizole has been shown in vitro to block ADH enzyme activity in dog, monkey and human liver. The concentration of fomepizole at which ADH is inhibited by 50% in vitro is approximately 0.1 µmol/L. No specific pharmacodynamics studies were conducted in humans. However, preliminary studies in patients with ethylene glycol/ methanol poisoning (S10, S11 and S12) provided evidence to support the mechanism of action of fomepizole in the proposed indications.

Dosage selection for the pivotal studies

Fomepizole has been shown in vitro to block ADH 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, three animals each were administered fomepizole, ethanol or left untreated (control group). The three animals in

¹⁴ Jacobsen D, et al. Kinetic interactions between 4-Methylpyrazole and Ethanol in Healthy Humans. Alcoholism: Clinical and experimental research. Vol.20, No.5. 1996.

the untreated group became progressively obtunded, moribund and died. At necropsy, all three dogs had severe renal tubular damage. Fomepizole or ethanol, given 3 h after ethylene glycol ingestion, attenuated the metabolic acidosis and prevented the renal tubular damage associated with ethylene glycol intoxication.

Several studies have demonstrated that Antizol® plasma concentrations of approximately 10 µmol/L (0.82 mg/L) in monkeys are sufficient to inhibit methanol metabolism to formate, which is also mediated by ADH. Based in these results, concentrations of Antizol® in humans in the range of 100 to 300 µmol/L (8.6 to 24.6 mg/L) have been targeted to assure adequate plasma concentrations for the effective inhibition of ADH.

In healthy volunteers, oral doses of Antizol® (10 to 20 mg/kg) significantly reduced the rate of elimination of moderate doses of ethanol, which is also metabolised through the action of ADH.

No specific studies were conducted to determine dosage selection for the pivotal studies.

Efficacy

Studies providing efficacy data

Pivotal efficacy studies

- Study S7 (OMC-4MP-3)

Evaluator's conclusions on clinical efficacy

for treatment of ethylene glycol poisoning

The efficacy of fomepizole treatment as an antidote for ethylene glycol toxicity has been documented in two uncontrolled studies submitted:

- Study S8 was a prospective study in 7 patients with severe EG poisoning and used the proposed dosing schedule for fomepizole (identical to the dosing recommendations in the proposed PI). Results of this study provided evidence to suggest that fomepizole (4MP) would be effective in preventing metabolism of EG to its toxic metabolites and that this would be evident in better clinical outcomes in terms of reduced mortality, morbidity, reversal of metabolic acidosis.
- Study S7 was a retrospective study which showed that prognostic outcome for the 26 patients with confirmed EG intoxication treated with 4MP was very good as 73% of patients survived with no sequelae, 15% of patients survived with some sequelae at endpoint (although these conditions tended to be mild and improved or resolved during patient follow-up). Two patients without benefit (1 death and 1 with long-term sequelae) were treated with 4MP more than 24 h after the intoxication. Hence, the effectiveness of 4MP in the treatment of EG intoxication appears to be closely related to the time at which the treatment is administered following intoxication. If treatment can be initiated very rapidly after ingestion of EG, its metabolism can be slowed and exposure to the toxic metabolites reduced.

However, interpretation of results from both studies S7 and S8 was confounded by concomitant use of ethanol and haemodialysis in conjunction with fomepizole, making it difficult to definitively assess the actual benefits of fomepizole in treatment of EG poisoning. Nevertheless, in the post-dialysis period(s), when ethanol concentrations were insignificant and the concentrations of ethylene glycol were >20 mg/dL, the administration of Antizol alone blocked any rise in glycolate or formate concentrations, respectively.

The systematic review of the literature identified a large number of case reports/series documenting the efficacy of 4MP in the treatment of ethylene glycol poisoning. The data from these publications provided supportive evidence of the efficacy of 4MP.

The META (Methylpyrazole for Toxic Alcohols) investigation by Brent et al (1999)¹⁵ in 19 patients with EG poisoning provided evidence that fomepizole is a safe and effective antidote in treatment of EG poisoning as data reported in this study led to approval of fomepizole for the treatment of EG poisoning in the United States. The plasma concentration of fomepizole that is necessary to inhibit ADH (approximately 0.8 µg/ml) was exceeded in this study and patients treated with concomitant ethanol were excluded from the study. The reduction in plasma glycolate concentrations and urinary oxalate excretion indicated that the metabolism of EG was inhibited. Furthermore, the inhibition of metabolite production coincided with the resolution of metabolic acidosis, which occurred at a mean of 3 h after the initiation of therapy. Renal function decreased during therapy in nine patients, all of whom had had abnormal renal function at enrolment. In contrast, the patients with normal serum creatinine concentrations at enrolment had no change in renal function.

A retrospective cohort study of 40 patients treated with fomepizole monotherapy for EG poisoning¹⁶ showed that the use of fomepizole as monotherapy without concurrent haemodialysis proved to be quite safe among patients without any metabolic acidosis or acute kidney injury. However, it is important to note that 60% of the patients had measurable ethanol concentrations which were in the therapeutic range (median >100 mg/dL). Interpretation was also limited due to retrospective, uncontrolled nature of the study; furthermore, there were no strict criteria mandating what pH level is considered too acidotic for fomepizole monotherapy and thus mandates haemodialysis.

Other case reports of EG poisoning treated with fomepizole were summarised and the results suggest that fomepizole is successful in preventing the metabolism of EG to its toxic metabolites, in reversing metabolic acidosis, and in preventing extensive renal damage. Furthermore, many of the case reports suggested that fomepizole along with supportive care (without haemodialysis) may be effective in patients with elevated EG levels, normal renal function and no metabolic acidosis at admission.

Hovda, et al (2011)¹⁷ reported the case of a young female with dissociative disorder who was admitted for EG poisoning a total of 154 times and was treated with fomepizole 99 times. Results from this case report suggest that fomepizole appears to be safe even when used frequently in the same patient. However, this is the only reference provided to support efficacy/ safety of repeated dosing with fomepizole.

Some studies/ case reports were provided to support evidence of efficacy of fomepizole for treatment of EG poisoning in paediatric patients. The retrospective study¹⁸ in 6 patients with age ranging from 22 months to 14 years) showed that haemodialysis with its inherent risks may be avoided in select paediatric patients with EG concentrations >50 mg/dL and normal renal function; the six paediatric patients with very high EG concentrations, normal renal function, and varying degrees of metabolic acidosis were

¹⁵ Brent, J., McMartin, K., Phillips, S., Burkhart, K. K., Donovan, J. W., Wells, M., & Kulig, K. (1999). Fomepizole for the Treatment of Ethylene Glycol Poisoning. *New England Journal of Medicine*, 340(11), 832–838.
<http://doi.org/10.1056/NEJM199903183401102>

¹⁶ Levine, M., Curry, S.C., Ruha, A.M., Pizon, A.F., Boyer, E., Burns, J., Bikin, D., Gerkin, R.D. (2012) Ethylene Glycol Elimination Kinetics and Outcomes in Patients Managed Without Hemodialysis. *Ann Emerg Med*, 59: 527 – 531.

¹⁷ Hovda et al 'Studies on ethylene glycol poisoning: One patient – 154 admissions. ' *Clinical Toxicology* (2011), 49, 478–484

¹⁸ Caravati, E. M., Heileson, H. L., & Jones, M. (2004). Treatment of Severe Pediatric Ethylene Glycol Intoxication Without Hemodialysis. *Journal of Toxicology -- Clinical Toxicology*, 42(3), 255–259.
<http://doi.org/10.1081/CLT-120037424>

successfully treated with fomepizole or ethanol (primarily fomepizole) without haemodialysis and most were discharged from the hospital within two to three days. Brent (2010)¹⁵ identified 14 published cases of paediatric patients treated with fomepizole. Six other case reports in paediatric patients were also summarised. Overall, the limited data available suggest that fomepizole, is effective and well tolerated in paediatric patients. Although the limited data reviewed here suggest that fomepizole (using the same dosage regimen as that used for adults) is safe and effective in paediatric patients, and that in the majority of cases of EG poisoning, haemodialysis may not be necessary, the data may be skewed by publication bias if those patients with bad outcomes were not published.

There are no well controlled studies of the use of fomepizole in the treatment of EG poisoning because of the nature of these events. The efficacy and safety of fomepizole were not specifically evaluated in elderly or in patients with renal/ hepatic impairment.

Overall, there was adequate evidence to support use of fomepizole in treatment of EG poisoning. The amount of toxin ingested, clinical level of intoxication and time to intervention are interrelated factors that influence the degree of treatment success.

Evaluator's conclusions on efficacy

for treatment of methanol poisoning

The evidence for efficacy of fomepizole treatment as an antidote for methanol toxicity was provided by two uncontrolled studies provided by the manufacturer (S7 and S13) involving 16 patients with methanol poisoning.

S13 was a well-conducted, prospective study which provided evidence for efficacy of fomepizole (4MP) treatment in 11 patients with methanol poisoning. Overall, 7/11 patients survived without sequelae, 3 patients survived with sequelae and there was 1 death. Fomepizole inhibited metabolism of methanol to toxic metabolites which was demonstrated by reduction in serum formate in all patients with detectable formate at baseline. Hence results from this study suggest that fomepizole, in conjunction with supportive care with or without haemodialysis, inhibits the conversion of methanol to its toxic metabolite, formate.

The case-by-case analysis of the 4 patients with confirmed methanol intoxication in Study S7 provided evidence to support efficacy and safety of 4MP in the treatment of methanol intoxication. However, interpretation was limited by retrospective nature of study and small sample size.

These efficacy studies and pharmacokinetic data have shown the recommended loading dose to be in the range of 10 to 20 mg/kg, followed by similar or lower doses every 12 h up to 48 h; then, due to enzyme induction, increased doses should be administered every 12 h until ethylene glycol or methanol blood levels are <20 mg/dL. If dialysis is employed to remove toxic metabolites of ethylene glycol or methanol, additional doses should be infused periodically throughout dialysis to compensate for its loss in the dialysate.

In addition to full clinical study reports provided to the sponsor (AFT Pharmaceuticals) by the manufacturer, the systematic review of the literature identified an additional two prospective studies^{19,15} that documented the efficacy of fomepizole in the treatment of poisoning associated with potentially fatal amounts of methanol in another 18 patients.

The role of haemodialysis in methanol poisoning is well-established when ethanol is the antidote but there are few reports and few kinetic data on dialysis when fomepizole is used as an antidote. Although the Phase III study (S13) leading to the FDA approval of

¹⁹ Hovda, K. E., Hunderi, O. H., TAFJORD, A.-B., Dunlop, O., Rudberg, N., & Jacobsen, D. (2005). Methanol outbreak in Norway 2002–2004: epidemiology, clinical features and prognostic signs. *Journal of Internal Medicine*, 258(2), 181–190.

fomepizole in methanol poisoning included dialysed patients, they were all dialysed according to the traditional dialysis indications from the time when ethanol was the only antidote. Based on data from the prospective case series study in 7 patients¹⁹ and another retrospective study in 14 patients²⁰, the authors suggest that methanol poisoning involving high methanol concentrations (> 50 mg/dL) without severe acidosis or visual impairment may be successfully treated by repeated dosing with fomepizole without dialysis.

Although fomepizole prevents the formation of toxic metabolites, dialysis is still required for elimination of methanol which is distinct from EG intoxication, where fomepizole may eliminate the need for dialysis.²¹

Three retrospective/ prospective study reports on methanol poisoning outbreaks in Norway¹⁹ and Czech Republic²² provided epidemiological, clinical and prognostic features from the large methanol outbreaks involving 210 patients. Methanol poisoning still has a high mortality, mainly because of delayed admission to hospital and late diagnosis. The use of buffer, antidote (ethanol and fomepizole were used in these studies) and haemodialysis is effective if initiated early. Visual disturbances, dyspnoea (including hyperventilation) and gastrointestinal (GI) symptoms were the most frequent clinical features, whilst severe metabolic acidosis (pH < 6.90 , base deficit (BD) > 28 mmol/L), coma and increased partial pressure of carbon dioxide (PCO₂) (lack of compensatory hyperventilation) were associated with poor outcome. Most of the patients who presented with symptoms were discharged without sequelae.

Other case report publications in adult and paediatric patients with methanol poisonings also provided supportive evidence for efficacy of fomepizole in treatment of methanol poisoning. However, it is important to note that dialysis was used in almost all of these patients.

Fomepizole is not intended to substitute for haemodialysis in patients with methanol poisoning. Concurrent haemodialysis is probably necessary to hasten removal of methanol in patients who present with high methanol levels, even if they present before the development of metabolic acidosis. However, fomepizole appears to be an easy and effective (although slightly expensive) substitute for ethanol in patients with methanol poisoning. By inhibiting hepatic metabolism of methanol and the accumulation of formic acid in the blood, it prevents the life- and vision-threatening complications of methanol poisoning.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

- Pivotal efficacy studies

²⁰ Mégarbane, B., Borron, S. W., Trout, H., Hantson, P., Jaeger, A., Krencker, E., ... Baud, F. J. (2001). Treatment of acute methanol poisoning with fomepizole. *Intensive Care Medicine*, 27(8), 1370–1378.

<http://doi.org/10.1007/s001340101011>

²¹ Brown MJ et al. Childhood Methanol Ingestion Treated With Fomepizole and Hemodialysis. *Pediatrics* 2001;108(4)

²² Zakharov, S., Kurcova, I., Navratil, T., Salek, T., Komarc, M., & Pelclova, D. (2015). Is the Measurement of Serum Formate Concentration Useful in the Diagnostics of Acute Methanol Poisoning? A Prospective Study of 38 Patients. *Basic & Clinical Pharmacology & Toxicology*, 116(5), 445–451.

<http://doi.org/10.1111/bcpt.12338>

Zakharov, S., Pelclova, D., Urban, P., Navratil, T., Diblik, P., Kuthan, P., ... Hovda, K. E. (2014). Czech mass methanol outbreak 2012: Epidemiology, challenges and clinical features. *Clinical Toxicology*, 52(10), 1013–1024. <http://doi.org/10.3109/15563650.2014.974106>

Six studies conducted in 63 patients to assess the safety and efficacy of fomepizole therapy for ethylene glycol poisoning (Studies S-7, S-8, S-9, S-10, S-11 and S-12), and interim safety data generated from 15 patients enrolled in an ongoing clinical study S13 to assess the safety and efficacy of fomepizole in the treatment of suspected methanol poisoning.

- Clinical pharmacology studies

Five clinical pharmacology studies conducted in 63 healthy subjects (identified in the NDA as Studies S-2, S-3, S-4, S-5 and S-6). Studies S-2 through to S-6 were all clinical pharmacology studies which assessed the pharmacokinetic and pharmacodynamic parameters of fomepizole.

Due to complexity of this literature based dossier, the safety sections of this evaluation report will be discussed as follows:

- evaluation and discussion of the safety results of the individual clinical studies in patients.
- evaluation and discussion of the safety results from each of the clinical pharmacology studies in healthy subjects.
- evaluation and discussion of the main safety results from other important published studies and case reports.
- evaluation and discussion of the Integrated summary of safety in combined dataset of 141 subjects (63 healthy subjects and 78 patients).

The sponsors have stated that the adverse reaction data in the proposed PI was based on data generated from this combined safety dataset of 141 (63 healthy subjects and 78 patients).

Patient exposure

In healthy volunteers

Overall, 53 healthy male subjects received fomepizole in the placebo-controlled Studies S2, S3, S4, S5 and S6. However, two of the cross-over studies (S-2 and S-5) involved two fomepizole treatment periods. In study S-2, six patients received fomepizole IV in one treatment period (with concomitant oral placebo) and oral fomepizole (with concomitant IV placebo) in another. In Study S-5, five patients received fomepizole and 'placebo' (in place of ethanol) in one period and 4 of the 5 received fomepizole and ethanol in another (the fifth patient dropped out prior to the second period). Thus, there were a total of 63 fomepizole subject-treatments (12 with fomepizole placebo concomitantly, five with ethanol 'placebo' concomitantly, and 46 without placebo) and 25 placebo subject-treatments (without fomepizole) in the five studies combined. Twelve of the fomepizole subject-treatments (S-2) involved both fomepizole and placebo (by different routes). Overall, 32 subjects received either single oral doses (n=27) or single IV doses (n=5) of fomepizole; 6 subjects received both IV and oral single doses in a cross-over study and 15 additional subjects received multiple oral doses every 12 h for up to 96 h.

It is important to note that only 5 subjects in the clinical pharmacology studies were treated with the proposed IV route of administration.

In patients with EG and methanol poisoning

Table 3 summarises the studies in patients which provided safety data. Study S-7 was a retrospective study of 38 patients treated for various poisonings over 14 years at a single centre in France. Cohort A included 26 patients treated for EG poisoning, Cohort B included 5 patients treated for methanol poisoning, and Cohort C included 7 patients treated for suspected but later unconfirmed EG poisoning. Study S-8 was a prospective study of 22 EG poisoned patients conducted by the sponsor in the U.S. Studies S-9 and S-10

were published reports that contained detailed descriptions of 4 patients whose data was also included in Study S-7. Studies S-11 and S-12 were published case reports of three additional patients poisoned with EG. Majority of dosing with fomepizole was by IV administration in all the EG/methanol poisoning studies (Table 3).

Table 3: Main studies in patients which provided safety data with brief summary of safety results

| Study No./Type | Title | Investigators / Authors Journal/Year | Design | No. of Patients/Subjects sex/ age range | Fomepizole (4MP) dosage | Safety Results |
|--|---|--|-----------------------------|--|--|---|
| S-7/ Retrospective | A Retrospective Open-label Study for Patients Treated in France with 4-Methylpyrazole (4MP) for Ethylene Glycol Poisoning | Baud FJ, et al Orphan Medical | Open-label, Clinical use | 38 patients: Cohort B: 5 patients 4 Males 1 Female Mean: 47 years Range: 28-57 years | Cohort B: Median loading dose: 10.2 mg/kg Range: 9.0-16.3 mg/kg Median Cumulative Dose: 19.7 mg/kg Range: 10.2-75.4mg/kg | Cohort B: 80% (4/5) alive with no sequelae, 20% (1/5) alive with sequelae. All patients: 25/38 reported 84 AEs including headache, vomiting, abdominal pain, anemia, fever. |
| S-8/ Prospective | An Open-label Phase III Pivotal Trial of the Antidotal Efficacy and Pharmacokinetic Profile of Antizol™ (fomepizole) for the Treatment of Ethylene Glycol Poisoning- Interim Report | Hollander J, Ford M, Brent J, Burkhardt K, Dart R, Curry S, McKay C, Douglas D Orphan Medical | Open-label, Clinical use | 22 patients 18(82%) Males 4(18%) Females Median: 42 years Range: 19-73 years | IV infusion, loading dose 15 mg/kg, then 10 mg/kg q12hX4, then 15 mg/kg q12h until EG <20mg/dl | Bradycardia, abdominal pain, headache, nystagmus, drowsiness, vertigo, hypotension, seizure, fever, tachycardia. 3 deaths not related to study drug. |
| S-9/ Clinical Treatment of Ethylene glycol (EG) poisoning | 4-Methylpyrazole May Be an Alternative to Ethanol Therapy for Ethylene Glycol Intoxication in Man. | Baud FJ, et al Clin Toxicol 1986-87 | Open-label, Clinical Use | 1) 19 y/o male 2) 26 y/o female 3) 28 y/o male (data for these patients also reported in S-7) | Oral or NG tube. Loading dose, then lower doses. Pt1: 15 mg/kg, then 5 mg/kg 11 hrs later, then 10 mg/kg BID, 4 days. Pt2: 20 mg/kg then 10 mg/kg q12h, 5 days. Pt3: 15 mg/kg and 5 mg/kg 12 hrs later | Rash, eosinophilia, mild AST elevation with CPK increase, decreased prothrombin time, mild transient hypoglycemia |
| S-10/ Clinical Treatment of EG Poisoning | Treatment of Ethylene Glycol Poisoning with Intravenous 4-Methylpyrazole | Baud FJ, et al N Engl J Med 1988 | Open-label, Clinical Use | 42 y/o male (data for this patient also reported in S-7) | IV infusion at 9, 21, 33, 45 and 57 hrs post EG ingestion. At these times, respective doses of 9.5, 7.0, 3.6, 1.2 and 0.6 mg/kg. | No adverse effects |

Table 3 continued: Main studies in patients which provided safety data with brief summary of safety results

| | | | | | | |
|---|--|---|-----------------------------|--|---|---|
| S-11/ Clinical Treatment of EG Poisoning | Efficacy of 4- Methylpyrazole in Ethylene Glycol Poisoning: Clinical and Toxicokinetic Aspects | Harry F, et al Hum Exp Toxicol 1994 | Open-label, Clinical use | 30 y/o male | IV infusion, loading dose 16.2 mg/kg; then q12h doses of 8.1, 5.4, 2.7 and 1.35 mg/kg | Mild transient AST elevation |
| S-12/ Clinical Treatment of EG Poisonings | 4-Methylpyrazole and Hemodialysis in Ethylene Glycol Poisoning | Jobard E, et al Clin Toxicol 1996 | Open-label, Clinical use | 1) 30 y/o male 2) 54 y/o male | IV infusion, Pt1: loading dose 10 mg/kg; then 4 hrs later 2.5 mg/kg/h over 2 hrs during 12-hour dialysis. Pt2: loading dose 20 mg/kg, then 1 hr later 1.5 mg/kg/h over 6 hours of dialysis. | Pt 1: Clinical recovery, no adverse effects. Pt2: Multiorgan failure, DIC, death |
| S-13/ Pro- spective | An Open-label Phase III Pivotal Trial of the Antidote Efficacy and Pharmacokinetic Profile of Antizol™ (fomepizole) for the Treatment of Methanol Poisoning | Brent J, Bukhardt K, Aarons C, Ford M, Donovan J, Akhtar J Dart R White S Orphan Medical | Open-label, Clinical use | 15 patients 11 males 4 females Mean: 40 years (Range: 18-61 yrs) | IV infusion, loading dose 15 mg/kg, then 10 mg/kg q12hX4, then 15 mg/kg q12h until EG <20mg/dL | 27 adverse events reported from 13/15 patients. Most frequent were agitation, anxiety, fever, headache. One patient died on study and one patient died subsequent to study, both due to severe methanol toxicity. |

Dosing characteristics varied among patients in the two pivotal methanol studies. In the retrospective study S-7 (Cohort B), fomepizole dosages and routes of administration varied depending upon the amount of toxin ingested, length of time between exposure and treatment, and mental status of the patient. In the prospective study (S-13), all patients were to receive IV fomepizole at an initial dose of 15 mg/kg, followed by 4 doses of 10 mg/kg every 12 hours, and 15 mg/kg every 12 h thereafter until methanol levels were <20 mg/dL. Patients receiving haemodialysis were given an additional dose before dialysis if more than 6 h had elapsed since their last dose, and this dose was to be repeated every 4 h during dialysis. Those receiving dialysis for longer than one hour were also to receive an additional fomepizole dose at the end of dialysis in addition to the next regularly scheduled dose, according to the following schedule:

- 1-3 hours: one-half of the next scheduled dose
- >3 hours: full dose equivalent to the next scheduled dose.

In Study S-7, three patients (60%) received IV fomepizole; the other two patients received an oral formulation. In Study S-13, all patients received the IV fomepizole formulation. The median loading dose of fomepizole for the 20 patients with suspected methanol poisoning was 15 mg/kg with a range of 9 to 22 mg/kg. Treatment periods ranged from single doses in seven patients to 13 doses over seven days in one patient. The highest cumulative dose administered was 8445 mg or 102.8 mg/kg (Table 4).

Table 4: Integrated fomepizole dosing characteristics

| Study | Study S-7 (N=5) | Study S-13 (N=16) | All Studies (N=20) |
|--------------------------------------|--------------------|----------------------|-----------------------|
| Loading dose (mg) | | | |
| Median | 600 | 1200 | 1073 |
| Minimum-Maximum | 500-1200 | 750-2170 | 500-2170 |
| Loading dose (mg/kg) | | | |
| Median | 10 | 15 | 15 |
| Minimum-Maximum | 9-15 | 15-22 | 9-22 |
| Duration of treatment (hours) | | | |
| Median | 16.8 | 6.2 | 12.2 |
| Minimum-Maximum | 0.5-168.0 | 0.5-60.0 | 0.5 - 168.0 |
| Total number of doses | | | |
| Median | 2 | 2 | 2 |
| Minimum-Maximum | 1-13 | 1-10 | 1-13 |
| Cumulative total dose (mg) | | | |
| Median | 1300 | 1690 | 1663 |
| Minimum-Maximum | 500-5050 | 750-8445 | 500-8445 |
| Cumulative total dose (mg/kg) | | | |
| Median | 14.0 | 29.2 | 25.0 |
| Minimum-Maximum | 6.0-25.0 | 15.0-102.8 | 6.0-102.8 |

The ongoing study S13 in patients with suspected methanol poisoning used the proposed dosing regimen for fomepizole (including during haemodialysis) as reflected in the 'dosage and administration' section of the proposed PI.

Safety issues with the potential for major regulatory impact

Liver toxicity

Mild, transient elevations in liver transaminases were reported in the earlier studies in healthy subjects but similar findings were not observed in the studies in patients.

Haematological toxicity

Eosinophilia is a known AE associated with fomepizole treatment.

Unwanted immunological events

Venous irritation and phlebosclerosis were noted in two of six normal volunteers given bolus injections (over 5 minutes) Antizol® at a concentration of 25 mg/ml. Minor allergic reactions (mild rash, eosinophilia) have been reported in a few patients receiving Antizol. Therefore, patients should be monitored for signs of allergic reactions.

Postmarketing data

No Periodic Safety Update Reports (PSURs) were provided in this submission.

Evaluator's conclusions on safety

Adverse effects reported with fomepizole use in adults include dizziness, lightheadedness, diarrhoea and headache. Elevation in blood pressure was observed in one report, but was also noted with equal frequency in placebo- administered volunteers. Transient elevation of liver transaminases (40%), serum triglycerides (30%), cholesterol (10%), phosphorous, and bilirubin was associated with multiple-dose fomepizole administration in Phase I studies, although lipid changes also appeared in placebo studies. Clinical use of fomepizole in adults showed only minimal adverse effects consisting of transient transaminase elevation, skin rash and eosinophilia. Besides the report of nystagmus and one AE of hypotension/ bradycardia which appeared to be directly related to IV fomepizole administration, no other major AEs were reported in the case reports.

The observational cohort studies comparing the safety (AEs and medication errors) of antidotal treatment with fomepizole versus ethanol in patients with EG/methanol

poisoning;²³ Although the results suggested a significantly worse side effect profile and higher rate of medication errors (including harmful errors) with ethanol compared to fomepizole, interpretation was limited by many confounding factors. Despite this and acknowledging that it would be very difficult to conduct prospective clinical trials comparing ethanol with fomepizole in these patients, the safety profile of fomepizole does appear to be more acceptable compared to that of ethanol.

No definitive clinical trials were conducted to evaluate safety in paediatric patients, elderly or patients with renal/ hepatic impairment.

The sponsors have stated that the objective of the Integrated Safety Summary (ISS) provided was to integrate adverse event (AE) data generated from the 12 clinical studies conducted to assess the safety of fomepizole in the treatment of EG and methanol poisonings. In USA, this integrated data was used to update the adverse reactions section of the current package insert (already approved for EG poisoning) upon marketing approval of Antizol for treatment of methanol or suspected methanol poisoning. However, the safety section of the proposed Australian PI does not include this information and should be modified to incorporate these AEs.

First round benefit-risk assessment

First round assessment of benefits

The benefits of fomepizole in the proposed usage are:

- Fomepizole or 4 Methylpyrazole (4MP) is a competitive inhibitor of alcohol dehydrogenase (ADH) and the affinity of fomepizole for human ADH is 80,000 and 8,000 times greater than methanol and ethanol, respectively.
- Fomepizole was effective in preventing metabolism of EG to its toxic metabolites showing better clinical outcomes in terms of reduced mortality, morbidity, reversal of metabolic acidosis.
- In some cases of EG poisoning with normal renal function and no metabolic acidosis on presentation, fomepizole may obviate the need for haemodialysis.
- Fomepizole, in conjunction with supportive care with or without haemodialysis, inhibits the conversion of methanol to its toxic metabolite, formate. By inhibiting hepatic metabolism of methanol and the accumulation of formic acid in the blood, it prevents the life and vision threatening complications of methanol poisoning.
- Fomepizole has no central nervous system depressant effects are observed at therapeutic doses.
- Monitoring of fomepizole blood levels is not necessary.
- Since fomepizole has a slower rate of elimination than ethanol, it has a stronger and more consistent duration of effective inhibitory activity.
- Fomepizole requires less frequent dosing to maintain effective blood levels.

First round assessment of risks

The risks of fomepizole in the proposed usage are:

²³Lepik KJ et al. Adverse Drug Events Associated With the Antidotes for Methanol and Ethylene Glycol Poisoning: A Comparison of Ethanol and Fomepizole. Ann Emerg Med. 2009;53:439-450
and Lepik KJ et al. Medication errors associated with the use of ethanol and fomepizole as antidotes for methanol and ethylene glycol poisoning. Clinical Toxicology (2011), 49, 391-401

- Lack of adequate prospective randomised controlled clinical trials but this would be difficult considering the acute nature and occurrence of proposed indications of EG or methanol poisonings.
- Lack of data on long-term safety implications including possible increase in sensitivity due to repeat exposure.
- Lack of definitive PK studies in patients with renal/ hepatic impairment.
- Interactions may occur with concomitant use of Antizol® and drugs that increase or inhibit the cytochrome P450 system (such as phenytoin, carbamazepine, cimetidine, ketoconazole), though this has not been studied.
- Expensive compared to ethanol.
- Venous irritation and phlebosclerosis; this was mainly seen following bolus injections over 5mins at 25 mg/mL.
- Common AEs associated with fomepizole treatment were vertigo, nausea, vomiting, abdominal pain, headache, unpleasant taste/ smell, eosinophilia and rash.

First round assessment of benefit-risk balance

Fomepizole has been shown to be a potent inhibitor of ADH, the enzyme responsible for the metabolism of ethylene glycol to its toxic metabolites, which can produce metabolic acidosis, severe CNS impairment, renal failure, and frequently death. In some cases of EG poisoning with normal renal function and no metabolic acidosis on presentation, fomepizole may obviate the need for haemodialysis.

Fomepizole, in conjunction with supportive care with or without haemodialysis also inhibits the conversion of methanol to its toxic metabolite, formate. By inhibiting hepatic metabolism of methanol and the accumulation of formic acid in the blood, it prevents the life and vision threatening complications of methanol poisoning. Fomepizole is not intended to substitute for haemodialysis in patients with methanol poisoning. Concurrent haemodialysis is probably necessary to hasten removal of methanol in patients who present with high methanol levels, even if they present before the development of metabolic acidosis.

The reported clinical use of 4MP has preceded the usual Phase I to III clinical studies for new drugs and therefore little is known about the optimal dosing in humans. However, several PK studies, literature references and clinical studies (retrospective and prospective) have established that the proposed dose of fomepizole (15 mg/kg loading doses followed by 10 mg/kg every 12 h with more frequent dosing during haemodialysis) is effective in maintaining therapeutic concentrations of fomepizole which inhibits ADH and hence biotransformation of EG and methanol to their toxic metabolites. The amount of toxin ingested, clinical level of intoxication, and time to intervention are interrelated factors that influence the degree of treatment success.

Overall, few clinically relevant AEs have been observed with fomepizole treatment. Potentially drug-related AEs include dizziness, light headedness, feeling of intoxication, vertigo, nausea, vomiting, abdominal pain, headache, unpleasant taste/ smell, eosinophilia, rash and local inflammatory reactions to venous infusion. Additionally, hypotension and seizure are of unknown relationship to fomepizole. Although these can be serious AEs, they are potential symptoms of ethylene glycol poisoning and assessment of their relationship to fomepizole is confounded in these severely intoxicated and metabolically compromised patients. Laboratory abnormalities possibly related to treatment include slight transient increases in liver enzymes, eosinophilia and elevated triglycerides and/or cholesterol, all without clinical manifestations.

The efficacy of fomepizole treatment as an antidote for ethylene glycol and methanol toxicity has been documented in multiple uncontrolled studies (both published and unpublished) and publications of individual patient case histories. Fomepizole has been shown to be successful in preventing the metabolism of ethylene glycol and methanol to their toxic metabolites, in reversing metabolic acidosis and in preventing extensive renal damage and visual impairment.

Ethanol, which has been the standard antidote for EG poisoning over the last 10 to 15 years, works by the same mechanism as fomepizole. However, the amount given must be carefully controlled, since ethanol itself is a hepatotoxin and CNS depressant. Patient management with ethanol is difficult because patients must be kept intoxicated for several days. Furthermore, ethanol is rapidly and erratically metabolised, requiring frequent dose adjustments to maintain therapeutic levels. Therapeutic blood levels of fomepizole can be maintained with twice daily dosing. Furthermore, only relatively mild CNS effects have been attributed to its use at therapeutic levels. Therefore, fomepizole is much safer and easier to use than ethanol.

Overall, the benefit-risk balance of Antizol (fomepizole, 4MP), given the proposed usage for treatment of ethylene glycol and methanol poisoning, is favourable.

First round recommendation regarding authorisation

It is recommended that Antizol (fomepizole, 4MP) be approved for the proposed indication of: 'Antizol is indicated as an antidote for ethylene glycol (such as antifreeze) or methanol poisoning either alone or in combination with haemodialysis (see Dosage and administration).'

However, the approval is subject to incorporation of suggested changes to the proposed PI, CMI and adequate response to Clinical questions (see Attachment 2).

Second round evaluation of clinical data submitted in response to clinical questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of fomepizole in the proposed usage are unchanged to those identified in the first round.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of fomepizole in the proposed usage are unchanged to those identified in the first round.

Second round assessment of benefit-risk balance

The benefit-risk balance of fomepizole, given the proposed usage is favourable.

Second round recommendation regarding authorisation

It is recommended that Antizol (fomepizole, 4MP) be approved for the proposed indication of: '*Antizol is indicated as an antidote for ethylene glycol (such as antifreeze) or methanol poisoning either alone or in combination with haemodialysis (see Dosage and administration).*'

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (Australia RMP Version 01 (dated 30 November 2014, DLP 26 November 2014) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 5.

Table 5: Summary of ongoing safety concerns

| Summary Ongoing Safety Concerns | |
|---------------------------------|---|
| Important identified risks | <i>Hypersensitivity to the active substance</i> |
| | <i>Drug interaction with ethanol – each decreases the elimination of the other. Also act in combination to reduced testicular mass.</i> |
| | <i>Impairment of fertility – reduced testicular mass</i> |
| | <i>Mutagenicity – Positive in Ames test against <i>E. coli</i> WP2uryA and <i>S. typhimurium</i> TA102.</i> |
| Important potential risks | <i>Carcinogenicity – no long term studies conducted with fomepizole</i> |
| | <i>Pregnancy – potential for effects on fetus not known</i> |
| | <i>Nursing Mothers – drug may be excreted in breast milk.</i> |
| Missing information | <i>None</i> |

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for all safety concerns and missing information.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities for Australia.

Reconciliation of issues outlined in the RMP report

Table 6 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA and an evaluation of the sponsor's responses.

The sponsor did not include a direct response to the RMP recommendations. Instead, a revised RMP was submitted, which in part addressed the recommendations. The actions taken by the sponsor are described in the table below, with discussion of whether or not the recommendation has been adequately addressed.

Table 6: Reconciliation of issues outlined in the RMP report

| Sponsor's response to first round recommendations with RMP evaluator's comment |
|---|
| <p>TGA recommendation 1: Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.</p> |
| <p><i>Sponsor's response:</i> The sponsor has not addressed the comments of the nonclinical evaluator.</p> |
| <p>RMP Evaluator comment: The RMP should be revised to incorporate the changes recommended in the Nonclinical Evaluation Report to ensure that the information contained in the RMP is technically accurate.</p> |
| <p>TGA recommendation 2: There appears to be a misspelling in the proposed indication for Antizol. This should be corrected by the sponsor. There are also inconsistencies in the use of Australian-English that should be made consistent throughout the documentation.</p> |
| <p><i>Sponsor's response:</i> The sponsor submitted a revised PI.</p> |
| <p>RMP Evaluator comment: This typographical error has been corrected.</p> |
| <p>TGA recommendation 3: Regarding off-label risks, the use of Antizol to treat ethanol intoxication cannot be excluded. Given the interaction identified with ethanol (affecting kinetics), and the serious effect on testicular mass/fertility, a stronger warning <u>against</u> use in treating ethanol intoxication is warranted. The Delegate may wish to consider that the sponsor explicitly advise against this use in the PI (as a Contraindication or Precaution).</p> <p>Furthermore, if not contraindicated, the sponsor must advise how the product is to be administered in cases of methanol or ethylene glycol PLUS ethanol intoxication, to include how treating physicians can ascertain this prior to administration. As interaction with ethanol is an identified safety concern, there should be reference to how to administer ANTIZOL (or not to administer) in cases presenting from exposure to ethylene glycol or methanol <u>and</u> ethanol.</p> |
| <p><i>Sponsor's response:</i> The sponsor has not addressed this recommendation in the revised PI.</p> <p>RMP Evaluator comment: This recommendation has been revised in consideration with ACSOM advice, and it included in the outstanding issues.</p> |
| <p>TGA recommendation 4: It is noted that the sponsor has not actually provided epidemiology information in the RMP relating to the incidence of indicated poisoning. The sponsor should provide this information in an updated RMP.</p> <p><i>Sponsor's response:</i> The revised RMP (version 02) included some epidemiology data for ethylene glycol and methanol poisoning in Australia from January 2012 to August 2014.</p> |

| Sponsor's response to first round recommendations with RMP evaluator's comment |
|---|
| <p>RMP Evaluator comment: The sponsor has adequately addressed this recommendation.</p> |
| <p>TGA recommendation 5: There are a number of precautions relating to the use of Antizol not reflected in the Summary of Safety Concerns:</p> <p>There are prominent warnings in the PI related to risks associated with Antizol being administered undiluted or by bolus injection. 'Medication errors' should be added as an Important Identified Risk with use of Antizol.</p> <p>The PI advises that the safety and effectiveness in paediatric patients have not been established. Given the possibility of accidental exposure to ethylene glycol or methanol by children, this patient group should be added as Important Missing Information in the Summary of Safety Concerns.</p> <p>The PI indicates that pharmacokinetics have not been sufficiently study in geriatric patients, between genders, or in patients with renal and hepatic insufficiency. Given the mechanism of action and pharmacology of Antizol, these patient groups should be included as Important Missing Information in the Summary of Safety Concerns.</p> |
| <p><i>Sponsor's response:</i> The revised RMP (version 02) included these safety concerns.</p> |
| <p>RMP Evaluator comment: This recommendation has been addressed, but these safety concerns should also have the planned risk minimisation activities included in the RMP.</p> |
| <p>TGA recommendation 6: Under 'Adverse Effects' in the provided PI, the following is presented: '<i>All other adverse events in this population were reported in approximately 3% or fewer of those receiving Antizol® and were as follows:</i>' There is no information actually provided after this statement – the sponsor should provide the specific adverse events reported with use of ANTIZOL.</p> |
| <p><i>Sponsor's response:</i> A description of the adverse events has been included in the revised PI.</p> |
| <p>RMP Evaluator comment: The sponsor has adequately addressed this recommendation.</p> |
| <p>TGA recommendation 7: The sponsor should provide with their response an updated RMP with a consistent set of safety concerns used for the Summary of Safety Concerns, the Pharmacovigilance Plan, and the Risk Minimisation Plan. For example, there are other safety concerns specified in the Risk Minimisation section of the RMP that are not included in the Summary. This includes:</p> <p>Identified risk: minor allergic reactions</p> <p>Identified risk: venous irritation and phlebosclerosis</p> <p>Identified risk: 'laboratory tests' – to include transient increases in serum transaminase concentrations and eosinophilia</p> |
| <p><i>Sponsor's response:</i> The revised RMP has in part addressed this recommendation.</p> |
| <p>RMP Evaluator comment: The Summary of Safety Concerns has been updated, as has the pharmacovigilance plan. The sponsor should ensure that all safety concerns are captured in the risk minimisation plan, with the proposed activities for each safety concern described.</p> <p>In addition, it is noted that 'laboratory tests' in themselves do not accurately capture the safety concern. Instead, it is recommended that this is separated into two safety concerns;</p> |

| Sponsor's response to first round recommendations with RMP evaluator's comment | |
|--|--|
| | hepatotoxicity (in line with the nonclinical evaluator's recommendations) and eosinophilia. |
| | TGA recommendation 8: From recommendation 7 above, the sponsor should be sure to nominate the relevant pharmacovigilance and risk minimisation activities against the updated Summary of Safety Concerns in the RMP. |
| | <i>Sponsor's response: see above</i> |
| | RMP Evaluator comment: see above. |
| | TGA recommendation 9: In reference to hypersensitivity, the sponsor should be consistent with inclusion of the additional text ' <i>or to any of the excipients</i> ' (for example, this reference to excipients is not included in the Summary of Safety Concerns). |
| | <i>Sponsor's response: The sponsor has added reference to the excipients.</i> |
| | RMP Evaluator comment: It is noted that in the revised PI that a statement has been added that fomepizole contains no excipients. Therefore, the reference to excipients should be removed from the hypersensitivity safety concern. |
| | TGA recommendation 10: The sponsor should be consistent with how patient groups and risks are referred to (e.g. 'elderly' population versus 'geriatric'). |
| | <i>Sponsor's response: This has been addressed in the PI, and variably updated in the RMP.</i> |
| | RMP Evaluator comment: The changes to the PI are acceptable. The RMP still contains a mix of terminology which should be updated in the next RMP version. |

Summary of recommendations

There are outstanding issues and additional recommendations.

Outstanding issues

Advice from the Advisory Committee on the Safety of Medicines (ACSM)

The key issues from the ACSM advice were:

- The committee endorsed the changes recommended by the RMP evaluator to the Summary of Safety Concerns.
- The committee advised greater consideration and information on ethanol toxicity, and warning against using fomepizole to treat ethanol toxicity, should be included in the PI. Advice on the recommended action for methanol/ethylene glycol and ethanol intoxication should also be provided in the PI.
- The committee recommended that the pharmacovigilance plan and risk management plan be updated to address all safety concerns.

The committee recommended inclusions of the following safety concerns

- Important potential risks:
 - Hypoglycaemia
 - Seizures

- Off-label use, including in:
 - Paediatrics
 - Diethylene glycol poisoning
 - Patients exposed to mixtures of poisons
 - In patients without positive identification of methanol and/or ethylene glycol poisoning
- Missing information:
 - Interactions with CYP450 inducers and inhibitors
 - Effects of race (including use in Aboriginal and Torres Strait Islander people)
 - Effects of gender [The RMP Evaluator notes this has been included as missing information in the revised RMP]
 - Interactions with disulfiram and medications for psychiatric disorders (anti-depressants, anxiolytics, antipsychotics)

New and outstanding recommendations

The following recommendations are based on consideration of the ACSOM advice, and the revised RMP and PI. TGA Recommendations 2, 4, 6 (from the round one RMP Evaluation) have been adequately addressed by the sponsor.

The following outstanding issues should be addressed:

TGA Recommendation 1: The sponsor has not made the revised the RMP with respect to the recommendations of the nonclinical evaluator. These should be addressed, with particular attention to the changes which impact on the Summary of Safety Concerns. The sponsor is reminded that any the addition of a safety concerns also requires a description of the pharmacovigilance and risk minimisation activities that will be conducted for that safety concern.

TGA Recommendation 3: The sponsor has not addressed the recommendation to include advice regarding the use of fomepizole in ethanol intoxication either alone or in combination with methanol and/or ethylene glycol poisoning. The PI should include:

- a. Guidance for use in patients with methanol and/or ethylene glycol intoxication, with concomitant ethanol intoxication. Given the reciprocal interactions and effects of ethanol and fomepizole, the Sponsor should indicate whether dose reduction or delay is warranted in these cases (preferably with data to support this inclusion or omission) or justify the absence of this information. In addition, the issue of sequential treatment with fomepizole following ethanol should be discussed.
- b. A clear statement that fomepizole is ineffective in treating ethanol intoxication, and would conversely prolong ethanol intoxication if administered.

TGA Recommendations 5, 7 and 8: These recommendations have been partly addressed, but the added safety concerns require the risk minimisation activities to be documented in the RMP. Routine activities are acceptable for these safety concerns; the corresponding PI statements should be included in the RMP.

TGA Recommendation 9: The safety concern for hypersensitivity should have the reference to excipients removed as the revised PI indicates that fomepizole is not formulated with any excipients.

TGA Recommendation 10: The RMP should be revised to consistently use the preferred terminology ('elderly' instead of 'geriatric').

The following additional recommendations are based on ACSOM advice:

The concerns raised by ACSOM regarding ethanol intoxication have been incorporated into the revised TGA Recommendation 3 (see above).

TGA Recommendation 11: The important potential risks and missing information identified by ACSOM should be added to the Summary of Safety Concerns, as shown in the table below. In addition, a description of the pharmacovigilance and risk minimisation activities that will be conducted for these safety concerns should be included in a revised RMP.

To assist the sponsor in capturing all the recommended additions to the safety specification, the Summary of Safety Concerns provided in version 02 of the RMP has been annotated below to include the recommended changes. Deletions are shown struck through, with additions underlined, with all changes highlighted for clarity.

| Summary - Ongoing Safety Concerns | |
|-----------------------------------|---|
| Important identified risks | Hypersensitivity to the active substance <u>or to any of the excipients.</u> [#] |
| | Drug interaction with ethanol – each decreases the elimination of the other. Also act in combination to reduced testicular mass |
| | Impairment of Fertility – reduced testicular mass |
| | Mutagenicity – Positive in Ames test against <i>E.coli</i> WP2urvA and <i>S. typhimurium</i> TA102 |
| | Medication errors- being administered undiluted or by bolus injection |
| | Minor allergic reactions |
| | Venous irritation and phlebosclerosis |
| | <u>Laboratory tests – transient increases in serum transaminase concentrations and</u> Eosinophilia. [#] |
| | <u>Hepatotoxicity (serum transaminase elevation)</u> ^{^, #} |
| | <u>CNS effects, including dizziness, vertigo and headache</u> [^] |
| Important potential risks | Carcinogenicity – no long term studies conducted with fomepizole |
| | <u>Use in</u> Pregnancy – potential for effects on foetus not known |
| | <u>Use in lactation</u> <u>Nursing Mothers</u> – drug may be excreted in breast milk. [#] |
| | <u>Muscle damage (creatinine kinase elevation)</u> [^] |
| | <u>Hypoglycaemia*</u> |
| | <u>Seizures*</u> |
| | <u>Off-label use, including in paediatrics, patients exposed to poisons</u> |

| Summary - Ongoing Safety Concerns | |
|-----------------------------------|---|
| | <u>other than ethylene glycol or methanol alone or in combination (including diethylene glycol), and use in patients without confirmed methanol or ethylene glycol poisoning*</u> |
| Missing information | <p><u>Use in</u> paediatric patients (<u>including neonates</u>)[^] - safety and effectiveness has not been established</p> <p>Any differences in the pharmacokinetics of fomepizole in <u>geriatrics</u> <u>the elderly</u>, between genders, <u>or in different ethnicity (including Aboriginal and Torres Strait Islander people)</u> <u>or in patients with renal and hepatic insufficiency</u>[#] have not been established.</p> <p><u>Use in</u> patients with renal impairment[#]</p> <p><u>Use in</u> patients with hepatic impairment[#]</p> <p><u>Effects on female fertility</u>[^]</p> <p><u>Drug interactions with CYP450 inducers and inhibitors*</u></p> <p><u>Drug interactions with disulfiram and medications for psychiatric disorders (anti-depressants, anxiolytics, antipsychotics)*</u></p> |

[^] = based on recommendations by the nonclinical evaluator; * = based on ACSOM recommendations; # = based on recommendations by the RMP evaluator, including those recommended for clarity. Note: The annotation symbols (^, *, #) should be removed from the Summary of Safety Concerns in the RMP.

Suggested wording for conditions of registration

The RMP requires significant revision to meet a standard that is acceptable. Therefore, at this stage no wording for the conditions of registration can be provided.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator concluded that pending resolution of the remaining issues, approval for registration is recommended with respect to the pharmaceutical chemistry aspects of the submission. The quality evaluator noted the following (please see Quality findings above for further details):

- The product contains no excipients or solvents and consists only of neat fomepizole filled into vials. Residual levels of the potentially genotoxic hydrazine and 4-nitrobenzaldehyde are controlled to acceptably low levels.
- The product must be diluted in at least 100 mL of 0.9% sodium chloride solution or 5% glucose solution before infusion intravenously.
- A shelf-life of 24 months, stored below 25°C, protected from light was considered appropriate based on the submitted stability data.

- Outstanding issues with impurities noted in the ACPM summary have now been resolved with the exception of GMP clearance for one site that is under evaluation by the Manufacturing Quality Branch.

Nonclinical

The nonclinical evaluator found the submission deficient in many aspects and could not support registration of fomepizole based on the nonclinical components of the submission. Overall the hybrid submission was of poor quality and did not address all requirements of the relevant ICH guideline for the nonclinical assessment of pharmaceuticals (ICH M3 (R2))¹¹ and there was a lack of critical assessment of the literature in the sponsor's Nonclinical overview and summaries. Of particular concern was the lack of data regarding the effects on the cardiovascular, respiratory and renal systems, the lack of the pharmacokinetic profile to assess the suitability of animal models, the effects of repeated dosing with fomepizole (lack of high quality data in more than one species for an adequate duration of dosing), and the effects of fomepizole on fertility, embryofetal and post-natal development.

The following were noted in the nonclinical evaluation:

- In vitro, fomepizole inhibited alcohol dehydrogenase with a K_i value of approximately 0.1–0.2 μM which is markedly lower than the predicted clinical fomepizole C_{max} . In vivo, fomepizole antagonised the effects of ethylene glycol poisoning in rats, dogs and monkeys and was also effective in preventing methanol poisoning in monkeys.
- Fomepizole was excreted predominantly in the urine as metabolites, with the urinary metabolite profile being qualitatively similar between rats and humans. Secondary pharmacology studies were not submitted.
- Fomepizole inhibited and induced CYP2E1 at clinically relevant concentrations and doses. Antipyrine metabolism was markedly inhibited by fomepizole, indicating inhibition of other CYPs at clinically relevant doses. The interactions with CYP2E1 and with the pharmacological target (alcohol dehydrogenase) have the potential to markedly alter ethanol metabolism, as well as the metabolism of other xenobiotics. In vivo data show fomepizole and ethanol reciprocally inhibit the elimination of each other. The interactions of fomepizole with other enzymes, receptors or transporters are unknown.
- In mice and repeat dose studies in dogs fomepizole CNS effects were observed, including impairment of the motor coordination in the CNS at subclinical doses in mice. Fomepizole also caused a transient decrease in body temperature and brain noradrenaline levels in mice. After 4 days dosing, brain noradrenaline levels were normal, but serotonin was increased.
- The LD₅₀ values for the IV dose in rodents were 1–2 times the maximum recommended human dose based on body surface area.
- In the repeat dose studies, CNS, liver enzyme elevations (that was severe and irreversible in some dogs) and muscle effects were seen. Clinically relevant doses fomepizole caused a marked increase in urinary volume, a marked metabolic alkalosis and hypokalaemia. Because the pharmacokinetics of fomepizole was not fully investigated in animals or humans there is uncertainty regarding the suitability of animal models used to investigate the toxicity profile.
- The genotoxicity investigation did not address all requirements of ICH guideline S2 (R1). Fomepizole was mutagenic in the bacterial mutation assay but did not cause chromosomal aberrations in vivo in the mouse micronucleus test. The evaluator concluded that fomepizole poses a genotoxic risk.

- No carcinogenicity studies were submitted. This was inconsistent with the positive genotoxicity findings but may be acceptable for the proposed indication.
- The reproductive toxicity of fomepizole was not studied in mammalian species. Placental transfer of fomepizole was demonstrated in pregnant rats. Fomepizole appeared to decrease testosterone levels and testicular mass in male rats, but the consequences of these changes on male fertility were not investigated.
- Based on a lack of animal data a Pregnancy Category B2 was recommended.

Clinical

Pharmacology

The pharmacology studies demonstrated that:

- Although not of direct relevance to the submission fomepizole is a rapidly and completely absorbed following oral administration of doses ranging from 7 to 50 mg/kg. The AUCs obtained for both the oral and intravenous doses of 7 mg/kg were similar and allowed the extrapolation of some oral data to the IV dosing. Tmax was within 1 to 2 h of single oral dosing
- Fomepizole is distributed rapidly and widely to total body water (volume of distribution (Vd) ranged from 0.58 L/kg in healthy volunteers to 1.0 L/kg in patient with ethylene glycol toxicity depending on the study)
- Fomepizole is metabolised to 4-carboxypyrazole (4-CP) that is excreted in urine.
- After single doses fomepizole is eliminated by Michaelis-Menten kinetics. At blood levels produced by initial doses of 7 mg/kg or greater 4MP elimination is saturated. After multiple doses the zero-order elimination rate increased and apparently became first order with a half-life of 1.5 to 2 hours.
- Fomepizole is dialysable; fomepizole levels fell at a median rate of 0.8 $\mu\text{mol}/\text{L}/\text{min}$ during dialysis and 0.33 $\mu\text{mol}/\text{L}$ off dialysis. The median clearance was 183 mL/min.

Pharmacodynamics

- In vitro studies demonstrated fomepizole blocks alcohol dehydrogenase activity in a number of animal species and in human liver.
- The in vitro 50% inhibitory concentration (IC50) was approximately 0.1 $\mu\text{mol}/\text{L}$ and the maximum inhibitory concentration (MIC) in humans was 10 $\mu\text{mol}/\text{L}$.
- The distribution to total body water suggests that 4MP has ready access to alcohol dehydrogenase in the liver, CNS and the eye.
- There were no specific PD studies conducted in humans although human efficacy and safety studies supported the action of fomepizole on ADH and that it blocks ethylene glycol and methanol metabolism.
- Fomepizole increases the half-life of ethylene glycol to 16 to 20 h.

Drug interaction studies

Drug interaction studies were limited to alcohols. An interaction study with alcohol showed an inhibition of the elimination of 4MP in the presence of ethanol, presumed to be related to the inhibition of the formation of 4-CP. The presence of ethanol is likely to

increase the duration of effect of fomepizole. The sponsor has assumed there will be interactions with the CYP enzyme system.

Efficacy

The sponsor submitted studies conducted by the manufacturer of Antizol and supplemented the studies with published literature.

Ethylene glycol

Manufacturer studies

S7 (OMC-4MP-3) was a retrospective, open label, single centre study of 38 patients with a mean age of 39 years (15 to 71 years) using patient data from 1982 to 1995. The study aimed to determine the efficacy, safety, tolerance and pharmacokinetic profile of 4MP in EG poisoned patients and methanol poisoned patients (outcomes for the methanol patients described later in the overview) and to determine the safety, tolerance and PK in patients with suspected poisoning that were later determined to have another diagnosis. The 4MP was administered according to the experience and practice of the treating physician. Patient follow up ranged from 1 day to 1 month. The patients were 74% male, with a mean weight of 65 kg and a mean height of 169 cm. Most (89%) were treated for documented or suspected EG toxicity and 13% were treated for documented or suspected methanol toxicity. At entry 21% presented comatose and 34% presented with a metabolic acidosis. EG was detected in the blood of 26 patients prior to treatment, and 7 were treated but the EG poisoning was not confirmed. The median EG level was 10.4 mg/dL (range 1.0 to 830.8 mg/dL) and 42% had EG levels <5 mg/dL. At entry 7 patients (27%) presented with severe toxicity, 4 (15%) were moderately intoxicated, 12 patients (46%) were mildly intoxicated and 3 had no signs of intoxication. Where the source was identified ethylene glycol was mostly ingested as antifreeze. Treatment commenced within 6 h for most (54%), 6 to 12 h for 8%, 12 to 24 h for 23%, more than 24 h for 8%.

The dosing of 4MP was per kg body weight using two different preparations of 4MP (21% received 4MP hydrochloride and 79% 4MP sulphate) and based on estimated EG. Treatment was with a mean loading dose of 11 mg/kg (range 0.2 to 19.5 mg/kg) with a mean of 3 doses (range 1 to 13) were administered over a mean treatment period of 2 days (1 to 7 days) and a mean cumulative dose of 1566 mg (range 200 to 6000 mg). Dosing intervals ranged from 1 to 12 h. 4MP was given orally to 32% of the patients and IV to the remaining 26 patients (68%). IV doses were diluted in either 5% dextrose or 0.9% sodium chloride. One patient was transitioned from oral to IV therapy because of vomiting. Four patients also received ethanol treatment.

Five EG patients underwent dialysis, 4 due to renal insufficiency from the EG toxicity and 1 because of a very high EG level. Mean number of dialysis sessions was 2.8 (1 to 8) and the mean duration of the first haemodialysis was 6.1 h.

The primary efficacy outcomes were mortality and morbidity. Survival with no sequelae was reported for 73%, survival with sequelae was reported for 15% (mild, and improving at the study endpoint of at the end of the follow-up period). The one death attributed to late intervention and severe toxicity on presentation occurred in a patient who also took flunitrazepam and NaOH.

Secondary efficacy analyses included evaluation of the effect of 4MP on the metabolic acidosis caused by the EG ingestion. EG concentrations decreased from a mean of 82.0 mg/dL to a median of 0.3 mg/dL at the end of follow up. In the EG only group the mean pH on entry was 7.3 (range 7.1 to 7.5) and by the study endpoint was 7.4 (7.4 to 7.5). Bicarbonate increased from a mean \pm SD 20.4 \pm 6.1 mmol/L (range 6 to 29 mmol/L) to 26.4 \pm 3.4 (20 to 30 mmol/L)

The investigator defined treatment efficacy determinations in preventing or diminishing toxicity were 38.5% definitely effective, 34.5% possibly effective and of no apparent benefit for 7 (27%) patients with mild intoxication or no apparent intoxication at presentation. Patient outcome was independent of the 4MP salt used or the route of administration. Although an outcome for the study no 4MP levels were collected for any of the patients.

S8 (OMC-4MP-1) was a prospective, open, label, multicentre, Phase III pivotal trial of the efficacy, tolerance and pharmacokinetics of fomepizole in 7 patients (6 male) with confirmed EG poisoning. Eligible patients were > 12 years old, presenting with a documented serum EG of >20 mg/dL, or a history (or strong suspicion) of EG ingestion along with arterial pH < 7.3, serum bicarbonate < 20 mEq/L, osmolar gap by freezing point depression > 10 mOsm/L, and/or oxalate crystals in urine. The main exclusion criterion was ethanol administration, known adverse reactions to pyrazoles and pregnant women.

Fomepizole was given IV as a 15 mg/kg loading dose diluted in 100 mL 0.9% sodium chloride over 30 minutes followed by 10 mg/kg (in 100 mL N Saline over 30 minutes) supplements every 12 h for 4 doses then 15 mg/kg every 12 h thereafter for a total duration of treatment dependent on poisoning severity and clinical sequelae. In addition IV fluids as 5% dextrose with supplemental potassium and bicarbonate to maintain normokalaemia and arterial pH above 7.3 were administered. Magnesium and vitamin supplements were discretionary. Arterial oxygen saturation was maintained at $\geq 90\%$ (unless unobtainable despite mechanical ventilation). Dialysis was permitted for patients presenting with EG > 50 mg/dL, severe metabolic acidosis or renal failure and the timing of fomepizole dosing.

The median age was 44 years (range 28 to 60 years), 6 out of the 7 patients were Caucasian. Two of the 7 patients were admitted with confirmed EG poisoning and the remainder were treated on suspicion. All had a metabolic acidosis (6 patients were severe and 4 patients with elevated lactate), 5 patients had renal impairment, 3 had hypocalcaemia and 4 had oxaluria. Six patients were considered to have severe intoxication, and the seventh with mild symptoms had an EG of 171 mg/dL. None had accidentally ingested the EG and in 4 patients the ingestant was identified as antifreeze. All 4 patients presenting to peripheral hospitals were administered ethanol prior to transfer and were subsequently treated with fomepizole. The time to ingestion was unknown for 2 patients but for the rest ranged from 10 to 40 h. Six patients had detectable ethanol levels and 3 were in or above the therapeutic range. The patients received between 2 and 5 doses of fomepizole.

The primary efficacy analysis was the prevention of mortality and severe morbidity (renal function, cardiac function and cranial neuropathies). Five patients presented with renal failure. Of those there was one death, 4 patients with ongoing renal failure not requiring haemodialysis, and 2 patients alive with no sequelae at the end of the study. All the renal failure patients had resolution or near resolution within 2 to 7 weeks after trial discharge. The death occurred after an acute myocardial infarction with cardiogenic shock, renal failure, severe lactic acidosis (pH 7.05) during the study.

The 6 patients with severe metabolic acidosis the pH had normalised although bicarbonate, while improving had not normalised for all. The only recurrence of metabolic acidosis was in the patient who died. Plasma glycolate levels ranged from 0 to 23.7 mmol/L. All patients with elevations had a progressive fall during therapy. One patient had a rise during therapy just prior to the next due dose that subsequently fell post-dosing. Three of the 4 patients with elevated urinary oxalates at baseline became negative for oxalates during therapy.

EG, plasma glycolate, ethanol, and fomepizole levels gradually declined prior to and following HD and all rapidly declined during HD.

Published literature

Methylpyrazole for Toxic Alcohols (META) Investigation (Brent et al 1999) included the 7 patients from the S8 study and 16 additional patients with EG poisoning. Four of the patients did not have EG poisoning, leaving 19 patients. At presentation 7 patients were comatose, 3 were inebriated, and 2 were lethargic, and 7 were awake. Nine presented with elevated serum creatinine and 15 had a metabolic acidosis. Seventeen underwent HD. Ethanol was detected in 12 patients and 4 of them had therapeutic concentrations (>100 mg/dL). The mean number of fomepizole doses was 3.5 (range 1 to 7) over a mean of 17.8 h (range 5 to 58).

The primary endpoint was the development of renal injury measured by serum creatinine, additional production of EG metabolites (either plasma glycolate or urinary excretion of oxalate) after fomepizole treatment and the development of cranial neuropathies. Plasma glycolate when elevated at enrolment progressively decreased, arterial pH and serum bicarbonate concentrations progressive increased in all patients. Clinical improvement was correlated with acid-base status. No patient had hypoglycaemia or deterioration of mental state after the initiation of fomepizole. Plasma fomepizole was around 183 to 366 μ mol/L during therapy and the elimination half-life was 19.7 h.

There was one death (described in S8). The 9 patients with renal failure at enrolment had a further increase in creatinine (peak values 212 to 1299 μ mol/L). All had late presentations with a more severe metabolic acidosis than those with normal renal function, although serum creatinine normalised in 6 of these patients. All patients with renal injury developed plasma glycolate concentrations of at least 98 mg/dL (12.9 mmol/L) at enrolment. No renal injury was evident in those with a normal creatinine and initial plasma glycolate < 10.1 mmol/L.

Levine et al (2012)²⁴ was an 8 year, retrospective, multicentre cohort study of 40 patients aged >15 years intoxicated with EG from 3 US centres, primarily to determine the elimination half-life of EG when fomepizole was used as monotherapy without HD, and secondarily to report mortality and development of renal failure with this approach. There were no criteria for this therapy option a priori but the decision was at the discretion of the medical toxicologist and tended to be in patients without a metabolic acidosis or renal dysfunction on admission. Detectable serum ethanol was not an exclusion criterion. The median age was 42, median peak EG concentrations were 127 mg/dL and the median number of fomepizole doses was 4. The median ethanol concentration was 118 mg/dL. The mean elimination half-life of EG was 14.2 h (95% CI 13.1 to 15.3 hours). One patient developed non-oliguric renal failure, not requiring dialysis.

Efficacy in children with EG poisoning

Carvati et al (2004)¹⁸ was a retrospective, open-label study of 6 children aged 22 months to 14 years treated for EG poisoning over a 4 year period. One received ethanol only, 2 received fomepizole only, and three received an ethanol load followed by fomepizole with treatment continued until serum EG was < 10 mg/dL. IV fluid and supplemental bicarbonate was also given, and the metabolic acidosis resolved within 24 h. The mean length of stay in intensive care unit (ICU) was 21 h and in the ward 33.7 h. The 22 month old had an episode of hypoglycaemia. All patients recovered without sequelae.

Brent et al 2010²⁵ was a systematic review of published cases of toxic alcohol poisoning treated with fomepizole (in a dosage regimen similar to adults). Of the 14 cases identified

²⁴ Levine, M., Curry, S.C., Ruha, A.M., Pizon, A.F., Boyer, E., Burns, J., Bikin, D., Gerkin, R.D. (2012) Ethylene Glycol Elimination Kinetics and Outcomes in Patients Managed Without Hemodialysis. *Ann Emerg Med*, 59: 527 – 531.

²⁵ Brent, J. (2010). Fomepizole for the treatment of pediatric ethylene and diethylene glycol, butoxyethanol, and methanol poisonings. *Clinical Toxicology*, 48(5), 401–406.
<http://doi.org/10.3109/15563650.2010.495347>

10 were for EG and 1 for diethylene glycol, 1 for butoxyethanol ingestion and 2 due to methanol poisoning. The 10 EG patients had a mean pH of 7.27 (7.03 to 7.38) serum bicarbonate of 13 mEq/L (2 to 25) and EG concentration of 2140 mg mg/L (130 to 3840). Eight were not dialysed. All 10 had resolution of their metabolic acidosis with fomepizole therapy. Two patients were initially commenced on ethanol therapy but switched to fomepizole because of adverse effects. The elimination half-life of EG, with fomepizole therapy, ranged from 9 to 15 h.

Baum et al²⁶ described the use of fomepizole in an 8 month old infant who drank up to 120 mL of EG, with a mild acidosis, an elevated osmolar gap and oxalate crystaluria, treated with fomepizole and dialysis. The use of haemodialysis reduced the fomepizole treatment time by an estimated 16 h.

Additional case reports

An additional 6 case reports from the literature supported the use in children and another 20 cases were gleaned from adult literature. There was one case of a young woman admitted with EG poisoning 154 times, treated with fomepizole 99 times, ethanol 60 times, combination ethanol and fomepizole 6 times, dialysis 73 times and buffer and antidote only 81 times. She had 10 admissions with evidence of some renal injury. She eventually died of EG toxicity (EG 81 mmol/L or 506 mg/dL). This single case of multiple fomepizole exposures did not reveal any detectable adverse effects on clinical examination, laboratory tests or autopsy.

Methanol poisoning

S7

This study included 5 patients with methanol toxicity. 4 were male with a mean age of 47 years (28 to 57 years). At enrolment 2 patients were severely intoxicated, 2 were mildly intoxicated and 1 patient was not intoxicated. All 5 patients were treated with 4MP but only 3 with IV therapy. The mean loading dose was 11.1 mg/kg and the median number of doses was 2 (1 patient received 13 doses in 7 days). Median baseline methanol was 102.1 mg (10 to 425.6 mg/dL), blood pH was normal for 4 of the 5 patients (the fifth had a pH of 7.26); the mean serum bicarbonate was 15.1 mmol/L. All 4 intoxicated patients had no detected blood methanol after treatment, those with an acidosis had it resolved, but persistent hypocalcaemia was seen in three of the 4 patients that presented with it at baseline. Four patients were discharged alive without sequelae and the fifth survived with the bilateral blindness that was present at hospital admission.

S13 (OMC-4MP-2)

This was a prospective, Phase III, open-label, multicentre, uncontrolled study to assess the safety and efficacy of Antizol (fomepizole) injection in 15 patients with methanol poisoning. The inclusion criteria included patients \geq 12 years, a documented elevated methanol level or if unavailable a clinical suspicion and at least two of: arterial pH $<$ 7.3, serum bicarbonate $<$ 20 mEq/L, and osmolar gap of $>$ 10 mOsm/L, methanol ingested $<$ 1 hour previously. Patients treated with therapeutic doses of ethanol were excluded. Due to laboratory error only 11 patients had documented elevated methanol levels at baseline. Most were male (n=9), Caucasian (n=10), with a mean age of 38 years (18 to 61 years). The time of methanol ingestion was unknown for 4 of the 11 patients. For the remainder only 2 had fomepizole administered within 6 h, with 1 within 6 to 12 h, 3 between 12 to 24 h and 1 $>$ 24 h after ingestion. The median pH was 7.38 (6.9 to 7.46), median serum bicarbonate was 15.0 mEq/L (3.0 to 22.5), and median methanol was 71.3 mg/dL (range

²⁶ Baum, et al. 'Experience and reason: Fomepizole treatment of ethylene glycol poisoning in an infant.' Pediatrics Vol. 106 No. 6 December 1, 2000 pp. 1489 -1491

23 to 612.1 mg/dL). Of the 6 patients with detectable formate levels, 5 were > 9 mmol/L (severe elevation) and 1 was in the range 1 to 9 mmol/L. Five patients also had detectable ethanol levels, of whom 3 had ethanol in the range 100 to 125 mg/dL given as first line therapy in the referring hospital. Three patients had abnormal visual acuity (five could not be assessed) and five had other visual signs or symptoms.

Fomepizole was commenced with a 15 mg/kg loading dose followed by supplemental dosing 12 hourly until methanol levels were < 20 mg/dL. Haemodialysis was permitted based on worsening metabolic acidosis, methanol level > 50 mg/dL, rate of decline of methanol of < 10 mg/dL /day, and evidence of ocular toxicity.

At study end 7 were alive without sequelae, 3 were alive with sequelae and 1 died. Of the 3 with sequelae 1 died 22 days after study end from toxic encephalopathy secondary to methanol poisoning, having entered the study comatose. Sequelae of the other two included unresolved left lower lobe (LLL) infiltrate from baseline and mild blurred vision (baseline hyperaemic optic disc). Of the 4 presenting comatose at baseline, 2 died and 2 showed marked improvement. The mental state of those awake at baseline remained unchanged. The patients with a metabolic acidosis (low serum bicarbonate, low blood pH and low PCO₂) had these parameters return to normal at the end of the study. No patient had an elevation of formate levels beyond the baseline measurement after the commencement of fomepizole. Four of the 7 patients dialysed had methanol levels > 20 mg/dL, but these 4 had formate levels < 1 mmol/L (not clinically significant). Within 48 h (on continuing fomepizole treatment) methanol levels were < 20 mg/dL and none had elevated formate levels.

Four patients were not dialysed. Their methanol levels ranged between 23.0 and 38.8 mg/dL and all had sub-therapeutic ethanol levels (0 to 67.8 mg/dL). In all patients formate levels remained at or decreased to undetectable levels in parallel with the declining methanol and ethanol levels. Patients with normal visual acuity at study entry and two of those that were not assessable at study entry had no visual changes (the other 2 died), and the remaining 3 patients had signs of improvement at study end or within 48 h of the conclusion of the study.

Zakharov, 2014²⁷ described a retrospective and prospective open-label study of 121 patients with methanol poisoning from black-market alcoholic beverages containing from 20% to 50% methanol that had also been sold at conventional outlets in the Czech Republic from September 2012 to January 2013. Eligible patients had a diagnosis of methanol poisoning made on history of ingestion of illicit spirit and a serum methanol > 20 mg/dL (6.24 mmol/L, 'toxic limit') and/or osmolar gap of > 20 mOsm/kg/water (H₂O) not explained by ethanol or a suspicion of methanol poisoning a detectable serum methanol and a raised anion gap metabolic acidosis. Clinical examination included ophthalmology examination and testing and CNS examination and a computed tomography (CT) brain in symptomatic patients. This study characterises the symptoms and laboratory findings of patients with methanol toxicity.

Twenty patients died before reaching hospital. Of the remaining 101 patients 80 were male with a median age of 53 (23 to 79) years and 21 were women with a median age of 57 years (16 to 69) who had consumed a median volume of 450 mL (males) to 200 mL (females). All patients with a metabolic acidosis were treated with bicarbonate aiming for full correction, and ethanol and/or fomepizole were given as antidotes in accordance with American Academy of Clinical Toxicology (AACT)/ European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) guidelines on methanol poisoning. Ethanol could be started in the ambulance. Fomepizole was in limited supply and was reserved for

²⁷ Zakharov, S, Pelclova, D, Urban, P, Navratil, T, Diblik, P, Kuthan, P, ... Hovda, K. E. (2014). Czech mass methanol outbreak 2012: Epidemiology, challenges and clinical features. *Clinical Toxicology*, 52(10), 1013-1024. <http://doi.org/10.3109/15563650.2014.974106>

patients with a serum methanol > 50 mg/dL (15.6 mmol/L) or formate > 40 mg/dL (8.9 mmol/L) and pH < 7.0, or methanol > 30 mg/dL (9.4 mol/L) and pH < 7.0 in patients unable to hyperventilate (PCO₂ > 23 mmHg). Treatment with fomepizole was stopped and replaced with ethanol when serum methanol was < 30 mg/dL (9.4 mmol/L) and a normal pH or 20 mg/dL if there was an acidosis. The rationale was to reduce the risk of incomplete alcohol dehydrogenase blockade by possible fluctuations of ethanol levels in the most severely poisoned patients especially during haemodialysis and to avoid respiratory depression in patients with a compensated metabolic acidosis. Dialysis was performed if patients had serum methanol > 50 mg/dL (15.6 mmol/L), metabolic acidosis with a pH < 7.3 or visual toxicity. The mode of dialysis (Intermittent hemodialysis (IHD), Continuous venovenous hemofiltration (CVVH) / haemodiafiltration (HDF)) depended on the haemodynamic stability of patient, the severity of the poisoning and the availability of the dialysis.

Only 11% of the patients were admitted within 12 h of ingestion another 35% within 48 h and in 18% the time of ingestion was unknown. From hospital records 56% were said to be alcohol abusers. Ethanol was detected on admission in 41 patients (median concentration 65 mg/dL, range 8 to 446 mg/dL), of whom 30 had received first aid ethanol in the ambulance. Three patients had negative methanol tests and 12 were below the cut-off of 20 mg/dL. On admission 25 were asymptomatic (including 18 given ethanol pre-hospital).

Hospital treatment measures included haemodialysis (CVVHD/HDF in 59% and IHD in 31%), ethanol (59%)/fomepizole (31%), and folate substitution (71%). Most (83%) also received bicarbonate. The 21 patients that died in hospital were significantly more acidotic, and the patients without sequelae were more likely to have compensated metabolic acidosis ($p < 0.001$). Of the 42 patients with visual symptoms on admission, 33% were symptomatic at discharge and 29% died. Patients without visual sequelae on discharge were significantly less acidotic and had lower serum methanol and formate. Coma on admission was more prevalent in patients with visual sequelae. Serum lactate reflected the severity of the poisoning and was highest in those that died.

Multivariate regression analysis showed coma, metabolic acidosis with pH < 7.0 and negative serum ethanol on admission to be the only independent parameters predicting death. Based on the ROC analysis at pH 6.6 the probability of death was 77% probability, and at pH < 7.0 was 21%.

Zakharov et al (2015)²⁸ was a prospective uncontrolled, observational study based on data from the above Czech mass methanol poisoning in 2012 and was designed similarly to the study above and included 38 patients with a median age of 51 years (37-62) of whom 28 were male. All had unintended methanol ingestions, and 10 had ingested uncontaminated ethanol products. Only 10% presented ≤ 12 h of ingestion, and 37% presented at > 48 hours. The more symptomatic patients had higher formate levels: the median formate of 15.2 mmol/L (inter-quartile range (IQR) 12.1 to 18.0 mmol/L), and 16.2 mmol/L with visual sequelae. Logistic regression showed a $> 90\%$ probability of poor outcome with serum formate concentration of 17.5 mmol/L.

Hovda et al 2005²⁹ reported a combined retrospective and prospective case series of 51 methanol poisonings from Norway from 2002 to 2004 that were retrospectively divided into three groups for analysis based on clinical outcome. Group I survived without

²⁸ Zakharov, S., Kurcova, I., Navratil, T., Salek, T., Komarc, M., & Pelclova, D. (2015). Is the Measurement of Serum Formate Concentration Useful in the Diagnostics of Acute Methanol Poisoning? A Prospective Study of 38 Patients. *Basic & Clinical Pharmacology & Toxicology*, 116(5), 445–451.

<http://doi.org/10.1111/bcpt.12338>

²⁹ Hovda, K. E., Hunderi, O. H., TAFJORD, A.-B., Dunlop, O., Rudberg, N., & Jacobsen, D. (2005). Methanol outbreak in Norway 2002–2004: epidemiology, clinical features and prognostic signs. *Journal of Internal Medicine*, 258(2), 181–190.

sequelae, Group II survived with sequelae and Group III died. Patients were given buffer (bicarbonate or trometamol) and antidote (ethanol, n=15 or fomepizole, n=36) and 37 received HD. Fomepizole was given has been described in previous studies. The patients were mostly male (n=39) with a median age of 53 years, median methanol level on admission 25mmol/L (80 mg/dL) (range 3.1 to 147.0 mmol/L). Only 12 were asymptomatic. Symptoms included visual disturbances (n=28), dyspnoea (n=21), gastrointestinal symptoms (n=22), coma (n=12), chest pain (n=6) and other (n=8). Eight presented with a respiratory arrest.

Overall there were 9 deaths and 5 patients with sequelae. Highest mortality was among those who presented with respiratory arrest (75% died) and coma (67% died). These patients were more acidotic (median pH 6.57, 25th centile 6.9, median base deficit 28 mM) at baseline. Methanol level at baseline was not a predictor of outcome. In the ethanol treated group 87% survived without sequelae and there were no survivors with sequelae, compared to 67% survivors without sequelae and 14% survivors with sequelae in the fomepizole group (but this was not a randomised trial).

Hovda et al 2005 prospectively studied 7 patients (5 male, 2 female, aged 41 to 69 years) with severe methanol poisoning treated with buffer, fomepizole and HD (mean 7 h) to evaluate the role of HD and to find a new indication for HD based on the patients initial clinical state. The patients were a part of cohort of patients from an outbreak of methanol toxicity from the consumption of illegal spirit (80% ethanol 20% methanol).

Patients were treated with fomepizole 15 mg/kg load then 10 mg/kg 12 hourly for 3 doses then 15 mg/kg/dose thereafter. The HD patients were given 10 mg/kg every 4 h (q4h). Doses were derived from the literature. All patients were dialysed. The timing of the dialysis was based on clinical findings with early HD commenced based on the degree of metabolic acidosis or visual disturbances that did not disappear with buffer and fomepizole alone. Severity of the poisoning and the outcome was correlated with the severity of the metabolic acidosis and the toxicity of the formate rather than methanol level if buffer and fomepizole were started early. Early, acidosis was found to be related to formic acid formation and later due to lactic acidosis secondary to the uncoupling of cytochrome oxidase by formate and the resultant tissue hypoxia. Dialysis clearance of methanol was 222 mL/min and of formate was 225 mL/min. The half-lives of formate and methanol were 1.7 h and 2.5 hours, respectively, explained by the higher intrinsic elimination of formate and the blockade of the elimination of methanol by fomepizole. The potential benefit of HD was the removal of methanol and formate and the correction of the metabolic acidosis. The authors did not recommend titration of HD to any particular methanol concentration but rather to remove formate and to assist with the correction of metabolic acidosis.

The authors proposed the use of HD in methanol poisoning in the critically ill patients with severe metabolic acidosis (base deficit > 20 mM) and/or visual disturbances with buffer and fomepizole. The authors recommend buffer and fomepizole for stable patients and consultation with a clinical toxicologist or experienced nephrologist prior to HD.

Hovda 2005 described the methanol kinetics in 8 patients with methanol poisoning treated with fomepizole and bicarbonate only, three of whom were later dialysed. The methanol kinetics was best described by a one compartment model with first order elimination.

META (Brent et al, 2001): This study also included 11 patients with methanol poisoning. Patients were included if they were > 12 years of age, serum methanol > 20 mg/dL (6.2 mmol/L) or a strong suspicions of methanol poisoning and a metabolic acidosis or an elevated osmolar gap. Ethanol treatment was an exclusion criterion although 3 patients were treated with therapeutic doses of ethanol at peripheral hospitals prior to enrolment. Patients had a mean age of 40 +/- 13 years. Where known the fluid ingested was mostly

windscreen wiper fluid. Where the intent of the ingestion was known 6 patients were suicidal, 2 intended inebriation and 2 were accidental ingestions. Mean plasma formic acid concentration was 80 mg/dL (17.5 mmol/L) range 0 to 198 mg/dL (0 to 43.8 mmol/L) in the group with visual disturbance and 7.4 mg/dL (1.6 mmol/L) range 0 to 24.5 mg/dL (0 to 5.33 mmol/L) in those without ($p=0.08$ for the difference of the two groups).

The fomepizole treatment regimen was 15 mg/kg loading dose, 10 mg/kg 12 hourly for the next three doses and 15 mg/kg thereafter. Median duration of treatment was 30 h (range 0.5 to 60) with a median of 4 doses. The target plasma concentration of fomepizole was 0.8 μ g/mL. The HD patients had a median interval of 1 treatment (1 to 4) and the initiation of HD was 90 minutes (14 to 160 minutes).

There was a strong initial correlation between initial arterial pH and plasma formic acid ($r= 0.92$, $p<0.001$). Formic acid concentrations fell in both groups with simultaneous resolution of metabolic acidosis, improvement in mental status and ocular effects. Methanol displayed first order kinetics in the non-HD patients. Nine of the 11 patients survived. The 2 that died were comatose at presentation, had an unknown time from ingestion to treatment, no detectable ethanol levels and very high serum formate levels.

Megarbane et al 2001²⁰ conducted a retrospective study of methanol poisoning treated with fomepizole in 3 ICUs in France, and found 14 patients (9 men, 4 women, median age 46 years) with a median plasma methanol concentration of delay of 13 h from ingestion to ICU admission, to assess the efficacy and safety of fomepizole in methanol poisoning and to test the hypothesis that fomepizole obviates the need for HD. Eight patients had co-ingested ethanol (median plasma concentration 195 mg/dL, range 12 to 530 mg/dL) and 3 had received ethanol as initial treatment. Fomepizole treatment was not standardised but most received a 15 mg/kg load and 10 mg/kg 12 hourly thereafter. HD was performed in the 4 patients with visual disturbances (3 with bilateral blindness and 1 with abnormal colour vision) and 1 underwent delayed peritoneal dialysis after 28 h of therapy for acute pancreatitis present on admission.

The patients without visual disturbance at baseline recovered without sequelae. There was some visual improvement in 1 of the 4 patients with visual disturbances (went from blindness to counting fingers several weeks after treatment). All the acidemic patients returned to a normal pH on fomepizole in 6 h (5 to 12 h), subnormal bicarbonate returned to normal in 21 h (4 to 34 h) and elevated anion gap returned to normal in 26 h (3 – 62 h). The 4 dialysis patients had more severe acidosis, lower serum bicarbonate and higher anion gap, although the baseline plasma concentrations of methanol were similar.

Paasma et al (2012)³⁰ was a retrospective analysis of 203 patients including the patients in the Hovda et al 2005 outbreak study in which 23 were given fomepizole and 171 were given ethanol as the antidote. There was a trend towards a favourable outcome in patients given fomepizole over ethanol or similar admission pH. Because of the small numbers one death in a patient with a late presentation influenced results (removal from the analysis resulted in a statistically significant difference in outcome).

Safety

The sponsor presented an integrated safety analysis of 141 patients from studies S7, S8, S11 S12 and S13 that had been prepared for the submission in the US. Overall 138 of the 141 (97.9%) combined subject/patient population reported at least one AE. A total of 262 events were reported. The most frequently reported AEs were headache (n=22; 15.6%),

³⁰ Paasma, R., Hovda, K. E., Hassanian-Moghaddam, H., Brahmi, N., Afshari, R., Sandvik, L., & Jacobsen, D. (2012). Risk factors related to poor outcome after methanol poisoning and the relation between outcome and antidotes – a multicenter study. *Clinical Toxicology*, 50(9), 823-831.
<http://doi.org/10.3109/15563650.2012.728224>

nausea (n=16; 11.3%), fever (n=11, 7.8%), acute renal failure (n=11, 7.8%), dizziness (n=10; 7.1%), increased drowsiness (n=9; 6.4%), bad metallic taste (n=8; 5.7%), vomiting (n=7; 5.0%) and agitation (6; 4.3%). Anaemia and abdominal pain/tenderness were each reported in five patients (3.5%). Hypotension, rash, feeling of burn/tingling in vein, diarrhoea, and light-headedness each were reported in four patients (2.8%).

Overall, 134 of the 141 subjects/ patients (95%) experienced 134 TRAEs. The most frequently reported were headache (n=20; 14.2%), nausea (n=15; 10.6%), dizziness (n=9; 6.4%), increased drowsiness (n=8, 5.7%) and bad taste/metallic taste (n=8, 5.7%). Other events included application site reaction, vomiting, rash, and abnormal smell. Where rated for severity most were mild or moderate in intensity. Hypotension and seizure in Study S-8 were rated severe with unknown relationship to study drug. Severe hiccups (possibly related to study drug) reported in Study S13 resolved three days after fomepizole dosing had discontinued. Other events included agitation, anxiety, dyspepsia, multiorgan system failure, disseminated intravascular coagulation, anuria and lymphangitis. Brief periods of light-headedness, decreased environmental awareness, and a feeling of drunkenness were correlated with high plasma levels of fomepizole. However, concomitant ethanol administration in some subjects reporting these AEs made assessment of causality difficult. Phlebosclerosis occurred in a Phase I study in subjects receiving a 25 mg/mL bolus injection over 5 minutes.

Deaths were reported during fomepizole treatment: one in Study S7, 3 in Study S8, 1 each in Studies S12 and S13. Two additional deaths occurred post study (a patient in Study S13 died 20 days post-study and another patient in study S7 died 11 months after treatment). The deaths appear related to the known sequelae of the ingestion rather than fomepizole.

Serious AEs (SAEs) were not systematically collected in all studies. In Study S7 three patients were transferred to other facilities for continuing treatment of adverse outcomes including fever, gastric pain, and vomiting in one patient; pre-existing tuberculosis in another patient; and acute pancreatitis and alcoholic ketoacidosis (both pre-existing) and suspicion of bacteraemia in a third patient. All three patients were lost to long term follow-up. Thirteen SAEs that occurred in ten patients in Study S8 were liver failure, myocardial infarction, and cerebral oedema in one patient each and acute renal failure in ten patients. These were judged by the study investigator to be due to EG or paracetamol poisoning, and unrelated to fomepizole treatment. There were 3 SAEs reported by two patients in Study S13: toxic encephalopathy in one patient and rhabdomyolysis and right deep vein thrombosis in the second patient. Both patients subsequently died. One patient in Study S7 was discontinued from treatment with fomepizole after two doses but no details were available.

Additional safety data were included from published literature:

While generally in agreement with the safety analysis above, additional AEs reported included transient elevation of liver transaminases, serum triglycerides, cholesterol, phosphorous, and bilirubin was associated with multiple-dose fomepizole administration in Phase I studies, although lipid changes also appeared in placebo studies. Vertigo, loss of appetite and increased uric acid in higher doses than those proposed. Clinical use of fomepizole in adults showed only minimal adverse effects consisting of transient transaminase elevation (in Study S11 this was < 1.5 x upper limit of normal (ULN)), skin rash and eosinophilia. Besides the report of nystagmus and one AE of hypotension/ bradycardia requiring intervention which appeared to be directly related to IV fomepizole administration (positive rechallenge) no other major AEs were reported in the case reports.

In the study by Megarbane et al (2001)²⁰ it was noted that prothrombin time, liver function tests, creatinine phosphokinase and platelet and white cell counts were stable during treatment. In this study three patients received 5, 6 and 16 doses respectively

(totals of 57.1 mg/kg, 88.2 mg/kg and 75.0 mg/kg), respectively. The observational cohort studies comparing the safety (AEs and medication errors) of antidotal treatment with fomepizole versus ethanol in patients with EG/methanol poisoning by Lepik^{31, 32} suggested a significantly worse adverse effect profile and higher rate of medication errors (including harmful errors) with ethanol compared to fomepizole, interpretation was limited by many confounding factors.

Safety in children was reported for 14 cases where fomepizole is used for EG (n=10), methanol (n=2) or other alcohols. Transient nystagmus was reported in an EG intoxicated child given fomepizole with a serum EG of 130 mg/L and a serum bicarbonate of 2 mEq/L.

Risk management plan

The TGA has evaluated but not accepted Australian RMP Version 02 (dated 26 June 2016, DLP 26 November 2014) for fomepizole. The RMP evaluator considered the sponsor had not adequately addressed the concerns in the first round report.

The issues of concern included:

- The concerns of the nonclinical evaluator had not been included in the RMP – Summary of Safety Concerns, with associated pharmacovigilance and risk minimisation activities.
- Issues around concomitant ethanol intoxication in ethylene glycol or methanol intoxication were not adequately addressed.
- The RMP did not include some of the safety statements in the PI.

Risk-benefit analysis

Delegate's considerations

Efficacy

Fomepizole has been approved internationally for some years and has been used in North America and Europe for the treatment of EG and methanol poisonings. It is included in the America Academy of Toxicology guidelines for the treatment of methanol poisoning, and is included on the WHO essential medicines list.

The sponsor provided a mixed submission of old studies described the sponsor as having been conducted by the manufacturer in the 1990s. This is supplemented with more recently literature. The clinical studies are open-label, observational studies, some prospective but most retrospective. Some patients are reported in more than one study. In some of the early studies the dosing protocol for fomepizole was not standardised and all patients received supportive care according to local protocols. In the recent studies the dosage regimens are standardised and consistent with the dosage regimen proposed by the sponsor. There have been changes to supportive care over time and changes to practices in critical care environments make comparisons of the older and more recent studies more difficult.

In animal models the action of fomepizole on alcohol dehydrogenase has been established. In human studies fomepizole treatment has been associated with an improvement in the

³¹ Lepik KJ et al. Adverse Drug Events Associated With the Antidotes for Methanol and Ethylene Glycol Poisoning: A Comparison of Ethanol and Fomepizole. Ann Emerg Med. 2009;53:439-450

³² Lepik KJ et al. Medication errors associated with the use of ethanol and fomepizole as antidotes for methanol and ethylene glycol poisoning. Clinical Toxicology (2011), 49, 391-401

clinical features of EG and methanol poisonings. Consistently, early intervention after the ingestion of the toxic alcohol produces more favourable clinical outcomes. Fomepizole increases the half-life of EG (from about 3 to 9 h to about 14 to 20 hours) and methanol (from about 8 to 28 h to around 50 h), reducing the proportion of the ingested dose converted to toxic metabolites. There are hard clinical outcomes from some studies with reversal or improvement of visual symptoms in some patients and discharge from hospital of patients that presented comatose. The nature of the studies does not allow comparison with standard care (that would include ethanol treatment) and congestions or early treatment with ethanol acts as a confounder in the results of many. No randomised controlled trials comparing ethanol and fomepizole have been presented.

Zacharov²² reported patients with ethanol or fomepizole treatment in the Czech methanol poisoning outbreak, with similar outcomes however fomepizole (for reasons of availability) was restricted to the most unwell patients and many had received ethanol as a treatment and all had ethanol as a co-ingestant.

EG and methanol can both be removed from circulation with haemodialysis. Haemodialysis can also remove glycolate, oxalate and formate. It also removes fomepizole and an amended dosage regimen is required during dialysis to ensure adequate blockade of alcohol dehydrogenase.

Safety and RMP

The safety of fomepizole was derived from manufacturer studies and published literature. The most commonly reported adverse events included dizziness, light-headedness, feeling of intoxication and vertigo. Nausea, vomiting, abdominal pain, headache, rash, eosinophilia and local inflammatory reaction to venous infusion were also reported. Less frequently hypotension and seizure were reported fomepizole. Laboratory abnormalities noted were transient increased in liver enzymes, eosinophilia and elevated triglycerides and/or cholesterol. Increased lactate, increased creatinine or urea and anaemia could be attributed to the toxicity from the ingested alcohol. Hypoglycaemia has been reported but it is not clear how much ethanol as a co-ingestant or treatment contributed to these events. Where the severity was reported the events were mild to moderate and tended to be short-lived. The safety is confounded by co-ingestants and the progression of toxicity from the toxic alcohols ingested. Although there is a concern from the nonclinical data about the mutagenic effects of fomepizole, and the carcinogenic potential has not been investigated, exposures are of short duration to address the acute toxicity of ethylene glycol or methanol. The one patient exposed to fomepizole 104 times (99 as the sole antidote) did not reveal any long term sequelae of repeated exposure although it may have been difficult to distinguish any consequences of repeated fomepizole exposure from repeated toxic alcohol exposure. The sponsor has provided a RMP that has aspects that require resolution for it to be acceptable.

Indication

The sponsor has described the efficacy and safety of fomepizole in the treatment of both ethylene glycol poisoning and methanol poisoning. In the majority of the studies of poisoned patients fomepizole has been used with dialysis of various modalities and with variable commencement and discontinuation criteria. Pending advice from the TGA's advisory committee the sponsor's proposed patient groups for the indication are supported.

The use of dialysis is a clinical decision based on the clinical presentation of the patient. The inclusion of a mention of dialysis as proposed by the sponsor may confuse the inexperienced prescriber and may imply that dialysis is optional (although it is not suggested this is the intent of the sponsor). Description of the use of fomepizole with dialysis along with dosage instructions can be included in the Dosage and Administration

section. It is not considered necessary to provide an example of a source of ethylene glycol in the indication and the Delegate therefore proposed the following:

Antizol® is indicated as an antidote for ethylene glycol or methanol poisoning.

Dose

There have been no formal dose ranging studies have been conducted to determine the optimal dose of fomepizole. The proposed dosage instructions are consistent with those used in the most recent studies where efficacy was demonstrated and with the current clinical practice guidelines.

Data Deficiencies

There are a number of data deficiencies in this submission:

- Drug interaction studies were limited
- There are limited data from patients with multiple dose exposure and no long term data.
- No head to head comparison with ethanol for patients of similar severity of poisoning.
- Small numbers of paediatric patients with EG and methanol were included in the submission.
- Data on the elderly or patients with chronic renal or hepatic disease prior to ingestion are limited, although some of the patients in the Czech study are likely to have had alcoholic-induced liver disease.

Conclusion

The sponsor has relied on old studies, most of which use salts of fomepizole, supplemented by literature where the form (salt or otherwise) of fomepizole used is not always identified. Most of the studies use fomepizole IV as is proposed by the sponsor. Extrapolation from these studies is required to the proposed product. The efficacy is derived only from case series, some prospective but the majority with some retrospective data collection. There is the potential for bias in the literature and with the open label sponsor studies. The confounding effect of ethanol on the efficacy and safety of fomepizole is of concern. Small numbers of patients were treated only with fomepizole, although there outcomes were similar to those where ethanol in combination with fomepizole was given. The purpose of many of the better conducted studies was to characterise methanol or ethylene glycol poisoning rather than specifically to determine the efficacy and safety of fomepizole, an already established treatment at the time the studies were conducted. Taking into account the limitations of the clinical safety information, the adverse effects of fomepizole appear mostly transient and manageable. Given the life-threatening nature of large ingestions of ethylene glycol or methanol the potential benefits of fomepizole treatment that it has been demonstrated with ethanol initial treatment and with dialysis, the overall benefit-risk profile is just favourable.

Summary of issues

- Does the submission include sufficient evidence to support the efficacy of fomepizole, particularly given the co-ingestion of or pre-treatment with ethanol?
- Is there sufficient evidence to provide dosing instructions for the transition from ethanol treatment to fomepizole treatment?
- Should the indications be for adults only given the limited paediatric data submitted?

- The nonclinical evaluator has identified mutagenicity of fomepizole. Is this risk sufficiently mitigated by the statement in the PI, given the likely duration of exposure of fomepizole?

Proposed action

The Delegate had no reason to say, at this time, that the application for fomepizole (Antizol) should not be approved for registration for the amended Indication:

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

Proposed conditions of registration

There will be a condition of registration to implement a RMP when the outstanding matters are resolved with the RMP team. Since a new version of the Australian RMP may result so no specific condition is proposed currently.

Questions for the sponsor

1. In which of the studies was the formulation proposed by the sponsor for registration in Australia used?
2. The META study¹⁵ determined the elimination half-life of fomepizole from plasma to be 19.7 hours. Please explain why this information is not proposed for the PI?
3. How widely available are ethylene glycol and methanol levels in Australia? Are ethylene glycol and methanol levels always reported as mg/mL or are they reported in mmol/L in Australia?
4. Please explain the rationale for a contraindication in patients without confirmed ethylene glycol and methanol poisonings. Does the sponsor propose alternative therapies should be used until an elevated ethylene glycol or methanol level can be obtained?
5. In its announcement in 2014 following approval of fomepizole in Japan, the Japanese sponsor announced it would conduct All Cases Surveillance to collect additional safety and efficacy data. Please provide a brief summary of the findings of this surveillance to date.
6. Ethanol intoxication may accompany toxic alcohol intoxication. The ACSOM recommended that guidance about the use of fomepizole in the ethanol intoxicated patient should be included in the PI. Please outline the available information that addresses this issue. Please draft dosing instructions for alcohol intoxicated patients for consideration by the ACPM.
7. The animal studies suggest liver toxicity and genotoxicity are of potential concern with fomepizole. Please outline the available human safety information regarding repeat dosing.
8. Please comment on the relevance of altered renal function in dogs, given the importance of good renal function for the effectiveness of fomepizole.
9. The sponsor has proposed a warning statement regarding muscle damage resulting from an increased creatine kinase for the PI. Please briefly summarise the evidence that supports this warning.
10. It is noted the GMP clearance has not been obtained for all sites. Please ensure all manufacturing sites have GMP clearance prior to the projected decision date.
11. The sponsor is encouraged to resolve any outstanding matters with the Australian RMP with the RMP team.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. The efficacy evidence for ethylene glycol poisoning and methanol poisoning is derived from open-label case series and includes some retrospective data. Has the sponsor provided sufficient evidence to support the use of fomepizole in the requested indication?
2. The nonclinical evaluator identified genotoxicity as a potential risk with the use of fomepizole in two types of bacteria. Is the mutagenicity of concern given the proposed indication for fomepizole? If so, is the risk adequately mitigated through the precautionary statement in the PI?
3. Accidental ingestion of ethylene glycol or methanol can occur in young children. Has the sponsor provided sufficient evidence to support the use in children? Can the adult data be extrapolated to children or should the indication include only adults?
4. Co-ingestions of ethanol and methanol or ethylene glycol can occur. Concomitant use of fomepizole and ethanol can prolong ethanol exposure. The ACSOM has recommended advice regarding the transitioning to/from ethanol therapy in the PI. Has sufficient evidence been provided in the submission to offer this advice in the PI or should the prescriber seek advice outside the PI (for example, Poisons Information Centre or local toxicologist)?
5. The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

1. *In which of the studies was the formulation proposed by the sponsor for registration in Australia used?*

The formulation proposed for Australia is simply the active drug substance fomepizole (4-methylpyrazole or '4MP') filtered and packed into vials under nitrogen. The studies in which the formulation proposed by the sponsor for registration in Australia was used in all, except the following studies:

- Study S7 OMC-4MP-3 which investigated 4MP hydrochloride and 4MP sulphate.
 - Megarbane et al 2001²⁰ supplied a higher concentration (5 mg/mL) of fomepizole but this does not matter as product diluted to allow for same dosage as proposed for the Australian product.
 - Study S9³³ similarly supplied a 5 mg/mL concentration of fomepizole that was diluted to allow for the same dosage as proposed for the Australian product.
 - Studies S11³⁴ and S12³⁵ also supplied a 5 mg/mL concentration of fomepizole, but dosing regimen used for these individuals differed from that proposed for the Australian product.
2. *The META study (Brent et al 1999) determined the elimination half-life of fomepizole from plasma to be 19.7 hours. Please explain why this information is not proposed for the PI?*

This is now included in the PI.

³³ Baud et al, 1986. Detailed clinical history of the 3 cases of EG intoxication treated with 4MP.

³⁴ Harry et al, 'Efficacy of 4MP in ethylene glycol poisoning: Clinical and toxicokinetic aspects'. Human and experimental toxicology (1994), 13: 61-64.

³⁵ Jobard, E., Harry, P., Turcant, A., Marie Roy, P., & Allain, P. (1996). 4-Methylpyrazole and Hemodialysis in Ethylene Glycol Poisoning. Clinical Toxicology, 34(4), 373-377. <http://doi.org/10.3109/15563659609013806>

3. *How widely available are ethylene glycol and methanol levels in Australia? Are ethylene glycol and methanol levels always reported as mg/mL or are they reported in mmol/L in Australia?*

AFT were advised by the TGA when applying for section 19A approval for this product that some Australian laboratories report the results for ethylene glycol and methanol in mmol/L, while others use mg/dL. Please advise if any further amendments are required to the PI and CMI as a consequence?

4. *Please explain the rationale for a contraindication in patients without confirmed ethylene glycol and methanol levels. Does the sponsor propose alternative therapies should be used until an elevated ethylene glycol or methanol level can be obtained?*

As stipulated in the Antizol Canadian product monograph, Antizol treatment should begin 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 greater than 3.2 mmol/L (20 mg/dL) or methanol concentration greater than 6.2 mmol/L (20 mg/dL).³⁶

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 hypocalcaemia. 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 during treatment, as transient increases in serum transaminase concentrations and eosinophilia have been noted with repeated Antizol dosing.³⁶

5. *In its announcement in 2014 following approval of fomepizole in Japan, the Japanese sponsor announced it would conduct All Cases Surveillance to collect additional safety and efficacy data. Please provide a brief summary of the findings of this surveillance to date.*

The Japanese sponsor Takeda has started a clinical trial entitled Specified Drug-use Survey of Fomepizole Intravenous Infusion 'Takeda' (All-case surveillance).³⁷ This study is an observational cohort prospective study that started on January 2015 in Japan. The estimation date for final collection of data for the primary outcome measure is June 2022. This study is currently recruiting patients.

The objective of the survey is to evaluate the safety and efficacy of fomepizole IV infusion in Japanese patients with ethylene glycol and methanol poisonings in daily medical practice.

The primary outcome is the frequencies of adverse events. Adverse event is defined as any untoward medical occurrence in patients where the drug has been administered or an unexpected exacerbation of the target disease. The frequencies of all adverse reactions will be tabulated by symptom, day of onset and severity.

The secondary outcome is the change from baseline in arterial blood pH. Summary statistics for arterial blood pH values and the changes from baseline will be calculated at each time point.

³⁶ Paladin Labs Inc. Product Monograph Antizol (fomepizole) Injection 1.5mL (1g/ml) Synthetic alcohol dehydrogenase inhibitor. s.l. : Version 4, 2015.

³⁷ Takeda Pharmaceutical Company Limited. In: Specified Drug-use Survey of Fomepizole Intravenous Infusion "Takeda" (All-case surveillance). ClinicalTrials.gov. [Online] March 2015. [Cited: ClinicalTrials.gov [Internet]. National Library of Medicine (US). 2000- Sep 2016.] <https://clinicaltrials.gov/ct2/show/record/NCT02415712> . NLM identifier: NCT02415712.

The recruitment information available indicates that the estimated number of patients to be enrolled is 168. All patients who have been confirmed as receiving the drug will be included regardless of the age and the sex. The participants will be followed from the first doses of the drug to 24 h after the last dose of the drug. This corresponds to an expected average of 3 days. The dose regimen of fomepizole will consist of an IV administration (infusion > 30 min) of one dose of 15 mg/kg followed by four doses of 10 mg/kg and 15 mg/kg for following doses.

The preliminary results reported to the Japanese regulatory authorities as part of Japan-PSUR dated August 2, 2016 are summarised in the following lines.

Study Patients

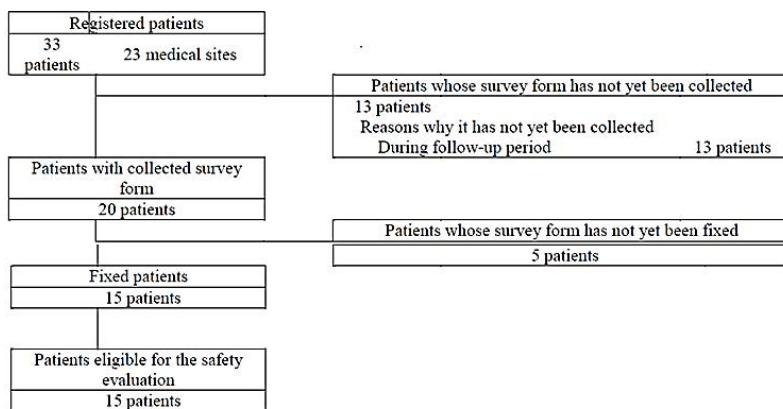
The information of 47 patients that met the inclusion criteria have been sent from 32 medical sites to the Central Registration Centre. Among them, two (2) patients were duplicate patients (the same patient). After excluding the duplicated patients, 17 patients were treated with fomepizole IV for ethylene glycol poisoning and 28 patients were treated for methanol poisoning.

Until now, 33 patients from 45 (deriving from 23 medical sites) were registered. Among them, survey forms were collected for 20 patients, and data from 15 patients was considered eligible for the safety evaluation. Final diagnosis for the 15 patients was as follows:

- Ethylene glycol poisoning in 1 patient,
- Suspected ethylene glycol poisoning in 1 patient,
- Methanol poisoning in 6 patients,
- And suspected methanol poisoning in 7 patients.

Please refer to figure below.

Figure 1: Disposition of patients: Preliminary results of the study Specified Drug-use Survey of Fomepizole Intravenous Infusion 'Takeda' (All-case surveillance), reported to the Japanese regulatory authorities.



Safety

Among patients eligible for safety evaluation collected by the end of the designated survey period, there was no occurrence of adverse drug reaction.

Serious adverse events

Among patients eligible for safety evaluation, the following serious adverse events reported between December 4, 2015 and June 3, 2016: acidosis (1), depressed level of consciousness (1), brain oedema (1), and decrease in blood pressure (1) in a total of two

(2) patients. The table below summarises the results of the survey concerning the list of incidence of serious adverse events during fomepizole therapy.

Table 7: Incidence of serious adverse events related to fomepizole therapy.
Preliminary results of the study Specified Drug-use Survey of Fomepizole
Intravenous Infusion 'Takeda' (All-case surveillance) reported to the Japanese
regulatory authorities.

| TIMING | DRUG USE-RESULTS SURVEYS | | | | | Total |
|--|---|---|---|---|--------|---------|
| | 1st 4 June 2014 to 3 December 2014 | 2nd 4 December 2014 to 3 June 2015 | 3rd 4 June 2015 to 3 December 2015 | 4th 4 December 2015 to 3 June 2016 | | |
| | 3 December 2014 | 3 June 2015 | 3 December 2015 | 3 June 2016 | | |
| | [1] Number of surveyed medical sites | 0 | 0 | 3 | 7 | 9 |
| [2] Number of surveyed pa patients | 0 | 0 | 4 | 11 | 15 | |
| [3] Number of patients with serious adverse events | 0 | 0 | 0 | 2 | 2 | |
| [4] Number of cases of serious adverse events | 0 | 0 | 0 | 4 | 4 | |
| [5] Rate of patients with serious adverse events ([3]/[2]*100) | - | - | 0.00% | 18.18% | 13.33% | |
| CATEGORY OF SERIOUS ADVERSE EVENTS | | | | | | |
| Metabolism and nutrition disorders | 0 | - | 0 | - | 0 | (6.67) |
| Acidosis | 0 | - | 0 | - | 0 | (6.67) |
| Nervous system disorders | 0 | - | 0 | - | 0 | (13.33) |
| Depressed level of consciousness | 0 | - | 0 | - | 0 | (6.67) |
| Brain oedema | 0 | - | 0 | - | 0 | (6.67) |
| Investigations | 0 | - | 0 | - | 0 | (6.67) |
| Blood pressure decreased | 0 | - | 0 | - | 0 | (6.67) |

6. *Ethanol intoxication may accompany toxic alcohol intoxication. The ACSOM recommended that guidance about the use of fomepizole in the ethanol intoxicated patient should be included in the PI. Please outline the available information that addresses this issue. Please draft dosing instructions for alcohol intoxicated patients for consideration by the APCM.*

Ethanol intoxication may accompany toxic alcohol intoxication. Many patients poisoned with methanol or ethylene glycol could present serum ethanol levels as a result of self-poisoning or initial treatment administration. This following discussion outlines the available information that, to our knowledge, addresses this issue.

Some of the first studies that investigated the interaction of ethanol and 4MP were those reported by Blomstrand et al. in 1980, and by McMartin et al. in 1988^{38,39}. The study of Blomstrand meant to investigate the mutual interaction of ethanol and 4MP in chronic and acute experiments, as well as the possible related functional and structural changes in hepatic and kidney functions.

For the chronic experiments, fomepizole (1.3 Mm; ADH inhibition 60%) was given to rats alone or in combination with 10% ethanol (1.7M)d during 38 weeks. Interestingly, it was shown that chronic administration of ethanol and 4MP led to an increased concentration of both ethanol and 4MP in the blood. Moreover, in which respects the toxicity of ethanol and 4MP, no obvious clinical symptoms during the long-term administration of 4MP and ethanol. Haematological values as well as liver and kidney function markers were unchanged. Also, no definitive lesion was found in electro-microscopy for the liver, kidney and heart.³⁸

The elimination of 4MP after saturation of the liver ADH with ethanol as well as the short term interaction of both compounds was also studied in acute experiments. In the elimination studies, ethanol (30 mmol/kg) was administered to rats 30 minutes before

³⁸ Rolf Blomstrand, Ake Ellin, Agneta Lof and Helene Ostling-Wintzell. Biological effects of Metabolic Interactions after chronic and acute administration of 4-MP and Ethanol to rats. Archives of Biochemistry and Biophysics, 1980, Vols. 199 (2) 591-605.

³⁹ Kenneth E. McMartin and Timothy Collins. Distribution of oral 4-Methylpyrazole in the rat: inhibition of elimination of ethanol. Clinical Toxicology, 1988, Vols. 26(7), 451- 466.

4MP (1 mmol/kg) intraperitoneally. During the whole study ethanol serum levels were kept above 9 mmol/L with doses of ethanol 10 mmol/kg. Accordingly with the results shown in the chronic studies, the results from this experiment showed that when ADH was saturated with ethanol, a much slower elimination of 4MP was recorded.³⁸

In order to further elucidate the mechanism of this interaction, an acute interaction study was carried out. In those studies fomepizole (425 µmol/kg) was administered alone or with ethanol (87 mmol/kg) during 4h, and the serum concentration of one fomepizole metabolites, 4-OH-MP, was measured. Interestingly, it was shown that there was a lower concentration of 4-OH-MP indicating that ethanol interferes with 4MP metabolism.³⁸

Years later, in 1988, McMurtin et al³⁹ conducted a similar study. 4MP was administered orally in doses of 5, 10, or 25 mg/kg alone or in combination with ethanol at 0, 1, 2 and 3 h (1 g/kg each h). At doses of 10 and 20 mg/kg, 4MP elimination appeared to be saturated showing an elimination rate of 10 µmol/L/h. When ethanol was administered, the rate of elimination of 4MP decreased at about 50%. Consistently, the urinary excretion of unchanged 4MP was increased during ethanol administration. These results corroborate the mutual inhibition of metabolism by ethanol and 4-methylpyrazole.³⁹

The first clinical investigation that addressed the interaction of ethanol and 4MP was the two double-blind, crossover studies, performed in healthy volunteers published by Jacobson et al. in 1996.⁴⁰

The objective of this publication was to determine whether moderate amounts of ethanol would alter 4MP elimination. Study A included three (3) groups of different 4MP concentrations (10 mg/kg, 20 mg/kg, 30 mg/kg) in which either ethanol or placebo were administered one hour after 4MP administration. (Group 1: 4MP (10 g/kg) ethanol (0.7 g/kg); Group 2: 4MP (20 mg/kg) + ethanol (0.7 g/kg); Group 3: 4MP (30 mg/kg) + ethanol (0.7 g/kg).

Study B, consisted of one group of four (4) subjects that received 4MP at a concentration of 5 mg/kg, along with either placebo or ethanol at the end of 4MP infusion (0.6 g/kg + 0.2 g/kg at 4 h and 8 h).⁴⁰

The results from Study A showed that 4MP significantly decreases the rate of ethanol elimination by about 40% at the three dose levels tested (10 mg/kg, 20 mg/kg and 30 mg/kg). Conversely, Study B showed that ethanol inhibited the rate of 4-CP urinary excretion, during the initial 10 h (-50%). After ethanol was cleared from the body, there was an apparent rebound in 4-CP excretion and the total recovery of 4-CP was not affected.⁴⁰

The interpretation of these results by the authors stated;

'In practice this will mean that 4MP levels will remain in the effective range for a longer period of time. As such, the presence of ethanol should increase the effectiveness of 4MP and certainly should not preclude the use of 4MP in such patients'.⁴⁰

In summary, all those studies help support the clinical data demonstrate that, Antizol at therapeutic doses significantly reduced the rate of elimination of ethanol by approximately 40% and that conversely, ethanol decreased the rate of elimination of Antizol by approximately 50% by the same mechanism.

Interestingly, the decreased rate of elimination of Antizol caused by ethanol was judged beneficial for the clinical use of fomepizole, as according to the authors, this could increase its effectiveness.⁴⁰ In contrast, no inference was made about the possible enhancement of ethanol CNS toxicity during fomepizole therapy.

⁴⁰ Jacobsen D, Sebastian CS, Dies DF et al. Kinetic interactions between 4-methylpyrazole and ethanol in healthy humans. *Alcohol Clin Exp Res*, 1996, Vols. 20(5): 804-809.

In order to explore the effect of 4MP on the neurobehavioral toxicity caused by ethanol, Paez et al⁴¹ conducted a murine study where mice were evaluated to perform in two (2) established and validated outcomes for ethanol-induced neurobehavioral toxicity: the rotarod test and the presence of righting reflex. Mice were pre-treated with 35 mg/kg of 4MP and afterwards administered incremental doses of ethanol (1 to 5 g/kg).⁴¹ As expected, the dose of ethanol at which 50% of the animals failed a particular outcome test [TD50] was decreased with 4MP administration for both the rotarod test and the righting reflex. In other words, 4MP significantly prolonged ethanol neurobehavioral toxicity in CD-1 mice.⁴¹

Because of those results, withholding fomepizole pre-treatment in suspected toxic alcohol ingestions was initially suggested Paez et al study.⁴¹ However, this recommendation received severe comments by emergency physicians:

*'Delaying fomepizole therapy until serum ethanol concentrations are available may be less costly to the hospital pharmacy or less likely to be proven unnecessary in hindsight. However, this decision could never be characterized as prudent in light of real-world delays encountered in obtaining serum concentrations of the various alcohols. It is also imprudent to suggest a safety benefit in delaying antidotal therapy for patients with suspected toxic alcohol ingestion'*⁴²

Moreover, three other physicians remarked:

*'Although 4MP is an expensive treatment, we believe that the severity of the adverse effects of toxic alcohol metabolism justifies its early use, and outweighs the risk of prolonged ethanol neurobehavioral toxicity, when there is a suspicion of toxic alcohol ingestion. In addition, it is not clear how a positive blood alcohol level should guide a delay in treatment with 4MP. While it is generally accepted that a serum ethanol concentration of 100 mg/dL is protective, it is not known how soon toxicity can be expected to develop as the serum ethanol concentration falls below 100 mg/dL. It would be impossible to predict with any accuracy how fast one person would metabolize ethanol and reach a serum concentration of 100 mg/dL. Inebriated patients who receive 4MP will remain stable and will not become more inebriated'*⁴³

In conclusion, if all the studies mentioned above help to understand the mutual inhibition of ethanol and 4MP, it is important to highlight the fact that those studies didn't address the current dose regimen of fomepizole. Most importantly, those studies were unable to describe the interaction of 4MP and ethanol during toxic alcohol intoxication.

The current dose regimen for Antizol, in place since 1999 for ethylene glycol poisoning and since 2002 for methanol poisoning⁴⁴, has been reported to be used to treat toxic alcohol poisoning regardless a concomitant alcohol intoxication with or without haemodialysis.^{45,46} To our knowledge, concomitant serum ethanol levels in toxic alcohol poisoned patients have not compromised the safety of fomepizole.⁴⁷

⁴¹ Ana Maria Paez, Timothy Maher and Lawrence Quang. Effects of 4-Methylpyrazole on Ethanol Neurobehavioral Toxicity in CD-1 Mice. Academic emergency medicine, 2004, Vols. 11(8) 820-6.

⁴² Marco L.A.Sivilotti MD, MSc; David NI Juurink MD, PhD. Comments to Paez et al study: Effects of 4-methylpyrazole on ethanol neurobehavioal toxicity in CD-1 mice. Acad. Emer Med. 2004; 11:820-6. s.l. : Journal of American Emergency Vol. 12, No. 6, 2005.

⁴³Beth Y. Ginsburg MD; Michael Anana, Oliver Mayorga MD, Robert S. Hoffman, MD. Comments to Paez et al study: Effects of 4-methylpyrazole on ethanol neurobehavioal toxicity in CD-1 mice. Acad. Emer Med. 2004; 11:820-6. 12(6): Journal of Academic Emergency Medicine, 2005.

⁴⁴ Guangduo Zhang, Kasumi Crews, Heather Wiseman, Nicola Bated, Knut Erik Hovda, John RH Archer, Paul I Dargan. Application to include fomepizole on the WHO List of Essential Medicines. November, 2012.

⁴⁵ Bruno Megarbane, Stephen W. Borron, Herve Trout, Philippe Hantson, Albert Jeager, Eliane Krencker, Chantal Bismuth, Frederic J. Baud.Treatment of acute methanol poisonign with fomepizole. Intensive Care Medicine, 2001, Vols. 27: 1370-1378.

Therefore, given the benefit/risk ratio observed for fomepizole in the treatment of toxic alcohol intoxication accompanied or not by ethanol, the lack of pertinent clinical data to make adjustments to our current validated dose regimen, and the opinion of experts in that matter, the sponsor is unable to draft a new dose regimen.

7. *The animal studies suggest liver toxicity and genotoxicity are of potential concern with fomepizole. Please outline the available human safety information regarding repeat dosing.*

The sponsor wishes to reiterate on the publication that addressed the potential long term effects of repeated use of fomepizole, which is the case report published by Hovda et al in 2011.⁴⁸ This publication presented the case report of a young patient that was admitted to the hospital 154 times for ethylene glycol poisoning with concentrations ranging from 25 to 700 mg/dl. During those episodes, fomepizole, ethanol, and both antidotes combined, were used as a therapy with or without haemodialysis (fomepizole 99 times, ethanol 60 times and both antidotes 6 times; haemodialysis 73 times). Although renal impairment was seen on ten (10) of the admissions, it was successfully normalised on all occasions.

According to the authors, the frequent use of fomepizole in this patient was not associated with any detectable side effects, neither on clinical examination and lab screening nor on the later autopsy. Precisely, the results of the autopsy revealed calcium oxalate crystals in the kidney, slight liver steatosis, and slight oedema of the lungs.

As stated by the authors: '*Except for the renal impairment, considered most probably caused by the calcium oxalate monohydrate crystal form EG metabolism, there were no sign of organ damage after repetitive use of fomepizole*'.⁴⁸

Since the birth date of Antizol (fomepizole) in December 1997, no serious unexpected drug reactions regarding the liver, or suggesting genotoxicity have been reported.⁴⁷

8. *Please comment on the relevance of altered renal function in dogs, given the importance of good renal function for the effectiveness of fomepizole.*

It is of note that a good renal function is necessary for the efficacy of fomepizole, as during a toxic alcohol intoxication therapy, both, the parent toxic alcohols and the fomepizole metabolites, are excreted by the renal route.

To this effect, five (5) studies concerning the effect of fomepizole in dogs were included in the present submission:

- Two of the above mentioned studies are founded by the sponsor: WIL Research study 258003 and 258004 and are repeated dose toxicity studies.^{49,50}
- The other three studies are publications derived from the literature.^{51,52,53}

⁴⁶Jeffrey Brent, Kenneth McMartin, Scott Phillips, Keith K. Burkhardt, J. Ward. Donovan, Melanie Wells, Ken Kulig. Fomepizole for the treatment of ethylene glycol poisoning. Engl J Med, 1999, Vols. 340:832-8.

⁴⁷ Paladin Labs (USA) Inc. 10th Periodic Safety Update Report for Antizol (fomepizole). International Birth Date: 04 Dec 1997 (USA) Period cover: 04 Dec 2013 to 03 Dic 2014, Date of report: 26 Jan 2015

⁴⁸Hovda, K.E., Julsrød, J., Øvrebø, S., Brørs, O., and Jacobsen, D. Studies on ethylene glycol poisoning: One patient – 154 admissions. Clinical Toxicology, 2011, Vols. 49, 478–484.

⁴⁹Orphan Medical, Inc. A dose range-finding toxicity study with intravenous 4-methylpyrazole in dogs. s.l. : Wil Research Laboratories, 1995. WIL-58003.

⁵⁰Orphan Medical Inc. An intravenous toxicity study with 4-Methylpyrazole in dogs. s.l. : WIL Research Laboratories Inc., 1995. WIL-25004

⁵¹Gregory F. Grauer, Mary Anna Hull Thrall, Barbara A. Henre and Jerry J. Hjelle. Comparison of the effects of ethanol and 4-Methylpyrazole on the pharmacokinetics and toxicity of ethylene glycol in the dog. Toxicology Letters, 1987, Vols. 35; 307-314.

⁵²Sharon M. Dial, Mary Anna Thrall, Dwayne W. Haman. 4-Methylpyrazole as treatment for naturally acquired ethylene glycol intoxication in dogs. JAVMA, 1989, Vol. 195.

⁵³Efficacy of 4-methylpyrazole for treatment of ethylene glycol intoxication in dogs. American Journal of Veterinary Research, 1994, Vol. 55.

Whereas the repeated dose toxicity studies aimed to detect the potential toxic effects of 4MP, the published reports explored the efficacy of fomepizole in Ethylene Glycol (EG) intoxicated dogs. Both types of studies are included in this discussion, as well as the available clinical information concerning the effect of fomepizole on the human renal function.

Repeated dose toxicity studies in dogs

The first sponsored study, WIL Research study 258003, consisted of a range finding study that explored fomepizole concentrations as high as 150 mg/kg.⁴⁹ The results of this study led to a second study which studied dosages of 10, 20 and 30 mg/kg and that was considered by the authors to be the definitive 4MP toxicity study.⁵⁰

In the definitive toxicity study, dosage levels 10, 20 and 30 mg/kg of 4MP were administered by a 0.5 h IV infusion twice a day during 14 days. The renal function and the changes in serum chemistry parameters as well as in the urinalysis were observed. The 20 mg/kg and the 30 mg/kg groups presented an increased mean urine volume and decreased mean urine gravity at Day 13. At Day 14, an electrolyte imbalance was also observed. In the 30 mg/kg and 20 mg/kg group an increase in sodium and bicarbonate was observed, whereas a decrease in potassium was only observed in the 30 mg/kg group. No other effects on urinalysis parameters were seen during the rest of the evaluations at any fomepizole concentration. Moreover, values of all the affected parameters were comparable to the control group at study Day 42.⁵⁰

Considering all effects of fomepizole (not only renal) the authors considered that:

- A dose of 10 mg/kg resulted in no drug related effects,
- A dose of 20 mg/kg was considered to have no-adverse effects (NOAEL),
- A dose of 30 mg/kg was considered to have drug related but not life threatening effects.

Any macroscopic or microscopic renal anomaly was reported in the study. All effects were reversible.⁵⁰

The sponsor wishes to expand on the following publications that studied the effect of fomepizole in EG intoxicated dogs, and which attributed to fomepizole a renal protector effect rather than a harmful one.

Effect of fomepizole in the renal function of Ethylene Glycol intoxicated dogs Three (3) studies concerning the effect of fomepizole in EG intoxicated dogs were presented in this submission (Grauer et al. (1987), Dial et al. (1989 and 1994). In all three (3) studies an altered renal function was present in dogs intoxicated with EG. Clinical features such as increase in urinary volume, increase serum urea nitrogen concentration and decrease serum bicarbonate concentration were studied.

The aim of Dial et al. first study was to investigate the effect of fomepizole in naturally acquired ethylene glycol intoxication in dogs, while the aim of the second one, was to compare the efficacy of fomepizole given after 5 or 8 h of an induced EG ingestion. In both studies, the overall clinical features presented by EG intoxicated dogs such as: polyuria, isothenuria, calcium oxalate dehydrate crystalluria, high anion gap metabolic acidosis and serum hyperosmolality, as well as ataxia, vomiting and depression, were considered EG related. In both studies, 4MP helped prevent the EG related renal damage and as shown in the second Dial et al study, fomepizole was more effective when the treatment was

initiated after 5h of EG ingestion compared to the same treatment initiated after 8 h of EG ingestion.^{52,54}

In Grauer et al study, nine (9) dogs intoxicated with EG (173 mmol/kg) were randomly assigned to three (3) groups:

- EG only,
- EG + ethanol (IV 19.3mmol/kg after 3h, 7h, 14 h, 24 h)
- EG+ 4MP (IV 0.24 mmol/kg after 3 h, 0.18 mmol/kg after 24h and 0.06 mmol/kg after 36 h).

EG induced toxicity was evaluated by measurement of serum bicarbonate levels as an index of metabolic acidosis and serum urea nitrogen as a measure of renal function. Moreover changes in the serum osmolality, the urine volume and the quantity of unchanged EG excreted were also studied.⁵¹

After the ingestion of EG, all dogs presented metabolic acidosis (diminution of serum bicarbonate concentrations). However, after six (6) h of EG ingestion, the dogs treated with ethanol and the dogs treated with 4MP presented a statistically significantly difference in serum bicarbonate concentrations compared to the dogs that did not receive any treatment, indicating an attenuation of the metabolic acidosis. In comparison to time zero (baseline), the serum bicarbonate concentrations decreased in all three (3) groups during the first 12 h after EG intoxication. However, in ethanol and 4MP treated groups, this decrement stabilised approximstely between 3 to 6 h.

As far as the serum urea nitrogen concentrations, EG intoxication caused a statistically significant elevation at 72 h after ingestion. This elevation in serum urea nitrogen concentrations, which could reflect renal failure, was prevented in the ethanol and 4MP treated dogs.⁵¹

EG intoxication was also responsible for an increased urine production of approximately 7 fold in all groups (EG, EG + ethanol, EG + 4MP) during the first 24 h. Because this increase in urine production was seen in the non-treated dogs, the sponsor inferred that it was EG related. In other words, EG intoxication caused an increase in urine volume that neither ethanol nor 4MP could significantly alter. However, between 3 and 72 h, the amount of EG excreted in the urine was significantly increased in the 4MP group compared with the control group (EG=48% versus EG+4MP=71%). The effect of 4MP on the increase of the excretion of intact EG could be the result of its inhibition on the alcohol dehydrogenase. In fact, by inhibiting the metabolism of EG, it was expected to observe an augmentation of intact EG excreted in the urine in the 4MP treated group compared to the control group where the intact EG concentration decreases as it is being metabolised.

Additionally, the authors stated that both therapies, ethanol and 4MP, increased the rate constant of EG excretion into the urine by approximately 70% between 3 and 72 h. This increase in EG clearance could be explained by the difference in renal function of the control group versus the treated groups (demonstrated by the augmentation in the serum urea nitrogen concentrations at 72 h). In fact, during renal impairment one would predict a reduction in drug clearance. Therefore, just taking into account the non-clinical dog studies, the sponsor might conclude that although the repeat dose toxicity studies showed that 20 mg/kg and 30 mg/kg of fomepizole could temporarily alter the renal function, during intoxication this effect is minor compared to the consequences of not treating the dogs.

⁵⁴ Sharon M. Dial, Mary Anna Hull Thrail, Dwayne W. Haman. Adverse Reaction Report. Case reference number PAL-0014-2010. s.l. : CIOMS form, 2010.

Clinical effect of fomepizole in the renal function

The publication that addresses the potential long term effects of repeated use of fomepizole, is the case report published by Hovda et al in 2011.⁵⁵ This publication presented the case report of a patient that was admitted to the hospital 154 times for ethylene glycol poisoning with concentrations ranging from 25 to 700 mg/dl. During those episodes, fomepizole, ethanol, and both antidotes combined, were used as a therapy with or without haemodialysis (fomepizole 99 times, ethanol 60 times and both antidotes 6 times; haemodialysis 73 times). Although renal impairment was seen on (10) ten of the admissions, it was successfully normalised on all occasions.

According to the authors, the frequent use of fomepizole in this patient was not associated with any detectable side effects, neither on clinical examination and lab screening nor on the later autopsy. As stated by the authors: '*Except for the renal impairment, considered most probably caused by the calcium oxalate monohydrate crystal form EG metabolism, there were no sign of organ damage after repetitive use of fomepizole*'.⁵⁵

Moreover, the authors added: '*Potential minor side effects from fomepizole could be 'hidden' behind the poisoning and metabolic acidosis itself; however, severe metabolic acidosis was hardly apparent, and the fact that she was discharged without any signs of sequelae after all episodes where fomepizole was used, makes this seem unlikely. This indicates that the use of fomepizole is safe even when used frequently*'

Therefore, the authors concluded that no adverse effects of fomepizole were registered supporting the safety of fomepizole.⁵⁵

Moreover, since the International birth date of Antizol, only one adverse drug reaction concerning the renal function has been reported.^{54,56} This case of one patient presenting renal failure and tubular necrosis was submitted to the FDA and Israel in June 2010 and was published by Zosel et al⁵⁷ the same year.

This publication describes the case of an ethanol intoxicated patient that was admitted following a choking event that led to a ventricular fibrillation cardiac arrest. Due to the development of tonic seizures, lorazepam was started but at an incorrect rate. Because propylene glycol was the diluent of the IV lorazepam solution, this medical error led to an overdose of lorazepam and consequently to a propylene glycol toxicity (659 mg/dL). Fomepizole was started and continued during 3 days along with continuous venovenous hemofiltration (CVVH) (15 mg/kg IV bolus followed by one dose of 10 mg/kg every 12 h; 4 doses of 10 mg/kg every 6 h; 15 mg/kg once a day along with CVVH). Although the acidosis was resolved and the propyl-glycol toxicity had decreased, the patient prognosis was poor as the patient presented an anoxic brain injury from the initial cardiac arrest. With the patients consent, the patient was extubated on hospital Day 12 and died within the next few minutes. According to the authors, although the patient's outcome was death, the patient's lactic acidosis was treated successfully with fomepizole and CVVH.⁵⁷

In the suspect adverse reaction report, the patient's renal pathology and subsequent decease was explained by the sequence of events following the accidental propylene glycol overdose. Therefore it was determined that the contribution of Antizol to the patient's renal pathology and subsequent decease was speculative.⁵⁶

⁵⁵ Hovda, K.E., Julsrud, J., Øvrebø, S., Brørs, O., and Jacobsen, D. Studies on ethylene glycol poisoning: One patient – 154 admissions. *Clinical Toxicology*, 2011, Vols. 49, 478–484.

⁵⁶ Paladin Labs (USA) Inc. 10th Periodic Safety Update Report for Antizol (fomepizole). International Birth Date: 04 Dec 1997 (USA) Period cover: 04 Dec 2013 to 03 Dec 2014, Date of report: 26 Jan 2015

⁵⁷ Amy Zosel, Elizabeth Egelhoff, Kennon Heard. Severe Lactic Acidosis After an Iatrogenic Propylene Glycol Overdose. *2:219*, 2010, *Pharmacotherapy*, Vol. 30.

Conclusion

In the repeat dose toxicity studies, an electrolyte imbalance as well as an increase in urinary volume was seen in dogs treated for 14 days, twice a day, with 20 mg/kg and 30 mg/kg 4MP. Whereas the increased sodium levels could be related to the increase in urinary volume, an increase in the potassium serum levels may prove beneficial in the metabolic acidosis resulted from EG toxicity.

On the other hand, the altered renal function (increase in urinary volume, increase serum urea nitrogen concentrations, decrease serum bicarbonate concentrations) observed in the EG intoxication studies, was related to the toxicity of EG itself. Fomepizole helped attenuate the metabolic acidosis, impede the impairment of renal function and increase the amount of intact EG excreted in the urine.

The clinical evidence available up to day, suggests that fomepizole does not present renal adverse effects when used recurrently.

9. *The sponsor has proposed a warning statement regarding muscle damage resulting from an increased creatine kinase for the PI. Please briefly summarise the evidence that supports this warning.*

The RMP evaluator requested that this information be incorporated into the RMP as an important potential risk. The sponsor therefore thought it prudent to include this warning statement in the PI as a result. Please advise if it should be removed.

10. *It is noted the GMP clearance has not been obtained for all sites. Please ensure all manufacturing sites have GMP clearance prior to the projected decision date*

Please note that GMP clearance has been obtained for all sites at the current time-point except for one site. This was submitted on 17 June 2015. P

11. *The sponsor is encouraged to resolve any outstanding matters with the Australian RMP with the TGA.*

The sponsor will liaise with the TGA team to resolve any outstanding issues with the Australian RMP.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) resolved to recommend to the TGA Delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Antizol liquid for dilution for infusion containing 1.5g/1.5mL of fomepizole to have an overall positive benefit-risk profile for the Delegate's amended indication;

Antizol is indicated for the treatment of ethylene glycol or methanol poisoning.

In making this recommendation the ACPM

- noted that fomepizole was designated as an orphan drug and it is a WHO essential medicine.
- noted that fomepizole has been approved internationally and has been used in North America and Europe for the treatment of ethylene glycol and methanol poisoning.
- expressed concern about the small number of paediatric patients with ethylene glycol and methanol poisoning included, but advised to include the limited paediatric data in the PI.
- was of the view that overall safety of fomepizole is acceptable and is better tolerated than ethanol.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

The committee is requested to provide advice on the following specific issues:

1. *The efficacy evidence for ethylene glycol poisoning and methanol poisoning is derived from open-label case series and includes some retrospective data. Has the sponsor provided sufficient evidence to support the use of fomepizole in the requested indication?*

The ACPM was of the view that there is very limited data to support the efficacy of fomepizole alone due to studies being highly inconsistent in design, and differing with respect to levels of intoxication with the toxic alcohol and ethanol, use of hemodialysis or ethanol pretreatment, and fomepizole dosing regimen. However, the committee agreed the benefit risk assessment is favourable despite the lack of robust data, taking into account these poisonings are rare in Australia and that it is unlikely that there may ever be large randomised clinical trials to support the indication. The committee also noted that the alternative treatment of these poisonings with ethanol also has difficulties.

2. *The nonclinical evaluator identified genotoxicity as a potential risk with the use of fomepizole in two types of bacteria. Is the mutagenicity of concern given the proposed indication for fomepizole? If so, is the risk adequately mitigated through the precautionary statement in the PI?*

The ACPM considered that identified genotoxicity may not be clinically relevant given the amended indication and acute exposure of patients to fomepizole. It was noted the risk was adequately outlined in the PI.

3. *Accidental ingestion of ethylene glycol or methanol can occur in young children. Has the sponsor provided sufficient evidence to support the use in children? Can the adult data be extrapolated to children or should the indication include only adults?*

The ACPM expressed concern that the PI does not exclude pediatric use but also does not provide any of the limited, pediatric data. There is no PK data provided to assist with extrapolation from adult to child. However, the committee noted that ADH activity reaches adult levels at about 5 years of age. The ACPM was of the view that the limited data available suggest that fomepizole (using the same dosage regimen as that used for adults) is effective and well tolerated in paediatric patients.

4. *Co-ingestions of ethanol and methanol or ethylene glycol can occur. Concomitant use of fomepizole and ethanol can prolong ethanol exposure. The ACSOM has recommended advice regarding the transitioning to/from ethanol therapy in the PI. Has sufficient evidence been provided in the submission to offer this advice in the PI or should the prescriber seek advice outside the PI (e.g. Poisons Information Centre or local toxicologist)?*

The ACPM advised that there is a reasonable chance that many patients will present with concomitant ethanol exposure, either self-administered or as an initial therapy. It is clear from the safety studies that early intervention after the ingestion of the toxic alcohol produces more favorable clinical outcomes. Therefore waiting for ethanol levels to drop to below therapeutic levels would be counterproductive. In addition, one of the

disadvantages of ethanol as an ethylene glycol or methanol antidote is the difficulty in predicting ethanol kinetics and it might be difficult to predict the impact of ethanol on an individual patient's fomepizole levels.

The committee considered that current studies do not provide any detailed information on the impact of ethanol on fomepizole efficacy. Therefore the ACPM agreed with the sponsor that it would be difficult to provide an evidence-based alternative regimen regarding transitioning to/from ethanol therapy. The PI currently provides information on the interaction between fomepizole and this advice could be repeated under Patient Management.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Antizol Fomepizole 1.5 g/1.5 mL concentrated injection vial for the indication of:

Antizol (fomepizole) is indicated for the treatment of ethylene glycol or methanol poisoning. (see Dosage and Administration).

Specific conditions of registration applying to these goods

The fomepizole Australian Risk Management Plan (RMP), version 4.0, dated 24 August 2016, data lock point 26 November 2014, included with submission PM-2015-02803-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Antizol approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at [<https://www.tga.gov.au/product-information-pi>](https://www.tga.gov.au/product-information-pi).

Attachment 2. Extract from the Clinical Evaluation Report

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