Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Fomepizole

Proprietary Product Name: Antizol

Sponsor: AFT Pharmaceuticals Pvt Ltd

Date of first round report: 6 April 2016

Date of second round report: 3 August 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviations	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

Abbreviations	Meaning
L	litre
LLN	Lower limit of normal
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
PO	Per Oral
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

1. Introduction

This is a Category 1 application for registration of a new chemical entity, Antizol Fomepizole liquid for dilution for infusion, 1.5g/1.5 mL vial.

1.1. Drug Class and Therapeutic Indication

Antizol is a pyrazole derivative, and a competitive inhibitor of the alcohol dehydrogenase (ADH) enzyme. The proposed indication for Antizol is:

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

1.2. Dosage Forms and Strengths

The submission proposes registration of the following dosage forms and strengths: *Antizol® is supplied as a sterile, preservative-free solution for intravenous use. The proposed marketed drug product, fomepizole for injection, is supplied in 2 mL glass vials containing 1.5 mL sterile liquid fomepizole free base as the drug substance. There are no diluents or additives. It is supplied in packages of four vials or one vial. Each vial contains 1.5 mL (1 g/mL) of fomepizole.*

1.3. Dosage and Administration

Preparation of fomepizole for intravenous infusion involves withdrawing the dose from the vial and injecting it into 100 mL of 0.9% sterile sodium chloride for injection, or into dextrose 5% in water.

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.

Dosage with Renal Dialysis: Antizol (fomepizole) Injection is dialysable and the frequency of dosing should be increased to every 4 h during haemodialysis.

2. Clinical rationale

Prior to the availability of specific therapies, approximately two-thirds of ethylene glycol (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 (Wacker WC, et al, 1965). 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 poisoning 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.

Fomepizole or 4 Methypyrazole (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.

3. Contents of the clinical dossier

3.1. 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 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.

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

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

Comment: The clinical overview was well written and the evaluators have no major disagreement with the contents of the document. The clinical summaries were not well-written with many grammatical and typographical errors.

The clinical submission had studies which were not labelled correctly. There was no consistency between study report numbers and actual reports presented. Furthermore, the actual reports were not in alignment with the Table of Contents (ToC). This made it very difficult for the evaluator to navigate through the dossier. There were 5 integrated summaries for Fomepizole:

- a 3-page integrated summary of benefits and risks of fomepizole in treatment of EG poisoning.
- an integrated summary of effectiveness data: This was submitted as a supplemental NDA to the FDA to seek approval for fomepizole for treatment of methanol poisoning.
- an integrated summary of safety.
- an integrated summary of effectiveness data, but this document could not be accessed.
- an integrated summary of safety data. However, this was just a 2-page document with an index of the actual integrated summary of safety that was provided in Section 8.8 above.

– There were 272 literature references: these were submitted under 7 subheadings:
  - 'LBS' had approximately 40 literature references, all of which were reviewed, evaluated and summarised in the report.
  - 'References provided with dossier clinical trial data' about 10 references which were all reviewed and evaluated.
  - 'Diethylene glycol references' about 8 of these were provided and read but none of these were directly relevant to this submission and so were not evaluated.
  - 'Historical control comparison references' about 54 references and 5 case reports were provided which were reviewed and those relevant to this submission were evaluated and summarised in the report.
  - 'Human PK references' about 17 references some of which were animal studies; these were read and when relevant evaluated.
  - 'Methanol references' about 34 references majority of which were dated before 1980 with some as early as 1941. These were read but none were considered directly relevant to this submission.
  - 'Section 8.13' Approximately 100 references were submitted in this section of the dossier and these were read and relevant ones evaluated and summarised in the evaluation report.

3.2. 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.

3.3. Good clinical practice

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.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 below shows the studies relating to each pharmacokinetic topic.

Table 1: 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
		- Multi-dose	S8 (EG poisoning) S13 (methanol poisoning)
	Hepatic impairment		None
	Renal impairment		S12- Jobard, 1996
	Neonates/infants/children/adolescents		None
	Elderly		None
Gender related	Males vs. females		None
PK interactions	Drug interaction study with ethanol		Jacobsen, 1990 (Study S4) Jacobsen, 1996
	Drug interaction study with EG		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.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Pharmacokinetics in healthy subjects

Comment: 6 studies in healthy subjects (S-2, S-3, Jacobsen, 1990, Jacobsen 1996, Maraffa, 2008 McMartin, 2012). However, it is important to note that detailed study reports and subsequent published articles were provided for studies S2 and S3[1] only.

It has been stated that Study S4 is actually the Jacobsen, 1990 reference, but this was provided under 'study report 6'. It appears that Study S6 is the Jacobsen, 1996 reference, but this is not clearly stated in the dossier and the sponsors have been asked to clarify. Furthermore, there was no Study S5 submitted in the dossier although it is mentioned in the various summaries.

4.2.2. Absorption

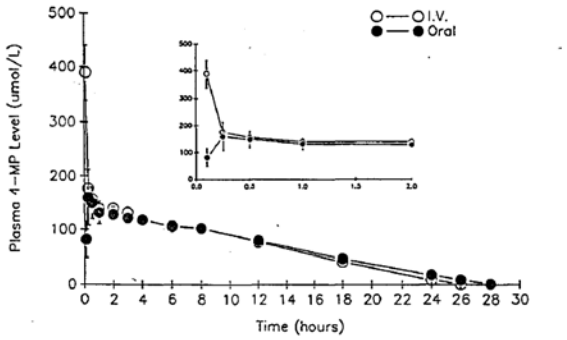
4.2.2.1. Sites and mechanisms of absorption

Results from studies S2 and S3 (described below) indicate that fomepizole (4MP) is rapidly and completely absorbed following both oral and IV dosing such that plasma concentrations of 4MP were identical within 30 minutes of administration of the oral and IV doses.

4.2.2.2. Bioavailability

Results from the Phase I single-dose, crossover Study S-**2** in 6 healthy males showed that the oral doses of 4MP were rapidly and completely absorbed, with a bioavailability of one. When the same acute dose (7 mg/kg) was given by either IV or oral routes, comparable AUC's were obtained reflecting similar plasma values after 30 minutes which may allow for the oral safety data from the rest of the studies in this section to be supportive of the IV use of fomepizole (Figure 1). Following absorption and distribution, 4MP was eliminated primarily by metabolism to 4-carboxypyrazole 4-CP, which was excreted in the urine. The rate of 4-CP excretion in the urine and of 4MP elimination from the plasma was identical after both oral and IV doses.

Figure 1: IV study Group averages of plasma 4MP levels over time



[1] S3 study report was the basis of two publications:
-Jacobsen et al. '4-methylpyrazole: a controlled study of safety in healthy human subjects after single, ascending doses.' Alcoholism, Clinical and Experimental Research, 1988; 12(4) :516-22.
- Jacobsen D, et al. 'Non-linear kinetics of 4-methylpyrazole in healthy human subjects.' Eur J Clin Pharmacal 1989; 37:599-604.

In Study S3 after oral administration, 4MP was rapidly absorbed and then slowly eliminated (Figure 2). In all dose groups, the time to peak plasma concentration was about 0.5 to 2 h. The mean peak plasma concentrations of 4MP (SEM) were 132 (17), 326 (18), 759 (196) and 1425 (49) µmol/L after doses of 10, 20, 50 and 100 mg/kg, respectively. Thus each mg/kg of 4MP dose produced an increase in the 4MP peak plasma concentration of about 13-16 µM.

Figure 2: Non-linear 4MP kinetics (Jacobsen et al)

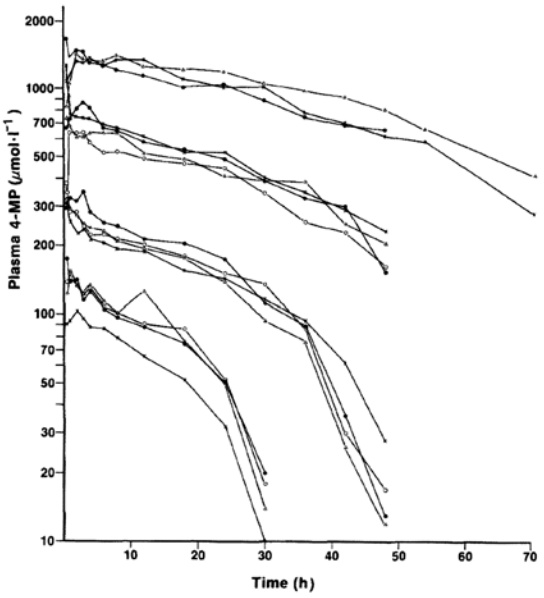
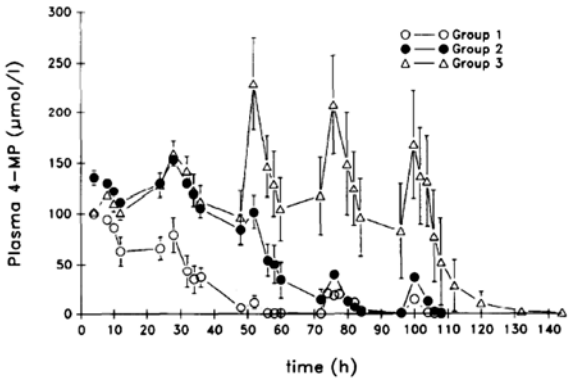


Fig. 1. Plasma elimination profiles of 4-MP in healthy male subjects plotted on log-linear coordinates. Healthy male subjects were given single oral doses of 10, 20, 50 and 100 mg 4-MP/kg b. wt. Number of subjects were 4, 4, 4, and 3 respectively. Within each group, individual elimination patterns (x, ●, ○, or △) were connected point-to-point. Each dose group can be distinguised by increasing plasma levels

Jacobsen, et al (1990): A placebo-controlled, double blind, multiple dose, sequential, ascending-dose study was performed to determine the tolerance of 4MP in 21 healthy volunteers. Oral loading doses of 4MP were followed by supplemental doses every 12 h through 5 days, producing plasma levels in the therapeutic range. Dose schedule in Group 3 (oral loading dose of 10 mg/kg, plus 5mg/kg every 12 h up to 36 h and then 10 mg/kg every 12 h up to 96 h) appeared to be the best at maintaining therapeutic levels for up to 5 days (Figure 3).

Figure 3: Plasma elimination profile of 4MP in heathy males given multiple doses.



Limitations of this study

This study only evaluated oral dosing with fomepizole and was mainly a tolerability study. It showed results which appear to be identical to those reported by McMartin, 2012.The sponsors have been asked to clarify this.

McMartin, 2012 reported a single dose, crossover study in 5 healthy male subjects followed by a double-blind, and multiple dose study in 21 healthy male subjects.

In the single dose study**,** the initial absorption and distribution of fomepizole was extremely rapid following oral and IV single dosing and there were virtually no differences in the plasma

concentrations after the different routes of administration within 15 minutes of dosing (Figure 1). The PK parameters after the oral and IV doses, calculated by regression analysis of the zero order elimination, show that the Vd and the AUC IV (0.58 ± 0.03 L/kg and 1885 ± 121) were virtually identical to that determined by the nonlinear model simulations (0.57± 0.03 L/kg and 1851±130) indicating compatibility between the two analyses.

In the multiple dose study**,** in Group 1 (loading dose of 4MP of 10 mg/kg followed by supplemental doses of 3 mg/kg every 12 h up to 96 h) and Group 2 (loading dose of 15 mg/kg plus 5 mg/kg/12 h up to 96 h), the plasma levels remained in the 50 to 150 μM range for about 36 to 60 h. Then the levels decreased markedly so that 4MP was detectable for only 8 h after the last administration. Thus, in order to produce relatively constant plasma levels throughout 5 days of treatment, the supplemental doses of 4MP were increased for subjects in Group 3 after 36 h of treatment (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) (Figure 4). Such a dosing schedule generally maintained plasma levels in the 100 to 200 μmol range throughout the 5 day treatment. Overall, the dose schedule in Group 3 (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) seems to be the best at maintaining therapeutic levels for up to 5 days. One of the original goals of the present study was to evaluate the effect of 4MP on the ethanol elimination rate as a model for its effect on ADH activity. Therefore, ethanol, 0.5 mg/kg, was given orally at 74 h to the subjects in Group 1 (Figure 4). This interaction was, however, difficult to interpret because the plasma 4MP levels were very low at 74 h. Thus, no ethanol was given to subjects in Groups 2 and 3. The 4MP and ethanol interaction was investigated in a separate study (Jacobsen, 1996) which is discussed below.

Figure 4: Plasma profile of 4MP in heathy males given multiple doses

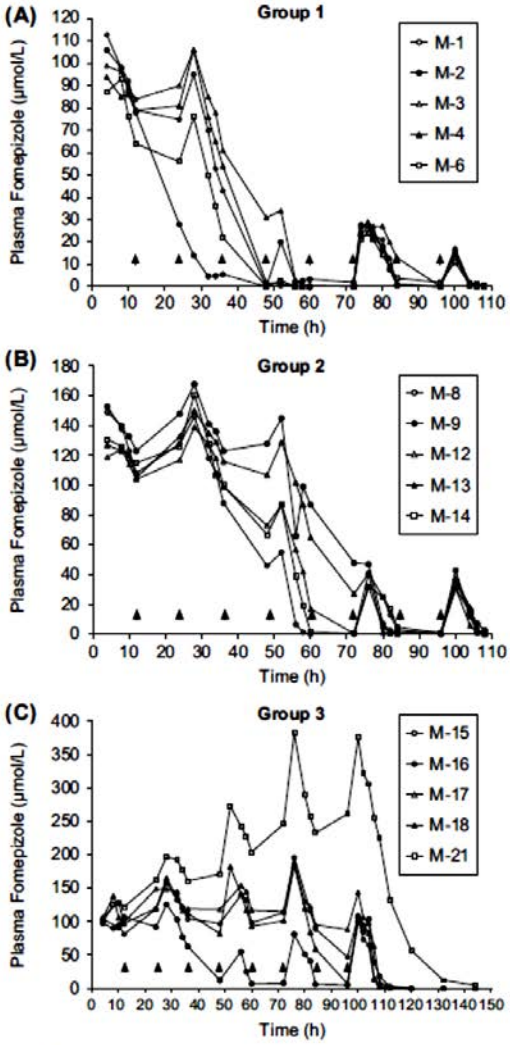


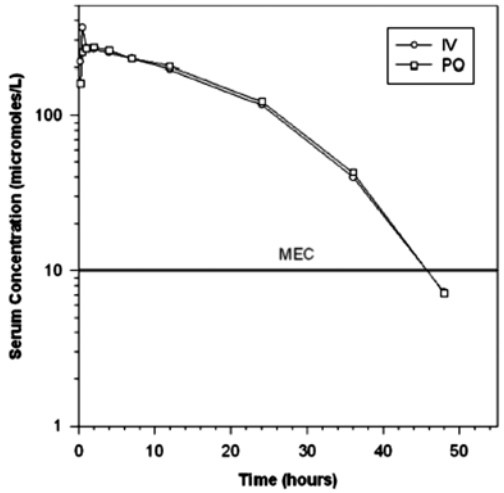
Fig. 4. Plasma fomepizole concentrations in healthy human subjects given multiple oral doses of fomepizole. (A, top) In Group 1, subjects received 10 mg/kg at 0 hour, then 3 mg/kg every 12–96 hours; (B, middle) in Group 2, subjects received 15 mg/kg at 0 hour, then 5 mg/kg every 12–96 hours; (C, bottom) in Group 3, subjects received 10 mg/kg at 0 hour, then 5 mg/kg every 12 hours up to 36 hours, and then 10 mg/kg/12 h to 96 hours. Arrowheads indicate timing of fomepizole doses.

Comment: Overall results from this well-conducted study confirmed that fomepizole is eliminated in human subjects following therapeutic doses by saturable, nonlinear kinetics and that, when humans are given multiple doses of fomepizole over a 5-day period, the rate of elimination of fomepizole was increased markedly (2- to 3-fold) within 3 days of such 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, thus indicating most probably an induction of metabolism of fomepizole. Supplemental doses of fomepizole need to be increased at the time that the enhanced elimination occurs (about 36 – 48 h) in order to maintain therapeutic fomepizole concentrations and validate the currently recommended dosing schedule for fomepizole in EG/methanol poisoned patients.

Marrafa J, et al (2008) reported a prospective, randomised, crossover trial in 10 healthy volunteers to describe comparative PKs of fomepizole after single oral and IV dose. Each received 15 mg/kg fomepizole, PO and by 30 minute IV infusion. PO fomepizole was rapidly absorbed with a bioavailability of ~100%. After oral and intravenous administration, the KM

ranged from 0.24 to 3.1 µmol/L (mean = 0.94; SD 0.98) and the V_{max} ranged from 6.5–31.4 µmol/L/hr (mean = 18.6; SD 9.6). The kinetics best fit a 2-compartment model with Michaelis-Menten elimination, which is consistent with previous studies in humans and animals showing a zero-order elimination process. The time above the presumed minimum effective concentration of 10 µmol/L ranged from 24 to 36 h (mean = 32.4 h; SD: 5.8), for both routes of administration (Figure 5).

Figure 5: Mean IV and PO fomepizole serum concentration over time



Comment: This was the first study that effectively determined a human Vmax and Km for PO and IV fomepizole. Oral and IV administration of fomepizole resulted in similar pharmacokinetic parameters.

4.2.2.3. Distribution

Volume of distribution

Both oral and IV doses were rapidly distributed, apparently to total body water (volume of distribution of 0. 6 L/kg). These data would imply that 4MP would gain access to and rapidly inhibit ADH activity in all tissues in the body including the main metabolic organ, the liver, and the potential target organs, the CNS, eyes and kidneys (Study S-2).

4.2.2.4. Metabolism

Interconversion between enantiomers

Not applicable.

Sites of metabolism and mechanisms / enzyme systems involved

Although there are no studies in humans showing that fomepizole is metabolised by cytochrome P-450, studies in rats and mice have shown that the primary metabolites of fomepizole are 4-hydoxymethylpyrazole (4-OHMP) and 4-CP with smaller amounts of an N-glucuronide. Following absorption and distribution, 4MP was eliminated primarily by metabolism to 4-carboxypyrazole (4-CP), which was excreted in the urine. The rate of 4-CP excretion in the urine and of 4MP elimination from the plasma was identical after both oral and IV doses (S-2).

Metabolites identified in humans

Up to 80 to 85% of a dose of fomepizole was collected in the urine as the primary metabolite (S-2), 4- carboxypyrazole (4-CP). 4-CP is not an inhibitor of alcohol dehydrogenase. Other minor metabolites of fomepizole are 4- hydroxymethylpyrazole, N-glucuronide conjugates of 4-carboxypyrazole and 4-hydroxymethylpyrazole (Weintraub and Standish, 1988). These metabolites are either inactive or are so weak (4-hydroxymethylpyrazole) that they could not contribute significantly to the inhibition of ADH seen with doses of fomepizole used clinically.

4.2.2.5. Excretion

Routes and mechanisms of excretion

In Study S-2, the urinary excretion of unchanged 4MP is not a major route of elimination as the total amount of 4MP recovered unchanged in the urine ranged from l to 3 % of the administered dose. No difference in urinary 4MP excretion was seen between subjects when treated that is, and orally. In earlier studies in human subjects, the primary metabolite of 4MP in the urine was 4-carboxypyrazole (4-CP), which accounted for about 72-86 % of the dose. There were no differences in the production and excretion of 4-CP between the two routes of administration, both in terms of the rate and of the total amount of excretion. 4-CP excretion was complete within 36 h in all subjects, except IV-3 who showed excretion through 48 h. As in previous studies, the major metabolite of 4MP was 4-CP, accounting for 54-82 % of the dose (mean, 65-66%).

S3 was the Phase I, placebo-controlled single dose, sequential, ascending dose study in 22 healthy males to determine the tolerability of 4MP at dose levels of 10 (n=4), 20 (n=4), 50 (n=4) and 100 mg/kg (n=3). Along with each dose group, there were two placebos except with the 100 mg/kg group where there was only one placebo. Single oral dose of 4MP (10-20 mg/kg) produced plasma levels within a probable therapeutic range. After oral administration, 4MP was rapidly absorbed and then slowly eliminated (Figure 2). In the 10 and 20 mg/kg groups, the elimination of 4MP from the plasma followed non-linear kinetics with mean rates of concentration decline of 3.66 and 5.05µmol/L/h, respectively. In the two highest dose groups, the elimination also appeared to be non-linear although PK sampling was not done long enough to confirm this. The average renal clearance of 4MP was low (0.016 mL/min) and only 3% of the administered dose was excreted unchanged in the urine, indicating metabolism as the major route of elimination.

Comment: Overall, results from this study showed that elimination of 4MP represented zero-order kinetics at the two lowest doses (10 and 20 mg/kg). At the 2 highest doses (50 and 100 mg/kg), the elimination of 4MP was most likely zero order although this could not be determined since the plasma concentration decline was not followed long enough. Hence, multiple dose studies would be required to confirm PKs of fomepizole at proposed dosing schedules.

It is important to note that the study report was the basis of 2 publications:

i. Jacobsen et al. '4-methylpyrazole: a controlled study of safety in healthy human subjects after single, ascending doses. 'Alcoholism, Clinical and Experimental Research, 1988; 12(4):516-22.

ii. Jacobsen D, et al. 'Non-linear kinetics of 4-methylpyrazole in healthy human subjects.' Eur J Clin Pharmacol 1989; 37:599-604.

Renal clearance

Renal clearance of fomepizole after acute treatment accounted for 1.4 to 3.5% of the dose across all studies and was not affected by the size of the dose. Significantly more of the metabolite 4-CP was excreted in the urine after higher doses. The rate of 4-CP excretion, however, was similar among the high and low dose groups, suggesting saturation kinetics occurs in the pathway of 4-CP formation and excretion.

4.2.2.6. Intra- and inter-individual variability of pharmacokinetics

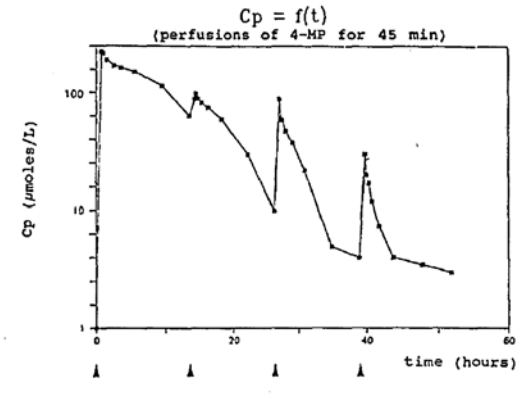
The plasma half-life of Antizol varies with dose, even in patients with normal renal function; intra and inter-individual variability has not been calculated.

4.2.3. Pharmacokinetics in the target population

4.2.3.1. S1

The first pharmacokinetic data for 4MP in patients with ethylene glycol poisoning was reported by Beng, et al, 1992. An initial dose of 10 to 20 mg/kg permits the achievement of plasma concentrations >10 µmol/L, which are therapeutically effective. This level can be maintained by the injection of lower doses every 12 h. The distribution volume of 4MP was 1 L/kg. Its body clearance is 0.70 mL/min/kg and renal clearance is much lower (0.03 mL/min/kg). Its kinetics is complex and dose dependent. It is first order at low doses (2-4 mg/kg) and zero order at high doses (8-16 mg/kg) (Figure 6). These same results were presented in another figure using Cartesian coordinates, the time being recorded for each dose starting from its moment of administration. It can be seen that in the elimination phase, for at least seven h, the lowering of the blood concentration for high doses is proportional to time, and depends little on the concentration indicating zero order elimination kinetics. Similar results have been observed in healthy subjects treated with 4MP.

Figure 6: Trend in the plasma concentration of 4MP with time. Each arrow head indicates administration of a new 4MP dose. Cp=f(t)



4.2.3.2. S11

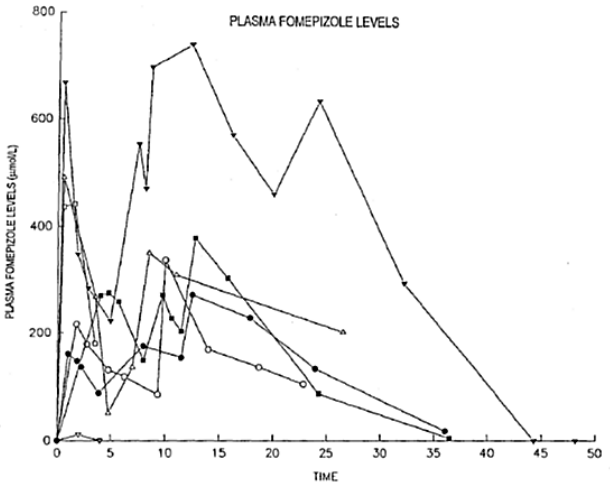
The single case report of ethylene poisoning in a 30-year old male showed that the EG half-life was 16 h during 4MP treatment compared to a normal half-life of 3h. Such a prolonged half-life especially strongly suggests reduced hepatic metabolism of ethylene glycol as a direct result of the presence of 4MP. Absence of ethanol in the plasma of this patient eliminated the possibility of ethanol contributing to the therapeutic effect of 4MP. It is important to note that the patient was conscious, had only mild acidosis and normal renal function on admission and was also administered 4MP within 3 h of accidental ingestion of ethylene glycol.

4.2.3.3. S8

In Study S-**8** (discussed in detail in section Other efficacy studies), six of the seven patients consistently had plasma levels of fomepizole that were therapeutic (>10 µmol/L or >0.82 mg/L). One of these six patients had a transient rise in plasma glycolate levels after levels fell following the initiation of fomepizole therapy (Figure 7. This occurred when his plasma fomepizole level had fallen to 118 µmol/L (9.7 mg/L), one of the lower levels observed for patients in this trial, although still well in excess of the fomepizole plasma level believed to be therapeutic (Figure 7). The two possibilities that would most likely explain this observation are 1) haemodynamic instability preventing clearance of any glycolate formed because of decreased delivery of the metabolite to the kidneys and dialyser, and/or 2) insufficient inhibition of ethylene glycol metabolism at this plasma level of fomepizole. This patient was in cardiogenic shock at the time of enrolment. At the time this elevated glycolate measurement was detected, he was hypotensive and it is likely that this contributed to the observed rise in plasma glycolate.

This conclusion is supported by the next plasma glycolate determination which showed a profound fall despite lower fomepizole levels (85.7 µmol/L or 7.0 mg/L).

Figure 7: PK results from patients poisoned with ethylene glycol in Study S8



Another patient had low measured plasma fomepizole levels at 2 h (10.8 µmol/L or 0.89 mg/L) and 4 h (0 µmol/L) after his loading dose, despite being apparently administered an appropriate dose (Figure 7). This patient refused further blood sampling after 4 h and subsequent fomepizole levels were not obtained. This patient presented with a baseline EG level of 51.0 mg/dL and had no detectable ethanol in his system. The patient was placed on dialysis but not until 8 h after the loading dose of trial drug was given. Both EG and plasma glycolate levels dropped for this patient prior to haemodialysis. The EG level dropped from 51 mg/dL to 18 mg/dL within the first 8 h. Similarly, the plasma glycolate levels dropped from 10 to 5.9 µmol/L within the first 4 h after the administration of the loading dose. It is unknown whether a dispensing error caused him to have such a low level. Despite the low levels of fomepizole in this patient, he did well and had no sequelae from his poisoning. The fomepizole level of 10.8 µmol/L (0.89 mg/L) obtained at two h post-loading dose, while less than predicted, should have been sufficient in inhibit EG metabolism. Fomepizole levels fell faster during haemodialysis than due to endogenous clearance alone. During haemodialysis, levels fell at a median rate of 0.80 µmol/L/minute (range 0.27 to 4.4). In the absence of haemodialysis, levels fell at a median rate of 0.33 µmol/L/minute (range 0.1 to 0.83). Fomepizole appeared to be effectively removed by haemodialysis and median clearance of fomepizole by dialysis was 183 mL/min (range 129 to 218).

Comment: Overall, data on fomepizole plasma levels from Study S-8 in seven patients treated with fomepizole for EG poisoning demonstrated that a loading dose of 15 mg/kg and supplemental dosing with 10 to 15 mg/kg every 12 h maintained fomepizole levels in the therapeutic range. Fomepizole was cleared more rapidly following haemodialysis suggesting that no frequent dosing with fomepizole may be required to maintain therapeutic levels.

4.2.3.4. S-13

In Study S-**13**, the fomepizole dosing regimen used in 11 patients with methanol poisoning consistently maintained plasma levels of fomepizole that were considered therapeutic (>10 µmol/L or >0.82 mg/L). Except for one patient[2], all patients received an initial fomepizole dose as a 30-minute infusion of 15 mg/kg (182.7µmol/kg). Subsequent dosing with fomepizole

[2] Due to the comatose status of Patient [information redacted], an error was made in estimating the patient's weight so that he actually received a loading dose of 22.0 mg/kg.

occurred via a defined protocol, but was somewhat variable among the patients due to variations in the timing and duration of haemodialysis periods, which influenced the fomepizole dosing. Hence, it was not possible to summarise plasma levels of fomepizole at designated time intervals. C_{max} ranged from 173-560 µmol/L, with mean and median values of 310 and 272, respectively. The peak often occurred following the initial dose (six of 11 patients), but sometimes after subsequent doses. Mean and median time to maximum concentration levels (T_{max}) values were 12.1 and 3.8 h, respectively. Because of the repeated fomepizole dosing, there were defined peaks and troughs in the plasma concentration profile in nine of 11 subjects. The trough level of fomepizole at steady state could be determined (C_{min} at time T_{min}). The mean and median C_{min} were 86 and 61µmol/L, while the mean and median minimum times T_{min} were 18.4 and 12 h, respectively. The number of blood sampling points after each dose of fomepizole was limited in Study S-13 because of the anticipated poor medical condition of many of these patients. Hence, the data points are insufficient to calculate the Michaelis-Menten parameters (K_m and V_{max}). However, the zero-order elimination phase could be computed in most cases after at least one dose of fomepizole to assess the nonlinear elimination of fomepizole in these patients.

These rates of elimination were determined repeatedly after multiple doses in some of the patients and were very consistent within each patient. The mean and median rates of fomepizole elimination were 13.0 and 14.8 umo1/L/h, respectively. The rate of fomepizole elimination in these patients was somewhat greater than those determined in healthy individuals after intravenous administration of 5 or 7 mg/kg doses of fomepizole (5.8 µmol/L/h in Jacobsen, 1989). During the haemodialysis periods, the total plasma clearance of fomepizole was primarily determined by dialysis, which is a first-order kinetic process. Hence, during the haemodialysis periods, the kinetic parameters demonstrated linear pharmacokinetics and the plasma clearance was approximately three times faster in patients undergoing dialysis than in undelayed patients. The mean and median Vct were 0.68 and 0.66 L/kg, respectively suggesting that fomepizole is distributed to the total body water in these patients and is similar to the Vd in healthy (0.74L/kg in Jacobsen, 1989).

4.2.4. Pharmacokinetics in other special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

Not evaluated.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

Jobard, 1996 (Study S12) reported two cases of severe ethylene glycol poisoning with renal failure who were treated with 4MP and haemodialysis; due to elimination of 4MP in the dialysate, a loading dose of 4MP 10-20 mg/kg was followed by continuous IV infusion of 1 to 1.5mg/kg/h during the 8-12 h of haemodialysis. The patient characteristics and clinical outcomes in these patients were summarised. S-12 determined PK parameters for fomepizole when used during dialysis in two aneuric patients. The plasma 4MP concentrations were 9 and 25.6mg/L at the beginning of dialysis in Patients 1 and 2 who received a loading dose of 10 and 20 mg/kg of 4MP, respectively. During dialysis, the plasma 4MP concentrations fell rapidly. In Patient 1, a 4MP infusion of 2.5 mg/kg/h for 2 h was needed to compensate the decrease of 4MP concentrations after four h of haemodialysis. Despite this infusion, the plasma 4MP concentrations were very low at the end of dialysis, but this was not deleterious for the patient because plasma EG concentrations were also very low over the same period. In contrast in Patient 2, continuous infusion of 4MP at a rate of 1.5 mg/kg/h during dialysis after a loading dose maintained plasma 4MP concentrations above 14 mg/L (Figure 8). The death of this patient admitted very late after massive EG ingestion with a flat electroencephalogram cannot be attributed to failure of treatment. The calculated volume of distribution of 4MP was 0.8 L/kg. The amount of 4MP eliminated in the dialysate reached about *45%* of the total elimination of 4MP for 12 and 8 h of haemodialysis for Patients 1 and 2, respectively.

Figure 8: Plasma 4MP and EG versus Duration of haemolysis

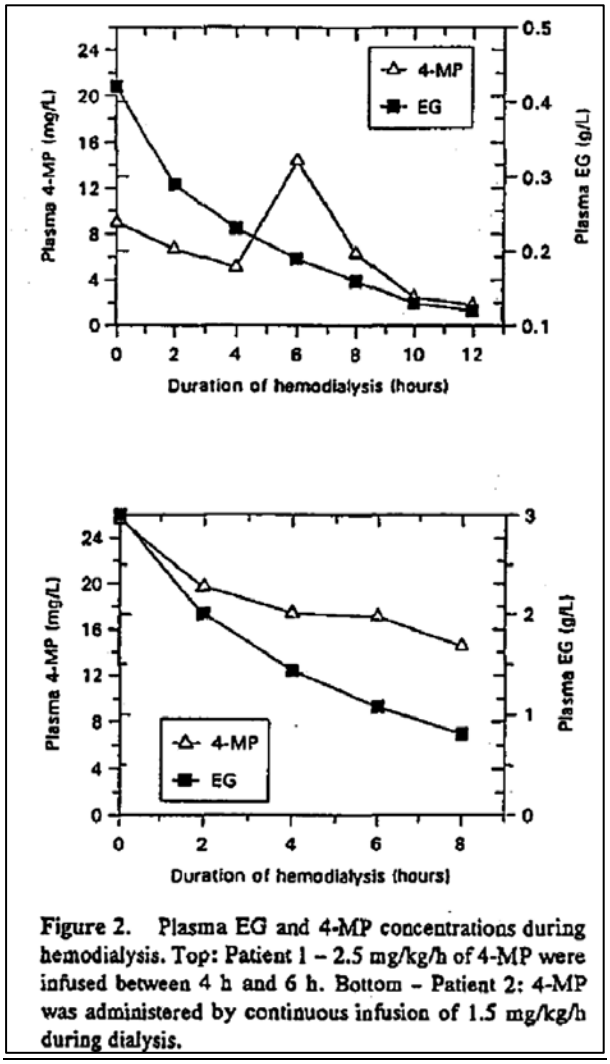


Figure 2. Plasma EG and 4-MP concentrations during hemodialysis. Top: Patient 1 – 2.5 mg/kg/h of 4-MP were infused between 4 h and 6 h. Bottom – Patient 2: 4-MP was administered by continuous infusion of 1.5 mg/kg/h during dialysis.

4.2.4.3. Pharmacokinetics according to age

Not evaluated.

4.2.4.4. Pharmacokinetics related to genetic factors

Not applicable.

4.2.4.5. Pharmacokinetics {in other special population / according to other population characteristic}

None.

4.2.5. Pharmacokinetic interactions

4.2.5.1. Pharmacokinetic interactions demonstrated in human studies

Fomepizole and ethylene glycol
Two publications, S-1 and S-11, describe drug interactions during the successful use of fomepizole to treat single cases of ethylene glycol poisoning. Ethylene glycol decreased the renal clearance of fomepizole from values of 1-2.5 mL/min in volunteers (S-2 and S-3) to 0.032 mL/min in a single reported case of poisoning treated with fomepizole (S-1). Likewise, it was shown that fomepizole prolonged the half-life of ethylene glycol in a single reported case of ethylene glycol poisoning from the reported values in the literature of approximately 3 h to approximately 16 h (S-11).

Fomepizole and ethanol
Previous studies in rats have shown that very large doses of ethanol can inhibit the elimination of 4MP from the plasma, presumably by inhibiting the cytochrome P-450 mediated oxidation of 4MP. Many patients poisoned with methanol or ethylene glycol will also exhibit moderate amounts of ethanol in the bodies (blood levels of 50 to 150 mg/dL), either because of co-consumption or because of initial therapeutic use of ethanol.

One of the original goals of the study reported by Jacobsen (1990) was to evaluate the effect of 4MP on the ethanol elimination rate as a model for its effect on ADH activity. Therefore, ethanol, 0.5 mg/kg, was given orally at 74 h to the subjects in Group 1. This interaction was, however, difficult to interpret because the plasma 4MP levels were very low at 74 h. Thus, no ethanol was given to subjects in Groups 2 and 3. The 4MP and ethanol interaction was investigated in a separate study which is discussed below.

Jacobsen D, 1996 was a study which examined whether moderate amounts of ethanol would alter 4MP elimination in healthy human subjects. This study was conducted in 2 parts:

Study A showed that single oral therapeutic doses of 4MP (10, 15 and 20 mg/kg) inhibited ethanol elimination in healthy humans by approximately 40%; 4MP concentrations in the range of 120 to 260 pmol/L were sufficient to inhibit ethanol elimination, thus to inhibit ADH activity.

In Study B, ethanol was administered in doses that would produce moderate blood levels likely to be observed in clinical situations. The ethanol dose schedule was sufficient to maintain blood ethanol levels in the range of 50 to 150 mg/dL for at least 6 h. This duration was needed to test for an effect on 4MP elimination, which was known to be slow and nonlinear. The inhibitory effect of ethanol was not readily apparent until 8 h after dosing (Figure 9).

Figure 9: Effect of ethanol on 4MP plasma concentration in healthy humans

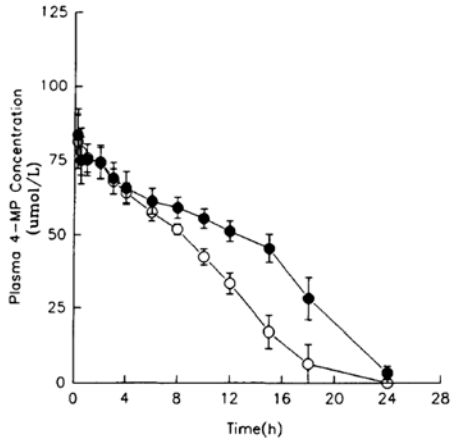


Fig. 3. Effect of ethanol on the plasma 4-MP concentrations in healthy humans. In a crossover design, subjects received an intravenous infusion of 4-MP (5 mg/kg over 30 min), followed by oral doses of ethanol (0.6, 0.2, and 0.2 at 0, 4, and 8 hr, respectively) in one session and similar doses of placebo in the other. Each point represents the group mean of the plasma 4-MP concentration ± SEM. ○, 4-MP + placebo; ●, 4-MP + ethanol.

Kinetic analysis of the plasma levels during the apparent zero-order elimination phase showed that ethanol inhibited the rate of concentration decline of 4MP by 50%. Ethanol did not alter the volume of distribution of 4MP. Ethanol significantly inhibited the rate of 4-CP excretion in the urine during the initial 10 h. After ethanol was cleared from the body, there was an apparent rebound in 4-CP excretion. Also, the total recovery of 4-CP was not affected by ethanol (51.0 *2* 6.8% of dose vs. 51.2 *2* 8.5% for placebo subjects). Neither the rate nor the total urinary excretion of unchanged 4MP (accounting for -2% of the dose) was affected by ethanol.

Comment: Overall, results from this study 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 and induction of the elimination of fomepizole by other enzyme inducers that affect the cytochrome P-450 enzyme system.

4.2.5.2. Clinical implications of in vitro findings

Not applicable.

4.3. Evaluator's overall conclusions on pharmacokinetics

4.3.1. Absorption and bioavailability

Although fomepizole is intended for use by the IV route in ethylene glycol and methanol poisoning it has also been studied by the oral route. Single acute oral doses (7 to 50 mg/kg) were rapidly absorbed (S-2, S-3, S-4, S-6) reaching maximum plasma concentrations in volunteers between 1 to 2 h after dosing. T-max occurred at various times later in studies of multiple oral doses (S-4), depending on the magnitude of the doses. Study S-2 demonstrates that when the same acute dose (7 mg/kg) was given by either IV or oral routes, comparable AUC's were obtained reflecting similar plasma values after 30 minutes. This allows for the oral safety data from the rest of the studies in this section to be supportive of the IV use of fomepizole.

4.3.2. Distribution

Fomepizole distributed rapidly and widely to the total body water with a volume of distribution between 0.60 to 1.0 L/kg depending on the study and subjects evaluated (healthy or patients with ethylene glycol/ methanol poisoning) (Table 2).

Table 2: Plasma 4MP levels oral dosing 7 mg/kg (85.3 µmol/kg)

Time (h)	IV-1R	IV-2	IV-3 (umol/L)	IV-4R	IV-5	IV-6R	x ± SEM*
0.1	107.7	21.2	17.4	178.0	48.9	143.1	81.7 ± 33.1
0.25	257.3	42.0	53.7	209.6	171.7	322.7	159.9 ± 52.1
0.5	237.8	80.3	110.1	187.6	125.2	244.6	149.6 ± 29.5
1	162.1	94.8	89.1	176.1	110.6	187.2	131.6 ± 20.8
2	145.1	102.3	114.6	141.2	102.8	179.8	128.1 ± 14.7
3	135.1	97.2	114.9	142.9	106.4	146.8	121.6 ± 9.9
4	128.4	91.9	108.7	142.4	99.6	151.2	118.8 ± 11.8
6	127.5	84.9	100.4	124.9	95.6	129.2	107.0 ± 8.6
8	118.4	79.5	97.5	116.3	91.1	128.7	102.6 ± 8.8
12	95.8	63.1	80.9	93.9	74.4	87.9	80.0 ± 5.4
18	67.5	51.1	56.2	45.2	46.6	35.3	46.9 ± 3.5
24	25.6	30.9	33.3	0.8	23.0	0.4	17.7 ± 7.2
26	2.6	19.5	17.2	0	5.7	0	8.5 ± 4.2
28	0	1.7	2.3	0	1.1	0	1.0 ± 0.4
30	0	0	0	0	0	0	0

*As discussed in the text, the group mean value was calculated from five subjects, excluding IV-1.

4.3.3. Metabolism and excretion

Fomepizole induced its own metabolism after 36 h of repeated dosing (S-4). After auto-induction, a first order kinetic model more closely described the elimination of fomepizole. 4-CP is formed from fomepizole after an initial cytochrome P-450 mediated hydroxylation that is followed by further oxidation. Up to 80% to 85% of a dose of fomepizole was collected in the urine as the primary metabolite (S-2), 4- carboxypyrazole (4-CP). 4-CP is not an inhibitor of ADH. Other minor metabolites of fomepizole are 4- hydroxymethylpyrazole, N-glucuronide conjugates of 4-carboxypyrazole and 4-hydroxymethylpyrazole (Weintraub and Standish, 1988). These metabolites are either inactive or are so weak (4-hydroxymethylpyrazole) that

they could not contribute significantly to the inhibition of ADH seen with doses of fomepizole used clinically.

Fomepizole is eliminated in human subjects following therapeutic doses by saturable nonlinear kinetics. Furthermore, when humans are given multiple doses of fomepizole over a 5-day period, the rate of elimination of fomepizole was increased markedly (2- to 3-fold) within 3 days of such 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, thus indicating most probably an induction of metabolism of fomepizole. Only 1 to 3.8% of the administered dose of fomepizole was excreted unchanged in the urine (S-2, S-3, S-4, S-5, S-6, S-11) regardless of the dose magnitude.

The plasma half-life of Antizol varies with dose, even in patients with normal renal function; intra- and inter-individual variability has not been calculated.

Most pharmacokinetic studies in humans have also suggested that fomepizole is eliminated by saturable, nonlinear kinetics after doses in the therapeutic range. This elimination is most likely due to metabolism since < 5% of the given dose is excreted unchanged in the urine.

4.3.4. 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, thus 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 36-48 h) in order to maintain therapeutic fomepizole concentrations. Data from the multiple dose part of study (Jacobsen, 1990) 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 h, if indicated, for 4 doses (to 48 h) and 15 mg/kg thereafter until blood levels of ethylene glycol are <20 mg/L. Oral dosing studies (S-3, S-4, S-6) that included doses of up to 100 mg/kg support the proposed clinical IV dosage.

4.3.5. Drug interactions

Results of Study S6 (Jacobsen, 1996) 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.

4.3.6. 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.

5. Pharmacodynamics

5.1. 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 in Section 4 above.

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

Antizol (fomepizole) is a competitive inhibitor of alcohol dehydrogenase (ADH) which catalyses the oxidation of ethanol to acetaldehyde. ADH also catalyses the initial steps in the metabolism of ethylene glycol and methanol to their toxic metabolites. Fomepizole (4MP) 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.

Ethylene glycol, the main component of most antifreezes and coolants, is metabolised to glycoaldehyde and oxalate. Glycolate and oxalate are the metabolic by-products primarily responsible for the metabolic acidosis and renal damage seen ethylene glycol toxicoses. The lethal dose of ethylene glycol in humans is approximately 1.4 mL/kg. Methanol, the main component of windshield wiper fluid, is slowly metabolised via alcohol dehydrogenase to yield formic acid. Formic acid is primarily responsible for the metabolic acidosis and visual disturbances (for example, decreased visual activity and potential blindness) associated with methanol poisoning. A lethal dose of methanol in humans is approximately 1- 2 mL/kg.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

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 PD studies were conducted in humans. Results from preliminary studies in patients (S10, S11, S12; Table 3) provide evidence that Antizol blocks ethylene glycol and methanol metabolism mediated by ADH in the clinical setting. Plasma concentrations of toxic metabolites of ethylene glycol and methanol failed to rise in the initial phases of fomepizole treatment. However, interpretation of the relationship of this effect to fomepizole therapy was confounded by haemodialysis and significant blood ethanol concentrations in many of the patients. Nevertheless, in the post-dialysis period(s), when ethanol concentrations were insignificant and the concentrations of ethylene glycol or methanol were > 20 mg/dL, the administration of fomepizole alone blocked any rise in glycolate or formate concentrations, respectively.

Table 3: Studies S10, S11 and S12: case reports of 4MP treatment of ethylene glycol

Authors, publication	Details of case reports	Treatment given	Clinical course/ sequelae	Conclusions/ comments
Baud, et al. "Treatment of ethylene glycol poisoning with	In a suicide attempt, a previously healthy 42-year-old man	Initial treatment consisted of gastric aspiration, oral	Clinical course was uneventful; patient	Repeated IV administration of 4MP was

Authors, publication	Details of case reports	Treatment given	Clinical course/ sequelae	Conclusions/ comments
intravenous 4-methylpyrazole." New England Journal of Medicine, Vol. 319, No. 2, July 1988. Reported as Study S10 in the dossier	ingested Approx. 1.5L of antifreeze solution containing 92.9% EG (23,500 mmol, or 1457 g). Vomiting and polyuria soon developed. On admission to the hospital 4.5 hours later, the patient was drowsy. His plasma bicarbonate level was 13mmol/L with an anion gap of 17.5 mmol/L, and his serum creatinine concentration was 82 µmol/L.	administration of activated charcoal. 4MP dose of 9.5, 7, 3.5, 1.2 and 0.5mg/kg at 9, 21, 33, 45 and 56 hrs till only traces of EG were present in plasma samples.	regained full consciousness, no seizures, EEG normal; metabolic acidosis did not recur; serum creatinine remained normal throughout hospitalisation; patient discharged from ICU after 3 days and from hospital after 7 days.	effective in this case of EG poisoning although normal renal function and rapid clinical improvement are necessary to allow use of specific antidotal treatment alone.
Harry et al, "Efficacy of 4-methylpyrazole in ethylene glycol poisoning: Clinical and toxicokinetic aspects." Human and experimental toxicology: 1994, 13: 61-64. Reported as Study S11 in the dossier	30-year-old man, 74kg, mentally retarded and slightly deaf accidentally ingested 100 g ethylene glycol; pt was conscious at admission. Initial EG plasma level was 3.5g/L with no ethanol.	Given gastric lavage and activated charcoal on admission. First IV dose of 4MP was 1200mg infused over 30mins within 3hrs of intoxication; subsequent doses of 4MP were 600, 400, 200 and 100mg given every 12 hours till plasma concentration of EG was <0.1g/L.	Elevated anion gap and metabolic acidosis disappeared within 4 h; no renal, neurological and cardiac toxicity due to hepatic EG metabolites and haemodialysis was not required. Urinary oxalate excretion and serum calcium remained normal throughout the first 20 h. Osmotic diuresis was observed which led to moderately	The EG half-life was 16 h during 4MP treatment. Compared to normal half-life of 3hrs. The prolonged half-life suggests reduced hepatic metabolism of EG as a direct result of the presence of 4MP. Prompt treatment with IV 4MP in a patient with EG poisoning with normal renal function was effective

Authors, publication	Details of case reports	Treatment given	Clinical course/ sequelae	Conclusions/ comments
			severe dehydration.	and safe.
Jobard, et al. "4-Methylpyrazole and haemodialysis in ethylene glycol poisoning." Clinical Toxicology, 34(4), 373-377 (1996). Reported as Study S12 in the dossier	Both patients intubated, ventilation; 30 yr old man given IV loading dose of 10 mg/kg 4MP, then haemodialysis started; between 4-6hr of dialysis, infusion of 2.5 mg/kg/h of 4MP given to compensate for loss of 4MP in dialysate. The 50yr old man given 4MP loading dose of 20mg/kg, one hr later haemodialysis started and maintenance dose of 4MP 1.5mg/kg/h infused during haemodialysis.	The 30 yr old man recovered from coma in 48 h, anuria and haemodialysis given for 8 days; hospital stay of 14 days and complete recovery observed. The 50yr old man had flat EEG and QRS complexes along with severe acidosis, anuria on admission, despite symptomatic treatment- he had haemodynamic instability and died 48hr after admission due to multiorgan failure and disseminated intravascular coagulation.	Data from these 2 patients suggested that in cases of severe EG poisoning with toxic plasma EG levels and renal failure, a 4MP loading dose of 10-20mg/kg followed by continuous infusion of 1 to 1.5mg/kg/h during the 8-12 hrs of haemodialysis may be effective.	

5.2.2.2. Secondary pharmacodynamic effects

Not evaluated.

5.2.2.3. Time course of pharmacodynamic effects

In the study reported by McMartin, 2012 (in healthy subjects, the time above the presumed minimum effective concentration of 10µmol/L ranged from 24 to 36 h (mean = 32.4 h; SD: 5.8), for both oral and IV routes of administration (Figure 1).

5.2.2.4. Relationship between drug concentration and pharmacodynamic effects

Based on animal studies, the presumed minimum effective concentration of fomepizole in humans is 10 µmol/L. These concentrations were associated with inhibition of metabolism of ethylene glycol in some preliminary studies in patients with ethylene glycol poisoning (refer section Summary of pharmacokinetics above).

In Study S11, the half-life of ethylene glycol was prolonged to 16 h during fomepizole treatment compared to a normal half-life of 3 h. Such a prolonged half-life suggests reduced hepatic metabolism of ethylene glycol as a direct result of the presence of fomepizole.

5.2.3. Genetic-, gender- and age-related differences in pharmacodynamic response

Not evaluated.

5.2.4. Pharmacodynamic interactions

Fomepizole can inhibit the metabolism of ethanol and ethylene glycol, and these substances in turn inhibit the elimination of fomepizole. Study S6 evaluated the inhibitory or interaction effects of fomepizole, ethanol and ethylene glycol all of which are substrate inhibitors of ADH. Results of this study in healthy subjects showed 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. Drug interactions with other ADH inhibitors and induction of the elimination of fomepizole by other enzyme inducers that affect the cytochrome P-450 enzyme system would be expected but were not specifically evaluated.

5.3. Evaluator's overall 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, S12) provided evidence to support the mechanism of action of fomepizole in the proposed indications.

6. 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 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 (8.6–24.6 mg/L) have been targeted to assure adequate plasma concentrations for the effective inhibition of ADH.

In healthy volunteers, oral doses of Antizol (10–20 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.

7. Clinical efficacy

7.1. Treatment of ethylene glycol poisoning

7.1.1. Pivotal efficacy studies (submitted by the Manufacturer)

7.1.1.1. Study S7 (OMC-4MP-3)

Study design, objectives, locations and dates
S-7 was a retrospective, open label study for patients treated in France with 4-methylpyrazole (4MP) for ethylene glycol poisoning. The main objectives of this study were: (1) To determine the- efficacy, safety, tolerance and PK profile of 4MP in ethylene glycol poisoned patients, (2) To determine the safety, tolerance and PK profile of 4MP in patients with suspected ethylene glycol poisoning, but who in fact were later determined to have no ethylene glycol poisoning, (3) To determine the efficacy, safety, tolerance and PK profile of 4MP in patients with methanol poisoning.

The first patient was treated in January 1982 and the last patient in December 1995. Retrospective data collection took place at one study centre in France during a six-month period from April 1996 to September 1996. Data was collected on paper Case Report Form from original patient case records and was entered into a single database on an ongoing basis. The database was frozen on October 14, 1996, after which study data was analysed.

Comment: Due to the retrospective nature of the study, patients were treated on 'compassionate grounds' and were not part of a prospective well-defined research program and were not subject to French GCP regulations. No ethics approval or informed consent was considered necessary since the anonymity of the patients was confirmed and the confidential nature of the documents seen and used in this study was respected at all times.

Inclusion and exclusion criteria

Data from a patient were to be collected if the patient was given 4MP therapeutically as an antidote for suspected ethylene glycol or methanol poisoning from 1981 to 1995. Patients were to be included whether or not they were actually confirmed to be poisoned with EG or methanol. The following data regarding how the diagnosis of EG poisoning was established were collected (if available): serum or blood EG level, urine EG level, osmolar gap, anion gap, arterial pH, serum bicarbonate, presence of oxalate crystals in urine.

The investigators assessed the clinical severity of intoxication based on blood and urine concentrations of EG or methanol, time of presentation after exposure and laboratory values, such as anion gap, pH and serum creatinine; the overall severity of the intoxication was based on the highest value found in any category.

Study treatments

4MP was administered as emergency treatment for acute EG poisoning according to the experience and normal practice of the treating physician. As far as possible, the following data related to 4MP treatment were collected for each patient eligible for the data collection: loading dose and all supplemental doses, amount of 4MP dose (mg/kg), time of dose, 4MP preparation (hydrochloride or sulphate salt), administration route (oral, IV), length of time of infusion, diluent used for administration, reason for discontinuation of 4MP dosing (for example, EG level below detectable limits).

Efficacy variables and outcome

The following data were collected while the patient was being treated with 4MP (if available): Clinical laboratory assessments: 4MP levels, EG levels (plasma or serum), urinary/ plasma oxalate level, ethanol level, arterial blood gases, lactate level, chemistry profile including

electrolytes, complete blood count, urinalysis, ECG, vital sign measurements and adverse events (AEs). If patients required haemodialysis as part of their treatment, the criteria for its initiation and its duration were recorded. After dosing with 4MP had been discontinued, the clinical laboratory assessments mentioned above were again collected.

The efficacy of 4MP treatment was based on the ability of 4MP to prevent mortality and severe morbidity associated with EG poisoning including kidney and cardiac function abnormalities. Secondary efficacy analyses included evaluations of the effect of 4MP on metabolic acidosis caused by EG ingestion.

Analysis populations, statistical methods

Data on 38 patients was collected, of whom 26 subjects presented with confirmed EG poisoning and were treated with 4MP (Cohort A). Five patients were treated with 4MP for methanol poisoning, all of whom had documented methanol levels in the blood (Cohort B). A further seven patients were treated with 4MP for suspected but later unconfirmed EG poisoning (Cohort C). The efficacy analysis was performed on patients treated with 4MP for confirmed EG poisoning (Cohort A). The safety analysis was performed on an Intention-to-Treat basis and included data from all 38 patients. Demographic, diagnostic, efficacy and safety data were presented in the form of tables, described by percentages for qualitative variables, and mean, standard deviation, median, maximum and minimum for quantitative variables.

Baseline data

Majority of the population of patients treated with 4MP for suspected EG poisoning were male (74%); the mean age of the patients was 39 years, ranging from 15 to 71 years. The criteria used to initiate dosing with 4MP were summarised; 34 of 38 patients (89%) were treated for suspected or documented EG poisoning. Documented plasma or serum EG levels were available at entry for only 5 patients and ranged from 3.9 to 200 mg/dL. Patient history alone was used to initiate dosing of 4MP in 12 cases (31.5%). At entry, 13 patients (34%) presented with metabolic acidosis with arterial pH ranging from 7.03 to 7.34. The serum bicarbonate level was below the lower normal limit (22 mmol/L) for all of these patients. An elevated anion gap was noted for 12 patients (31.6%), ranging from I8 to 40 mmol/L. Four of the 5 patients with documented or suspected methanol ingestion had methanol levels ranging from 10 to 269 mg/dL at entry. The history of intoxication was summarised; the type of product ingested was known for 11 of 29 patients. In general, the product most commonly ingested was liquid antifreeze (21 patients; 55%). Ethanol was noted as a co-ingestant for seven patients (18%) while 3 patients had other co-ingestants (flunitrazepam, benzodiazepine and chloroform). Seventeen patients (45%) consumed the intoxicating product(s) unintentionally, 10 patients (26%) consumed that: intoxicating product deliberately for self-harm reasons. The reason for intake was not known for 11 patients (29%).

The mean time between intoxication (date of product ingestion) and treatment with 4MP (date of entry into trial) for the 38 patients treated was less than one day (0.61 ± 0.84 days: data available for 31 patients). Five patients had a time-lag more than one day between intoxication and treatment with 4MP (one patient died and 2 presented sequelae at follow-up). The median serum or blood EG level at baseline for all 37 patients with EG data was 2.7 mg/dL (range from 0 to 830.8 mg/dL). The median serum or blood EG level in Cohort A at baseline was 10.4 mg/dL; majority (15/26: 58%) had blood EG levels < 20 mg/dL, with 11/26 (42%) of patients having EG levels of under 5mg/dL. Four patients had EG levels over 100 mg/dL at baseline. Vital signs at baseline were summarised. In Cohort A, 65% of patients were awake, 27% were comatose and 3% were lethargic. Plasma oxalate data were only available for 6 patients of whom 3 had levels higher than ULN and all 3 patients had confirmed EG poisoning (Cohort A). Ethanol was detected in the blood of 15 patients (45%) and baseline blood ethanol levels ranged from 0.46 to 180 mg/dL. In Cohort A. the mean blood pH at baseline was 7.3, ranging from 7.1 to 7.5; 8 patients (36%) had blood pH below the normal limit. In Cohort A, majority (94%) of patients

with data available presented blood lactate levels above ULN (mean blood lactate was 7.5 mmol/L, ranging from 1.5 to 44 mmol/L), had low serum bicarbonate levels (mean of 20.4 mmol/L), mean BUN was 5.3 mmol/L with 5/26 (19%) of patients having BUN above ULN; creatinine concentrations were high with 9/23 (39%) having levels above ULN. Patients also tended to be hypocalcemic (data available for 21 patients) and majority of patients (61.9%) presented serum calcium below the LLN (2.3 mmol/L) and 4 patients had serum calcium levels under 2.0 mmol/L.

At entry, 7 patients (18%) were noted to have received treatment with ethanol as an antidote before arrival at the hospital and a further 4 patients (l0.5%) received ethanol during 4MP treatment. Two different preparations of 4MP were used to treat patients with suspected or confirmed EG intoxication: 8 of 30 (21%) were treated with 4MP hydrochloride (4MP HCI) while remaining 30 patients (79%) were treated with 4MP sulphate (4MP SO_4) was given orally to 13 of 38 patients (34%), while 20 patients (68%) received 4MP intravenously; one patient was initially given 4MP by mouth with subsequent doses given IV. Treatment with 4MP was initiated based on the estimated EG intake and the clinical status of the patient The mean loading dose of 4MP given for all patients was 11 mg/kg, ranging from 0.2 to 19.5 mg/kg with similar doses used in Cohort A. Overall, 10 patients received just 1 dose of 4MP, while all other received multiple doses (mean number of doses was 3 with maximum of 13 doses given to one patient). The doses of 4MP were administered in 0.9% sodium chloride injection, and 5% dextrose injection, as the investigator deemed appropriate. When administered intravenously, it was infused over 45 minutes. Doses were given at regular intervals (ranging from 1 hour to 12 h) while treatment periods ranged from one dose on one day to 13 injections over 7 days. The mean duration of treatment was 2.1 days; 17 patients (45%) treated with 4MP received treatment for less than 12 h (including the 10 patients treated with just one dose of 4MP), 8 patients (21%) received treatment for 24-48 h and 5 patients were treated for 48-72 h (13%)[3]. The mean total dose of 4MP administered per patient was 1565.8 mg for all patients (ranging from 200 to 6000mg) and it was l674 mg in Cohort A.

Efficacy results (in Cohort A or 26 patients with confirmed EG poisoning)

The mean concentration of EG at baseline for the 26 patients in Cohort A was 82.0 mg/dL which decreased over the treatment period and was negligible at the end of follow-up (median was 0.3mg/dL ranging from 0 to 16.4mg/dL) with 50% of patients being 0 mg/dL.

The mean blood pH also returned to within normal limits by the end of 4MP treatment. The serum bicarbonate levels which were low at inclusion (mean=20.4 mmol/L for the 25 patients with data available, 12 patients had levels under LLN) had increased to 26.4 mmol/L at endpoint (last recorded measurement) with majority of patients (60%: missing data for 1 patient) having serum bicarbonate levels within the normal range.

The final outcome status for the 26 patients with confirmed EG intoxication showed that the majority of patients were alive with no sequelae (73%). One patient died as a result of the intoxication. Review of the death narrative revealed that this [information redacted] year old patient with multiple product intoxication was comatose with multiple complications and only started 4MP treatment, 2 days after the intoxication. Four patients (15%) were reported to present sequelae upon discharge. The investigator considered that 4MP was definitely effective in preventing or diminishing toxicity in 10 cases (38.5%) and was possibly effective in preventing or diminishing toxicity in 9 cases (34.6%). Seven patients (27%) were noted to have no apparent beneficial effect from treatment with 4MP: 2 patients had not consumed sufficient EG to be judged intoxicated, 3 patients were only mildly intoxicated at admission. Both patients without benefit (1 death and 1 long-term sequelae) were treated with 4MP more than 24 h after the intoxication. No differences in clinical outcome was observed between the 4MP HCL (n=8)

[3] One patient had undetermined duration of treatment as time of administration were not available.

and 4MP SO_4 (n=30) preparations or between patients treated with oral or intravenous 4MP preparation.

Six patients underwent haemodialysis (16%). Four of these six patients were dialysed due to renal insufficiency caused by EG ingestion, one patient was dialysed due to an extremely high level of EG in the plasma (830 mg/dL) and the remaining patient was dialysed for methanol ingestion. The number of haemodialysis required ranged from 1 to 8 (mean number administered was 2.8); the mean duration of the first haemodialysis was 6.1 h.

Comment: In this pivotal retrospective study involving 26 patients with confirmed EG intoxication, the median baseline EG concentration was 10.4 mg/dL, ranging from 1.0 to 830.8 mg/dL. Patients were, on the whole, treated rapidly after intoxication although 5 patients received therapeutic intervention more than 24 h after ingestion of intoxicant. Fifty-eight percent (58%) of the patients in Cohort A were mildly intoxicated or presented with no clinical signs of intoxication and severe intoxication was reported for seven cases (27%). The dosages and routes of 4MP administration in this study, varied depending on the amount of toxin ingested, length of time between exposure and treatment and mental status of the patient.

Overall prognostic outcome for the patients with confirmed EG intoxication treated with 4MP was very good as 73% of patients survived and had no sequelae of intoxication at endpoint. A further 15% of patients survived but presented with some sequelae at endpoint, although these conditions tended to be mild and improved or resolved during patient follow-up. One death was reported in the study occurring after late therapeutic intervention for a severe multi-substance intoxication (EG, flunitrazepam, sodium hydroxide). Seven patients were noted to have no apparent beneficial effect from treatment with 4MP: 2 patients had not consumed sufficient EG to be judged intoxicated, 3 patients were only mildly intoxicated at admission. Both patients without benefit (1 death and 1 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 this study was limited by the following confounded factors:

i. 7 patients (18%) were noted to have received treatment with ethanol as an antidote before arrival at the hospital and a further 4 patients (10.5%) received ethanol during 4MP treatment,

ii. Haemodialysis was used along with 4MP treatment in 7 patients,

iii. Retrospective nature of the study (important information may have been missed in the data collection).

7.1.1.2. Study S-8 (OMC-4MP-1)

Study design, objectives, locations and dates

S-8 was an open label, multi-dose, multi-centre, Phase III pivotal trial of the antidotal efficacy and pharmacokinetic profile of fomepizole for the treatment of patients with confirmed EG poisoning.

The objectives of this study were to determine the efficacy and tolerance of fomepizole in the treatment of EG poisoned patients; to determine the relationship between the time-response curve of fomepizole and its pharmacokinetic profile; to correlate the pharmacokinetic profile of

fomepizole with its inhibitory effects on EG metabolism; and to determine the safety of fomepizole administration in EG poisoned patients.

The first patient was treated on 5 November 1995 and the last patient was treated on 15 July 1996. Twenty-one trial centres in USA were initiated as potential enrolment sites. For purposes of this interim report (dated 29 October, 1996), only four of those sites actually enrolled patients into the trial. This trial was conducted according to Good Clinical Practices (GCP) guidelines.

Inclusion and exclusion criteria

The main inclusion criteria were: Male and female patients, over 12 years of age, who presented with a documented serum EG level of >20 mg/dL; OR a history (or strong clinical 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; OR recent (<1 hour) documented history of a potentially toxic amount of EG and osmolar gap >10 mOsm/L, were eligible for participation in the trial. Signed written consent was also required prior to initiation of the trial. The main exclusion criteria were: administration of ethanol to the patient at the investigator's hospital; known adverse reaction to pyrazoles and pregnant females.

Study treatments

The study treatment was fomepizole (4-methylpyrazole, 4MP) at a concentration of 1000 mg/mL in single unit-dose 5 mL amber glass vials containing 1.5 mL sterile fomepizole. Loading dose: fomepizole 15 mg/kg diluted in 100 mL normal saline (NS) delivered intravenously (IV) over 30 minutes. Supplemental doses: fomepizole 10 mg/kg (in 100 mL NS, IV over 30 min) every 12 h for 4 doses, then 15 mg/kg (in 100 mL NS, IV over 30 min) thereafter. Duration of treatment was dependent on severity of poisoning and resulting clinical condition (estimated to be 2-4 days).

In addition to the fomepizole treatment described above, a standardised treatment protocol was to be followed until 6 h after the final fomepizole dose. This protocol included establishing a primary IV line to deliver 5% dextrose/normal saline at a rate determined by investigator; administration of potassium supplementation to keep serum potassium in the normal range; and administration of intravenous bicarbonate therapy to keep arterial pH >7.3. The amount of bicarbonate administered was to be at the discretion of the investigator considering the patient's age, cardiovascular and renal status, and base deficit. Magnesium and further vitamin supplementation were administered at the discretion of the investigator. All patients were kept on a cardiac monitor for the duration of the trial, and arterial oxygenation was to be maintained at 290% (unless this degree of oxygen saturation was unobtainable with artificial ventilation). Blood pressure support and general supportive care were provided as deemed appropriate by the investigator.

In cases of severe EG poisoning, haemodialysis was required. Patients who presented with an EG level of >50 mg/dL, or who met one of several criteria representing severe metabolic acidosis or renal failure, were treated with haemodialysis in addition to fomepizole therapy. The dialysability of fomepizole is significant, and for this reason, the dosing of fomepizole was adjusted to account for haemodialysis. Patients were dosed with every four h during the dialysis procedure. Dosing at the termination of haemodialysis was dependent on the length of time that haemodialysis lasted. Patients who were dialysed for less than one hour, continued per protocol with the next dose 12 h after the last dose. Patients who were dialysed for one to three h were given half of the next scheduled dose, and then continued the every 12 hour dosing protocol. For those patients who were dialysed for greater than three h, the next dose of fomepizole was administered at the end of haemodialysis and treatment continued following the every 12 hour dosing protocol.

Efficacy variables and outcomes

Measurements related to the reversal of metabolic acidosis included serum pH and serum bicarbonate. Measurements related to the inhibition of EG metabolism were plasma glycolate and urinary oxalate levels. Assessments related to the morbidity associated with EG poisoning included collection of adverse experiences associated with the poisoning. Of specific interest were measurements associated with renal function including BUN, serum creatinine, and urinalysis. Assessments related to cardiac function included monitoring of vital signs and electrocardiograms. Cranial nerve assessments were also conducted.

The efficacy outcomes evaluated were: Mortality, Morbidity (cardiac and renal), Metabolic Acidosis and Clinical Outcome. The primary efficacy analysis included an assessment of the ability of fomepizole to prevent the mortality and severe morbidity associated with EG poisoning. The morbidity analyses also included assessments of the ability of fomepizole to prevent potential abnormalities to renal function, cardiac function and the cranial nerves. Secondary analyses included evaluations of 1) the metabolic acidosis, 2) EG and glycolate PKs and 3) fomepizole PKs.

Safety parameters evaluated were: Adverse experiences, Clinical laboratory tests, Vital signs, Electrocardiograms, Ophthalmic examinations, Cranial nerve examinations, Concomitant medication use. PK parameters of EG, its metabolites and that of fomepizole were also evaluated.

Analysis populations, sample size, statistical methods

This trial was designed to enrol ten (10) patients poisoned with EG. For the purpose of this interim report, a total of seven (7) patients were enrolled. More patients are expected to be enrolled. All seven patients enrolled in the trial were included in all of the efficacy analyses.

The sample size (n=10) was based on the number of patients that the sponsor anticipated could be enrolled at the trial sites within 12 to 18 months. No statistical considerations were made with respect to sample size. For efficacy analyses, tabulations and summary statistics were calculated, where appropriate, related to evaluations of metabolic acidosis and fomepizole PKs.

Baseline data

The study included 7 patients (6 male and 1 female), the average age was 43.4 ± 12.5 years; median age was 44 years (range: 28 to 60 years). Six of the patients treated were Caucasian; one patient was Afro-American. Two of the seven patients were enrolled based on documented EG poisoning with serum EG level of >20 mg/dL. The other five patients were enrolled based on a suspicion of EG poisoning and clinical and laboratory evidence suggestive of EG poisoning. All patients demonstrated evidence of metabolic acidosis (six severe) and five patients demonstrated some level of renal function impairment at baseline. Six of 7 patients were considered severely intoxicated upon presentation. Six of the seven patients ingested EG intentionally for self-harm (suicide) and one patient ingested EG for an inebriating effect. Antifreeze was confirmed as the ingestant in 4 of 7 patients, while the specific ingestant was not known for the remaining 3 patients. Four of the 7 patients presented at outlying hospitals and 3 of 7 presented at the investigator's site. Each of the 4 patients that presented to an outlying hospital was treated with ethanol prior to transfer and subsequent treatment with fomepizole. The time between EG ingestion and treatment with fomepizole at the investigator's hospital was not known for 2 patients and ranged from 10 to 40 h for the other patients.

All seven of the patients had baseline EG levels >20 mg/dL with mean of 107.5 ± 58.9 mg/dL. At baseline, 3 of the patients presented comatose, 2 were lethargic, 1 was inebriated and 1 was awake. At baseline, all 7 patients had arterial pH below the LLN and 6 of 7 had serum bicarbonate below the LLN. These results are as expected in patients with metabolic acidosis. Four of 7 patients had lactate levels above the ULN. BUN tended to be within the normal limits although 1 of 7 patients had a BUN below the lower limit. Creatinine concentrations were above

the ULN in 5 of 7 patients at baseline indicating abnormalities in renal function. Three of 6 had their Total calcium below the LLN. Additionally, 4 of 7 patients had oxalate crystals detected in their urine. Six of 7 patients presented with detectable ethanol levels and 3 of 7 patients had ethanol levels in or above the therapeutic range (100 to 130 mg/dL) upon trial entry. No abnormalities were observed for the vital signs at baseline. Six of the seven patients were severely intoxicated at presentation; the seventh patient was only mildly intoxicated at presentation, but given the EG level at baseline for this patient (171 mg/dL), it is expected that this patient may have succumbed to the types of sequelae (acute renal failure or even death) without treatment. The patients were given between 2 and 5 doses of fomepizole each. The total fomepizole dose for these seven patients ranged from 1800 to 6750 mg (25. 8 to 45 mg/kg, respectively); the highest single dose administered to a patient during this trial was 15.7 mg/kg.

Efficacy results

Clinical outcome

At trial completion, one patient was dead, four patients were alive with sequelae (acute renal failure) and two patients were alive without sequelae. The patient that died and the four that had renal injury at the end of the trial were severely intoxicated at baseline. Each of the patients with acute renal failure had renal insufficiency upon presentation. Of the four patients with acute renal failure at the end of the trial, all had complete to near complete resolution of their renal failure within 2 to 7 weeks after trial discharge. Each required treatment with haemodialysis after trial discharge but no longer required haemodialysis at last follow-up.

Six patients presented with severe metabolic acidosis and all six had resolution of their acidosis as evidenced by a normal serum pH within 4 h of treatment with fomepizole. Only one patient redeveloped of metabolic acidosis while receiving treatment; this patient developed a severe lactic acidosis secondary to cardiogenic shock and hypotension. One patient who entered the trial with mild metabolic acidosis had a normal pH within 2 h of trial drug administration. The last measured values of pH showed that 5 of 6 patients had pH within the normal range. While the serum bicarbonate levels had not yet normalised for all patients, significant improvement was observed over the course of the trial.

Levels of glycolate prior to the administration of fomepizole ranged from not detectable (in one patient) to 23.7 mmol/L. All patients had a rapid reduction in plasma glycolate levels after the initiation of fomepizole therapy although one patient showed a rise in glycolate levels during the trial. This patient had a rapid and progressive fall in glycolate levels from 23.7 mmol/L (pre-fomepizole) to 9.5 mmol/L at 4.75 h after the initial of therapy. This was followed by a rise of plasma glycolate concentration to 18.4 mmol/L 6 h after his fomepizole loading dose, at a time when he was scheduled to receive his next dose. All subsequent plasma glycolate determinations in this patient were lower and progressively fell. Three of the four patients with microscopic oxaluria at presentation had their urines turn negative for oxalate during the trial while one patient still had microscopic oxaluria at the end of study.

Morbidity Associated with Ethylene Glycol Poisoning: Two patients had normal serum creatinine levels at enrolment into the trial and neither of them developed an abnormal serum creatinine level over the course of the trial. The remaining five patients had signs of renal insufficiency on presentation with baseline serum creatinine ranging from 1.5 to 3 mg/mL and these progressively rose during the trial to a maximum of 2.5 to 14.7. All of these patients had severe metabolic acidosis (pH 7.05 to 7.35, bicarbonate 6 to 10.8 mEq/L) at presentation. Plasma glycolate levels were markedly elevated in 4 patients (median 16.8 mmol/L, range 12.9 to 23.7) and urine oxalate concentration was markedly elevated (5.19, 2.29, and 2.69 mmol/L) in three patients and borderline (1.27 and 1.54 mmol/L) in two patients. One patient who was in profound renal failure and cardiogenic shock at the time of presentation died shortly after entry into the trial. All four surviving patients with renal injury had completed to near complete resolution of their renal failure within 2 to 7 weeks after trial discharge. All no longer required haemodialysis at last follow-up. No clinically significant systemic abnormalities were noted on

cardiac function, as assessed by vital signs, serial clinical examinations, and daily electrocardiograms. There were no cranial nerve abnormalities that developed over the course of the trial.

Graphs of the plasma fomepizole, plasma EG, plasma glycolate and plasma ethanol levels over time for each patient were presented and these indicate when fomepizole doses were administered to each patient, and when haemodialysis was used. These figures demonstrate that EG, plasma glycolate, ethanol, and fomepizole levels gradually declined prior to and following haemodialysis and rapidly declined while the patients were on haemodialysis.

Comment: This was a prospective study in 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.

However, interpretation of results was confounded by the following limitations:

i. The study enrolled only 7 patients,

ii. Concomitant ingestion of ethanol which is a generally accepted treatment for EG poisoning. Ethanol often consumed prior to and along with EG ingestion, but in this study ethanol was also administered as an emergency treatment at outlying hospitals prior to patient's transfer to the trial site for 4 of the 7 patients.

iii. Concomitant treatment with haemodialysis was another confounding factor. Although the study design included an assumption that up to 50% of patients would require haemodialysis, in fact all the patients in this study required haemodialysis due to initial high levels of EG, unstable serum chemistry due to metabolic acidosis and decreased renal function.

Due to concomitant use of ethanol and haemodialysis in conjunction with fomepizole, it is very difficult to definitively assess the actual benefits of fomepizole in treatment of EG poisoning. However, EG and plasma glycolate levels declined prior to and following haemodialysis suggesting the role of fomepizole in blocking the conversion of EG to its toxic metabolites.

7.1.1.3. Other efficacy studies

Efficacy from published studies

Methylpyrazole for Toxic Alcohols (META) Investigation (Brent et al. 1999)

Between 1995 and 1997, the authors studied 23 consecutive patients with confirmed or possible EG poisoning (7 of which were included in S8). The study was well conducted at centres in USA and used proposed doses of fomepizole (loading dose of 15 mg/kg followed by 10 mg/kg every 12 h till 48 h and then again 15mg/kg after that to compensate for increased fomepizole metabolism). The inclusion/exclusion criteria were well-defined. Four of the 23 enrolled patients were found to not have EG poisoning (EG levels <20 mg/dL and did not meet any other inclusion criteria either). The main endpoints of the study were the development of renal injury (high serum creatinine concentrations), additional production of EG metabolites (an increase in either the plasma glycolate concentration or the urinary excretion of oxalate after the administration of fomepizole), and the development of cranial neuropathies.

At presentation, 7 of the 19 patients were awake, 7 were comatose, 3 were inebriated and 2 were lethargic. Nine patients had high serum creatinine concentrations, and 15 had metabolic acidosis and low serum bicarbonate concentrations. The initial arterial pH value was inversely correlated with the plasma glycolate concentration (r=¡0.84, P<0.05) (Figure 10).

Figure 10: Plasma glycolate versus arterial pH at the time of enrolment in 18 patients

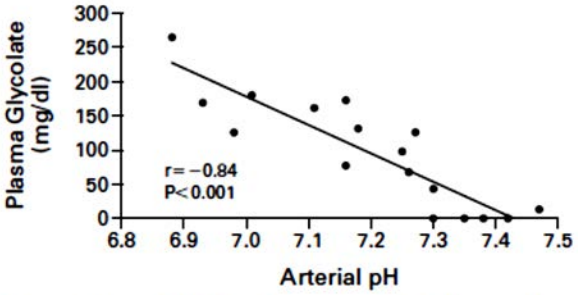


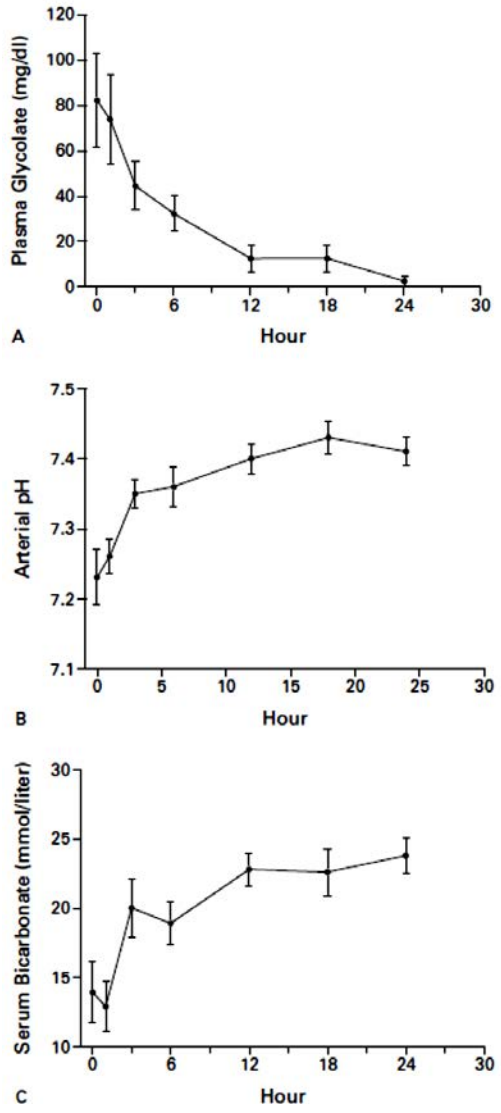
Figure 2. Plasma Glycolate Concentrations in Relation to Arterial pH at the Time of Enrollment in 18 Patients with Ethylene Glycol Poisoning.

Plasma glycolate and pH were measured within one hour of each other. The line was determined by least-squares regression analysis. To convert the values for plasma glycolate to millimoles per liter, multiply by 0.132. Seventeen data points are shown because 2 of these 18 patients had overlapping values.

Seventeen patients underwent haemodialysis. Ethanol was detected in 12 patients and 4 of them had therapeutic concentrations (>100 mg/dL). The 19 patients were given an average of 3.5 doses of fomepizole (range, 1 to 7) over an average of 17.8 h (range, 5 to 58).

Plasma glycolate concentrations decreased progressively in all the patients. Concomitantly, arterial pH values and serum bicarbonate concentrations increased progressively (Figure 11).

Figure 11: Mean plasma glycolate concentrations, arterial pH and serum bicarbonate concentration over time on the first day of 4MP therapy in 19 patients



Clinical improvement was correlated with the normalisation of acid-base status. None of the patients had a spontaneous deterioration in mental status or hypoglycemia after the initiation of therapy. The plasma fomepizole concentration during therapy usually ranged from 15 to 30 µg/mL (183 to 366 µmol/L) but occasionally, the values were lower. The mean half-time of elimination of EG from plasma was 19.7±1.3 h. None of the patients in whom plasma glycolate concentrations were undetectable at enrolment had measurable concentrations during therapy. Urinary oxalate excretion decreased in all the patients during treatment with fomepizole.

Eighteen of the 19 patients survived their acute illness. The patient who died had an arterial pH of 7.05 and an acute myocardial infarction before enrolment. He died from cardiogenic shock 22 h later. None of the patients had cranial neuropathy. All nine patients with high serum creatinine concentrations at enrolment had a further increase (peak value, 2.4 to 14.7 mg/dL [212 to 1299 µmol/L) during treatment. These nine patients presented later and had more severe acidosis at the time of presentation than those who had normal serum creatinine concentrations. However, the serum creatinine concentration became normal in six of the nine patients, and ranged from 1.5 to 3.8 mg/dL (133 to 336 µmol /L) in the other three patients at the time of the last measurement. All the patients in whom renal injury developed had plasma glycolate concentrations of at least 98 mg/dL (12.9 mmol/L) at enrolment. No signs of renal

injury developed in any patient whose initial plasma glycolate concentration did not exceed 76.8 mg/dL (10.1 mmol/L) or whose initial serum creatinine concentration was normal.

Comment: Overall, the results of this study suggest that fomepizole is a safe and effective antidote in the treatment of EG poisoning. The plasma concentration of fomepizole that is necessary to inhibit ADH (approximately 0.8 µg/mL) was exceeded in this 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, at a mean of three h after the initiation of therapy. Renal function decreased during therapy in nine patients, all of whom had abnormal renal function at enrolment. In contrast, the patients with normal serum creatinine concentrations at enrolment had no change in renal function.

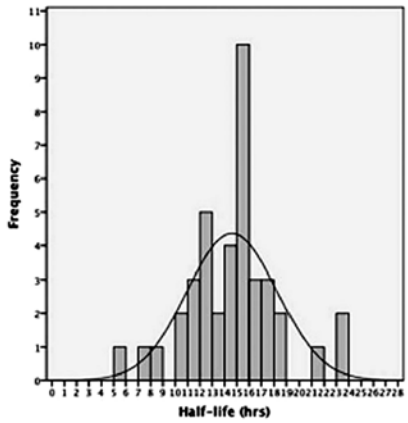
Data reported in the Methylpyrazole for Toxic Alcohols (META) investigation, led to approval of fomepizole for the treatment of ethylene glycol poisoning in the United States.

The main limitation of this study was the lack of a control group. However, due to the morbidity and mortality associated with EG poisoning, inclusion of an untreated control group was not possible. Furthermore, interpretation was confounded by presence of therapeutic levels of ethanol in 4 patients and use of haemodialysis in 17 patients.

Retrospective study of Fomepizole (Levine et al. 2012)

Levine et al. (2012) performed a retrospective, multicentre cohort study of 40 patients older than 15 years intoxicated with EG using data from 3 specialist centres in USA over 8 years. The primary purpose of this study was to determine the elimination half-life of ethylene glycol when fomepizole was used as monotherapy without haemodialysis. A secondary purpose was to report mortality and development of renal failure in patients treated with this approach. It is important to note that the decision to treat with fomepizole as monotherapy and not use haemodialysis had not been based on any set criteria. The choice had been made at the discretion of the medical toxicologist treating each patient. In general, toxicologists treated patients with fomepizole alone when metabolic acidosis (pH<7.3; anion gap>25 mEq/L) or renal dysfunction was absent on admission. The 40 patients included in this case series had a median age of 42 years, median peak EG concentrations of 127mg/dL and median number of doses of fomepizole per patient was 4 (3-5 doses); only 3-4 patients showed mild acidosis (pH<7.3, anion gap>25mEq/L). The mean elimination half-life for EG was 14.2 h (SD 3.7 h), with a 95% confidence interval of 13.1 to 15.3 h (Figure 12). Only 1 patient developed non-oliguric renal insufficiency (peak serum creatinine of 2.1 mg/mL), who recovered and did not require haemodialysis.

Figure 12: Serum EG elimination half-life (mean 14.2 h±3.7 SD) n=40



Comment: The estimations of EG elimination half-life during fomepizole monotherapy have previously been based on small numbers of patients. This case series of 40 patients displayed a mean elimination half-life of 14.2 h, which is shorter than but similar to the half-life of 16.9 h reported in the META study[4] for patients without renal failure. Another difference from the META study was that patients who received concomitant ethanol were not excluded in this case series; 24 patients in this case series (60%) had measurable serum ethanol concentration at presentation, the median of which was 118 mg/dL. The remaining patients had no ethanol in the blood at presentation and did not receive ethanol as an antidote.

This was a retrospective cohort study of patients treated with fomepizole monotherapy rather than a prospective randomised controlled study. There were no strict criteria mandating what pH level is considered too acidotic for monotherapy and thus mandates haemodialysis. Nonetheless, no patient in this series had profound metabolic acidosis or renal dysfunction and among patients without any metabolic acidosis or acute kidney injury the use of fomepizole as monotherapy without concurrent haemodialysis proved to be quite safe. 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), 6confounding interpretations regarding actual efficacy of fomepizole as an antidote for EG poisoning.

Efficacy in paediatric patients from published studies

In the retrospective study by Caravati, et al, 2004, six patients with an age range of 22 months to 14 years were admitted for treatment of EG poisoning over a four-year period. Initial serum EG concentrations ranged from 62 to 304 mg/dL (mean 174.0 mg/dL). Only patients with EG concentrations >50 mg/dL were used as haemodialysis is often considered at this level and this study hoped to evaluate other treatment options in patients with severe EG poisoning. The lowest measured individual serum bicarbonates ranged from 4 to 17mEq/L. Serum creatinine of all patients was normal at presentation) and only 3 patients had 1+ oxalate crystaluria on initial urinalysis. The severity of illness ranged from severe acidosis and lethargy to mild acidosis and alertness. All patients were initially admitted to intensive care. One patient received ethanol only, two patients received fomepizole only, and three patients received a loading dose of ethanol and then were converted to fomepizole therapy. None of the patients received haemodialysis. Treatment was continued until the serum EG was <10 mg/dL. Metabolic acidosis resolved with intravenous fluid and supplemental bicarbonate within 24 h. The mean length of stay in intensive care was 21h and in the ward was 33.7 h. One episode of hypoglycemia occurred in a 22 month-old. All patients recovered without evidence of renal insufficiency or other major complications.

Comment: Overall, this study provided preliminary evidence that haemodialysis with its inherent risks (bleeding, infection, thrombosis, hypovolemic, hypotension, and electrolyte abnormalities) 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 successfully treated with fomepizole or ethanol (primarily fomepizole) without haemodialysis and most were discharged from the hospital within two to three days. However, this study did have some limitations:

[4] In the META study, among the 19 patients included in the final analysis, 17 patients also underwent haemodialysis. With the data from patients who received fomepizole before receiving haemodialysis, the ethylene glycol concentrations exhibited first-order elimination kinetics, with a mean elimination half-life of 19.7 hours. Of patients with normal renal function, the elimination half-life was 16.8 hours.

i. Retrospective data collection from medical records has limitations as all clinical information may not be accurately recorded and several complications may have been missed.

ii. Small number of patients and lack of long-term follow-up after discharge.

Brent, et al (2010) did computerised search of the U.S. National Academy of medicine and Embassy databases to identify published cases of paediatric patients treated with fomepizole. This search strategy identified 14 published cases: 10 due to EG poisoning, 1 due to diethylene glycol poisoning, 1 due to butoxyethanol ingestion, and 2 due to methanol poisoning. The median age of these cases was 5.5 years old. For the 10 ethylene glycol poisoned patients, the median recorded values of their arterial pH was 7.27 (range 7.03–7.38), serum bicarbonate concentration was 13 mEq/L (range 2–25), and EG concentration was 2,140 mg/L (range 130–3,840). Eight of these patients were not haemodialysed (these 8 patients had EG levels as high as 3,500 mg/L and serum bicarbonate concentrations as low as 4 mEq/L. All 10 patients with EG poisoning had resolution of their metabolic acidosis and recovered without sequelae. The half-times of EG elimination ranged from 9 to 15 h during fomepizole therapy, which is faster than the 19.7 h reported in adults. The two patients who ingested diethylene glycol or butoxyethanol all recovered without sequelae. One of the two children who ingested methanol was haemodialysed although both cases had similar severity. Most cases used the current U.S. approved regimen. Two cases were originally treated with ethanol but switched to fomepizole because of adverse effects. In both cases, the adverse reactions to ethanol resolved once fomepizole treatment was initiated.

Comment: Overall, the limited data available suggest that fomepizole, using the same dosage regimen as that used for adults, is efficacious and well tolerated in paediatric patients. In many cases of paediatric EG poisoning treated with fomepizole, haemodialysis may not be necessary despite high concentrations and the presence of metabolic acidosis.

Although the data reviewed here suggest that fomepizole 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.

Baum, et al (2000) reported the first case of treatment with fomepizole in an infant with EG poisoning: An 8 month old infant who drank up to 120 mL of EG and developed minor acidosis, significantly elevated osmolal gap and oxalate crystaluria. He was treated with fomepizole and haemodialysis. Even after the completion of haemodialysis, fomepizole appeared to effectively block the production of EG toxic metabolites and to allow the resolution of acidosis; Haemodialysis was used in this infant in light of evidence that significant EG had been ingested and that some degree of EG conversion to toxic organic acids had occurred. The use of fomepizole alone in this patient may have been effective, despite the prolongation of EG half-life to approximately 9 h. The reduction in EG concentration accomplished by haemodialysis would have required approximately 16 additional h if treated with fomepizole alone. The authors suggest that future studies must weigh the benefits of a lengthier but less invasive treatment with fomepizole alone against the risks associated with acute haemodialysis.

7.1.1.4. Case reports

There are 6 case reports in paediatric patients which have been summarised in Table 4 and provide preliminary evidence of efficacy of fomepizole in treatment of EG poisoning in paediatric patients.

Table 4: Case reports of EG poisoning in paediatric patients.

	Authors, publication	Details of case reports	Treatment given	Clinical course/ sequelae	Conclusions/ comments
1	Baum, et al. 2000. 'Fomepizole treatment of EG poisoning in an infant.' Paediatrics Vol. 106 No. 6 December 1, 2000 pp. 1489 - 1491	This is the first report of fomepizole treatment of EG poisoning in an infant. 8-month-old male infant who drank up to 120 mL of EG & developed acidosis and oxalate crystalluria. Renal function was normal, with serum BUN of 10 mg/mL and creatinine of 0.2mg/mL. Arterial blood gas pH of 7.32 , osmolal gap of approx. 60 mOsm/kg.	Treated with fomepizole: loading dose of 15mg/kg IV and haemodialysis. Even after the completion of haemodialysis, fomepizole appeared to effectively block the production of EG toxic metabolites and to allow the resolution of acidosis.	The patient recovered within 48 hrs. IV fomepizole (total dose, 45 mg/kg) appeared to allow the correction of metabolic acidosis even after completion of haemodialysis, and prolonged EG half-life to approx. 9 hours	Fomepizole appeared to prevent the metabolism of EG to toxic acids even after haemodialysis was discontinued. The authors suggest EG-poisoned patients who present with normal renal function and acid-base status might do well when treated with fomepizole but without haemodialysis.
2	Benitez, et al. 2000: 'Nystagmus Secondary to Fomepizole Administration in a Pediatric Patient.' Clinical Toxicology, 38(7), 795–798 (2000)	6-year old presented to the emergency department mottled, comatose with Kussmaul respirations. Initial arterial blood gases: pH 7.11, PO_2 200, HCO_3 2, base excess 229 and within 20 minutes her pH dropped to 7.03.	Fluid-resuscitated, $NaHCO_3$, thiamine, and pyridoxine. Within 4 hours of admission, a loading dose of fomepizole (15 mg/kg) was infused due to the severity of the patient's clinical status, haemodialysis was initiated but discontinued temporarily due to catheter thrombus formation. The initial (3-hour post-admission) EG was 13	The child recovered uneventfully	She developed coarse vertical nystagmus within 2 hours of fomepizole infusion frequently cited adverse events, such as headache, nausea, and dizziness was not reported. Overall, fomepizole appeared safe in this patient although she developed transient nystagmus.

	Authors, publication	Details of case reports	Treatment given	Clinical course/ sequelae	Conclusions/ comments
			mg/dL. EG was 5 mg/dL 3 hours after haemodialysis this then was discontinued. No further fomepizole was administered		
3	Boyer, 2001. 'Severe EG ingestion treated without haemodialysis. ' *Pediatrics* 2001;107;172	13-year-old female ingested approx. 4 fluid ounces of antifreeze BUN=11.0 mg/dL, creatinine 0.8 mg/dL, and glucose 105 mg/dL. Anion gap was 14 mg/dL. An arterial blood gas showed pH 7.38, osmolar gap of 53 mosM/L. The measured serum EG was 103 mg/dL.	Ethanol was given at primary hospital; Six hrs after EG ingestion she received fomepizole 15 mg/kg IV loading dose. Arterial pH remained above 7.35. fomepizole, 10 mg/kg, was given every 12 hrs for total of 5 doses. Serum EG was after 23 mg/mL after 24hrs after ingestion, 13mg/ml by 36 hrs.	Discharged after 3 days with no sequelae. At discharge on the third hospital day, she had BUN= 10 mg/ml & serum creatinine = 0.6 mg/mL	Authors suggest that use of fomepizole averted IV ethanol infusion & haemodialysis, limited the duration of intensive care monitoring & decreased overall cost of treatment. However, important to note that patient had normal renal function at admission.
4	Detaille, 2004. 'Fomepizole alone for severe infant EG poisoning.' Pediatr Crit Care Med 2004; 5:490 – 491	5-month old boy ingested 200ml of antifreeze solution. Presented with metabolic acidosis-bicarbonate=11.1mmol/L, anion gap=31mOsm/L, hypercalcaemia=4mmol/L, plasma EG=-56.4mmol/L; normal renal function.	Antidotal therapy with a total of seven doses of fomepizole given IV with an interval of 12 hrs (15 mg/kg as loading dose, then 10 mg/kg). Total of 7 doses reqd. Haemodialysis was not performed	The infant made a complete recovery with no change in renal function. Discharged after 96hrs. Plasma fomepizole concentrations ranged from 4.5 to 21 mg/mL during the treatment, with a mean peak concentration of 18.9+ 2.2	Although not yet approved for this indication in the child, fomepizole seemed safe and effective and may simplify treatment in selected cases of EG poisoning reducing need for haemodialysis.

	Authors, publication	Details of case reports	Treatment given	Clinical course/ sequelae	Conclusions/ comments
				mg/ml.	
5	Hann G, 2012. 'Antifreeze on a freezing morning: ethylene glycol poisoning in a 2-year-old' *BMJ Case Reports* 2012; doi:10.1136/bcr.07.2011.4509	2-year old accidental ingestion of antifreeze presented with severe metabolic acidosis; pH=7.24, anion gap=16.7, lactate=20mmol/L, bicarbonate=9.1mmol/L; EG=84.6mg/ml	fomepizole infusion given 4hrs after arrival to hospital, After the second dose of fomepizole, the EG level fell to 31 mg/l. Child continued to improve clinically. Two more doses of fomepizole were given over the next 24 h, making a total of four doses, until the EG level was undetectable	The child was discharged after 7 days, having fully recovered with no sequelae to EG poisoning and no adverse effects of fomepizole	Fomepizole, when available, is a safe alternative to ethanol in the treatment of children with EG poisoning. *Comments: Dose of fomepizole administered to the child was not mentioned in the case report.*
6	Harry, 1998. 'Ethylene glycol poisoning in a child treated with 4MP. '*Pediatrics* 1998;102;e31	A 4yr old girl accidentally ingested unknown amount of antifreeze & admitted 4hrs later. EG poisoning was confirmed by a metabolic acidosis, with an anion gap of 29 mmol/L and an osmolar gap of 50 mOsm/L. Seven hours after ingestion, the metabolic acidosis increased	4MP antidotal treatment given 7hrs after EG ingestion by IV loading dose of 15mg/kg given over 1hr followed by 2 doses of 10mg/kg infused 12 and 24hrs later. No ethanol or haemodialysis was given.	The child was discharged on the fourth day without metabolic, hepatic, renal, or hematologic disturbance.9 days later, results of the clinical examination were normal, and biological parameters revealed no complications of EG poisoning nor of 4MP treatment	The efficiency of 4MP treatment was confirmed by the rapid correction of metabolic acidosis without alkalization and by the increase in EG half-life. No adverse effect of 4MP was observed

Baud et al, 1986 presented 3 cases of acute EG poisonings that were treated in the ICU of a single hospital in France from 1981 to 1983. During that period, no patients admitted for EG poisoning were treated with ethanol. This study reports the uneventful course of three cases of acute accidental EG intoxication treated with oral administration of 4MP. The diagnosis of EG intoxication was confirmed by the determination of plasma and urine EG concentrations. 4MP was given orally at an initial dose of 15 mg/kg body weight followed by 5 mg/kg after 12 h and

thereafter, 10 mg/kg 4MP was given orally every 12 h until plasma EG concentrations became undetectable. Review of the detailed clinical history provided evidence to support efficacy and safety of 4MP especially when given soon after EG intoxication (it was given 4, 16 and 6 h after intoxication in the 3 cases respectively) but before convulsions, coma or renal failure have occurred.

Comment: This literature reference was submitted as Study S9 in the dossier.

The uneventful recovery in these patients raises the question whether these EG intoxications would have been life-threatening without 4MP treatment. However, these 3 cases did show that 4MP helped in inhibiting EG metabolism evidenced by reduced oxalemia.

Baud et al, 1988 reported successful treatment with 4MP in a 42-year old man who ingested 1.5 litres of antifreeze solution (in an suicide attempt) containing 92.9% ethylene glycol. No haemodialysis was required and he was given 4MP nine h after EG ingestion and clinical course was uneventful with patient discharged on third day from ICU and seventh day from hospital. Similar results were reported in another case report (Harry, 1994).

Comment: The above single case reports by Baud (1988) and Harry (1994) were submitted as studies S10 and S11, respectively in the dossier. Both these single case reports (Baud, 1988 and Harry, 1994) suggested efficacy of early treatment with 4MP without need for any other treatment in patients with EG poisoning with normal renal function.

Two publications (Baud et al. 1986 and Baud et al. 1988) presented cases of patients that made up part of the study population of the retrospective Study S-7.

Jobard, 1996 reported two cases of severe EG poisoning with renal failure that were treated with 4MP and haemodialysis; due to elimination of 4MP in the dialysate, a loading dose of 4MP 10-20 mg/kg was followed by continuous IV infusion of 1 to 1.5mg/kg/h during the 8-12 h of haemodialysis). Data from these 2 patients suggested that in cases of severe EG poisoning with toxic plasma EG levels and renal failure, a 4MP loading dose of 10-20 mg/kg followed by continuous infusion of 1 to 1.5 mg/kg/h during the 8-12 h of haemodialysis may be effective.

Comment: The Jobard (1996) literature reference was submitted as Study S12 in the dossier.

Case reports of ≤ 3 intoxicated patients

Comment: The sponsor's **C**linical summary of efficacy states that of the 27 cases identified in 20 case reports in the systematic review that concerned 3 or fewer patients per publication. The baseline status of these patients, treatment and clinical outcome was supposed to be summarised in an Appendix.

However this appendix was not provided in the dossier.

These case reports have been evaluated and summarised in Tables 2 and 3; 17 patients were administered fomepizole IV by the intravenous route. 3 subjects were administered 4MP orally via nasogastric tube and all three were reported in the same publication (Baud, 1986). One study did not describe the method of administration (Ahmed, 2014). Overall, 19 of the 20 patients reported in the clinical case report literature of the use of fomepizole in the treatment of EG poisoning survived, and 1 patient died 48 h after admission due to multiorgan failure. The patient had a very high level of acidosis (pH 6.5) at presentation and the time between ingestion and treatment was unknown (Jobard, 1996, S12).

Hovda, et al, 2011 summarised the case of a 26-year old female with a dissociative disorder who was admitted with EG poisoning a total of 154 times. She was treated with fomepizole 99 times, ethanol 60 times (with a combination of both six times) and dialysis 73 times. Her admission data before initiation of treatment was summarised. This patient had potentially lethal poisoning on most occasions but was usually admitted early. Early admission was also

consistent with only 10 admissions with a renal impairment (creatinine above 80 µmol/L, max 155 µmol/L; her baseline creatinine seemed to be between 60 and 70 µmol/L). Her renal function seemed to normalise after each of these 10 incidents. The correlation between serum-EG and osmolar gap (OG) was good ($r^2 = 0.76$) suggesting that OG is a good surrogate marker for EG. Eventually she died with an EG concentration of 81 mmol/L (506 mg/dL). The frequent use of fomepizole in this young patient was not associated with any detectable side effects; neither on clinical examination and lab screening, nor on the later autopsy. Despite repeated episodes of EG poisoning, her kidney function seemed to normalise after each overdose. She was treated with buffer and antidote without haemodialysis 81 times without complications, supporting the safety of this approach in selected cases.

Comment: This study provided information on intra-individual variations in kinetics of EG and its metabolites. It also provided data on long-term effects of repeated use of fomepizole or on the outcome frequent EG poisonings. Results suggest that fomepizole appears to be safe even when used frequently in the same patient. However, this is the only available evidence for safety / efficacy of repeated administration of fomepizole in the same patient.

Since their earlier publications (case studies Baud et al. 1986, 1988), the authors treated 38 patients with fomepizole alone for clinical suspicion of EG poisoning. 11 patients had plasma EG concentrations of ≥20 mg/dL. In these 11 patients, fomepizole was given orally in 4 cases, intravenously in 6 cases and via both routes in 1 case. Fomepizole was administered every 12 h until EG concentrations became undetectable. Median number of doses administered to each patient was 3 and the median loading dose of fomepizole was 800 mg. Four patients had renal injury (serum creatinine concentration of 100 µmol/L or more). Between patients with (n=4) and without (n=7) renal injury, plasma ethylene glycol concentrations at admission were similar (p=0.09), and arterial pH was significantly lower (p=0.04) reflecting the impact of the duration of time between poisoning and administration of antidote. Early administration of fomepizole is essential if toxic metabolism is to be prevented. Three of the 11 patients underwent haemodialysis: two due to renal insufficiency and acidosis; another patient with normal renal function but very high plasma EG concentration (8.31 g/L) was dialysed (Borron, et al, 1999).

7.1.2. Analyses performed across trials (pooled analyses and meta-analyses)

Not applicable.

7.1.3. 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 provided by the manufacturer:
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) 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 three 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 poisoning (Levine, et al, 2012) 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 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) reported the case of a 26-year old 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 study (Caravati, 2004) 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 successfully treated with fomepizole or ethanol (primarily fomepizole) without haemodialysis and most were discharged from the hospital within two to three days. Brent (2010) identified 14 published cases of paediatric patients treated with fomepizole. Six other case reports in paediatric patients are also summarised in Table 2. 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 exist no well controlled studies of the use of fomepizole in the treatment of EG poisoning because of the nature of these events. The efficacy/ 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.

7.2. Treatment of methanol poisoning

7.2.1. Pivotal efficacy studies (provided by the manufacturer)

7.2.1.1. Study S7 (Cohort B)

In addition to studying the effect of fomepizole on the treatment of EG poisoning, Study S7 (discussed above) also evaluated its efficacy in the treatment of methanol poisoning. Of the 38 patients initially enrolled, 5 were treated for methanol toxicity. These 5 patients were referred to as cohort B in Study S7. Majority of patients in Cohort B were males (n=4, 80%) with mean age of 47years (28-57years). At admission, the investigator assessed that 2 patients (40%) were severely intoxicated, 2 patients (40%) were mildly intoxicated and l patient (20%) was not intoxicated. Three of these patients were awake (60%), one was inebriated (20%) and one was lethargic (20%). All 5 patients were treated with 4MP sulphate; 3 received IV 4MP while 2 patients received oral treatment. The mean loading dose of 4MP used was 11.1 mg/kg (700mg), ranging from 9 to 16.3 mg/kg. Patients tended to receive multiple doses of 4MP, with the mean number of doses being 4 (median: 2 doses). One patient received a total of 13 doses of 4MP over a 7 day period. A mean cumulative total dose of 1935mg 4MP was administered (range: 500 mg to 5050 mg).

Median baseline blood methanol was 102.1 mg/mL, ranging from I0 to 425.6 mg/mL. At the final evaluation, no methanol was detected in the blood of any of the four intoxicated patients. At baseline the mean blood pH was within normal range (mean pH 7.4) and only one patient had clinically significant low pH (7.26) which returned to normal within 9 h of dosing with 4MP. At baseline, three patients presented blood bicarbonate levels below the LLN; the mean serum bicarbonate level for the population at entry into the study was low (15.1 mmol/L). At endpoint, the level had increased and was within the normal range (22.5 mmol/L) and only 1 patient had a serum bicarbonate concentration below the LLN (21.5 mmol/L). However, this was very close to the normal limit (22 mmol/L) and was not clinically significant. The renal parameters were normal at baseline and end of the study; calcium levels were low at baseline in 4 patients and remained low in 3 of the 4 patients.

At the last study evaluation, four of the five patients in this study treated with 4MP for suspected or documented methanol intoxication, were alive with no sequelae (80%) while one patient was alive with sequelae due to intoxication (bilateral blindness after severe methanol intoxication, although this condition was presented at hospital admission). The investigator assessed that treatment with 4MP was definitely or possibly effective in preventing or diminishing toxicity for four patients. No beneficial effect was noted for the fifth patient who was considered by the investigator not to be intoxicated at admission to hospital.

Comment: Overall, 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 (n=5).

7.2.1.2. Study S13 (OMC-4MP-2)

Study design, objectives, dates and locations

The second study, S13, was a prospective, Phase III, open-label, multicentre, uncontrolled study to assess the safety and efficacy of Antizol (fomepizole) Injection in patients with methanol poisoning. The objectives of this study were to: determine the efficacy and tolerance of Antizol in the treatment of methanol poisoned patients; determine the relationship between the time response curve of Antizol and its PK profile; correlate the PK profile of Antizol with its inhibitory effects on methanol metabolism, and determine the safety of Antizol administration in methanol poisoned patients. The study was conducted by Orphan Medical with patients enrolled from January 1996 to October 1997 at 6 centres in USA. This trial was conducted in accordance with the current guidelines for Good Clinical Practices (GCPs).

Inclusion/ exclusion criteria

The main inclusion criteria were: age ≥ 12 years; written informed consent and documented serum methanol level >20 mg/dL or if methanol level was not immediately available, patients with a history of methanol ingestion, or a strong clinical suspicion of methanol intoxication (if a history was not obtainable) plus at least two of the four following criteria:

- Arterial pH <7.3
- Serum bicarbonate <20 mEq/L
- Osmolar gap by freezing point depression >10 mOsm/L
- Recent (less than 1 h) documented history of an ingestion of a potentially toxic amount of methanol.

The main exclusion criteria were: Ethanol given therapeutically to the patient at the investigator's hospital; Known adverse reaction to pyrazoles; Pregnant female.

Study treatments

The patients described in this report received an initial loading dose of Antizol administered at a dose of 15 mg/kg followed by supplemental doses every 12-h until methanol levels were <20 mg/dL. Except for one patient, all patients received an initial Antizol dose as a 30 minute infusion of 15 mg/kg (182.7 pmol/kg). Due to the comatose status of one patient, an error was made in estimating the patient's weight so that he actually received a loading dose of 22.0 mg/kg. Patients with significant metabolic acidosis or visual sequelae (with severe intoxication) and who met criteria for haemodialysis as defined in the protocol[5], were also medically managed with haemodialysis. Additional patient management included bicarbonate therapy, cardiac monitoring, vitamin supplementation, blood pressure support, and oxygenation as appropriate.

[5] Arterial pH <7.1; Drop in arterial pH > 0.05 units despite bicarbonate supplementation after completion of the Antizol loading dose; Drop in serum bicarbonate of > 5 mEq/L despite bicarbonate supplementation after completion of the initial loading dose of Antizol;; Inability to maintain arterial pH >7.3 despite bicarbonate therapy; Measured methanol level of >50 mg/dL; Methanol levels declining at a rate of <10 mg/dL/24-hours. Any of the following visual symptoms: a. Significant blurring of vision b. Double vision c. Large number of spots before eyes d. Significant decrement in visual acuity (greater than one line on a standard hand-held Snellen eye chart) ; e. Sense of seeing through a 'snowfield'. Any of the following visual signs: a. Peri-papillary oedema b. Hyperaemia of the optic discs. Markedly retarded pupillary light reflex d. Central scotomata Any of the following visual signs: a. Peri-papillary oedema b. Hyperaemia of the optic discs c. Markedly retarded pupillary light reflex. d.Central scotomata

Efficacy endpoints, statistical considerations

The primary efficacy variables that were established a priori for this study were reversal of or lack of development of metabolic acidosis, inhibition of methanol metabolism as assessed by formate, and assessment of morbidities associated with methanol poisoning. The efficacy analyses included an assessment of the ability of Antizol to prevent the mortality and severe morbidity associated with methanol poisoning; tabulations and summary statistics were calculated. No statistical considerations were made with respect to sample size. The sample size was based on the number of patients that the sponsor anticipated could be enrolled at up to 25 sites within 12 to 18 months.

Participants

Fifteen patients were initially enrolled in this study. Due to laboratory error, it was subsequently determined that four of these patients did not have documented blood methanol concentration levels at baseline. Thus, 11 of the 15 patients were included as efficacy evaluable patients. All 15 patients who were enrolled in this study were included in the assessment of safety in the final clinical study report.

Baseline data

Majority of the patients were male (n=9), Caucasian (n=10) and the mean age was 38 years (range: 18-61 years). Overall, 7/11 (64%) of the patients entered the study with moderate or severe intoxication. The most common reason for methanol ingestion was suicide attempt (n=6) followed by inebriating effect (n=2) and accidental (n=2). The time of methanol ingestion was unknown for four of 11 patients (36%) For the remaining seven patients, treatment with Antizol was initiated within 6 h for two patients (18%), between 6 and 12 h for one patient (9%), between 12 and 24 h for three patients (27%) and > 24 h for one patient (9%). At baseline, the median pH level was 7.38 (Range: 6.90- 7.46). Five of 11 patients (45%) had arterial pH levels <7.35. The median serum bicarbonate level was 15.0 mEq/L (range 3.0- 22.5). All eleven evaluable patients had baseline serum methanol levels > 20 mg/dL (median=71.3 mg/dL, range: 23.0 to 612.1 mg/dL). Seven of 11 patients (64%) presented with formate levels in the non-detectable range (< 1 mmol/L). Among the remaining six patients, one (9%) had a formate level in the moderate range (1 to 9 mmol/L) and the remaining five patients (45%) had formate levels in the severe range (>9 mmol/L). All five of these patients received baseline ocular scores indicative of severe intoxication. Five of 11 efficacy evaluable patients (45%) presented with detectable ethanol levels and 3 patients (27%) had ethanol levels in or above the presumed ethanol therapeutic range (100 to 125 mg/dL) upon study entry. All three had received ethanol as a first line therapy at a referring hospital, prior to transport to the trial site. Four patients (36%) had no visual abnormalities at baseline, one (9%) had mild to moderate visual dysfunction[6], and one patient (9%) had severe visual dysfunction[7]. Five patients (45%) were not evaluable due to either coma (N=4) or uncooperative behaviour (N=1). Only 1 patient was hypotensive with a baseline blood pressure of 100/38 mmHg. No other clinically significant abnormalities were observed for vital sign measurements at baseline.

Results

Clinical outcome

At study completion, seven patients (64%) were alive without sequelae, three patients (27%) were alive with sequelae, and one patient (9%) died. Five of the seven patients who ended the trial alive and without sequelae had overall baseline severity scores of moderate (N=2) to severe (N=3). Life support was terminated 20 days after completion of the study for one of the

[6] presented with a score of 20/100

[7] One patient could only count fingers and also presented with sluggish pupillary reactivity and peri-papillary oedema of his right eye. {This patient had previously documented optic nerve damage in his right eye and a prosthetic left eye)

patients with sequelae at the end of the study, Cause of death was attributed to brain stem herniation due to toxic encephalopathy secondary to severe methanol toxicity and this patient entered the study comatose. The sequelae described by the Investigator's for the remaining two patients were left lower lobe infiltrate for one patient (which was present at baseline and continued throughout the study) and mild blurring of vision for another patient (unknown aetiology although, the patient presented with hyperaemia of the optic disc at baseline).

Four of 11 patients (36%) were comatose at baseline. The time of methanol ingestion was unknown for these patients. At the end of the trial, two of these patients showed marked improvement in mental status, one patient died during the trial, and one patient remained comatose and subsequently died post-trial due to severe methanol toxicity. Of the remaining seven patients, the number of h from time of methanol ingestion to initiation of trial drug therapy varied from 3.3 h to 26.75 h. For the 5 patients who were awake at baseline, mental status remained unchanged at the end of the trial, even though the number of h to trial drug initiation varied from 3.3 h to 23.5 h. For the remaining two patients, both demonstrated some improvement in mental status by the end of the trial.

Nine of 11 (82%) efficacy evaluable patients had low serum bicarbonate levels, five (45%) had low blood pH measurements, and eight (73%) had low PCo_2 levels at baseline. At the end of the study, the majority of patients had normal values for each of these parameters, demonstrating a reversal of baseline metabolic acidosis.

Inhibition of methanol metabolism

Five patients (45%) presented with non-detectable (<1 mmol/L) plasma formate levels prior to the administration of Antizol, one patient (9%) presented with a mild (1-9 mmol/L) severity level, and five patients (45%) presented with severe toxic (>9 mmol/L) levels of formate. No patient developed elevated formate levels after initiation of Antizol therapy. Levels decreased within 4 h of initiation of Antizol therapy in all patients who presented with detectable baseline plasma formate levels. All patients had non-detectable levels of formate at the end of the trial.

At the end of haemodialysis, four of seven patients still had methanol levels> 20 mg/dL (range: 21.7- 33.2 mg/dL), two of whom had detectable but non-therapeutic levels of ethanol (~ 16.5 mg/dL). All four patients ended haemodialysis with insignificant plasma formate levels (<1 mmol/L). Within 48 h after the end of haemodialysis, all four patients had methanol levels <20 mg/dL and none of these patients developed an increase in formate levels throughout the post-haemodialysis period.

Presenting methanol levels for the 4 patients who did not receive haemodialysis in this study were 37.4, 38.8, 36.7 and 23.0 mg/dL, respectively. Presenting ethanol levels were below the accepted therapeutic range (67.8, 10.7, 0 and 0 mg/dL, respectively). In each case, plasma formate levels quickly declined to non-detectable levels, or remained at non-detectable levels in conjunction with reduction in methanol and ethanol levels throughout the course of treatment with Antizol. Thus, treatment with Antizol, and not ethanol, played a primary role in the prevention of any increase in the concentration levels of the toxic metabolite, formate.

Formate levels <1 mmol/L are considered to be background levels in these patients. The data suggests that Antizol, in conjunction with supportive care with or without haemodialysis, inhibits the conversion of methanol to its toxic metabolite, formate.

For the three patients that presented with normal visual acuity and were asymptomatic for other visual signs or symptoms at baseline, none developed any visual changes throughout the course of the study. For the four patients who could not be visually assessed at baseline, two ended the study with normal visual acuity, one died during study and one died subsequent to study. For the remaining patients, three showed signs of improvement by the end of the study and one patient showed no signs of improvement until 48 h after the end of the study.

Four patients had sinus tachycardia at study entry that resolved by the end of the study for 2 of the patients. An ECG was not conducted at the end of the study for the other 2 patients. No significant abnormalities were noted in cardiac function for the remaining seven efficacy evaluable patients. There were no cranial nerve abnormalities other than ocular nerve findings previously present that developed throughout the course of the study for any patient.

Comment: This was a well-conducted 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.

7.2.2. Other studies

7.2.2.1. Efficacy from published studies

Methylpyrazole for Toxic Alcohols (META) Investigation (Brent et al. 2001)

Study design, inclusion/ exclusion criteria

Brent and co-workers performed a prospective multicentre study of fomepizole treatment in 11 patients with methanol poisoning between 1995 and 1997. The main inclusion criteria were patients aged > 12 years old with serum methanol >20 mg/dL (6.2 mmol/L) or if there was a history or a strong suspicion of methanol ingestion, in addition to at least two of the following three findings: an arterial pH <7.3, a serum bicarbonate concentration <20 mmol/L, or a serum osmolality gap of >10 mOsm/kg of water. Main exclusion criteria were ethanol treatment, known adverse reaction to pyrazoles and pregnancy.

Study treatment

Fomepizole was administered as a 15 mg/kg loading dose, followed by 3 doses of 10 mg/kg every 12 h. From the fifth dose, 15 mg/kg was given to compensate for increased metabolism.

Endpoints, statistical considerations

Outcomes measured were preservation of visual acuity, resolution of metabolic acidosis, inhibition of formic acid production, achievement of therapeutic plasma concentrations of fomepizole with the dosing regimen, residual illness or disability and death. Mean values were compared with use of Student's unpaired t-test and nominal variables with use of Fisher's exact test. Correlations were determined with the Pearson correlation coefficient.

Baseline data

The mean ($\pm$SD) age of the 11 patients was 40±13 years. Of the 9 patients for whom the ingested product was known, 8 had drunk windshield-wiper fluid, and one had ingested gas-line antifreeze. Methanol was ingested to attempt suicide in six patients, to cause inebriation in two, accidentally in two, and for unknown reasons in one. Three patients had initial plasma ethanol concentrations of at least 100 mg/dL (21.7 mmol/L); all three had received ethanol at referring hospitals before they were enrolled in the study. There was a strong inverse correlation between the initial arterial pH values and the plasma formic acid concentration ($r=0.92$, $P<0.001$). Of the three patients who had undetectable plasma formic acid concentrations at the time of presentation, only one patient had a high plasma ethanol concentration. For the group as a whole, there was no correlation between the initial plasma formic acid and ethanol concentrations ($P=0.96$). Seven patients had visual abnormalities, manifested as symptoms, decreased visual acuity, or other abnormal results on examination. The mean plasma formic acid concentration in this group was 80 mg/dL (17.5 mmol/L) with a range of 0 to 198 mg/dL (0 to 43.0 mmol/L), compared to a much lower 7.4 mg/dL (1.6 mmol/L) with a range of 0 to 24.5 mg/dL (0 to 5.33 mmol/L) in the patients with no visual abnormalities ($P=0.08$). All patients who could be evaluated had normal extra ocular movements. No patient reported

diplopia, seeing spots, or the sensation of seeing through a snowstorm. The median duration of treatment with fomepizole was 30 h (range, 0.5 to 60), and the patients received a median of 4 doses (range, 1 to 10). The seven patients who underwent haemodialysis received a median of one treatment (range, one to four). The median interval between enrolment and the initiation of haemodialysis was 90 minutes (range, 14 to 160).

Results

After the institution of fomepizole therapy, plasma formic acid concentrations fell in all patients, with simultaneous resolution of the metabolic acidosis and improvements in mental status and visual symptoms and signs. No patient had hypoglycemia after the initiation of therapy. Methanol elimination in patients who did not undergo dialysis followed first order kinetics with a half-life of 54 h. Plasma fomepizole, measured a total of 155 times during therapy in all patients, was at or above the target concentration of 0.8 µg/mL on all but three occasions. Nine of the 11 patients survived. Seven patients who presented with visual disturbances due to methanol poisoning recovered without visual impairment. The two patients that died were comatose at presentation, had an unknown time from ingestion to treatment, had non-detectable levels of ethanol in serum and had very high levels of serum formate at presentation. Both patients died of anoxic brain injury.

Comment: This study was similar to the 2 pivotal studies evaluated above with similar study design, endpoints and patient characteristics and the results of this prospective study in 11 patients suggest that fomepizole is a safe and effective antidote for use in the treatment of methanol poisoning.

7.2.2.2. Prospective case series study of severe methanol intoxications treated with Fomepizole (Hovda et al. 2005)

Study design, objectives

Prospective case series study on methanol, formate and dialysis kinetics in 7 cases of severe methanol poisoning treated with buffer, fomepizole and haemodialysis (average 7 h, range 5 – 8). The objective of this prospective kinetic study on methanol and formate in seven methanol-poisoned patients was to evaluate role of haemodialysis when using the new antidote-fomepizole and to find a possible new indication for dialysis based on the patient's initial clinical status.

Study participants

The patients were part of an outbreak where illegal spirit consisting of 20% methanol and 80% ethanol were consumed.

Study treatments

Six patients were initially given sodium bicarbonate, while 1 patient received trometamol (Tribonat) as a buffer. Two patients were given IV ethanol before being transferred to the investigating hospital where they received fomepizole. Fomepizole (Fomepizole, OPI Orphan Pharma international, Paris, France) was given as a bolus dose of 15 mg/kg IV diluted in isotonic saline, and then 10 mg/kg every 12 h, all doses given over 30 minutes. From the fifth dose and on, 15 mg/kg were given in order to compensate for increased metabolism. During dialysis, fomepizole was given by 10 mg/kg every 4 h.

The doses were based on clinical studies [Jacobsen et al. 1990] and the META Study [Brent et al. 2001] and similar to the proposed doses for fomepizole. Haemodialysis was performed in all patients for 5 to 8 h and when terminated, serum methanol was below 10 mmol/L. Four patients were dialysed early after diagnosis was obtained, while three were dialysed 'electively' the next day. The decision for early or elective dialysis was done on the basis of the patients' clinical condition; the degree of metabolic acidosis or visual disturbances present which did not disappear with buffer and antidote alone. Of the 4 patients who received dialysis after diagnosis,

3 also received massive supportive treatment due to their clinical condition (antibiotics for sepsis; mechanical ventilation and vasopressors because of respiratory and circulatory failure).

Results

This study included 5 males and 2 females with ages ranging from 41 to 69 years. The severity and outcome of methanol poisoning were correlated to the toxic effects of formate and the degree of metabolic acidosis and not to the serum methanol, provided alkali and antidotal treatment had been started. This was shown in this study by patients 6 and 7 who had the highest serum methanol levels at admission, but no clinical features. The early acidosis is due to the production of formic acid whereas lactic acid production occurring in the later stages of poisoning is due to tissue hypoxia caused by formate uncoupling of cytochrome oxidase [Hovda et al. 2005, Jacobsen and McMartin 1986, 1997].

Elimination kinetics for methanol and formate before, during and after haemodialysis in all 7 patients showed that the elimination rate of methanol was clearly increased during haemodialysis and apparently followed first order kinetics with a mean R2 of 0.98 (range 0.96 – 1.00). No rebound effect in serum methanol due to redistribution was observed after dialysis was terminated.

Despite similar dialysis clearance, the half-life of formate is shorter than that of methanol, average being 1.7 and 2.5 h, respectively. This is explained by a higher intrinsic elimination of formate (metabolism and a variable renal excretion), whereas methanol metabolism is blocked and the renal and pulmonary excretion is small. As such, dialysis represents 83% of the total body clearance of methanol and 68% of the total body clearance of formate in these patients. The median dialysis clearance of methanol was 222 mL/min (range 204 – 232, n = 5) and for formate 225 mL/min (range 220 – 229, n = 2). The potential benefit of dialysis is due to the removal of methanol, the correction of the metabolic acidosis and removal of the toxic metabolite formate. Due to their small molecular weight, small volume of distribution, and lack of protein binding, both methanol and formate are easily dialysed [Jacobsen et al. 1990].

As demonstrated by the effective block of methanol metabolism by fomepizole in all 7 patients and the clinical improvement after this treatment combined with aggressive correction of acidosis, there is really no longer any recommended serum methanol concentration for discontinuation of dialysis (for example, 10 mmol/L [Jacobsen and McMartin 1986, 1997]). The efficacy of haemodialysis in removing methanol is undisputable. If methanol analyses are not available, the length of haemodialysis may best be guided by calculations of the osmolality gaps [Hovda et al. 2004, 2005].

Comment: 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 leading to the FDA approval of 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 [Brent et al. 2001).

Based on data from the above prospective case series study and another retrospective study discussed below [Megarbane et al. 2001, 2004], the authors propose that the indications for haemodialysis in methanol poisoning using fomepizole as the antidote may therefore be separated into two categories:

- The critically ill patient, with severe metabolic acidosis (base deficit > 20 mM) and/or visual disturbances, should be given buffer, fomepizole and haemodialysis as soon as possible. The main effect of dialysis is then to remove the toxic anion formate and to assist in correcting the metabolic acidosis, thereby also reducing formate toxicity. The removal of methanol per se is not life-saving in this setting, because fomepizole prevents further production of formic acid.

- The stable patient, with little to moderate metabolic acidosis and no visual disturbances, should be given buffer and fomepizole. The indication for haemodialysis should then be discussed with an experienced nephrologist and/or clinical toxicologist.

  The efficacy of fomepizole and the significant different side effect profile from ethanol gives the treating physician the possibility to delay or even drop dialysis in this setting, and thereby change the triage, as patients will not develop more clinical features from methanol poisoning when fomepizole and bicarbonate is given.

  However, the evidence for the above guidelines is only preliminary and would require confirmation in prospective studies.

7.2.2.3. Retrospective study of methanol intoxications treated with Fomepizole (Mégarbane et al., 2001)

Study design, objectives

This was a retrospective clinical study in three intensive care units in university-affiliated teaching hospitals in France between 1987 and 1999. The objective was to assess the efficacy and safety of fomepizole in methanol poisoning and to test the hypothesis that fomepizole obviates the need for haemodialysis in selected patients.

Study participants

The study included 14 methanol-poisoned patients admitted to ICUs and treated with fomepizole. Patients were classified according to requirement for dialysis and whether ethanol was self-administered or prescribed.

Study treatments

Fomepizole was administered orally (n=4) or IV (n=10). The IV form was diluted in 250 mL isotonic saline and infused over 45 mins by an infusion pump. Fomepizole dosing varied by practitioner but was generally administered twice daily. A loading dose of 15 mg/kg was followed by doses of 10 mg/kg every 12 hour until plasma methanol became undetectable. Median dose was 10.8 mg/kg. Patients with a plasma methanol concentration of 50 mg/dL received a median of 4 doses. Haemodialysis was performed only in the 4 patients with visual disturbances. Two patients received sodium bicarbonate, seven folinic acid and eight thiamine and pyridoxine. One patient underwent delayed peritoneal dialysis (28 h after initiation of fomepizole therapy) for acute pancreatitis present on admission.

Baseline data

There were 9 men and 5 women with median age of 46 years. The ingested products were cooking alcohol (n=7), pure methanol (n=4), windshield washing fluid (n=1) and undetermined (n=2). There was a history of alcoholism in 12 cases. Reasons for methanol ingestion included suicide (n=10), unintentional misuse (n=2) and unknown (n=2). The median delay between intoxication and ICU admission was 13 h (range: 3-48 h). On admission, 9 patients were awake, one inebriated, 2 lethargic and 2 comatose (both of whom required mechanical ventilation); 3 patients presented with bilateral blindness and one with colour vision impairment (optic nerve damage on ophthalmological examination). Only 1 patient had hypotension and 3 had tachycardia; median respiratory rate was 18/min (14-40) with 6 patients presenting with tachypnoea (respiratory rate >20/min). Only 1 patient underwent gastric lavage and 3 received activated charcoal prior to ICU admission. The median initial plasma methanol concentration was 50 mg/mL (4-146 mg/dL). Eight patients co-ingested ethanol with median initial plasma concentration of 195 mg/dL (12-530 mg/dL) and 3 patients received ethanol as initial treatment. Median arterial pH was 7.34 (7.11-7.51), serum bicarbonate 17.5 mmol/L (3-25 mmol/L), anion gap 22.1 mmol/L (11.8-42.2), arterial lactate 2.2 mmol/L (0.7-6.9) and serum creatinine 84 µmol/L (50-128).

Results

Except for the 4 patients with visual disturbances at admission, all patients recovered without sequelae. Visual disturbances improved in only 1 blind patient who could count fingers several weeks after discharge. The median ICU stay was 5 days (2-20). The 6 that were not haemodialysed with plasma methanol <50 mg/mL had uneventful hospital courses; 4 patients with methanol of at least 50 mg/mL were not haemodialysed and recovered completely.

On admission, 8 patients had subnormal arterial pH which returned to normal with fomepizole therapy within 6 h (5-12 h); 11 patients had subnormal bicarbonate which returned to normal in 21 h (4-34 h) and 11 patients had elevated anion gaps which returned to normal within 26 h (3-62 h). The 4 patients receiving haemodialysis had significantly lower pH, lower serum bicarbonate and larger anion gaps despite insignificant differences in plasma methanol concentration than the non-haemodialysed patients[8]. These differences suggested a delay in seeking treatment which likely contributed to their visual impairment. Neither fomepizole nor haemodialysis improved visual impairment.

Comment: Results from this retrospective case series suggest that in patients presenting with high methanol concentrations (>50 mg/dL) but without severe acidosis or visual impairment may be successfully treated by repeated dosing with fomepizole without dialysis. Although interpretation was limited due to retrospective nature of this study, it did provide some evidence to support the findings observed in the prospective case series study discussed in Hovda, 2005 above.

7.2.2.4. Combined retrospective and prospective case series study of methanol poisonings from large outbreak in Norway 2002-2004 (Hovda 2005).

Study design, objectives

This was combined prospective and retrospective case series study of 51 hospitalised patients in Norway who were confirmed poisoned with methanol. This was one of the largest study where both serum methanol[9], acid-base status and in some cases, even serum formate levels were measured. This was also the first large-scale outbreak in which fomepizole was used as an antidote.

Patient characteristics, methods

Overall, 51 patients were admitted from September 2002 until December 2004, of who 33 were admitted in 2002, 13 in 2003 and five in 2004. Nine patients died in hospital (hospital mortality 18%), five patients were discharged from hospital with sequelae (10%), whereas one died 1 year later from cerebral sequelae. Eight patients who died outside hospital were diagnosed as methanol poisonings on autopsy. The patients were retrospectively separated into three groups according to the outcome: Group I: patients who survived without sequelae; Group II: patients who survived with sequelae; Group III: patients who died. Comparisons between the admission data in the different groups were initially performed by the use of Kruskal–Wallis nonparametric test. The statistically significant parameters were then compared group by group using Mann–Whitney U-test. The significant parameters were separated by 25-, 50- and 75-percentiles in order to look for possible threshold values for the different parameters. The correlation between pH and pCO_2 was performed by interaction term using regression analysis.

[8] The 2 subgroups of patients with and without haemodialysis were compared using the Mann-Whitney test with the significance level set at p=0.05.

[9] Methanol in serum was measured by a gas chromatographic method with flame ionization detection and a headspace injector (sensitivity 1.3 mmol/ L and day-to-day coefficient of variation 5%).

Study treatment

Patients were given buffer (bicarbonate or trometamol; Tribonat, Baxter Germany) aiming at a full correction of acidosis within the first h. In addition, they were given ethanol (15 patients) or fomepizole (36 patients) as antidotes, and haemodialysis (37 patients). Fomepizole (Fomepizole, OPi Orphan Pharma International, Paris, France) was given as a bolus dose of 15 mg/kg IV diluted in isotonic saline, and then 10 mg/kg every 12 h, all doses given over 30 min. From the fifth dose and on, 15 mg/kg was given in order to compensate for increased metabolism. During dialysis, 10 mg/kg fomepizole was given every 4 h.

Results

There were 39 males and 12 females with a median age of 53 years. Median S-methanol in all the groups on admission was 25.0 mmol/L (80 mg/dL) (range 3.1– 147.0 mmol/L). Of those 39 (77%) who were symptomatic upon admission, 28 patients (55%) presented with visual disturbances, 21 (41%) with dyspnoea, 22 (43%) with gastrointestinal (GI) symptoms, 12 patients (24%) were comatose, six (12%) with chest pain and eight (16%) with other symptoms (mainly fatigue). Eight patients (16%) presented with respiratory arrest.

Overall, 35/51 patients survived without sequelae, 7 patients survived with sequelae and 9 patients died. About 60% of the patients discharged with sequelae had visual disturbances on admission, 40% had GI symptoms, dyspnoea, coma and respiratory arrest. Respiratory arrest and coma on admission were robust markers of poor outcome: 6 of 8 (75%) patients admitted with respiratory arrest died and 8 of 12 (67%) comatose patients died. Although the patients with the most severe outcome also had the highest serum methanol, the differences between the groups surviving without sequelae, surviving with sequelae, and the patients who died, were not significant (P=0.289, using Kruskal–Wallis nonparametric test). The patients who died were more acidotic [median pH 6.57, median base deficit (BD) 28 mmol/L) than the patients discharged with sequelae and those discharged without. There was a significant difference between these three groups regarding pH ($P < 0.001$) and BD (P=0.001), but not regarding HCO_3 (P= 0.207). The three groups were further separated by the 25-, 50- and 75-percentiles, in order to look for possible threshold values regarding different prognosis. It is important to note that the 25-percentile (pH below 6.90) almost completely separated the dying patients (Group III) from those surviving (Group I)[10]. Amongst the patients surviving, there was a trend towards decreased pCO_2 when pH was decreasing, whilst the trend was opposite amongst the patients dying, the difference between groups being highly significant ($P < 0.001$). In 13 of the dialysed patients, serum methanol levels were obtained before start of, and after termination of, haemodialysis. During dialysis the mean half-life of the serum methanol concentration was 2.4 h.

Comment: Epidemiological, clinical and prognostic features from the large methanol outbreak in Norway in 2002-2004 provided evidence to support use of fomepizole in treatment of methanol poisoning. 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 this study) and haemodialysis is effective if initiated early. Visual disturbances, dyspnoea (including hyperventilation) and GI symptoms were the most frequent clinical features, whilst severe metabolic acidosis (pH < 6.90, BD > 28 mmol/dL), coma and increased pCO_2 (lack of compensatory hyperventilation) were associated with poor outcome. Most of the patients who presented with symptoms were discharged without sequelae.

[10] The one patient dying in the 50-percentile group (pH 6.90–7.19), was admitted with the tentative diagnosis of stroke and methanol poisoning was therefore diagnosed late. He is therefore an outlier amongst the dead (pH 7.13, pCO2 2.0 kPa). This patient also explains one of the two deaths in the 50-percentile of the BD values in Figure 4b, which without him would distinguish survivors well at a BD <28 mmol L.

7.2.2.5. CZECH mass outbreak of Methanol poisonings (Zakharov, 2014)

Study design, objectives

This was a combined prospective and retrospective case series study of 121 patients with confirmed methanol poisoning. A large outbreak of methanol poisonings in the Czech Republic between September 2012 and January 2013 was attributed to the consumption of illegal methanol-containing strong alcoholic beverages sold on the black market or at conventional outlets. The objective of the present study was to report the data from the mass methanol poisoning in the Czech Republic in 2012 addressing the general epidemiology, treatment, and outcomes, and to present a protocol for the use of fomepizole ensuring that the antidote was provided to the most severely poisoned patients in the critical phase.

Patient characteristics, methods:

Diagnosis was made when (i) a history of recent ingestion of illicit spirits was available and serum methanol was higher than 20 mg/dL (6.24 mmol/L) and/or an osmolal gap >20 mOsm/kg/H_2O (that could not be explained by ethanol) was found, or (ii) there was a history/clinical suspicion of methanol poisoning; serum methanol was above the limit of detection with at least two of the following: pH<7.3, serum bicarbonate<20 mmol/L (20 mEq/L), and anion gap (calculated with potassium) >20 mmol/L (20 mEq/L). Of the 121 cases that were identified, 20 died out of hospital and 101 were hospitalised.

The clinical examination protocol included complete ocular examination with standard ophthalmologic tests (visual acuity, visual fields, colour vision, contrast sensibility, fundoscopy), cerebral computed tomography (CT) in symptomatic patients and standard neurological examination. The patients were considered to have visual sequelae (VS) of acute methanol poisoning if the symptoms of toxic neuropathy of the optic nerve were documented on admission/ during hospitalisation, with pathologic findings on visual acuity, visual fields, colour vision, and contrast sensitivity, or persisting lesions on fundoscopy with other symptoms of visual damage on discharge from the hospitals. The patients were considered as having CNS sequelae of poisoning if the symmetrical necrosis and haemorrhages of basal ganglia were present on computed tomogram of the brain. The hospitalised patients were divided into three groups according to the outcome: Group I: Survivors without sequelae; Group II: Survivors with visual and/or CNS sequelae; Group III: Patients who died.

The admission laboratory data in the different groups were compared on a group by group basis using Two-Sample Assuming Unequal Variances (Equal Means), Two-sample F-Test for Variances, Bias test, and two-sample Kolmogorov–Smirnov test. Data was expressed as medians with range and arithmetic means with confidence interval, as appropriate. For comparison of the obtained results, common statistical tests have been used (t-Test: Two-Sample Assuming Equal Variances, t-Test: Two-Sample Assuming Unequal Variances (Equal Means), Two-sample F-Test for Variances, Bias test and ANOVA). Multivariate logistic regression was used to evaluate the different independent variables for mortality, whereas cumulative logit proportional odds model was used for various sequelae. The p-values were based on the likelihood-ratio tests. For the multivariate regression analysis, the whole population of 101 hospitalised patients was used without stratification. All statistical calculations were carried out with a level of significance $\alpha < 0.05$.

Study treatment:

Bicarbonate was given as a buffer to patients with metabolic acidosis aiming at full correction; ethanol and/or fomepizole were given as antidotes. Uniform indications were applied for antidotal treatment and elimination techniques according to the AACT/EAPCCT practice guidelines on the treatment of methanol poisoning. Because there was limited availability of fomepizole, the following antidote-saving approach was used: a) if fomepizole was not available, the standard scheme of ethanol administration to rapidly achieve the protective serum concentration of 100–150 mg/dL (21.7 – 32.6 mmol/L) was initiated as soon as possible; b)

fomepizole treatment was prioritised in patients with serum methanol >50 mg/dL (15.6 mmol/L) [or formate higher than 40 mg/dL (8.9 mmol/L)] and pH <7.0, or methanol >30 mg/dL (9.4 mmol/L) and pH < 7.0 in patients unable to hyperventilate (pCO_2 > 3.07 kPa or 23.0 mmHg); c) treatment with fomepizole was stopped and followed by ethanol administration when methanol concentration decreased below 30 mg/dL (9.4 mmol/L) given a normal pH, or 20 mg/dL (6.2 mmol/L) if metabolic acidosis was not yet corrected.

The rationale for this approach was to decrease the risk of incomplete ADH blocking by possible fluctuations of ethanol levels in the most severely poisoned patients, especially during haemodialysis, and to avoid respiratory depression caused by ethanol in patients hyperventilating to compensate the acidosis. Haemodialysis was performed if the patients fulfilled any of the following criteria: serum methanol higher than 50 mg/dL (15.6 mmol/L), metabolic acidosis with a pH<7.30, or had visual toxicity. The mode of dialysis, intermittent haemodialysis (IHD) or continuous veno-venous haemodialysis/ haemodiafiltration (CVVHD/HDF), was based on several factors, such as the haemodynamic stability of a patient on admission, or the severity of poisoning, but availability also played an important role.

Results:

Of the 101 patients treated at hospitals, there were 80 males with median age of 53 (23-79) years and 21 females with median age of 57 (16-69) years. Only 11% (n=11) of the patients were admitted within 12 h after the methanol ingestion, 35% (n=35) within 48 h, and 37% (n=37) later than 48 h and was unknown in 18% (n=18) of the cases. All of the patients who died were admitted more than 24 h after ingestion. According to the history from the discharge reports, 56% of the hospitalised patients were daily alcohol abusers. The type of toxic alcohol was known in 78 cases, and the approximate quantity in 67 cases. The median amounts of toxic spirits (volumes of the formulated spirits) consumed by males was 450 mL (range 100–1500 mL) and by females 200 mL (range 80–500 mL). Forty-one patients had detectable ethanol before hospital antidote treatment, with a median concentration of 65 mg/dL (8–446 mg/mL), that is, 14.1 mmol/L (1.7 – 96.8 mmol/L); 30 of them were administered ethanol as a ‘ first aid antidote ‘ by ambulance medical staff during the transfer to a hospital and 6 patients were not tested for serum ethanol before the antidote treatment was started Three patients were found with negative methanol levels and positive formate and twelve were found with a methanol concentration below the ‘ toxic limit ‘ (20 mg/dL or 6.24 mmol/L). On admission, 25/101 (25%) of patients were asymptomatic, 18 of them with measurable ethanol in blood (all of them were given pre-hospital ethanol). The most common clinical symptoms on admission are shown in Table 5. Detailed information about the treatment given is presented in Table 6. In total 10/101 (10%) did not receive any antidote: 3 of these recovered without sequelae[11], 2 recovered with sequelae[12] and 5 patients died[13]. A total of 26/101 (26%) patients did not receive haemodialysis: 21 of them did not meet criteria for haemodialysis and, all of them survived without sequelae; two patients died upon admission and in 3 cases haemodialysis was not applied because of the negative serum methanol, coma on admission, and severe metabolic acidosis corrected by the bicarbonate infusions with no definite diagnosis of methanol poisoning till death (the first cases in the outbreak). Overall, 26/101 (26%) did not receive folate of whom 10 died, 3 survived with visual sequelae and 13 survived without sequelae.

[11] All 3 had low serum methanol on admission (6, 10 and 20mg/dL) and no metabolic acidosis.
[12] One patient with serum methanol of 17 mg/dL (5.3 mmol/L), pH 7.2, and serum ethanol of 228 mg/dL, or 49.5 mmol/L (self-administered shortly before admission), and one patient admitted in coma with severe metabolic acidosis and negative serum methanol
[13] 3 of them were diagnosed post-mortem and 2 patients died on admission before any specific treatment was initiated.

Table 5: Most common clinical symptoms on admission in 101 patients

Table 1. Laboratory data on admission on 101 hospitalized patients according to the outcome groups (medians, ranges, IQR).

	Age [Years]	Serum-Methanol [mmol/L]	Serum-Ethanol [mmol/L]	Serum-Formate [mmol/L]	Serum-Lactate [mmol/L]	pH	pCO_2 [kPa]	HCO_{3c} [mmol/L]	BD [mmol/L]	AG, [mmol/L]	S-glucose [mmol/L]	Time to treatment [hours]
Group I	53	21.7	3.0	10.6	2.1	7.31	4.35	17.8	−6.1	22	6.4	32
($n = 60$)	23–74	0–228.1	0–96.8	0–22.5	0.7–12.8	6.67–7.46	0.97–6.55	2.0–27.2	−0.1–−38.1	11–58	4.4–24.5	7–96
	24	36.9	18.3	14.7	1.6	0.25	1.42	14.0	−18.0	12	1.9	28
Group II	53	43.9	0.0	14.4	5.9	7.02	3.2	5.1	−21.0	32	9.6	42
($n = 20$)	33–73	6.2–218.5	0.0–49.5	8.9–21.2	0.5–16.3	6.65–7.39	1.3–5.2	2.5–18.7	−6–−36	17–50	5.5–19.8	12–72
	20	33.1	11.7	4.6	5.1	0.42	1.5	7.5	−15.0	8	6.3	22
Group III	57	29.0	0.0	15.5	9.5	6.75	4.4	5.2	−29.0	39	12.5	48
($n = 21$)	16–79	0–148.9	0.0–0.0	5.2–25.2	0.9–19.4	6.57–7.32	1.2–11.5	2.2–13.4	−11–36	19–49	2.9–21.6	24–72
	17	37.3	0.0	3.2	6.4	0.28	1.8	4.0	−7.0	10	6.3	39
Total ($n = 101$)	53	27.8	0.0	13.4	3.1	7.20	4.23	9.1	−17.0	28	7.3	48
	16–79	0.0–228.1	0.0–96.8	0–25.2	0.5–19.4	6.57–7.46	1.0–11.5	2.0–27.2	−0.1–−38	11–58	2.9–24.5	7–96
	22	41.6	11.0	10.9	6.1	0.46	2.0	16.5	−23.0	17	5.0	24
P_{I-II}	0.275	0.044*	0.188	0.001*	0.002*	<0.001*	0.016*	<0.001*	<0.001*	0.009*	0.003*	0.414
P_{I-III}	0.235	0.711	<0.001*	0.074	<0.001*	<0.001*	0.141	<0.001*	<0.001*	<0.001*	<0.001*	0.134
P_{II-III}	0.921	0.167	<0.001*	0.968	0.020*	<0.007*	0.616	0.194	0.009*	0.106	0.187	0.501

Group I – survivors without sequelae, Group II survivors with sequelae, Group III died.
BD, base deficit; AG, anion gap; OG, osmolal gap; IQR, interquartile range.
P_{I-II}, P_{I-III}, P_{II-III} – results of Chi^2 test of difference in laboratory parameters between the Groups I, II, and III ((statistically significant differences).
To convert from mmol/L to mg/dL use the following conversion factors: methanol – 3.205; ethanol – 4.608; formate – 4.603; lactate – 9.009; glucose – 18.018. To convert bicarbonate and base deficit from mmol/L to mEq/L use the conversion factor 1.0. To convert kPa to mmHg (torr) use the conversion factor 7.501.

Table 6: Treatment given in 101 patients separated by the three outcome groups

	Alkalization	Ethanol	Fomepizole	Folates	CVVHD/HDF	IHD
Group I ($n = 60$)	24 (40%)	49 (82%)	8 (13%)	47 (78%)	19 (32%)	20 (33%)
Group II ($n = 20$)	17 (85%)	10 (50%)	8 (40%)	17 (85%)	13 (65%)	5 (25%)
Group III ($n = 21$)	18 (86%)	11 (52%)	5 (24%)	11 (52%)	13 (62%)	5 (24%)
Total ($n = 101$)	59 (58%)	70 (69%)	21 (21%)	75 (74%)	45 (45%)	30 (30%)
P_{I-II}	<0.001*	0.005*	0.010*	0.519	0.008*	0.486
P_{I-III}	<0.001*	0.008*	0.260	0.023*	0.015*	0.416
P_{II-III}	0.948	0.879	0.265	0.025*	0.837	0.929

Notes: Group I – survivors without sequelae, Group II survivors with sequelae, Group III died.
CVVHD/HDF, continuous veno-venous hemodialysis/hemodiafiltration; IHD, intermittent hemodialysis.
P_{I-II}, P_{I-III}, P_{II-III} – results of Chi2 test of difference in treatment given between the Groups I, II, and III (*Statistically significant differences).

Outcome and prognosis:

There were 21 fatalities in hospital (hospital mortality 21%), other 20 patients died at home or before reaching hospital, giving a total mortality of 34%. Twenty patients (20%) were discharged from hospital with sequelae, with visual impairment diagnosed in nine, CNS impairment in four cases and both visual and CNS sequelae in seven cases. Among the 25 asymptomatic patients on admission, there were 24 (96%) survivors without sequelae, one patient got visual sequelae, and none died. The patients with symptoms of visual toxicity on admission (42/101) got visual sequelae on discharge in 33% of cases, and died in 29% of cases. On admission these patients had gastrointestinal symptoms in 71% of cases, dyspnoea in 55%, and chest pain in 21%. Overall, 36% (15/42) of these patients became comatose during the transfer to the hospitals or shortly upon admission to the emergency departments of hospitals, 5% of them had episodes of respiratory arrest. Most of these patients (83%) were administered sodium bicarbonate to correct metabolic acidosis, 90% were treated with antidote (ethanol in 59% and fomepizole in 31% cases) and haemodialysis (CVVHD/ HDF in 59% and IHD in 31%) and 71% of them were administered folate. The patients without visual sequelae on discharge were significantly less acidotic than those with visual damage ($p< 0.01$), and had lower serum methanol and formate (both $p< 0.01$). Coma upon admission was significantly more prevalent in the patients with visual sequelae ($p< 0.05$). The hospital treatment measures (haemodialysis, antidotes, folate substitution) in the patients without visual sequelae did not differ from the other groups. The 21 patients who died were more acidotic than the survivors with and without sequelae, and the difference in pH and base deficit was significant between all three groups.

Among the patients who recovered without sequelae, there was a trend toward lower pCO_2 when pH was increasing, while the opposite trend was seen among the dying patients (pH decreased/pCO_2 increased) ($p< 0.001$). Multivariate regression analysis evaluating the partial effect of laboratory and clinical features on mortality found coma, metabolic acidosis with pH<7.0, and negative serum ethanol on admission to be the only independent parameters predicting death. Arterial blood pH was the most important predicting parameter for the multivariate logistic regression model (logit) of risk of death. The probability of death changed

exponentially from approximately 77% for the cut-off pH of 6.6, 21% for the cut-off pH of 7.0. For the serum ethanol concentration on admission as the independent parameter predicting mortality the AUC was 0.77 (95% CI 0.68 – 0.86) There were no significant differences in mortality rate between any of the treatment modalities (IHD vs. CVVHD/ HDF, ethanol vs. fomepizole, or folate substitution 'yes/ no'). In the survivors, the difference in the prevalence of visual sequelae was not significant between those with and without folate therapy (p= 0.08). Most of the survivors with folate substitution (48/63, 76%), and half of those without folate therapy (8/16, 50%) were treated with haemodialysis.

Comment: Of the 101 patients treated at hospitals, 21 were administered fomepizole. There were no significant differences in mortality rate between either of the antidote treatment modalities (ethanol vs. fomepizole) despite fomepizole being reserved for patients with more severe methanol poisonings. Severity of metabolic acidosis, state of consciousness, and serum ethanol on admission were the only significant parameters associated with mortality. The type of dialysis or antidote did not appear to affect mortality. Recommendations that were issued for hospital triage of fomepizole administration allowed conservation of this valuable antidote in this massive poisoning outbreak for those patients most in need.

The main strengths of this study were:

i. The most comprehensive data ever presented after a methanol outbreak.

ii. Most of the essential clinical and laboratory data on admission were collected during the hospitalisations using standardised forms distributed to the hospitals by the TIC during the first weeks of the outbreak.

iii. The groups of patients were comparable by age, circumstances of poisoning, latency period, and size; most of the collected data exhibited normal distribution.

iv. The effect of each treatment modality and laboratory parameter on outcome was evaluated after adjustment for the effect of the remaining treatment modalities and laboratory parameters within the multivariate regression analysis.

Some of the limitations of this study were:

v. Data on some patients (such as history of poisoning and clinical symptoms on admission) were retrospective with their limitations.

vi. Possible variations in the time, amount and patterns of toxic spirits intake, individual differences in the methanol and formate metabolism, as well as the possible variations in the available modalities for treatment in different hospitals.

7.2.2.6. Zakharov et al, 2015: A prospective study in 38 patients with methanol poisoning

Study design, objectives

This was a prospective, uncontrolled observational study based on data from the Czech methanol mass poisoning in 2012 (Zakharov, 2014).

Patient characteristics, methods:

Patients were eligible if they met the following criteria: confirmed methanol poisoning, documented circumstances of methanol ingestion and time to diagnosis, and sufficient laboratory data, including arterial blood pH, serum methanol, and lactate and ethanol concentrations on admission. A diagnosis of methanol poisoning was made based on similar criteria to those described above in Zakharov, 2014. The patients were further divided into three groups according to the outcome: Group I, survivors without health sequelae; Group II, survivors with visual and/or central nervous system (CNS) sequelae; and Group III, patients

who died. Study treatments, comparison of admission data and analysis of results were same as that described for Zakharov, 2014 above.

Results

The 38 patients had a median age of 51 (37-62) years and included 28 males and 10 females. Only 10% of the patients were admitted within 12 h after the methanol ingestion, 53% within 48 h and 37% later than 48 hr. The type of toxic alcohol was known in 34 cases and the approximate quantity in 27 cases. The median amount of toxic spirits (volumes of the formulated spirits) consumed was 450 mL (range 100–800 mL). The methanol poisoning occurred due to unintentional ingestion of methanol-tainted ethanol in adulterated strong alcoholic beverages. Ten (26%) patients had co-ingested other alcoholic beverages without toxic amounts of methanol (wine, beer, whisky, home-made spirits) concomitantly.

The group of survivors without sequelae differed significantly in serum formate and lactate concentrations from the two other groups. A significant correlation was found between the aggregate concentration of serum formate and serum lactate and the severity of metabolic acidosis. In two patients, the serum concentrations of methanol on admission were under the limit of toxicity of 6.24 mmol/L. In both subjects[14], the measurement of formic acid proved to be useful for diagnostics and clinical management. In 12 patients, the methanol concentrations were under 15.6 mmol/L on admission, that is, under the serum level indicating haemodialysis; nevertheless, the median formate concentration in these 12 cases was 8.6 mmol/L (range 4.1–14.2 mmol/L), indicating the need for the application of enhanced elimination methods according to the present AACT/EAPCCT practice guidelines on the treatment of methanol poisoning.

The symptomatic patients had significantly higher serum formate concentrations than the asymptomatic ones (median of 2 mmol/L): the median serum formate in the patients with visual disturbance was 15.2 mmol/L (IQR 13.5–16.9 mmol/L), and in those with dyspnoea, it was 15.4 mmol/L (IQR 12.1–18.0 mmol/L), but signs of visual toxicity were present in one patient with serum formate as low as 3.7 mmol/L. Finally, the lowest serum formate concentration in a patient with coma on admission was 9.3 mmol/L, and the median for comatose patients was 15.7 mmol/L (IQR 12.8–18.5 mmol/L). The differences in serum formate concentrations in symptomatic patients depending on clinical features were not significant (all $p > 0.05$).

Most of the patients were severely acidotic on admission; therefore, bicarbonate was given aiming for full correction of the metabolic acidosis. All the patients were administered antidotes to block ADH, and ethanol was administered more often as a cheaper and more available antidote, whereas fomepizole was applied mainly in severely ill patients.

There were six fatalities in hospital, 15 patients (39%) were discharged from hospital without sequelae, and 17 patients (45%) had health sequelae of methanol poisoning. Among them, visual impairment was diagnosed in three cases, CNS impairment in five cases and both visual and CNS sequelae in nine cases. Patients with visual sequelae were found to have a median serum formate concentration on admission of 16.1 mmol/L (IQR 14.3–19.9 mmol/L). Patients with CNS sequelae had a median serum formate concentration of 15.9 mmol/L (IQR 14.2–19.5 mmol/L). The patients with both visual and CNS sequelae had a median serum formate concentration of 19.1 mmol/L (IQR 14.3–20.6 mmol/L). Finally, those who died had a median serum formate concentration of 15.2 mmol/L (IQR 13.8–15.9 mmol/L). The bivariate logistic regression (logit) model showed that the probability of a poor outcome (death or survival with sequelae) was higher than 90% in the patients with a serum formate concentration of at least 17.5 mmol/L, a serum lactate concentration of at least 7.0 mmol/L and/or an arterial blood pH

[14] In one case, the serum formate was very high, 15.2 mmol/L, confirming that in late-presenting patients, most of the methanol might be bio transformed into this metabolite. In the other case, the serum formate was at the upper reference limit, confirming minor methanol poisoning.

lower than 6.87. Receiver operating characteristics (ROC) curve analysis was used to examine how the serum formate concentration alone and combined with the serum lactate concentration predicted survival without visual and CNS sequelae. It showed that the corresponding areas under the curve (AUC) were 0.64 (95%CI 0.44–0.85) I for the serum formate and 0.75 (95% CI 0.56–0.93) for 'S-formate + S-lactate'. The difference between the two was not significant (p = 0.23), because the analysis was based on data from only 38 patients.

Comment: This was the most comprehensive data on formate measurements after methanol poisonings and results suggested that:

i. Serum formate concentration is a more reliable indicator of the severity of poisoning in patients presenting 48 or more h after toxic spirit ingestion, when much of the ingested methanol might already have been metabolised or in unclear cases with the serum methanol concentrations are close to the toxic limit.

ii. Serum formate unlike serum methanol concentration alone or with serum lactate concentration, as well as the severity of metabolic acidosis, should be used as decisive parameters for the application of haemodialysis in subjects with serum methanol <15.6 mmol/L in underdeveloped countries where resources are scarce, checking methanol levels with gas chromatography may not be possible and the enzymatic measurement of serum formate may be more practical.

Limitations of this study were as follows:

iii. Confounding factors due to nature of retrospective data (history, of poisoning, amount of toxic spirits and clinical symptoms on admission).

iv. Individual differences in methanol and formate metabolism.

7.2.2.7. Paasma et al, 2012

Retrospective observation case series of methanol-poisoned patients from Norway (Hovda, et al., 2005), Estonia, Tunisia and Iran who were identified by positive serum methanol and had a blood acid-base status drawn on admission. Overall, 203 patients were included in the study, of which 32 were given fomepizole and the remaining 171 were administered ethanol alone. There were 48 deaths and 34 patients were discharged with neurological sequelae.

Using data from all patients, multiple-regression analysis and the ROC curve identified pH and coma to be the strongest prognostic factors, which is consistent with results from previous studies. A pH < 7.00 was found to be the strongest risk factor for poor outcome, along with coma (Glasgow Coma Scale (GCS)< 8) and a $pCO_2 \geq$ 3.1 kPa in spite of a pH< 7.00. Despite the low number of patients in the fomepizole group, the analysis suggested a *trend* (non-significant) toward a leftward shift in morbidity and mortality (that is, better outcomes) regarding the pH, but this difference was not significant. In spite of the severe metabolic acidosis reflected by low pH, more patients who were administered fomepizole survived with sequelae instead of dying compared with patients with a similar pH treated with ethanol.

Due to the small number of fomepizole patients, the analysis was more sensitive to outliers, such as one of the patients in the fomepizole Group III who died despite having a pH of 7.13 on admission. The diagnosis of this patient was delayed, and treatment was not initiated until 6 h after admission, at which time the patient was already much more acidotic (pH 6.8) and in a coma. Without this one outlier, the difference between the two antidote groups would be significant (p= 0.038). Further, there was a trend toward hyperkalaemia in the poor-outcome fomepizole groups (Group II and III), whereas many of the surviving patients treated with ethanol suffered from sequelae despite having a normal serum-K (not significant). Finally, patients in the ethanol group seemed to die significantly more often despite (spontaneous) hyperventilation relative to patients in the fomepizole group (p=0.034). The authors proposed a risk assessment chart to predict the patient's outcome based on admission data.

Comment: Interpretation from the above analysis was confounded by the following factors:

i. Not possible to compare the outcomes from the two antidotes directly in retrospective studies as the morbidity and mortality associated with methanol poisoning depend on the time from methanol intake to the initiation of treatment, the amount of formic acid produced and the degree of metabolic acidosis.

ii. Possible variations in the time from intake to the start of treatment, and the available modalities for treatment (other than the antidote).

iii. The limited number of patients in the fomepizole group, the analysis was more susceptible to the effects of outliers. Hence the positive trend observed in this study would require a prospective study and also a larger fomepizole group to confirm any benefits of fomepizole over ethanol.

7.2.3. Fomepizole treatment for methanol poisonings in paediatric patients

Brent et al. 2010 reviewed the published literature to identify published cases of paediatric patients treated with fomepizole; 14 patients were identified as being of relevance to the topic, of which 2 were intoxicated with methanol. Both cases had a similar degree of severity and one was haemodialysed. Both patients recovered without reported sequelae and did not have any reported adverse events of fomepizole administration (Brent, 2010).

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 (Brown, et al, 2001).

7.2.4. Other studies

Hovda 2005 report serum methanol kinetics in 8 patients treated with bicarbonate and fomepizole only. This was a prospective case series study of 8 patients with methanol poisoning, who were selected to fomepizole and bicarbonate treatment only, because of moderate metabolic acidosis. Three of the patients were later dialysed, because of high serum methanol concentrations and very slow methanol elimination.

7.2.4.1. Results

Upon admission the median pH was 7.27 (range 7.12–7.50), median base deficit was 15 mmol/L (5–22 mmol/L) and median serum methanol was 20.4 mmol/L (65 mg/dL) (range 8.4–140.6 mmol/L). The kinetics of methanol during fomepizole treatment in six patients was best described by a first-order elimination one-compartment model.

The mean correlation coefficient (R2) describing the first-order elimination model in all eight patients was 0.95 (range 0.90–0.99). The mean plasma half-life ($T_{1/2}$) of methanol during fomepizole treatment was 52 h (range 22–87); the higher the serum methanol, the longer the $T_{1/2}$. Mean half-life of serum formate was 2.6 h, when methanol metabolism was assumed blocked by fomepizole and no folinic acid was given. This rapid formate elimination in non-acidotic patients may be explained by high renal excretion of formate.

Comment: Based on their data, the authors suggest that methanol-poisoned patients with moderate metabolic acidosis (pH>7.10 and base deficit <22 mmol/L) and visual disturbances that are reversed by the initial bicarbonate administration may safely be treated with fomepizole only. However, it is important to note that dialysis does shorten the period of hospitalisation when the serum methanol is high (>19 mmol/L or 60 mg/dL).

7.2.4.2. Case reports

From the literature, detailed information regarding 8 individual cases including 2 paediatric methanol intoxications, were identified. These case reports 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.

7.2.5. Analyses performed across trials (pooled analyses and meta-analyses)

After approval of Antizol (fomepizole, 4MP) was granted by the FDA for treatment of ethylene glycol poisoning, a supplemental NDA was submitted to seek approval for the use of Antizol as an antidote for methanol or suspected methanol poisoning. This integrated summary was provided in the sponsor's submission.

7.2.6. Evaluator's conclusions on clinical 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 10-20 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 (Hovda et al 2005 and Brent et al. 2001) 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 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 patients (Hovda, 2005) and another retrospective study in 14 patients [Megarbane et al. 2001, 2004], 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 (Brown, et al, 2001).

Three retrospective/prospective study reports on methanol poisoning outbreaks in Norway (Hovda, 2005) and Czech Republic (Zakharov, 2014 and 2015) 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 GI symptoms were the most frequent clinical features, whilst severe metabolic acidosis (pH < 6.90, BD > 28 mmol/L), coma and increased pCO_2 (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 (Table 2) and paediatric (Table 3) 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.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy studies

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.

8.1.2. 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 S-6 were clinical pharmacology studies assessing the pharmacokinetic and pharmacodynamic parameters of fomepizole.

8.1.3. Pivotal studies that assessed safety as a primary outcome

None.

Comment: Due to complexity of this literature based dossier, the safety sections of this evaluation report will be discussed as follows:
Section 8.4.1: evaluation and discussion of the safety results of the individual clinical studies in patients.
Section 8.4.2: evaluation and discussion of the safety results from each of the clinical pharmacology studies in healthy subjects.
Section 8.4.3: evaluation and discussion of the main safety results from other important published studies and case reports.
Section 8.5: 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).

8.2. Pivotal studies that assessed safety as a primary outcome

None.

8.3. Patient exposure

8.3.1.1. 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.

8.3.1.2. 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/ Retro-spective	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/ Pro-spective	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, Burkhart 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 P, 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 8 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 Antidotal Efficacy and Pharmacokinetic Profile of Antizol™ (fomepizole) for the Treatment of Methanol Poisoning	Brent J, Burkhart 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.

8.3.2. Safety results of the individual pivotal studies in patients

Brief summary of the safety results in studies in patients was provided in Pivotal efficacy studies above.

8.3.2.1. Study S7

All 38 patients that received fomepizole regardless of actual intoxication status were included in the analysis of safety; 25/38 patients (66%) reported 84 AEs including headache, vomiting, abdominal pain anaemia and fever. Ten AEs were reported in 3/5 patients (60%) of patients in Cohort B. The majority of these AEs were judged by the investigator to be mild to moderate. No serious adverse events were reported and no patient discontinued the trial. No clinically significant laboratory abnormalities were noted at last evaluation.

8.3.2.2. Study S8

Overall, 22 patients were treated for suspected or confirmed EG poisoning in this open-label, prospective study. All patients received 4MP via intravenous infusion; loading dose 15 mg/kg, then 10 mg/kg q12h for 4 doses then 15 mg/kg until EG <20 mg/dL. The most frequent AE was acute renal failure which occurred in patient who had signs of established renal insufficiency at presentation and was not related to treatment as renal injury is the most common major complication of EG poisoning. There was one death which was attributed to the severe intoxication and significant time delay to treatment and unrelated to the treatment regimen. One case of hypotension also occurred in this patient and the relationship with the study drug was deemed unknown by the investigator and occurred in a patient who had evidence of a concurrent acute myocardial infarction on presentation. The patient rapidly developed cardiogenic shock and died; this patient also experienced seizure. Four other AEs were judged to be related to the study drug by the investigator, of which each occurred once over the course of the study. These were emesis, headache, abdominal pain and vertigo. Other AEs were unrelated to study medication as judged by the investigators. There were non-clinically significant abnormalities noted for ECG, cranial nerve assessments, or ophthalmic evaluations. With the exception of the hypotension noted for one patient, no clinically significant vital sign abnormalities were observed. No clinically significant laboratory abnormalities were noted with the exception of those related to the effect of the EG poisoning itself. In contrast to the observations in earlier studies in healthy subjects (S2 and S4), no elevations in liver enzymes were observed in this trial.

8.3.2.3. Study S13

The highest cumulative dose of fomepizole in this study was 8445 mg. Due to the comatose status of one patient an error was made in estimating the patient's weight so that he actually received a loading dose of 22 mg/kg. The patient tolerated the dose well and completed the study alive with ongoing baseline sequelae of lower left lung infiltrate. Overall, 37 AEs were reported by 13/15 patients (87%). The majority were mild to moderate and considered related to concurrent illness (67%). The most frequently reported AEs were agitation (33.3%) anxiety (20%), fever (20%) and headache (13.3%). Three SAEs were reported by two patients (toxic encephalopathy, rhabdomyolysis and right deep vein thrombosis) and both patients died (one patient during the study and the other patient 20 days after end of the trial). Both deaths were due to toxic encephalopathy secondary to severe methanol poisoning. No patients discontinued due to an AE. There were no clinically significant abnormalities for cranial nerve assessment, vital signs or physical examinations.

8.3.2.4. Study S10

Baud et al, 1986: The only obvious AE in this study was a skin rash in one of three patients and possible eosinophilia in two others.

8.3.2.5. Study S11

Harry, et al, 1994: This was a case of a 30 year old male with EG poisoning treated with IV fomepizole (loading doses of 16.2 mg/kg or followed by q12h doses of 8.1, 5.4, 2.7 and 1.35 mg/kg). During 5 days of hospitalisation the only observed AE of 4MP treatment was a mild transient elevation in AST activity to 36 IU/L on the third day (normal <30 IU/L). Examination of the patient 15 days later revealed no clinical or biochemical abnormality.

8.3.2.6. Study S12

Jobard, et al, 1996: This study reported the cases of two patients severely intoxicated with EG. The first patient made a full clinical recovery without any AEs. The second patient suffered multiorgan failure and death. The authors concluded that the death of this patient admitted very late after massive EG ingestion with a flat electroencephalogram cannot be attributed to failure of treatment

8.3.3. Safety results of the individual clinical pharmacology studies in healthy subjects

8.3.3.1. Study S2

Safety and PK study of 6 healthy males between the ages of 23 and 35 using single IV bolus or oral doses of 7 mg/kg. Safety results included mild and brief instances of light-headedness, skin rash, venous irritation, phlebosclerosis, nausea and headache after IV doses. Some elevation in triglycerides, CPK and ketonuria was observed, although none were clinically significant.

8.3.3.2. Study S3: Jacobsen et al, 1988 and 1989

Single ascending oral dose study of the safety of fomepizole (10, 20, 50 and 100 mg/kg) in 22 healthy males ages 20-40: No side effects were observed at 20 mg/kg dose. Slight nausea observed at 10 mg/kg. At 50 or 100 mg/kg nausea, vertigo, dizziness, feeling of drunkenness, loss of appetite and increases uric acid were reported. Slight transient liver impairment (elevation of liver transaminases) was observed but was not consistent with increasing doses of fomepizole (4MP given orally).

8.3.3.3. Study S4: Jacobsen, 1990

Subjective side effects were reported in 50% of the placebos (3/6) and 47% of the drug subjects (7/15). The side effects reported at various times in both groups were dizziness, light-headedness, diarrhoea and headache. All effects were rated mild and of short duration and no relationship with the study drug as apparent. Six (40%) of the drug subjects had an increase in

one or both serum transaminase levels. The elevation was mild, and in all of these subjects the follow-up values had not returned to normal when measured about 1 to 2 weeks following completion of the study.

8.3.3.4. Study S5

All subjects subjectively evaluate their side effects on a 1-3 scale. All subjects were also checked for objective signs or side effects at each vital sign checkpoint. Other than the predictable side effects related to moderate ethanol consumption, the side effects reported by these subjects were abnormal taste and small, local tingling, mild nausea, dizziness, headache and diarrhoea. An instance of hyperglycaemia was also reported. There was no irritation or phlebosclerosis reported in the 9 subjects who were given fomepizole as a 30 minute IV infusion.

8.3.3.5. Study S6 (Jacobsen, 1996)

This was a study which evaluated the mutual inhibitory effect between ethanol and 4MP on their elimination following single oral doses of 10, 15 and 20 mg/kg of 4MP with and without ethanol in a double-blind, placebo controlled, crossover study; the second part of the study involved IV 4MP with oral ethanol or placebo.

Comment: The actual reference provided by the sponsor did not provide any safety results for this study. However, the following was provided in the sponsor's Summary of clinical safety: '*The major AEs experienced by these subjects were related to the moderate intoxication produced by the ethanol. The subjects all reported subjective effects that would be considered characteristics of ethanol, but with equivalent occurrence whether given 4MP or placebo. Side effects observed included lethargy, facial flush, nausea, vomiting, blurred vision, hangover and diarrhoea. No laboratory abnormalities related to 4MP were observed*.' However, the source of this data was not provided and the sponsors have been requested to clarify.

8.3.4. Additional Safety results from the published studies and case reports

8.3.4.1. Prospective and retrospective studies:

In the single patient that was treated for EG poisoning 154 times (99 of which were with fomepizole only, and 6 with combination fomepizole and ethanol), except for renal impairment (most probably caused by the calcium monohydrate crystals from EG metabolism), there were no signs of organ damage after repetitive use of fomepizole as judged from findings on admission to hospital, on discharge from hospital, and on the autopsy performed at her eventual death. This suggested that the use of fomepizole is safe even when used frequently (Hovda, et al, 2011).

Of the 38 patients administered fomepizole for clinical suspicion of EG poisoning and reported by Borron et al. 1999, side-effects that were regarded as possibly related to fomepizole occurred in four patients, probably related in 1 patient and definitely related in one patient. Side-effects included two events each of pain/inflammation at the site of injection and transient eosinophilia, and one event of generalised cutaneous eruption.

In patients treated for EG poisoning reported by the Methylpyrazole for Toxic Alcohols (META) study group (Brent et al., 1999), no AEs were rated as definitely or probably related to fomepizole. Adverse events that were possibly related to fomepizole were bradycardia (2 patients), seizure (2 patients) and headache (2 patients).

In the META study for methanol poisoning (Brent et al., 2001), AEs in six patients were classified by the treating physicians as possibly related to fomepizole. These were phlebitis, dyspepsia, anxiety, agitation, hiccups, reaction at the infusion site, transient tachycardia, transient rash and a 'strange' feeling. Each of these events occurred in only one patient, except for agitation, which was reported by two patients. The rash that occurred after four doses of fomepizole in one patient who had a history of allergic reactions to sulphonamide drugs and

who was also receiving methadone, clonidine, lorazepam, and vitamins. He received two additional doses of fomepizole, with no recurrence of the rash.

Levine et al. (2012) did not report any AEs that were related to treatment with fomepizole in 40 patients with EG intoxication without haemodialysis.

In another retrospective study for the treatment of methanol poisoning (Mégarbane et al., 2001), most patients received between 1 and 4 doses of fomepizole. However, three patients received 5, 6 and 16 doses, representing total doses of 4000, 6000, and 5025 mg (57.1, 88.2 and 75.0 mg/kg), respectively. Despite these relatively high cumulative doses, AEs were rare. Nausea and headache occurred in one patient, lymphangitis, a burning skin sensation and mild transient eosinophilia in the patient receiving 16 doses, and fever was observed in two patients (one of whom received 4 doses). During fomepizole treatment, prothrombin time, liver function tests, creatine phosphokinase and platelet and white blood cell counts remained stable.

8.3.4.2. Adverse drug events associated with the use of ethanol vs. fomepizole

Lepik, et al (2009) reported a cohort study which investigated patients aged ≥ 13 years if they were hospitalised between 1996–2005 for methanol or ethylene glycol poisoning and treated with at least 1 dose of ethanol or fomepizole. The primary outcome was at least 1 adverse drug event, expressed as adverse drug event rate per person-day of antidote treatment. Association between time to first adverse drug event and antidote type was modelled by Cox regression, adjusted for confounders. Overall, 223 charts were reviewed and 172 analysed. The fomepizole treated cases had higher pre-treatment APACHE II scores[15] than the ethanol-treated cases, indicating more severe illness at baseline. Use of non-antidote treatments was similar between treatment types, although a higher proportion of fomepizole treated cases receiving haemodialysis and sodium bicarbonate. All fomepizole- and 115 (88%) of ethanol-treated cases received antidote exclusively by the intravenous route. Median antidote duration was approximately 24 h for both groups. Fifteen cases received both antidotes, all switched from ethanol to fomepizole. Toxicologists identified at least 1 adverse drug event in 74 of 130 (57%) ethanol-treated and 5 of 42 (12%) fomepizole-treated cases. CNS symptoms accounted for most adverse drug events (48% ethanol-treated, 2% fomepizole treated). Severe adverse drug events occurred in 26 of 130 (20%) ethanol-treated (coma, extreme agitation, cardiovascular) and 2 of 42 (5%) fomepizole-treated (coma, cardiovascular). Serious (life-threatening) adverse drug events occurred in 11 of 130 (8%) ethanol-treated (respiratory depression, hypotension) and 1 of 42 (2%) fomepizole-treated (hypotension, bradycardia) cases. Median adverse drug event onset was within 3 h after the start of either antidote. Ethanol and fomepizole adverse drug event rates were 0.93 and 0.13 adverse drug events per treatment-day, respectively. Adjusted hazard ratio was 0.16 (95% confidence interval 0.06, 0.40) suggesting a 6-fold reduction in AEs rate in the fomepizole group compared with ethanol.

Comment: The above results should be interpreted with caution due to the following limitations of this cohort study:

i. This was an observational study and cases were not randomised to treatment groups.

ii. Number of patients in the fomepizole group was much lesser compared to the ethanol group (40 vs 130).

iii. Use of hospital chart data, which are susceptible to misclassification (for example, incorrect documentation of symptom onset times) and missing information (which could underestimate event frequency).

iv. Chart abstracters and reviewers were not blinded to the study.

[15] Acute physiology and Chronic Health Evaluation II is a severity of disease classification system (Kraus, et al, 1985) and is one of the several ICU scoring systems;

v. Overall, it is very difficult to come to any definitive conclusions regarding comparative safety of fomepizole vs ethanol as an antidote for EG/methanol poisonings due to co-ingestants, other treatments, effects of toxic alcohol poisoning and other medical conditions.

Lepik, et al (2011) described and compared the frequency, type, outcome and underlying causes of medication errors associated with ethanol and fomepizole. Using the same cohort as the previous study (Lepik et al. 2009) the authors used Fisher's exact test to determine differences in the proportion of ethanol and fomepizole treated cases with medication error and univariate logistic regression to identify risk factors associated with harmful dosage errors.

There were 145 ethanol- and 44 fomepizole-treated cases with similar baseline characteristics with exception of fact that voluntary poison control service consultation occurred in 100% of fomepizole- but only 50% of ethanol-treated cases. There was ≥ 1 medication error in 113/145 (78%) ethanol- and 20/44 (45%) fomepizole-treated cases (p = 0.0001) with more ethanol-related errors involving excessive dose, inadequate monitoring and inappropriate antidote duration. Harmful errors occurred in 19% of ethanol and 7% of fomepizole-treated cases (p=0.06) and were largely due to excessive antidote dose or delayed antidote initiation. Occurrence of harmful dosage error was reduced in cases with Poison Control Centre consultation, odds ratio (95% CI) 0.39 (0.17, 0.91), haemodialysis 0.37 (0.16, 0.88), or fomepizole versus ethanol 0.24 (0.06, 1.04). Poison Control Centre consultation and haemodialysis treatment had a significant protective effect against harmful dosage errors, with odds ratios (OR), (95% CI) of 0.39 (0.17, 0.91) and 0.37 (0.16, 0.88), respectively. Use of fomepizole reduced the risk of harmful dosage error relative to ethanol, OR (CI 95%) 0.24 (0.06, 1.04), but did not achieve statistical significance. Overall, the authors concluded that fomepizole was less prone to medication error than ethanol. Error-related harm was most commonly due to excessive antidote dose or delayed antidote initiation.

Comment: Overall, fomepizole was less prone to medication error than ethanol. Error-related harm was most commonly due to excessive antidote dose or delayed antidote initiation. However, the above results should be interpreted with caution due to the following limitations of the above study:

i. This was an observational study and cases were not randomised to treatment groups.

ii. Number of patients in the fomepizole group was much lesser compared to the ethanol group (44 vs 145).

iii. Poison Control Centre consultation occurred in 100% of fomepizole-treated patients compared to only 50% of the ethanol-treated patients; this is especially important as consultation had a significant protective effect against harmful dosage errors.

iv. Documentation of medication errors by hospital chart review is susceptible to missing information. Information was less complete for ethanol than for fomepizole-treated cases.

v. Chart abstracters and reviewers were not blinded to the study.

8.3.4.3. Case reports

In addition to the case reports provided by the manufacturer, two other case reports identified in the systematic review presented treatment emergent AEs associated with fomepizole.

Transient nystagmus within 2 h of IV infusion of 15 mg/kg fomepizole in a 6-year old girl that ingested ethylene glycol and the event lasted one hour. However, the more commonly cited AEs associated with fomepizole, such as headache, nausea and dizziness were not obvious in this patient (Benitez, 2000).

Lepik et al (2008) reported a case of hypotension and bradycardia associated with IV fomepizole infusion. A 59-year old man presented to hospital 10 years after EG ingestion with ataxia, slurred speech, metabolic acidosis, heart rate 70/min, blood pressure 160/100 mmHg. Treatment with haemodialysis and fomepizole began 7.5 h after admission. Severe bradycardia (29/min) and hypotension (69 mmHg systolic) occurred immediately following a 30 minute IV infusion of the first (19 mg/kg) fomepizole dose, but was rapidly corrected with 1 mg atropine. Transient bradycardia (48/min) and hypotension (89/57 mmHg) recurred immediately after the second (10 mg/kg) fomepizole dose, also given during dialysis. There was a dose dependent symptoms intensity and recurrence with rechallenge (with fomepizole) that suggest a causal relationship between fomepizole and the adverse events experienced. The authors concluded that the patient probably suffered an idiosyncratic reaction to fomepizole. This patient was included in the cohort of patients in subsequent publications by these authors (Lepik et al. 2009, 2011).

The other case reports did not provide safety data.

8.4. Integrated summary of safety (ISS)

The objective of the ISS provided was to integrate 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.

8.4.1. Adverse events:

8.4.1.1. AEs in patients

Overall, 60 of the 78 patients (76.9%) experienced at least one AE. The 60 patients included 25 of the 38 patients in Study S-7 (84 events), 19 of the 22 patients in Study S-8 (69 events), 13 of the 15 patients in Study S-13 (27 events), and all three patients reported in Study S-11 and Study S-12 (4 events). A total of 184 AEs were reported. The body systems most affected were Body as a Whole (51.3%), Nervous System (33.3%), Respiratory System (30.8%), Digestive System (26.9%), Urogenital System (25.6%) and Cardiovascular System (23.1%). The most frequently reported AEs were fever (14.1%) and acute renal failure (14.1%). Other common AEs were headache (11.5%), vomiting (7.7%) and agitation (7.7%).

8.4.1.2. AEs in healthy subjects[16]

The most common AE was nausea, which occurred in 14 subjects receiving fomepizole (22%) and in one subject (4%) on placebo. Headache was reported by 13 fomepizole subjects (21%) and two placebo subjects (8%). Although these events occurred with greater frequency among fomepizole-treated subjects, the temporal relationship to dosing was not consistent. An unpleasant taste was sometimes associated with both oral and intravenous administration of fomepizole (8 subjects, 13%); 3 subjects (5%) complained of an abnormal smell with IV dosing. Dizziness was reported by 9 subjects who received fomepizole (14%), especially at higher oral dosage levels (50 and 100 mg/kg) and by one placebo subject (4%).

8.4.1.3. AEs in combined healthy subjects and patients (n=141)

Overall 138 of the 141 (97.9%) combined subject/patient population reported at least one AE. A total of 262 events were reported. The body systems most often involved were Body as a Whole (38.3%), Nervous System (37.6%) and Digestive System (29.1%). The most frequently reported

[16] AEs that occurred in healthy subjects were counted for each specific treatment period during which the event occurred. Thus, identical events occurring in the same subject during different treatments were counted once for each treatment period.

AEs were headache (n=22; 15.6%), 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%). All other events were reported in <2.1% of patients.

8.4.2. Drug-related AEs

8.4.2.1. AEs in patients

Overall, 53 of the 78 patients (67.8%) experienced 53 drug related AEs. The body systems most affected were Body as a Whole (23.1%), Nervous System (11.5%), Cardiovascular (7.7%) and Hemic/Lymphatic (7.7%). The most frequently reported drug-related AEs were headache (n=7; 9.0%), abdominal pain (n=4; 5.1%), vomiting (n=3, 3.8%) and fever (n=3, 3.8%). Majority of AEs for which severity assessments were' made were mild or moderate in intensity. Hypotension and seizure in Study S-8 were rated severe with unknown relationship to study drug. The severe hiccups (possibly related to study drug) reported in Study S13 resolved three days after fomepizole dosing had been discontinued. The remaining AEs were not rated in intensity or relationship to study drug by the Investigator and were entered into the database as 'unknown' for both of these categories. These included agitation, anxiety, dyspepsia, headache (N=1), multiorgan system failure, disseminated intravascular coagulation, anuria and lymphangitis.

8.4.2.2. AEs in healthy subjects[17]

AEs were not rated for intensity or by relationship to study drug per FDA guidelines in the healthy subject studies (N=63). Brief periods of light-headedness, decreased environmental awareness, and a feeling of drunkenness were also reported with IV and high oral doses. These events correlated with high plasma levels of fomepizole and were probably drug-related. However, concomitant ethanol administration in some subjects reporting these AEs made assessment of causality difficult. The only events definitely attributed to treatment with fomepizole were phlebosclerosis, abnormal smell, and bad taste, the latter occurring during both IV and oral administration. Phlebosclerosis occurred only in subjects receiving a 25 mg/mL bolus injection over 5 minutes (Study S-2). This concentration and infusion rate was higher than those used in the subsequent intravenous study, S-5 (2 mg/mL over 30 minutes). None of the five subjects in S-5 developed phlebosclerosis in either fomepizole treatment period.

8.4.2.3. AEs in combined healthy subjects and patients (n=141)

Overall, 134 of the 141 subjects/ patients (95%) experienced 134 drug-related AEs. The body systems most affected were Nervous System (25.5%), Body as a Whole (22.7%), Digestive System (17.7%) and Special Senses (11.3%). The most frequently reported drug-related AEs 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%). The incidence of all remaining events was <2.8% and included application site reaction, vomiting, rash, and abnormal smell. AEs were not rated for intensity or by relationship to study drug per FDA guidelines in the healthy subject studies (N=63). Therefore, all events noted in this group were included as 'unknowns.

8.4.3. Deaths, SAEs and discontinuations due to AE

Six deaths were reported during fomepizole treatment: one in Study S7, 3 in Study S8, 1 each in studies S12 and S13. Two additional deaths were reported post study (a patient in Study S13

[17] AEs that occurred in healthy subjects were counted for each specific treatment period during which the event occurred. Thus, identical events occurring in the same subject during different treatments were counted once for each treatment period.

died 20 days post-study and another patient in Study S7 died 11 months after treatment. Review of the death narratives suggested that the deaths did not appear to be related to fomepizole treatment.

AEs collected in Study S7 were not assessed for seriousness according to the FDA definition. However, six serious events that resulted in the death of one patient were life-threatening (metabolic acidosis, collapse, acute renal failure, anuria- all present prior to fomepizole administration; convulsions and fever) and the investigator rated all of these events as severe and not related to study drug. Three other patients in Study S7 were transferred to other facilities for continuing treatment of adverse experiences. Prolongation of hospitalisation would be considered as serious by the FDA definition. The events were 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 AEs that occurred in ten patients in Study S8 were considered serious. All 13 of these events (liver failure, myocardial infarction, and cerebral oedema in one patient each and acute renal failure in ten patients) were judged by the Investigator to be due to EG or acetaminophen poisoning, and unrelated to fomepizole treatment.

In Study S12, the events leading to death in one case were multi-organ system failure and disseminated intravascular coagulation, which were life-threatening, although no assessment of seriousness was reported by the Investigator.

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. All three events were coded by the Investigator as severe and not related to study drug. Both patients subsequently died.

One patient in Study S7 was discontinued from treatment with fomepizole after two doses but no details were available. In Studies S8 and S13, seven patients were discontinued after being enrolled and after receiving a loading dose of fomepizole and repeat laboratory reports indicated that none of these patients had ingested ethylene glycol (N=3) or methanol (N=4) . All patients were included in safety assessments of the respective study reports. No patient discontinued due to an AE.

8.5. Post-marketing experience

No PSURs were provided in this submission.

8.6. Safety issues with the potential for major regulatory impact

8.6.1. 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.

8.6.2. Haematological toxicity

Eosinophilia is a known AE associated with fomepizole treatment.

8.6.3. Serious skin reactions

None.

8.6.4. Cardiovascular safety

None.

8.6.5. 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.

8.7. Other safety issues

8.7.1. Safety in special populations

8.7.1.1. Paediatric patients

Brent et al (2010) reported 14 published cases related to fomepizole treatment in paediatric patients with EG (N=10), methanol (n=2) or other (diethylene glycol & butoxyethanol, n=2) poisoning. The one adverse effect reported during fomepizole therapy was transient nystagmus in a 6-year-old with a serum EG concentration of 130 mg/L and a serum bicarbonate concentration of 2 mEq/L.

8.7.1.2. *Elderly patients*

Not evaluated.

8.7.1.3. Renal, Hepatic impairment

Not evaluated.

8.7.2. Safety related to drug-drug interactions and other interactions

No specific studies were conducted to evaluate safety of fomepizole when administered with other ADH inhibitors or drugs that act on the CYP-450 enzyme system.

8.7.3. Overdose, abuse potential

Nausea, dizziness and vertigo were noted in healthy volunteers receiving 50 and 100 mg/kg doses of Antizol (at plasma concentration of 290–520 µmol/L, 23.8 – 42.6 mg/L). These doses are 3-6 times the recommended dose. This dose-dependent CNS effect was short-lived in most subjects and lasted up to 30 h in one subject. Antizol is dialysable, and haemodialysis may be useful in treating cases of overdosing.

Fomepizole is not recommended in pregnant/ nursing women or paediatric population unless the benefits outweigh the risks.

8.8. Evaluator's overall conclusions on clinical 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 (Lepik, 2009 and 2011). 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 (discussed in section 8.4.2 above). 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 ISS provided was to integrate 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.

9. First round benefit-risk assessment

9.1. 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.

9.2. First round assessment of risks

The risks of fomepizole in the proposed usage are:

- 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 (for example, 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 25mg/mL.
- Common AEs associated with fomepizole treatment were vertigo, nausea, vomiting, abdominal pain, headache, unpleasant taste/ smell, eosinophilia and rash.

9.3. 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, lightheadedness, 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 10-15 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.

10. 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 in section 11 of this evaluation report.

11. Clinical questions

11.1. Pharmacokinetics

2. *It appears that Study S6 is the Jacobsen, 1996 reference. However, this is not clearly stated in the dossier and in fact the clinical summary of safety in Module 2 mentions that Study S5 is Jacobsen, 1996 which contradicts with the tabular summary provided in the ISS. Furthermore, there was no Study S5 submitted in the dossier although it is mentioned in the various tabular summaries. Could the sponsors provide clarification on the identity and location of these PK studies in the dossier?*

3. The actual reference (Jacobsen, 1996) provided did not provide any safety results for Study S6. However, the following was provided in the sponsor's Summary of clinical safety: '*The major AEs experienced by these subjects were related to the moderate intoxication produced by the ethanol. The subjects all reported subjective effects that would be considered characteristics of ethanol, but with equivalent occurrence whether given 4MP or placebo. Side effects observed included lethargy, facial flush, nausea, vomiting, blurred vision, hangover and diarrhoea. No laboratory abnormalities related to 4MP were observed*.' However, the source of this data was not provided and it is requested that the sponsors provide clarification.

11.2. Pharmacodynamics

None.

11.3. Efficacy

Paediatric methanol or ethylene glycol poisonings: Brent et al. 2010 reviewed the published literature to identify published cases of paediatric patients treated with fomepizole. Fourteen patients were identified as being of relevance to the topic, of which *210* were intoxicated with ethylene glycol. (sponsor's Clinical summary of efficacy)

4. *There appears to be a typographical error in the above statement which should read 10 of the 14 patients. Could the sponsors please confirm this?*

Study report of OMC-4MP-2 had the following: '*Seven of 11 patients* (64%) presented with formate levels in the non-detectable range (less than 1 mmol/L). Among the *remaining six patients,* one (9%) had a formate level in the moderate range (1 to 9 mmol/L) and the remaining five patients (45%) had formate levels in the severe range (>9 mmol/L).'

5. *The above paragraph is inaccurate as there were only 11 patients in all. Please provide clarification.*

Jacobsen, et al (1990) reported placebo-controlled, double blind, multiple dose, sequential, ascending-dose study has been performed to determine the tolerance of 4MP in 21 healthy volunteers. Oral loading doses of 4MP were followed by supplemental doses every 12 h through 5 days, producing plasma levels in the therapeutic range. Dose schedule in Group 3 (oral loading dose of 10 mg/kg, plus 5 mg/kg every 12 h up to 36 h and then 10 mg/kg every 12 h up to 96 h) seems to be the best at maintaining therapeutic levels for up to 5 days.

6. *Results of the Jacobsen, 1990 study appear to be identical to those reported by McMartin, 2012. The sponsors have been asked to clarify this.*

In the pivotal, Phase III, open-label Study S8 (OMC-4MP-2), the study reports submitted mentions that 21 trial centres in USA were initiated as potential enrolment sites. For purposes of this interim report (dated 29 October, 1996), only four of those sites actually enrolled patients into the trial.

6. *Did this study continue to enrol patients and if so could the sponsors provide an updated final study report?*

Brown, 2001. 'Childhood methanol ingestion treated with fomepizole and haemodialysis.' *Paediatrics* 2001;108;e77. This literature reference in Module 5.4 has the following sentence on page 2 of 5: 'Serum methanol concentration measured by gas chromatography was *35 g/dL*'

7. *There appears to be an error as it should read 35 mg/dL. Could the sponsors please provide clarification?*

11.4. Safety

None.

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

The clinical questions raised by the evaluators in first round evaluation report are mentioned first followed by the sponsor's response and then the evaluator's comments on the sponsor's response.

12.1. Pharmacokinetics

12.1.1. Question 1

It appears that Study S6 is the Jacobsen, 1996 reference. However, this is not clearly stated in the dossier and in fact the sponsor's Clinical summary of safety mentions that Study S5 is Jacobsen, 1996 which contradicts with the tabular summary provided in the ISS. Furthermore, there was no Study S5 submitted in the dossier although it is mentioned in the various tabular summaries. Could the sponsors provide clarification on the identity and location of these PK studies in the dossier?

Sponsor response:
Please note that there are two different studies both by Jacobsen in 1996 that have very similar formats. One (S5) was provided in section 5351 (study report 3) and S6 was provided in section 5351 (study report 4).

Evaluation of response:

The sponsor's response is satisfactory.

12.1.2. Question 2

The actual reference (Jacobsen 1996) provided did not provide any safety results for Study S6. However, the following was provided in Module 2 summary of clinical safety: 'The major AEs experienced by these subjects were related to the moderate intoxication produced by the ethanol. The subjects all reported subjective effects that would be considered characteristics of ethanol, but with equivalent occurrence whether given 4MP or placebo. Side effects observed included lethargy, facial flush, nausea, vomiting, blurred vision, hangover and diarrhoea. No laboratory abnormalities related to 4MP were observed.' However the source of this data was not provided and it is requested that the sponsors provide clarifications.

Sponsor response:
Safety data is only provided in S6. In the summary of safety, there is a heading 'S5/Jacobsen 1996'. This is incorrect, this should just be S5. Reference to S5 is not extensive in the clinical overview and clinical summary. Also in the summary of safety there is a heading 's6'. Safety data is only in the full clinical S6 study report, which is why only S6 is mentioned.

Evaluator of response:
The sponsor's response is satisfactory.

12.2. Pharmacodynamics

None.

12.3. Efficacy

12.3.1. Question 3

Paediatric methanol or ethylene glycol poisonings: Brent et al 2010 reviewed the published literature to identify published cases of paediatric patients treated with fomepizole. Fourteen patients were identified as being of relevance to the topic, of which 210 were intoxicated with ethylene glycol.

There appears to be a typographic error in the above statement which should read 10 of the 14 patients. Could the sponsors please confirm this?

Sponsor response:

This was a simple typographic error, and should read '10 of the 14 patients'.

Evaluation of response:

The sponsor's response is satisfactory.

12.3.2. Question 4

Study report of OMC-4MP-2 had the following: 'Seven of 11 patients (64%) presented with formate levels in the non-detectable range (less than 1 mmol/L). Among the remaining six patients, one (9%) had a formate level in the moderate range (1 to 9 mmol/L) and the remaining five patients (45%) had formate levels in the severe range (>9 mmol/L).

The above paragraph is inaccurate as there were only 11 patients in all. Please provide clarification.

Sponsor response:

The sponsor agrees there seems to be an error in calculation. Unfortunately, the raw data cannot be located.

Evaluation of response:

The sponsor's response is satisfactory.

12.3.3. Question 5

Jacobsen et al (1990) reported placebo-controlled, double blind, multiple dose, sequential, ascending-dose study has been performed to determine the tolerance of 4MP in 21 healthy volunteers. Oral loading doses of 4MP were followed by supplemental doses every 12 h through 5 days, producing plasma levels in the therapeutic range. Dose schedule in Group 3 (oral loading dose of 10 mg/kg, plus 5 mg/kg every 12 h up to 36 h and then 10 mg/kg every 12 h up to 96 h) seems to be the best at maintaining therapeutic levels for up to 5 days.

Results of the Jacobsen 1990 study appear to be identical to those reported by McMartin 2012. The sponsors have been asked to clarify this.

Sponsor response:

Jacobsen 1990 and McMartin 2012 do provide the exact same results and are likely the same patients (both studies were done with 21 patients in Shreveport, Louisiana). For whatever reason, McMartin 2012 does not reference Jacobsen 1990 and the main authors are the same.

Evaluation of response:

The sponsor's response is satisfactory.

12.3.4. Question 6

In the pivotal, Phase III, open-label Study S8 (OMC-4MP-2), the study reports mentions that 21 trial centres in US were initiated as potential enrolment sites. For purposes of this interim report (dated 29 October 1996), only four of those sites actually enrolled patients into the trial. Did this study continue to enrol patients and if so could the sponsors provide an updated final study report.

Sponsor response:
The sponsors provided an updated final study report.

Review of this updated report indicated that the efficacy and safety results were identical to those already discussed in section 7.2.1.1. Of the 15 enrolled patients at 6 study sites, only 11 were evaluated for efficacy. Overall, the updated study report did not provide any new information and this Phase III open-label study provided evidence to support the efficacy/ safety of fomepizole in treatment of methanol poisoning.

12.3.5. Question 7

Brown 2001. 'Childhood methanol ingestion treated with fomepizole and haemodialysis'. Paediatrics 2001; 10; e 77. This literature reference has the following sentence on page 2 of 5: 'Serum methanol concentration measured by gas chromatography was 35 g/dL'.

There appears to be an error as it should read 35 mg/dL. Could the sponsors please provide clarification?

Sponsor's response:

This was a simple typographic error and should read 35 mg/dL.

Evaluator's comments:

The sponsor's response is satisfactory.

12.4. Safety

None.

13. Second round benefit-risk assessment

13.1. 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 Section 9.1.

13.2. 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 Section 9.2.

13.3. Second round assessment of benefit-risk balance

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

14. 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).'

15. References

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