Application to Include Fomepizole on the WHO Model List of Essential Medicines

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1. Summary Statement of the Proposal for Inclusion, Change or Deletion

Fomepizole is proposed for inclusion in the WHO Model List of Essential Medicines for the treatment of toxic alcohol and glycol poisoning, principally methanol and ethylene glycol, in adults and children.

Fomepizole was approved by the United States Food and Drug Administration (FDA) for treatment of ethylene glycol poisoning in 1997, and for methanol poisoning in 2000, and is recommended by the American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT). Ethanol, the traditional antidote for these indications, is not approved by the FDA and is generally no longer recommended by clinical toxicologists as the first-line treatment.

Toxic alcohols and glycols are widely available. Poisoning with ethylene glycol is most often due to ingestion of antifreeze, while methanol poisoning is generally associated with homemade or smuggled alcoholic beverages to which methanol has been added as it is significantly cheaper than ethanol. These may result from intentional ingestions associated with self-harm attempts, or from unintentional, accidental ingestion. Epidemics of methanol poisoning (caused by ingestion of contaminated beverages) and of diethylene glycol poisoning (caused by adulterated medications), continue to be a public health concern worldwide, predominantly in developing countries among economically disadvantaged communities.

Toxic alcohol and glycol poisoning can be associated with severe morbidity and mortality. Exposure to toxic alcohols and/or glycols can result in metabolic acidosis and serious complications such as acute renal failure (especially ethylene glycol) and blindness/permanent neurological dysfunction (methanol). The main reason for poor outcome is late diagnosis and late and/or inadequate treatment.

The toxicity associated with the toxic alcohols and glycols is due to their metabolism by the enzyme alcohol dehydrogenase to toxic intermediates. Fomepizole prevents formation of the toxic metabolites by competitively inhibiting alcohol dehydrogenase. Ethanol can also be used as an antidote and acts through the same mechanism.

Experimental studies have demonstrated the ability of fomepizole to inhibit alcohol dehydrogenase, and animal studies have shown that fomepizole reverses the toxic effects of methanol and ethylene glycol poisoning.

Prospective observational clinical studies and retrospective case reviews of ethylene glycol and methanol poisoning have provided evidence that fomepizole:

- effectively blocks the enzyme alcohol dehydrogenase, and thereby inhibits formation of the toxic metabolites of ethylene glycol and methanol
- prevents or improves renal dysfunction associated with ethylene glycol poisoning, and visual impairments associated with methanol poisoning
- prevents metabolic acidosis and arrests development of further metabolic acidosis in patients who present with an established acidosis.

Uncontrolled clinical studies and numerous case reports/case series have consistently shown that fomepizole is associated with positive outcomes when used to treat ethylene glycol and methanol poisoning. It is well-tolerated at therapeutic doses and associated with few serious side effects.

Compared to ethanol, fomepizole appears to be an equally or more effective antidote. In addition fomepizole offers several practical advantages:

- the dosing schedule is standardised and easier to administer
- the pharmacokinetics are more predictable

- there is no need to monitor the serum concentration of fomepizole whereas ethanol requires frequent blood monitoring every 1-2 hours
- some patients can be treated without concurrent haemodialysis, reducing the need for critical care support
- it has a better adverse event profile than ethanol and does not cause CNS depression or respiratory depression
- is associated with fewer medication errors (prescription, administration and monitoring errors).

Although fomepizole carries a much higher acquisition cost, fomepizole monotherapy may be equally or more cost effective than ethanol therapy due to savings on additional hospital costs that are required for ethanol therapy (intensive care unit admission, haemodialysis and laboratory support).

In summary fomepizole is an effective and safe antidote for the management of toxic alcohol and glycol poisoning. Fomepizole has considerable advantages over ethanol as an antidote for toxic alcohol and glycol poisoning. There have been a number of recent large outbreaks of toxic alcohol and glycol poisoning where fomepizole has not been available. Wider access to fomepizole would improve the management of patients both in large outbreaks and individual poisonings, allowing simpler, safer and more effective treatment of this potentially life threatening poisoning.

2. Name of the Focal Point in WHO Submitting or Supporting the Application

Ms. Joanna Tempowski (IPCS)

3. Name of the Organisation(s) Consulted and/or Supporting the Application

Funding to support the drafting of this application was provided by EUSA Pharma. However, EUSA Pharma have not reviewed this document and provided no intellectual input into the drafting of the document; no individuals received personal funding from EUSA Pharma.

4. International Nonproprietary Name (INN, Generic Name) of the Medicine

The international non-proprietary name of the medicine is fomepizole. Commonly used synonyms include 4-methylpyrazole, 4-MP, 4-methyl-1*H*-pyrazole.

5. Formulation Proposed for Inclusion

Fomepizole is available as solutions for intravenous infusion in its base or sulphate form. Fomepizole base is available in 1.5 mL injection vials as a 1 g/mL concentrate. Fomepizole sulphate is also available in packs of five 20 mL injection vials with a fomepizole concentration of 5 mg/mL, equivalent to 100 mg fomepizole. These solutions can also be administered via the oral route.

6. International Availability

Fomepizole is commercially available in the United States, Canada, Europe and many other parts of the world. Manufacturers of fomepizole include AGEPS Laboratoire and X-Gen Pharmaceuticals.

The following table outlines the international availability of fomepizole.

Country	Name	Concentration	Company	Form
North America				
United States and Canada	Antizol®	1 g/mL	Paladin Labs	Fomepizole base
United States	Fomepizole (generic)	1 g/mL	Mylan LLC	Fomepizole base
	Fomepizole (generic)	1 g/mL	X-Gen Pharmaceuticals	Fomepizole base
	Antizol®	1 g/mL	Paladin Labs	Fomepizole base
Europe				
EU member states except France. Switzerland, Iceland, Norway, Macedonia, Croatia, Kosovo, Bosnia-Herzegovina, Serbia, Montenegro and Turkey	Fomepizole EUSA Pharma	5 mg/mL	EUSA Pharma	Fomepizole sulphate
France	Fomépizole AP-HP	5 mg/mL	AGEPS Laboratoire	Fomepizole sulphate
Middle East				
Israel	Antizol®	1 g/mL	Orphan Medical, Israel	Fomepizole base
Asia				
Korea, Taiwan, China, Hong Kong, India, Singapore, Malaysia, Pakistan, Philippines, Thailand, Indonesia and Japan	Fomepizole EUSA Pharma	5 mg/mL	EUSA Pharma	Fomepizole sulphate

7. Whether Listing is requested as an Individual Medicine or as an Example of a Therapeutic Group

Listing is requested on as an individual medicine within Section 4.2 “Antidotes and other substances used in poisonings – Specific”.

8. Information Supporting the Public Health Relevance

8.1 Epidemiological Information on Disease Burden of Toxic Alcohol and Glycol Poisoning

8.1.1 Toxic Alcohols and Glycols

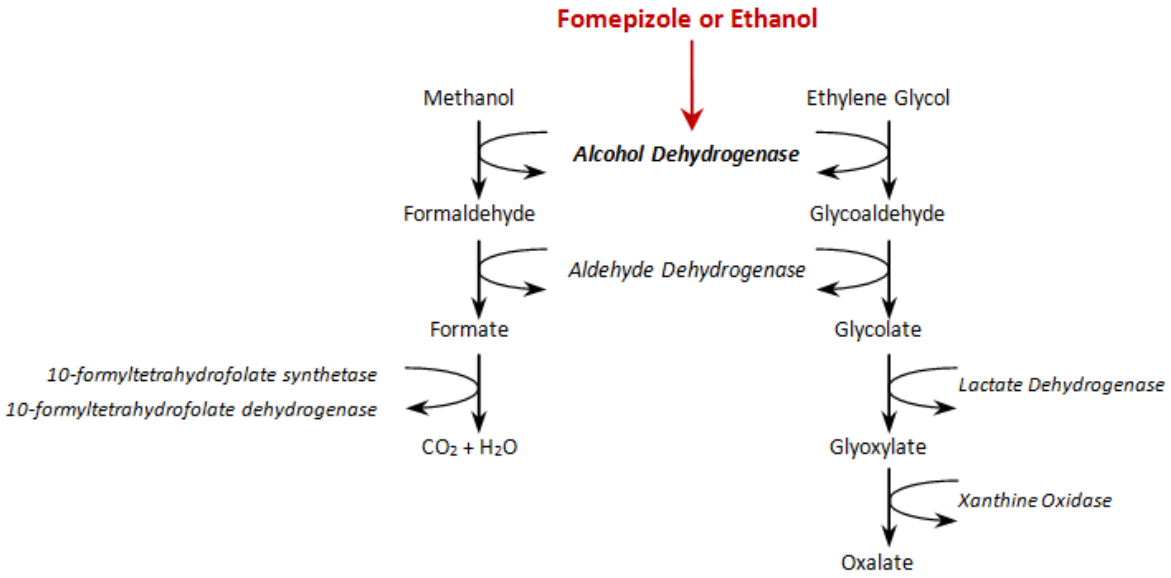
Toxic alcohols and glycols are hydroxyl-containing compounds with either one (alcohol) or two (glycol) hydroxyl groups. The terms toxic alcohols and glycols commonly refer to ethylene glycol and methanol, as well as the less common diethylene glycol and glycol ethers. Of these, ethylene glycol and methanol are found throughout the world in commercially available products such as antifreeze, screenwash and fuel additives. Their wide availability accounts for the majority of poisoning cases, which are caused by accidental or intentional ingestion. Although relatively uncommon, poisoning with these agents is associated with severe morbidity and mortality. Untreated methanol poisoning has been associated with a high mortality rate of 28% and a rate of visual deficits or blindness in 30% of survivors (Bennett et al., 1953). The visual disturbances and the neurological impairments seen in these poisonings appear to be

permanent in nature (Paasma et al., 2009). While most cases of poisoning involving this group of chemicals are caused by methanol or ethylene glycol exposure, some incidents are the result of epidemics of diethylene glycol contamination. These are primarily caused by the illegal substitution of diethylene glycol in medications for the more expensive but essentially non-toxic glycol or glycerine compounds. Exposures to propylene glycol, polyethylene glycol, glycol ethers and other toxic alcohols and glycols have also been documented but these tend to be isolated incidents and are much rarer.

Mechanism of Toxicity of Toxic Alcohols and Glycols

Toxic alcohol and glycol poisoning share many similarities. There is little toxicity associated with toxic alcohols and glycols themselves (Brent, 2009). Instead, toxic alcohols and glycols are metabolised to toxic intermediates as a result of oxidation via alcohol dehydrogenase and aldehyde dehydrogenase (see Figure 1). It is these metabolites that are responsible for the metabolic acidosis seen in poisoned patients (Kraut and Kurtz, 2008) and mediate the effects of toxic alcohol and glycol poisoning. For example, methanol itself has a relatively low level of toxicity (Barceloux et al., 2002) but is metabolised to formaldehyde via alcohol dehydrogenase, and then to formic acid via aldehyde dehydrogenase. Formic acid is a weak acid and is generally found in the ionised form, as formate, in plasma. It is formic acid/formate which is responsible for the retinal and optic nerve damage seen in patients with severe methanol intoxication, hence the blindness associated with methanol. In order to prevent the major adverse effects of intoxication, the antidotes used to treat toxic alcohol and glycol poisoning (ethanol and fomepizole) act to competitively inhibit alcohol dehydrogenase, blocking metabolite formation.

Figure 1. Diagram Showing the Metabolism of Ethylene Glycol and Methanol (adapted from Fujita et al., 2004)



Poisoning with toxic alcohols and glycols occurs for a variety of reasons, e.g. intentional ingestions relating to alcohol abuse or self-harm attempts, unintentional or accidental consumption, and epidemics caused by contaminated food/beverages or medications adulterated with toxic alcohols or glycols (Tables 1 and 2). Occasional cases of poisoning have also been described via inhalation of toxic alcohol-containing products as a result of substance abuse (Kulstad et al., 2001), and iatrogenic administration of drug formulations containing toxic alcohols and glycols (Rodriguez et al., 1993; Zosel et al., 2008). Exposure to toxic alcohols and glycols can result in metabolic acidosis, with serious complications such as acute renal failure (especially ethylene glycol), blindness (methanol) and permanent neurological dysfunction, all of which contribute to a high morbidity and mortality rate. The main contributing factor to poor outcome is late diagnosis and delayed treatment (Hovda et al., 2005c).

8.1.2 Ethylene Glycol

Ethylene glycol is commonly found in antifreeze, the major source of exposure in toxic alcohol and glycol poisoning outside epidemics. Most cases of poisoning caused by ethylene glycol occur through its intentional consumption as an inexpensive alcohol substitute or as part of an intentional self-harm attempt. It is also not an uncommon source of paediatric ingestions due to the sweet taste conferred by ethylene glycol (McMahon et al., 2009). Unlike methanol, ethylene glycol poisonings are largely isolated incidents and it is the most common cause of toxic alcohol and glycol poisoning in the United States. In 2007, the United States Toxic Exposure Surveillance System reported 5731 exposures where ethylene glycol was the primary toxic agent (Bronstein et al., 2008), more than double the number of reports of methanol poisoning (2283 exposures).

8.1.3 Methanol

Methanol poisonings can occur as isolated incidents caused by unintentional (accidental) or intentional ingestion, but also in epidemics. In the latter situation, methanol poisoning is generally associated with homemade alcoholic beverages, “moonshine” liquor, where methanol has been used to fortify illicit spirits due to the relative low cost of methanol compared to ethanol. These epidemics are most prevalent in developing countries (Paasma et al., 2009), often affecting large numbers with high mortality rates (Table 1), e.g. 44% of patients died in an Estonian outbreak of methanol poisoning in 2001 (Paasma et al., 2007). Because symptoms of methanol poisoning are often non-specific (it is referred to by some authors as the “great imitator”) diagnosis can be difficult and many poisonings and even outbreaks may pass unnoticed. A large number of fatalities before admission to hospital are likely to contribute to the underreporting of methanol poisonings (Paasma et al., 2009).

In these cases it is often the economically disadvantaged who are affected. For example, the victims of the mass methanol poisoning in West Bengal (2011) were farmers and rickshaw drivers who could not afford branded liquor (ProMED-mail, 2012a), and the 71 deaths from the 2011 outbreak in Sudan were among homeless youths aged 13-25 (Abdul Rahim and Al Shiekh, 2012).

Table 1. Selection of Recent Methanol Outbreaks (adapted from Hovda, 2011)

Year	Location	Affected	Fatalities	References
1998	Madagascar	?	200	BBC News (2002)
1998	Nis, Serbia	>90	43	Transitions Online (1998)
1998	Murang´a, Kenya	?	>100	Highbeam Business (1998)
1998	Shanxi Province, China	>200	27	BBC News (1998)
1998	Phnom Penh, Cambodia	>400	60	Levy et al. (2003)
1998	Vietnam	34	5	ProMED-mail (1999)
1999	Mai Mahiu, Kenya	34	5	Levy et al. (2003)
1999	Embu, Kenya	?	24	Levy et al. (2003)
1999	Narsingdi, Bangladesh	?	121	Levy et al. (2003)
2000	Nairobi, Kenya	661	140	Levy et al. (2003), Ahmad (2000)
2000	San Salvador, El Salvador	>200	117	Levy et al. (2003)
2000	San Vincente, El Salvador	19	19	Levy et al. (2003)
2000	Newfoundland, Canada	>12	2	CBC News (2000)
2000	Feni, Bangladesh	>100	56	Levy et al. (2003)
2001	Thika, Kenya	?	120	Levy et al. (2003)
2001	Pärnu, Estonia	154	68	Paasma et al. (2007)
2001	Bombay, India	>120	27	
2002	Mecca/Jizan Province, Saudi Arabia	?	19	Levy et al. (2003)
2002	Antananarivo, Madagascar	40	11	Levy et al. (2003)

Year	Location	Affected	Fatalities	References
2002	Taiwan	?	9	
2002-2004	Norway	59	17	Hovda et al. (2005)
2003	Botswana	>45	9	BBC News (2003)
2004	Istanbul, Turkey	?	21	ProMED-mail (2005)
2004	Shiraz, Iran	>60	17	
2004	Kenya	?	23	
2005	Istanbul, Turkey	?	23	
2005	Magadan, Russia	?	33	Fox News (2005)
2005	Kenya	174	49	China Daily (2005)
2006	Nicaragua	801	48	PAHO (2006)
2006	Urals, Russia	60	3	
2006	Irkutsk Region, Russia	?	13	
2006	Teheran, Iran	42	6	
2008	Ulan Bator, Mongolia	>32	>11	USA Today (2008)
2008	Karnataka & Tamil Nadu, India	285	150	BBC News (2008)
2009	Central Uganda	77	27	ProMED-mail (2009)
2009	Kolkata, India	?	26	The Indian Express (2009)
2009	Delhi, India	?	>30	Pandey,A (2009)
2009	Karnataka, India	?	170	Tribune (2011)
2009	Orissa Bolangir, India	21	9	Orissa Current News (2009)
2009	Gujarat/Ahmedabad, India	>275	136	Sify News (2009)
2009	Bali/Lombok, Indonesia	45	25	The Australian (2009)
2010	Uttar Pradesh, India	?	10	BBC News (2010a)
2010	Kampala, Uganda	189	89	ProMED-mail (2010)
2010	Nairiobi, Kenya	?	>17	BBC News (2010b)
2010	Makassar, Indonesia	5	3	Jakarta Globe (2010)
2010	Kampong Cham province, Cambodia	?	17	Phnom Penh Post (2010)
2011	Kuril Archipelago, Russia	19	4	RIA Novosti (2011)
2011	Khartoum, Sudan	>137	71	Abdul Rahim and Al Shiekh (2012)
2011	Los Rios, Ecuador	>770	51	The Economist (2011)
2011	West Bengal, India	>370	170	ProMED-mail (2012a); BBC News (2011)
2011	Haiti	40	18	PAHO (2011)
2011	Bodrum, Turkey	22	5	Hürriyet Daily News (2011)
2011	Central Province, Kenya	?	29	Allafrica.com (2011)
2011	Kolkata, India	>167	143	San Francisco Chronicle (2011)
2012	Andhra Pradesh, India	37	17	ProMED-mail (2012a)
2012	Orissa, India	100	31	BBC News (2012)
2012	Cambodia	367	49	ProMED-mail (2012b)
2012	Tegucigalpa, Honduras	48	24	News Track India (2012)
2012	Czech Republic and Slovakia	>105	33	Prague Daily Monitor (2012)

Methanol epidemics have also occurred in developed countries. Hovda et al. (2005c) reported a mass poisoning outbreak between 2002 and 2004 in Norway that led to the deaths of 17 out of 59 cases (33% mortality rate). An outbreak starting in September 2012 in the Czech Republic has, by November 2012, resulted in the deaths of more than 30 individuals; more than 90 have been admitted to hospital, with many survivors left blind or brain damaged, and at least 17 additional individuals have been found dead outside hospital (Personal Communication Hovda and Pelclova). It is suggested in this outbreak that criminal gangs used methanol as a substitute in order to evade the high excise tax on ethanol (Crane, 2012).

Methanol poisoning also arises as a result of exposure to commercially available products, especially screenwash. In the United States, 13524 cases associated with methanol poisoning were reported

between 1993 and 1998, with screenwash accounting for 61% of exposures (Davis et al., 2002). In non-fatal methanol poisonings in Turkey, ingestion of cheap eau-de-colognes was reported to be the main source of exposure (Kalkan et al., 2003). These poisoning cases are largely related to alcohol abuse, with intentional ingestion occurring when alcoholics are deprived of their beverage of choice. This is especially true in developed countries. A Swedish case series of methanol poisonings from 1995 to 1999, reported that 74% of patients had a history of alcohol abuse (Personne et al., 2001).

8.1.4 Diethylene Glycol

The prevalence of diethylene glycol poisoning is low. However, it is also associated with a high mortality rate. The majority of diethylene glycol poisoning cases have occurred during epidemics, usually when diethylene glycol has been used as a substitute in medications for the more expensive but essentially non-toxic glycol or glycerine compounds normally used (Schep et al., 2009). In 1937 the first documented poisoning epidemic caused by diethylene glycol, the Massengill disaster, was reported in the United States. In this incident, diethylene glycol was used as the solvent in a sulphanilamide elixir and had not been tested for toxicity before it was marketed. It led to the deaths of 105 adults and children out of the 353 individuals who had received the medication, and prompted the passage of the 1938 Federal Food, Drug and Cosmetic Act requiring the demonstrable safety of a product before it is marketed (Junod, 2000). Since then epidemics have continued to occur (Table 2), predominantly in developing countries where poor manufacturing practices and lack of safety regulation enforcement are prominent (Abubukar et al., 2009). Like methanol epidemics, these also have high mortality rates. Between 1995 and 1996, 85 children died out of 109 known to be affected in a diethylene glycol poisoning epidemic in Haiti, a fatality rate of 81% (O'Brien et al., 1998).

In Panama in 2006, an official estimate at the time attributed 78 deaths to an outbreak of diethylene glycol-contaminated cough syrup (Rentz et al., 2008). As of January 2012, the official number of deaths had risen to 282 (AFP, 2012) and it is likely that this is still an underestimate; according to other reports, the number of deaths in this outbreak could be as high as 365 (Bogdanich and Hooker, 2007) or 426 (Walker, 2007). This is indicative of the difficulty in accurately assessing the number of victims affected by such an epidemic.

Toxic alcohol and glycol poisoning is often not suspected by doctors in such epidemics, especially in poor countries with limited resources and with prevalence of other diseases (Bogdanich and Hooker, 2007). For example in Panama an epidemic was originally erroneously identified as Guillain-Barré syndrome, a rare neurological disorder that can mimic the initial stages of diethylene glycol poisoning (Walker, 2007). Furthermore the majority of deaths from diethylene glycol poisoning occur in the community rather than after admission to a medical facility, further contributing to the overall underreporting of poisoning cases (Bogdanich and Hooker, 2007).

Table 2. Diethylene Glycol Outbreaks (adapted from O'Brien et al., 1998; Schep et al., 2009)

Year	Location	Contaminated Product	Source of Diethylene Glycol (DEG)	Fatalities	References
1937	USA	Sulphanilamide	DEG excipient	105	Kesten et al. (1937)
1969	South Africa	Sedatives	DEG replaced propylene glycol	7	Wax (1996)
1985	Spain	Sulfadiazine	DEG excipient	5	Cantarell et al. (1987)
1986	India	Glycerine	Industrial-grade glycerine	21	Pandya (1988)
1990	Nigeria	Paracetamol	DEG replaced propylene	47	Okuonghae et al.

Year	Location	Contaminated Product	Source of Diethylene Glycol (DEG)	Fatalities	References
			glycol		(1992)
1990-1992	Bangladesh	Paracetamol	DEG replaced propylene glycol/glycerine	236	Hanif et al. (1995)
1992	Argentina	Propolis	DEG excipient	29	Drut et al. (1994)
1995-1996	Haiti	Paracetamol syrup	DEG replaced glycerine	88	O'Brien et al. (1998)
1998	India	Cough expectorant	DEG replaced glycerine	33	Singh et al. (2001)
2006	Panama	Cough syrup	DEG replaced glycerine	282	AFP (2012)
2006	China	Armillarisin-A	DEG replaced glycerine	12	Lin et al. (2008)
2008	Nigeria	Teething syrup	DEG replaced glycerine	84	Polgreen (2009)

8.1.5 Other Alcohols and Glycols

Poisoning caused by other alcohols and glycols are much rarer and can occur from a range of alcohols, glycols and glycol ethers. Notable cases of propylene glycol poisoning have occurred in medical settings due to iatrogenic administration. Propylene glycol is thought to have a low toxicity hence its application as a diluent in many pharmaceuticals including oral, topical and injectable formulations (notably injectable diazepam), which are insoluble in water (Glover and Reed, 1996; Szajewski, 1994). However, serious toxicity can occur if an individual is exposed to a high dose over a short period of time. Incidents of iatrogenic poisoning with propylene glycol have been documented, such as from pharmacy dispensing errors (Brunet et al., 2009) or overdoses of medicines that contain propylene glycol used as a solvent e.g. lorazepam (Zosel et al., 2008). Poisoning with other alcohols has also been reported through unintentional ingestion, such as 2-butoxyethanol found in commercially available household and industrial cleaning products (Hung et al., 2010).

8.1.6 Disease Burden

Toxic alcohol and glycol poisoning is prevalent throughout the world, with the most common exposures due to ethylene glycol and methanol. Mass toxic poisonings continue to have serious health consequences and high mortality rates in developing countries (ProMED-mail, 2012b), with methanol epidemics relating to "moonshine" liquor affecting the most economically disadvantaged. Diethylene glycol outbreaks have also resulted in high numbers of fatalities, especially in countries with poor safety regulations.

Although data relating to the numbers affected by toxic alcohol and glycol poisoning is limited, the available data are likely to be a significant underestimation of the actual number of cases. This is true not just for developing countries, where many deaths occur before admission to a medical facility, but also in developed countries such as the United States where reporting of poisoning cases is not mandatory (Brent, 2009).

8.2 Assessment of Current Use

8.2.1 Treatment of Ethylene Glycol and Methanol Poisoning in Adults and Children

Fomepizole and ethanol are antidotes used for toxic alcohol and glycol poisoning. Fomepizole acts by competitively inhibiting alcohol dehydrogenase and binding preferentially to the enzyme. This prevents the further formation of the toxic metabolites which are responsible for the major adverse effects of ethylene glycol and methanol poisoning (see Figure 1).

The toxicity of ethylene glycol and methanol poisoning is mediated via their metabolites. Ethylene glycol and methanol have relatively low levels of toxicity, whereas their metabolites glycolic acid and oxalic acid (ethylene glycol), and formic acid (methanol) are responsible for the metabolic acidosis seen in poisoned patients. These metabolites are generally found in plasma in the ionised form as glycolate, oxalate and formate and we will use these terms in the rest of this document to refer to both the ionised and non-ionised metabolites.

The initial step in the metabolism of ethylene glycol and methanol to their toxic metabolites involves oxidation by liver alcohol dehydrogenase. The efficacy of fomepizole and ethanol as antidotes for these poisonings is based on their preferential binding to alcohol dehydrogenase. Ethanol competes with ethylene glycol and methanol as substrates for alcohol dehydrogenase (binding 500-1000 times stronger to the enzyme as compared to methanol) (Hovda, 2009), whereas fomepizole acts as a competitive antagonist of the enzyme (binding 80000 times stronger than methanol) (Hovda, 2009). Both ethanol and fomepizole inhibit the metabolism of the parent ethylene glycol and methanol and prevent the accumulation of their toxic metabolites.

The indication for using fomepizole to treat ethylene glycol and methanol poisoning is based on the blood concentration of the toxic substance. If this information in unavailable, evidence of metabolic acidosis and an elevated anion gap or osmolal gap can be used as diagnostic and/or surrogate indicators, especially when a consistent history of ingestion is present (Hovda et al., 2004; Jacobsen et al., 1997). Recently, a simple enzymatic method for measuring formate has been suggested as an alternative diagnostic tool for methanol poisoning (Hovda et al., 2011). This is a much simpler and cheaper yet highly sensitive and specific way of diagnosing methanol poisoning.

Fomepizole was approved by the United States Food and Drug Administration (FDA) for the treatment of ethylene glycol poisoning in 1997, and for methanol poisoning in 2000, for individuals aged 12 or over. The American Academy of Clinical Toxicology (AACT) and European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) recommend fomepizole as the first-line antidote in the treatment of both types of poisoning (Barceloux et al., 1999; Barceloux et al., 2002), with ethanol to be used if fomepizole is unavailable. Fomepizole was also approved by the European Medicines Agency (EMA) in 2001 for use in methanol poisoning. In many countries fomepizole is considered to be first-line treatment, based on its efficacy and in particular, better adverse effect profile compared with ethanol. Whilst ethanol has been used to treat ethylene glycol and methanol poisoning since the 1940s, it is not FDA approved for either of these indications (McMahon et al., 2009). Ethanol use is commonly associated with adverse effects such as central nervous system (CNS) depression, hypoglycemia, hypothermia and agitation (see Section 11.4.1). The only contraindication to fomepizole use is a previous allergic reaction to methylpyrazoles; this has not been reported (Brent, 2009). The main disadvantage of fomepizole over ethanol is its higher acquisition cost. Anecdotally, this appears to have prevented the widespread use of fomepizole as an antidote.

Despite this, fomepizole has been used in Europe and North America for the management of individual cases of ethylene glycol/methanol poisoning and in developing countries during epidemics of methanol and diethylene glycol poisoning. In the 2006 outbreak of methanol poisoning in Nicaragua, Jazz Pharmaceuticals donated 1200 vials of fomepizole, the equivalent of 300 courses of treatment (PAHO, 2006), with a further donation made later that year during the diethylene glycol epidemic in Panama (PR Newswire, 2006). Furthermore, 103 boxes (515 vials) of fomepizole were recently donated by the Norwegian NBC Centre, EUSA Pharma, Swedish Orphan Biovitrum, and the Norwegian Medicinal Depot during an outbreak of methanol poisoning in the Czech Republic (Cameron, 2012; Pelclova, personal communication 2012).

8.2.2 Other Indications

An oral formulation of fomepizole, Convivia™, which could potentially lower systemic acetaldehyde concentrations resulting from acetaldehyde dehydrogenase 2 (ALDH2) deficiency, an inherited metabolic disorder affecting 40-50% of East Asian populations, is being developed by Raptor for the treatment of alcohol intolerance (Raptor Pharmaceuticals Corp., 2012). This disorder is associated with the accumulation of acetaldehyde, a carcinogenic intermediate of ethanol metabolism. As well as immediate unpleasant symptoms (e.g. facial flushing and tachycardia), elevated concentrations of acetaldehyde can increase risks of long-term serious health problems, such as digestive tract cancers. A Phase IIa clinical trial has demonstrated that it is effective in reducing tachycardia (ClinicalTrials.gov, 2008). Other uses of fomepizole that have not been approved by the FDA include the treatment of diethylene glycol and propylene glycol poisoning, prevention of the disulfiram/ethanol reaction and suppression of acetaldehyde accumulation in alcohol-sensitive patients (Barceloux et al., 1999).

8.3 Target Population

The target population for treatment with fomepizole includes all children and adults with confirmed toxic alcohol or glycol poisoning and those with suspected poisoning in whom management with an antidote is clinically indicated. Fomepizole use is particularly relevant in populations with high levels of alcohol abuse, especially in economically disadvantaged areas where homemade alcoholic beverages are consumed as a substitute for more expensive branded alcohols. It is also applicable in countries at risk of medication-associated poisonings as a result of inadequate implementation of safe manufacturing standards, poor enforcement of drug quality controls and where intentionally deceptive drug manufacturing practices are known to have occurred (Abubukar et al., 2009). Children are a target population as unintentional (accidental) poisonings can occur in this group. Although the safety and effectiveness of fomepizole in paediatric patients have not been formally established, case reports have suggested fomepizole to be safe and effective (Brent, 2010; De Brabander, 2004).

There is only one animal study on kinetics of fomepizole in pregnant rats, showing a five times higher concentration of fomepizole in the foetus as compared to the maternal serum (Gracia et al., 2012). Thus far, no studies on the long-term effects on the foetus have been performed. It is not known whether fomepizole is excreted in human milk. Therefore, caution is required when fomepizole is considered for use in pregnant and breast-feeding women. Fomepizole is currently classified as an FDA Pregnancy Category C drug. This means that potential benefits may warrant the use of this drug in pregnant women despite potential risks (Federal Register, 2008).

9. Treatment Details

9.1 Dosage Regimen and Duration

9.1.1 Adults

Intravenous Administration

The intravenous dosage regimen recommended by the American Academy of Clinical Toxicology (AACT) is a loading dose of 15 mg/kg, followed by maintenance doses of 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours thereafter to compensate for increased fomepizole metabolism (Barceloux et al., 1999; Barceloux et al., 2002; McMartin et al., 2012; see Section 9.2 below).

An alternative dosage regimen for the treatment of ethylene glycol poisoning is shown in Table 3. A loading dose of 15 mg/kg is administered, followed by maintenance doses of 10 mg/kg every 12 hours up to 48 hours. The number of maintenance doses and the doses after 48 hours depend on the initial concentration and time course of ethylene glycol concentrations (SPC, 2011).

Table 3. Fomepizole Dosing in Patients with Ethylene Glycol Poisoning

Fomepizole Dose (mg/kg body weight)					
Loading Dose	2nd Dose (12h)	3rd Dose (24h)	4th Dose (36h)	5th Dose (48h)	6th Dose (60h)
15	10	10	10	7.5 to 15	5 to 15

Treatment during Haemodialysis

As fomepizole is dialysable, treatment must be altered compensate for the loss of fomepizole in the dialysate. Two protocols have currently been proposed for this:

1. Administration of an initial loading dose of 15 mg/kg, followed by maintenance doses according to Table 4 (Adapted from AHFS, 2003).

Table 4. Fomepizole dosing in Patients Requiring Haemodialysis

Dose at the Beginning of Haemodialysis	
If <6 hrs since last fomepizole dose	If ≥6 hrs since last fomepizole dose
Do not administer dose	Administer next scheduled dose (10 mg/kg up to 48 hrs, then 15 mg/kg after)
Dosing during Haemodialysis	
Dose every 4 hrs (10 mg/kg up to 48 hrs, then 15 mg/kg after)	
Dosing at the Time Haemodialysis is Completed	
Time between the last dose and the end of haemodialysis	
<1 hr	Do not administer dose at the end of haemodialysis
1-3 hrs	Administer ½ of next scheduled dose
>3 hrs	Administer next scheduled dose
Maintenance Dosing off Haemodialysis	
Give next scheduled dose 12 hours from last dose administered	

2. Administration of a continuous intravenous infusion of 1 mg/kg/hour for the entire duration of haemodialysis following a loading dose of 15 mg/kg (SPC, 2011; Mégarbane, 2010).

The appropriate dose should be injected into at least 100 mL of 0.9% sodium chloride or dextrose 5%, and the contents infused slowly over 30 minutes.

Fomepizole administration should continue until serum ethylene glycol or methanol concentrations are undetectable or <20 mg/dL, and the patient is asymptomatic with a normal blood pH value (SPC, 2011).

Oral Administration

Several cases of ethylene glycol and methanol poisoning have been successfully treated using orally administered fomepizole (Baud et al., 1986-7; Borron et al., 1999; Hantson et al., 1999). There is evidence that this is well tolerated and produces similar blood concentrations of fomepizole as when administered intravenously (Maraffa et al., 2008; McMartin, 2012). The intravenous administration remains the standard route particularly in cases of life threatening and/or established poisoning (Mégarbane et al., 2008).

9.1.2 Children

Intravenous Administration

Although the dosage regimen has not been established for paediatric patients, safe and effective use has been reported using the same protocol as for adults (Boyer et al., 2001; Brent, 2010; Detaille et al., 2004).

9.1.3 Other Toxic Alcohols

Fomepizole has not been approved for the treatment of poisonings by other toxic alcohols such as diethylene glycol and propylene glycol. At present, treatment is recommended as for ethylene glycol and methanol poisoning (Kraut and Kurtz, 2008; Mégarbane et al., 2002). Several cases have been reported where fomepizole was used successfully in the treatment of diethylene glycol poisoning (Borron et al., 1997; Brophy et al., 2000).

9.1.4 Validation of the Current Fomepizole Treatment Regimen

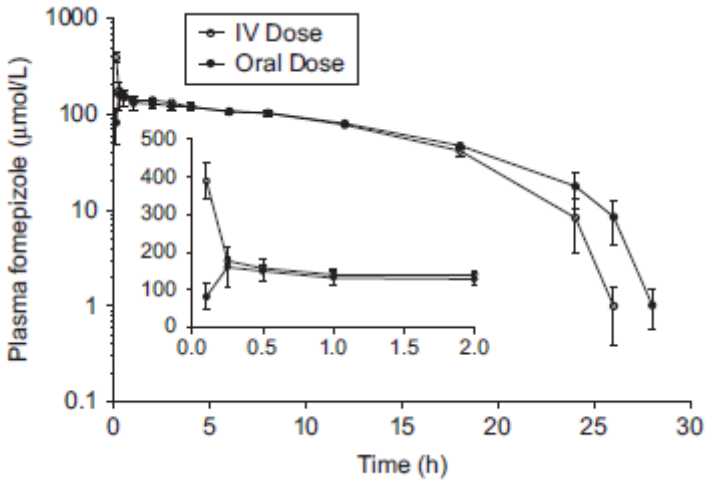
The current AACT/EAPCCT dosing recommendations for fomepizole in poisoned patients have recently been validated in a pharmacokinetic study. Although the current recommendations have been in place since 1999 for ethylene glycol poisoning (Barceloux et al., 1999) and 2002 for methanol poisoning (Barceloux et al., 2002), some reports have questioned the need to increase the fomepizole dose after 48 hours (Mégarbane et al., 2005).

As the pharmacokinetics of fomepizole had not been well described in humans, particularly after multiple dosing as in the case of therapeutic use, McMartin et al. (2012) investigated the metabolism and kinetics of fomepizole in healthy human subjects. In this double-blind study, 21 male volunteers were randomly assigned to one of three groups, with five subjects administered multiple oral doses of fomepizole and two subjects administered placebo in each group. Subjects in group one received a loading dose of 10 mg/kg, followed by maintenance doses of 3 mg/kg every 12 hours up to 96 hours. Group two subjects received doses of 15 mg/kg plus 5 mg/kg/12 hrs up to 96 hours and group three subjects received doses of 10 mg/kg plus 5 mg/kg/12 hrs up to 36 hours, then 10 mg/kg/12 hrs up to 96 hours.

The justification for using oral administration of fomepizole as opposed to intravenous administration was that the kinetics of oral and intravenous fomepizole are assumed to be equivalent as previous studies have reported that oral fomepizole is completely bioavailable, comparable to intravenous fomepizole (Marraffa et al., 2008). In addition, McMartin et al. (2012) initially compared single oral and intravenous doses of fomepizole (7 mg/kg) in healthy volunteers and found that both oral and intravenous administration resulted in extremely rapid initial absorption and distribution of fomepizole, such that virtually no differences in plasma concentrations were observed between the two routes of administration within 15 minutes of dosing (Figure 2). They found that the area under the plasma

elimination curve for oral and intravenous administration were similar (1918 ± 100 and 1885 ± 121 respectively).

Figure 2. Fomepizole is eliminated from plasma by saturable, nonlinear kinetics in healthy humans after single oral or intravenous doses (7 mg/kg). Note the y-axis is a log scale. The inset shows the concentrations during the first 2 hours only, plotted on linear coordinates. Each point represents the group mean of the plasma fomepizole concentration ± SEM, n = 5 per group. (Fig. 1. from McMartin et al., 2012)



The multiple dose study found that plasma levels of fomepizole remained relatively constant for 36-50 hours in groups one and two, after which it markedly decreased and was detectable for only eight hours after the last dosing (Figure 3). By comparison, group three subjects in which supplemental doses of fomepizole were increased after 36 hours showed that plasma concentrations of fomepizole remained within therapeutic levels for five days. The minimum plasma concentration of fomepizole that is necessary to inhibit alcohol dehydrogenase and therefore assumed to be therapeutically effective is 0.8 µg/mL (10 µmol/L) based on preclinical animal studies (Brent et al., 2001; McMartin et al., 1975; McMartin et al., 1980).

Figure 3. Plasma fomepizole concentrations in healthy human subjects given multiple oral doses of fomepizole. (A, left) 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, right) 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/12hrs to 96 hours. Arrowheads indicate timing of fomepizole doses. (Fig 4. from McMartin et al., 2012)

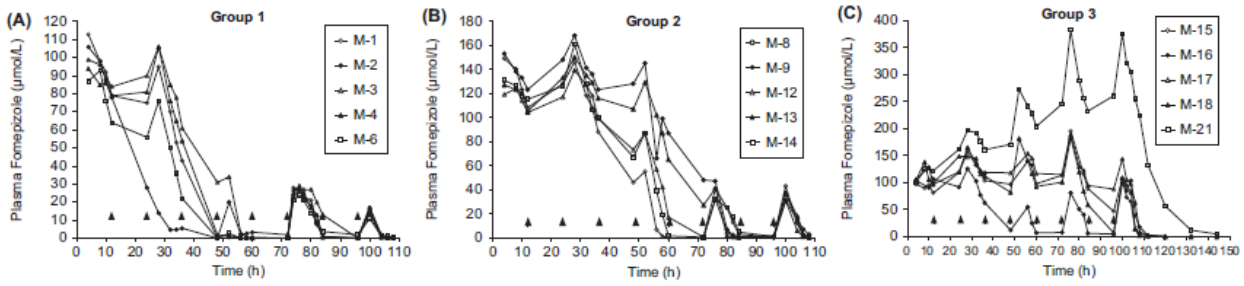


Table 5. Increased elimination of fomepizole from plasma after multiple oral doses. (Table 3 from McMartin et al., 2012)

	Elimination Rate (µmol/L/hr)					
Time (hrs)	Group 1	n	Group 2	n	Group 3	n
4-12	2.8 ± 0.6	4	3.3 ± 0.7		*	
28-36	6.3 ± 0.3	4	5.9 ± 0.7		6.4 ± 0.8	4
52-60	*		8.3 ± 0.7		10.3 ± 0.7	5
76-84	*		*		13.7 ± 1.8	5
The apparent zero order rate of elimination was determined from the slope of the least squares regression analysis of the plasma fomepizole levels during the respective time periods for each subject. n □ number of subjects used for respective time periods (<5 when there was inadequate data for determination of elimination rate). Values represent the mean ± SEM. *Data points were not sufficient for determination of elimination rate.						

The rate of fomepizole elimination increased 2-3 times within three days of multiple dosing (Table 5), suggesting that constant plasma levels were unable to be maintained in group one and two subjects because of the increased fomepizole elimination with repeated dosing. The increase in fomepizole elimination was also associated with enhanced urinary excretion of 4-carboxypyrazole, the primary metabolite of fomepizole, indicating that the increased elimination of fomepizole was most likely due to induction of its metabolism, probably via cytochrome P-450. In order to maintain therapeutic fomepizole concentrations, doses of fomepizole need to be increased at the time enhanced elimination occurs, around 36-48 hours. This supports the current treatment regimen of increasing the fomepizole dose at 48 hours.

9.1.5 Treatment Criteria

Fomepizole treatment should be initiated immediately upon suspicion of significant ethylene glycol or methanol exposure to prevent the metabolism of these compounds into toxic metabolites. Various criteria that indicate the need for alcohol dehydrogenase inhibitors have been developed, these include (Barceloux et al., 1999; Barceloux et al., 2002; Mégarbane, 2010):

- Serum ethylene glycol or methanol concentration >20 mg/dL *or*
- Documented recent history of ethylene glycol or methanol ingestion with increased osmolal gap >10 mOsm/kgH_2O *or*
- History of ethylene glycol or methanol ingestion with at least two of the following criteria:
    - Arterial pH <7.3
    - Serum bicarbonate <20 mmol/L
    - Osmolal gap >10 mOsm/kgH_2O
    - Urinary oxalate crystals present (only in ethylene glycol poisoning cases)

9.2 Need for Special Diagnostics

It is important that ethylene glycol and methanol poisoning are diagnosed rapidly in order for therapy to be most effective. Gas chromatography can provide accurate diagnosis by determining the concentrations of ethylene glycol and methanol in the plasma however this can be limited by the time it takes to perform the analysis and the required analytical techniques are often unavailable. Furthermore, the toxic alcohols may have been completely metabolised before admission to hospital. Therefore due to the urgent nature of treatment, diagnosis often relies on interpreting other readily available laboratory

tests. An arterial blood gas analysis can be used to detect the presence of a metabolic acidosis, while the concentrations of electrolytes, bicarbonate, glucose, urea, creatinine and the serum osmolality (freezing point rather than vapour pressure method) can be obtained in order to calculate the anion and osmolal gaps. Evidence of a metabolic acidosis and elevated anion and osmolal gaps can often be used to aid the diagnosis of ethylene glycol and methanol poisoning (Hovda et al., 2004; Jacobsen and McMartin, 1997). A variety of other conditions can also lead to an increase in osmolal gap, such as renal failure, shock and diabetic ketoacidosis. This low specificity of osmolal gap for toxic alcohol means that its role in diagnosis is debatable. However, it can provide a useful tool when used in conjunction with clinical history, examination and other diagnostic tests (Krasowski et al., 2012). The main obstacle, however, is the fact that the areas where large outbreaks of toxic alcohol poisonings most often occur often do not have access to many of the tests used in the diagnosis of toxic alcohol poisoning including specific ethylene glycol/methanol assays and osmolality analyses.

A new method of diagnosing methanol poisonings by measuring the toxic metabolite formate has recently been suggested based on an old and well proven enzymatic-spectrophotometric method (Hovda et al., 2011). The method is highly sensitive and specific, cheap, takes less than 30 minutes to perform and can be used on a standard spectrophotometer which exists in most biochemistry laboratories around the world. Current studies are also investigating the potential to exchange the glucose dehydrogenase (GDH) enzyme on the paper strip of bedside glucose meters (using the GDH-NAD—method) with formate dehydrogenase (FDH). This would allow existing bedside glucose meters to be used for diagnosis of methanol poisoning with a single drop of blood within 30 seconds, potentially making the use of any laboratory equipment unnecessary for diagnosis (Hovda, 2011).

A clinical sign that is specific for methanol poisoning is pseudopapilitis. In this, the usually sharp margins between the papilla (where the optic nerve enters the eye) and the retina become blurred and hyperaemic. This can look somewhat similar to papilloedema, but in pseudopapilitis the papilla does not protrude into the eye, rather, it is at the same level as the retina (Roe, 1948).

Urinalysis may reveal the presence of oxalate crystals, which can support the diagnosis of ethylene glycol poisoning (Jacobsen and McMartin, 1997); however this is a late feature and is not always present. Antifreeze products can contain fluorescein, which may cause the urine to fluoresce under a Wood lamp (Winter et al., 1990). However, studies have demonstrated that this is not a reliable screening tool for suspected antifreeze ingestion in children, and it is therefore not part of routine investigation (Casavant et al., 2001; Parsa et al., 2005).

9.3 Treatment or Monitoring Facilities and Skills

9.3.1 Treatment Monitoring

No specific laboratory monitoring of plasma fomepizole concentration is required during treatment (Detaille et al., 2004; see Section 10.5.3). Plasma ethylene glycol levels should be monitored every 12-24 hours (OPi, 2004). For details on the laboratory monitoring required during ethanol treatment, see Appendix 2.

9.3.2 Need for Haemodialysis

Haemodialysis enhances the elimination of ethylene glycol and methanol from the blood, as well as their metabolites, and should be considered under certain circumstances. Previous recommendations were that haemodialysis was considered if the serum ethylene glycol or methanol concentrations were ≥50 mg/dL, or in the case of renal failure or severe metabolic acidosis (Stokes and Aueron, 1980;

Barceloux et al., 1999; De Brabander et al., 2005). Patients with serum ethylene glycol or methanol concentrations significantly higher than 50 mg/dL have been successfully treated with fomepizole alone without haemodialysis (Bacis et al., 2003; Boyer et al., 2001; Detaille et al., 2004; Hovda et al., 2005b). Serum concentrations above 50 mg/dL alone are therefore no longer considered to be an independent criterion for initiating haemodialysis. This is particularly the case for ethylene glycol, which has a half-life of 15-17 hours during fomepizole therapy. However, methanol has a longer half-life (50-80 hours) during fomepizole therapy. Therefore, patients may be on therapy for more than a week and physicians may consider using haemodialysis to shorten the duration of fomepizole therapy.

Although some patients with methanol poisoning can be treated with fomepizole alone without haemodialysis, critically ill patients with a severe metabolic acidosis (base excess less than 15) and/or visual disturbances should still be treated with haemodialysis in addition to fomepizole (Hovda and Jacobsen, 2008). If patients require transport to another centre for haemodialysis, or the capacity for haemodialysis is overwhelmed during a toxic alcohol outbreak, the efficacy of fomepizole as an antidote and its favourable adverse effect profile allow treating physicians the potential to postpone or avoid dialysis even in patients with severe poisoning (Hovda and Jacobsen, 2008).

In cases where haemodialysis is necessary, specialist equipment is required and staff must be adequately trained. In 2006, it was estimated that close to 80% of the world dialysis population is treated in Europe, North America and Japan (Aviles-Gomez et al., 2006). As such, there is the potential that low income countries may not have appropriate access to haemodialysis or need to transfer patients for haemodialysis. Therefore, being able to manage patients with high ethylene glycol/methanol concentrations using fomepizole alone without haemodialysis is a significant advantage over ethanol.

10. Summary of Comparative Effectiveness in a Variety of Clinical Settings

10.1 Identification of Clinical Evidence

Literature searches were performed to find clinical studies relating to fomepizole or ethanol use in toxic alcohol or glycol poisoning using EMBASE and MEDLINE (see Appendix 1 for search terms used). The AACT Practice Guidelines on the Treatment of Ethylene Glycol Poisoning (Barceloux et al., 1999) and Methanol Poisoning (Barceloux et al., 2002), and International Programme on Chemical Safety (IPCS) reviews of fomepizole (Baud et al., 2003), ethylene glycol (Jouglard, 2001) and methanol (Bozza-Marrubini et al., 2001) were used to identify relevant papers. Clinical trials databases were also searched for the term “fomepizole” and key researchers were contacted for any unpublished data.

A search for non-clinical studies was not conducted. Instead, a number of experimental and animal studies were identified in the IPCS review of fomepizole (Baud et al., 2003) and a selection of relevant papers (Blomstrand and Ingemansson, 1984; Clay and Murphy, 1977; Grauer et al., 1987; Li and Theorell, 1969; McMartin et al., 1975; Reynier, 1969) are described in this section.

Only English language papers were included. No time restriction was applied.

The evidence found comprises retrospective case series, case reports, and prospective clinical trials of the efficacy of fomepizole in ethylene glycol and methanol poisoning. No randomised, controlled studies currently exist in the literature. The clinical evidence presented in this section is from retrospective case series and prospective clinical studies. Individual case reports were excluded as their evidence quality is low.

The clinical details of the prospective observational studies and retrospective case series are summarised in Appendix Tables 2 and 3 and an assessment of their quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach in Appendix Table 6.

10.2 Experimental Evidence of Efficacy of Fomepizole

10.2.1 *In vitro* Studies

Experimental studies have demonstrated the ability of fomepizole to inhibit alcohol dehydrogenase, with 500-1000 times greater affinity for the enzyme than ethanol (Li and Theorell, 1969; Reynier, 1969). The study by Li and Theorell (1969) was the first to suggest a potential role for fomepizole as a clinically useful agent in toxic alcohol and glycol poisoning. Their results showed fomepizole to be a powerful competitive inhibitor of human liver alcohol dehydrogenase *in vitro*.

10.2.2 Animal Studies

Fomepizole

Animal studies in monkeys reported the ability of fomepizole to reverse the toxicity of lethal doses of methanol (McMartin et al., 1975) and ethylene glycol (Clay and Murphy, 1977). Fomepizole had a profound inhibitory effect on the oxidation of methanol and was capable of preventing or reversing the metabolic acidosis induced by methanol. A single intramuscular dose of 50 mg/kg fomepizole also inhibited $^{14}CO_2$ production from ^{14}C-methanol by 75%, and when signs of methanol toxicity e.g. vomiting, weakness and general behaviour distress were allowed to develop, administration of fomepizole resulted in a resolution of these effects (McMartin et al., 1975). Fomepizole has also been shown to reverse the toxic ocular effects of methanol in cynomolgus monkeys. Intramuscular fomepizole was administered at doses of 20 mg/kg every 15 hours from 5 hours after methanol administration until the serum methanol concentration was <1 mM. In these animals, no signs of ocular toxicity were observed on ophthalmoscopy and electroretinography examinations (Blomstrand and Ingemansson, 1984). Prior to fomepizole administration, formate concentrations rose rapidly, but after fomepizole administration these then rapidly declined. However, 15 hours after the administration of fomepizole, formate began to accumulate when there was no detectable fomepizole in the plasma. This strongly suggests that fomepizole was responsible for preventing the accumulation of formate.

The ability of fomepizole to prevent and reverse metabolic acidosis was also demonstrated in a monkey model of ethylene glycol toxicity. Pigtail monkeys were administered fomepizole doses of 50 mg/kg every 6 hours for 24 hours either intravenously or intraperitoneally (Clay and Murphy, 1977). Administration of ethylene glycol alone produced a profound metabolic acidosis but no toxicity was observed when fomepizole was administered 30 minutes after ethylene glycol exposure. Fomepizole doses administered 6 and 14 hours after ethylene glycol exposure were also effective in reversing the metabolic acidosis. However, delayed fomepizole administration at 15 and 21 hours after exposure resulted in a much slower reversal of acidosis. This showed that the efficacy of fomepizole in ethylene glycol poisoning is closely related to the timing of administration relative to ethylene glycol exposure, with a delay in treatment being associated with poorer efficacy.

Fomepizole Compared with Ethanol

In dogs, the efficacy of fomepizole for the treatment of ethylene glycol poisoning was compared to ethanol and no treatment. Repeated administration of fomepizole or ethanol 3 hours after ethylene glycol exposure was found to be similarly effective in preventing the metabolic acidosis and renal

impairment associated with ethylene glycol intoxication (Grauer et al., 1987). However, ethanol treatment exacerbated the ethylene glycol-induced CNS depression and induced recumbency, whereas dogs treated with fomepizole had less severe CNS depression and ataxia after the administration of the first dose and these signs improved over time. In addition, dogs treated with fomepizole were clinically normal within 24 hours, whereas ethanol-treated dogs remained either severely ataxic or recumbent for 36 hours and depressed for 72 hours. In ethanol-treated dogs, the combination of diuresis produced by ethylene glycol ingestion and the significant CNS depression related to ethanol treatment meant that intravenous fluid therapy was necessary to prevent life-threatening dehydration. From 3-72 hours after ingestion, repeated administration of fomepizole significantly increased urinary excretion of unchanged ethylene glycol in animals without renal failure, 71% of the ethylene glycol ingested was excreted unchanged in urine compared to 51% for ethanol-treated dogs and 48% for untreated animals.

10.3 Clinical Evidence of Efficacy of Fomepizole

The clinical use of fomepizole in humans was first reported in the late 1980s for treatment of ethylene glycol poisoning (Baud et al., 1986-1987), and in 1997 for methanol poisoning (Burns et al., 1997). Subsequent to these initial reports, two multi-centre prospective clinical trials were conducted to assess the efficacy of fomepizole for these indications (Brent et al., 1999; Brent et al., 2001).

The outcomes which have been investigated in clinical studies to demonstrate the influence of fomepizole on patient survival include:

- blocking metabolism of the parent alcohol and thereby inhibition of the formation of the toxic metabolites, urinary oxalate, plasma glycolate and formate
- prevention or improvement in renal dysfunction associated with ethylene glycol poisoning, demonstrated by changes in serum creatinine, and visual impairments associated with methanol poisoning
- prevention or resolution of metabolic acidosis, demonstrated by changes in arterial pH and serum bicarbonate.

10.3.1 Quality of Evidence

To date, no randomised controlled studies comparing treated subjects with either untreated subjects or placebo-controls have been conducted as it would be unethical to withhold treatment for poisonings associated with high morbidity and mortality (Brent et al., 1999). There have also been no studies directly comparing fomepizole with ethanol for the management of toxic alcohol or glycol poisoning. The infrequent nature of these intoxications and variation in circumstances of the poisoning e.g. time to admission, amount of toxin ingested, renders it difficult to conduct true randomised clinical trials, and to recruit sufficient numbers of patients.

The body of evidence supporting the efficacy of fomepizole is derived from prospective, observational clinical studies (Brent et al., 1999; Brent et al., 2002; Hovda et al., 2005a; Hovda et al., 2005b; Hovda et al., 2005c; Sivilotti et al., 2000), and retrospective case reviews (Borron et al., 1999; Caravati et al., 2004; Green, 2007; Levine et al., 2012; Mégarbane et al., 2001; Paasma et al., 2012) discussed below and summarised in Appendix Tables 2, 3 and 6.

Although these clinical studies appear to be well designed and executed, when rated using the GRADE approach they are of low to moderate quality. The prospective observational studies lacked control groups. The retrospective studies have several limitations, e.g. case notes may be incomplete or inaccurate, the decision to treat was not based on set criteria but made at the discretion of the treating

physician, and there may have been local variations in diagnostic equipment and treatment quality (see Appendix Table 6).

However, it is important to note that positive outcomes due to fomepizole are consistently reported across all the studies, and are supported by numerous case reports.

The findings from these studies are summarised below. Details of the studies are included in Appendix Tables 2, 3 and 6.

10.3.2 Fomepizole Treatment in Ethylene Glycol Poisoning

Prospective Observational Studies

The efficacy of fomepizole in ethylene glycol poisoning was demonstrated by a multi-centre, prospective observational clinical trial conducted by the Methylpyrazole for Toxic Alcohols (META) Study Group in the US. A consecutive series of 19 adult patients with confirmed ethylene glycol poisoning (either a serum ethylene glycol concentration of ≥20 mg/dL, or a suspicion of ingestion and specified laboratory measurements), were treated with intravenous fomepizole. Fomepizole was administered at a loading dose of 15 mg/kg followed by 10 mg/kg every 12 hours for 48 hours, after which the dose was increased to 15 mg/kg every 12 hours to compensate for increased fomepizole elimination.

17 patients underwent haemodialysis (Brent et al., 1999). No patients were administered ethanol at the participating study centres, however, patients were not excluded from the study if they had co-ingested ethanol (4 patients) or if they had received ethanol treatment at a referring hospital before transfer to a study centre (8 patients) (Sivilotti et al., 2000).

18 out of the 19 patients survived their acute poisoning. Fomepizole treatment was associated with a progressive decrease in plasma glycolate in all patients, and correction of acidosis with concurrent rises in arterial pH and serum bicarbonate concentrations. The patient who died suffered cardiogenic shock 22 hours after enrolment, following an acute myocardial infarction before enrolment.

Further analysis and toxicokinetic analysis of the data from this study by Sivilotti et al. (2000) showed that fomepizole effectively inhibited alcohol dehydrogenase-mediated oxidation of ethylene glycol at the doses used. Additional evidence of efficacy was provided by the observed decrease in ethylene glycol elimination with fomepizole loading and subsequent increase after the discontinuation of fomepizole therapy. They reported that the ethylene glycol elimination half-life during fomepizole monotherapy (therapeutic fomepizole concentrations in the absence of ethanol or haemodialysis) was 19.7 ± 1.3 hours. After fomepizole concentrations had decreased to below the target minimum of 10 µmol/L (after fomepizole therapy was discontinued), the half-life of ethylene glycol was <8.6 ± 1.1 hours. In untreated patients, the elimination half-life of ethylene glycol has been reported as 3-8.6 hours (Barceloux et al., 1999). Their analysis also showed that the presence of ethanol had no appreciable effect on ethylene glycol elimination confirming a very high degree of metabolic inhibition by fomepizole alone.

Retrospective Case Series

Several retrospective case series on the treatment of ethylene glycol poisoning with fomepizole were identified in different clinical settings. These have also reported the successful treatment of these patients using fomepizole, including many who did not receive haemodialysis.

Caravati et al., (2004) showed fomepizole to be an effective treatment for paediatric patients. They reviewed data from 6 paediatric patients admitted with ethylene glycol poisoning ranging in severity from mild acidosis (lowest measured serum bicarbonate ranged from 4-17 mmol/L) and alertness to severe acidosis and lethargy, and with serum ethylene glycol concentrations ranging from 62-304 mg/dL

(mean 174 mg/dL); these concentrations can be associated with life-threatening toxicity. All patients had normal renal function (creatinine levels) at presentation. Two cases were treated with fomepizole only and three patients received a loading dose of ethanol but were switched to fomepizole after transfer from an outlying hospital. These patients were all treated without haemodialysis and their metabolic acidosis resolved within 24 hours of admission. All patients recovered and were discharged without sequelae or renal insufficiency.

The effectiveness and safety of fomepizole as sole treatment for ethylene glycol poisoning, without adjunctive haemodialysis, in patients with normal renal function, was demonstrated in a retrospective cohort study of 40 patients over an 8 year period (Levine et al., 2012). All patients had good outcomes despite median peak serum ethylene glycol concentration of 127 mg/dL (interquartile range [IQR] 84-226 mg/dL).

A report of a series of 38 patients with suspected ethylene glycol poisoning treated with fomepizole provides additional evidence of efficacy and safety of fomepizole without haemodialysis in patients without renal failure (Borron et al., 1999). All patients were given a loading dose of fomepizole on admission. 11 patients were subsequently found to have ethylene glycol plasma concentrations of ≥20 mg/dL (median concentration 81 mg/dL, IQR 50-277 mg/dL) and given fomepizole, orally in four cases, intravenously in six cases, and by both routes in one case. Only three patients were treated with haemodialysis, in two cases because of renal insufficiency and acidosis and in one case because of a very high plasma ethylene glycol concentration of 831 mg/dL. One patient died within a few hours of admission, having been admitted with multi-organ failure. In the seven patients with normal renal function, there was no subsequent deterioration of serum creatinine concentration after the initiation of fomepizole therapy.

One report on a single patient admitted a total of 154 times with ethylene glycol poisoning studied potential adverse effects of repeated use of fomepizole (Hovda et al., 2011). No adverse effects of fomepizole were registered. The kinetics of ethylene glycol and glycolate during treatment with fomepizole were also studied. The median ethylene glycol concentration was 250 mg/dL (25-700 mg/dL). Median half-life of ethylene glycol during fomepizole treatment was found to be 12.9 hours before dialysis, and 2.4 hours during dialysis. The mean glycolate half-life was found to be 3.2 hours before dialysis. The outcome was also evaluated with fomepizole (99 times), ethanol (60 times), and both antidotes used (six times) – both with (73 times), and without (81 times) haemodialysis. The outcome was good on all 154 admissions, both with and without dialysis. The renal impairment seen on ten of the admissions normalised on all occasions.

10.3.3 Fomepizole Treatment in Methanol Poisoning

Prospective Observational Studies

A further prospective clinical trial by the META Study Group showed fomepizole to be effective in methanol poisoning, preventing methanol metabolism and the resultant metabolic acidosis (Brent et al., 2001). 11 consecutive patients with either a serum methanol concentration of ≥20 mg/dL, or a suspicion of ingestion and specified laboratory measurements, were treated with fomepizole using the same dosing regimen as the META Study Group clinical trial for ethylene glycol poisoning (see Section 10.3.2). Seven patients who had visual disturbances at presentation also underwent haemodialysis.

Therapeutic plasma concentrations of fomepizole were achieved with the dosing regimen used. Plasma fomepizole concentrations, measured a total of 155 times during therapy in all patients, were at or

above the target concentration of 10 µmol/L on all except three occasions. Efficacy was evidenced by a good outcome in 9 out of the 11 patients (two patients died of anoxic brain injury) and a decrease in plasma formate concentrations in all patients, with simultaneous resolution of the metabolic acidosis, and improvements in mental status and visual symptoms and signs. This reduction of formate concentrations indicated that methanol metabolism had been inhibited by fomepizole.

Fomepizole prevented formate production in four patients who did not receive haemodialysis, suggesting that haemodialysis may not be necessary for patients without acidosis or visual impairment, treated with fomepizole.

Experience of using fomepizole in a large methanol outbreak in Norway has been described by Hovda et al. (2005c). 51 patients were admitted with confirmed methanol poisoning, probably caused by a single batch of methanol-tainted liquor. Fomepizole was easier to administer than ethanol as it was given in twice daily bolus dosing compared to the difficult infusion regime of ethanol and did not require therapeutic drug monitoring. In addition, fomepizole did not cause respiratory depression and many patients could be treated outside the intensive care unit or required only a brief stay. Morbidity and mortality were high, particularly in patients with severe acidosis on admission. 36 patients received fomepizole and 29 survived. The seven patients who died were admitted with a mean pH of 6.66 (range 6.34-7.13). Four patients who were treated with fomepizole survived but with sequelae.

Eight patients from the Norwegian outbreak who had low to moderate acidosis were selected for treatment with buffer and fomepizole alone, without dialysis (Hovda et al 2005a). Three of these patients were later dialysed due to a very long methanol half-life during fomepizole treatment. All patients recovered uneventfully with the exception of one patient who was discharged with visual disturbances – due to language difficulties he was not known to have visual disturbances, even on admission, and as a result he was not dialysed according to the treatment protocol. It was therefore considered safe that dialysis was avoided in patients with low to moderate acidosis regardless of methanol concentration.

Hovda et al. (2005b) assessed the kinetics of formate and haemodialysis in seven severe cases of methanol poisoning from the same Norwegian outbreak. They showed that fomepizole was effective in preventing methanol metabolism in methanol-poisoned patients without severe metabolic acidosis or visual disturbances, despite delayed haemodialysis. Two patients, who were dialysed electively the day after admission, displayed no clinical signs e.g. metabolic acidosis, despite having the highest methanol concentrations on admission (329 mg/dL and 450 mg/dL) and were discharged without sequelae. The lack of metabolic acidosis seen in these patients suggests that little methanol was metabolised to formate. This provided further evidence to support the treatment of this level or severity of poisoning with fomepizole alone without haemodialysis.

Retrospective Case Series

Evidence that fomepizole rapidly resolves metabolic acidosis in methanol poisoning was provided by a retrospective study of 14 methanol-poisoned patients treated with oral (n = 4) or intravenous (n = 10) fomepizole (Mégarbane et al., 2001). These included four patients who underwent haemodialysis for visual impairments present on admission and three patients who had been administered ethanol therapeutically; one patient was administered ethanol by a referring physician, in the other two cases fomepizole treatment was instituted on the basis of complications – one patient developed stupor during ethanol therapy and the other developed acute pancreatitis.

All patients survived and recovered without sequelae, except those with visual disturbances that were present on admission. Improvements in the level of consciousness were noted in these patients and no

new signs or symptoms of methanol poisoning occurred after the initiation of fomepizole treatment. Four patients had plasma methanol concentrations of ≥50 mg/dL and were treated without haemodialysis. These patients recovered fully without any sequelae and included the patient with the highest methanol concentration (146 mg/dL), in whom ethanol was not used. Analysis of methanol toxicokinetics demonstrated that fomepizole blocked methanol metabolism effectively. The median elimination half-life of plasma methanol during fomepizole monotherapy was calculated to be 22.9 hrs (range 15.9-56.5 hrs) and the median total clearance was 17.6 mL/min (range 10.5-34.6 mL/min). Linear regression between methanol elimination half-life and plasma methanol concentration measure from the start of fomepizole monotherapy was highly significant (R^2 = 0.98, p = 0.0009). On the basis of these results, the authors suggested that in patients without severe metabolic acidosis and normal renal function, methanol poisoning may be successfully treated using fomepizole without haemodialysis. This was in contrast to prior recommendations that haemodialysis is indicated in patients with serum methanol concentration >50 mg/dL to remove the pre-existing toxic metabolites.

Nevertheless, haemodialysis remains an important adjunctive therapy, especially in cases of late admission in patients with severe metabolic acidosis.

10.4 Ethanol Treatment in Ethylene Glycol and Methanol Poisoning

Ethanol has been used for toxic alcohol and glycol poisonings since the 1940s (Agner et al., 1949; Roe, 1946). However, unlike fomepizole, it is not FDA approved for either indication. Whilst the efficacy of fomepizole for ethylene glycol and methanol poisoning has been evaluated in prospective clinical trials, no such trials exist for ethanol.

Many case series have reported the use of ethanol as treatment for ethylene glycol and methanol poisoning (Brahmi et al., 2007; Ekins et al., 1985; Lister et al., 2005; Paasma et al., 2007; Palatnick et al., 1995).

An early prospective study evaluated the clinical outcomes of seven consecutive patients treated with ethanol and concurrent haemodialysis. Ekins et al. (1985) reported survival in all patients, with only one patient discharged with severe ocular damage. However, it is unclear whether the positive outcomes seen in this study were due to ethanol treatment or the concurrent use of haemodialysis.

Based on a study of three methanol-poisoned patients, Palatnick et al. (1995) determined the half-life of methanol to be 30.3-52.0 hours when ethanol was administered without haemodialysis, but as short as 3.5 hours when ethanol therapy was combined with haemodialysis. The authors recommended the concurrent use of haemodialysis with ethanol to reduce the period of stay in an intensive care unit and to reduce the period of risk for toxicity and potential complications of ethanol treatment. The authors also observed that maintaining a therapeutic ethanol concentration of ≥100 mg/dL was difficult. Ethanol concentration after loading was measured a total of 49 times. In more than 87% of these measurements the ethanol concentrations were subtherapeutic. This difficulty in maintaining therapeutic ethanol concentration is consistent with other reports in the literature which have also reported the difficulty of maintaining therapeutic concentrations of ethanol, especially during haemodialysis, and reported that fluctuations of serum ethanol concentration place patients at risk of subtherapeutic or toxic serum ethanol concentration (see Section 11.4.2).

Lister et al. (2005) described a retrospective case series of 27 patients treated with ethanol for ethylene glycol or methanol poisoning, 26 of whom also had concurrent haemodialysis. They found that 25 out of 27 patients (93%) survived despite difficulties in achieving target serum ethanol concentrations. Only one

patient was discharged with renal dysfunction as a result of ethylene glycol toxicity and no visual deficits associated with methanol were reported, although incomplete reporting of the visual disturbances associated with methanol was noted as a limitation of this study. The authors concluded that neither in their study nor the clinical trials of fomepizole (Brent et al., 1999; Brent et al., 2001) was it possible to distinguish the role of antidote therapy from the role of timely and adequate haemodialysis in producing a favourable outcome. They also noted that the reported effectiveness of fomepizole without the use of haemodialysis (Borron et al., 1999; Mégarbane et al., 2001) may offer an advantage over ethanol treatment, especially in centres where haemodialysis is unavailable, and that the recommended fomepizole dose regimen was advantageous in situations where frequent laboratory monitoring or continuous intravenous infusion facilities are unavailable. The only disadvantage of fomepizole listed by the authors is its higher acquisition cost.

The patient outcomes reported in a recent series of severe methanol poisonings in Tunisia, treated with ethanol due to the unavailability of fomepizole (Brahmi et al., 2007), contrast with those reported when fomepizole was used in Norway (Hovda et al., 2005c; see Section 10.3.3). 16 patients were admitted 4-24 hours after ingestion (median 9.5 hours) with a delay in obtaining medical consultation of 6-48 hours (median 36 hours). At presentation, CNS effects including vertigo, headache and coma were seen in 11 cases, visual disturbances including blurred vision, visual impairment, dyschromatopsia and bilateral blindness were reported in 10 cases, and 3 patients had haemodynamic failure and shock. The median serum methanol concentration at presentation was 140 mg/dL (range 19-362 mg/dL) and median pH was 7.22 (range 6.80-7.42), with metabolic acidosis seen in all but one patient. Intravenous ethanol was administered in 13 patients and haemodialysis instituted in 11 patients. Three patients (19%), who were admitted comatose, died within six hours of admission from refractory shock. Visual deficits were reported in 69% of patients.

Fomepizole, recommended as a first line antidote but unavailable in Tunisia, has been reported to reduce and reverse visual impairment (Mbia, 2002). As a result, Brahmi et al. suggested fomepizole to be included on government lists of necessary antidotes.

Paasma et al. (2007) described an outbreak in 154 patients in Estonia in 2001 where ethanol was the only available antidote. Of these, 111 patients were admitted to hospital alive with confirmed methanol poisoning, of whom 25 (23%) died. The remaining 43 patients with confirmed methanol poisoning died outside hospital, giving a total mortality rate of 44%. The patients who died had a significantly lower pH (median pH 6.78), compared to the ones who survived with sequelae (median pH 7.14), or without sequelae (median pH 7.19). Other important prognostic factors were consciousness on admission, and the patients' ability to hyperventilate. The authors evaluated the consciousness of the patient both on admission and after one hour (after the initiation of ethanol treatment), and found that 29/72 (40%) of the patients who were awake fell into coma following ethanol treatment. Two of these also developed respiratory arrest and needed rapid intubation, and this group had a poorer outcome compared to the ones who stayed awake.

10.5 Comparison of Fomepizole versus Ethanol Treatment

Two studies compared fomepizole with ethanol using retrospective data. A study by Corley and McMartin (2005) assessed the efficacies of fomepizole and ethanol for ethylene glycol intoxication and another by Paasma et al. (2012) compared the two in methanol outbreaks.

10.5.1 Comparison of Fomepizole and Ethanol in Ethylene Glycol Poisoning

Corley and McMartin (2005) used a pharmacokinetic model to assess the efficacies of fomepizole and ethanol treatment. A human physiologically based pharmacokinetic (PBPK) model, developed in a

companion paper, was adapted to include treatment regimens that alter the kinetics of ethylene glycol and glycolate; these included haemodialysis, ethanol and fomepizole treatment. The original PBPK model was based on the extensive data on the kinetics and mode of action of ethylene glycol and its metabolite, glycolate, in humans. This PBPK model was able to successfully simulate the ethylene glycol and glycolate concentrations as measured in several case reports and series, and thereby validating the use of this model. This resulting model was then used to evaluate the effectiveness of various treatment regimens based on the modelled kinetics of ethylene glycol and glycolate.

The PBPK model suggested that fomepizole is more effective at inhibiting ethylene glycol metabolism to glycolate than ethanol, based on its significantly lower dissociation constant when the simulations are conducted at the normal therapeutic levels for each treatment. The simulation indicated that fomepizole treatment should lower blood glycolate concentrations more rapidly, along with a lower urinary glycolate excretion. The results implied a more complete inhibition of metabolism by fomepizole compared to ethanol, as indicated by the slower elimination of ethylene glycol from the blood, and higher excretion in the urine. The model also suggested that if administered early enough in a clinical situation, fomepizole can be more effective than ethanol or haemodialysis in preventing the metabolism of ethylene glycol to its more toxic metabolites.

However, haemodialysis remains an important treatment option if treatment is instituted after a significant amount of ethylene glycol is metabolised or if renal toxicity has occurred. Since alcohol dehydrogenase inhibitors only prevent formation of toxic metabolites, haemodialysis which also removes the pre-existing toxic metabolites in addition to their parent compounds, remains an important adjunctive therapy, especially in cases of late admission and in patients with severe metabolic acidosis.

10.5.2 Comparison of Fomepizole and Ethanol in Methanol Poisoning

In a recent retrospective study, Paasma et al. (2012) evaluated factors associated with sequelae and death in order to compare treatment with fomepizole to ethanol. In this study, patient data from previous outbreaks of methanol poisoning from Norway (1979 and 2002-2005), Estonia (2001), Tunisia (2003-2004), and additional data obtained from two different centres in Iran (Tehran 2004-2009 and Mashhad 2009-2010) were used. By combining data from different methanol epidemics in different parts of the world where laboratory analyses and clinical features were available, the study attempted to diminish the influence of confounders such as local variations of diagnostic equipment and treatment quality.

203 patients met the inclusion criteria for this study: confirmed methanol poisoning and arterial blood gas drawn on admission before any treatment was initiated. Subjects were grouped into three categories based on patient outcomes – survivors without sequelae, survivors with sequelae (visual disturbances or brain damage on discharge) and patients who died (Table 5). Despite a large patient sample size, there were still a limited number of patients treated using fomepizole, especially in regards to those who died. Fomepizole was only used in the Norwegian outbreak in 32 patients (2002-2005).

Table 6. Different Outcome Groups As Related to Different Admission Parameters (from Paasma et al., 2012)

Antidote	**Survivors without Sequelae*** (n = 121)	**Survivors with Sequelae*** (n = 34)	**Patients who Died** (n = 48)	**Overall** (n = 203)
Fomepizole	22 (68.75%)	4 (12.5%)	6 (18.75%)	32 (100%)
Ethanol	99 (57.89%)	30 (17.54%)	42 (24.56%)	171 (100%)
*Sequelae defined as visual disturbances or brain damage on discharge				

Their analysis showed a trend towards a better outcome regarding the pH in the fomepizole group relative to the ethanol group. However, this difference was not significant. In spite of severe metabolic acidosis (low pH), more patients administered fomepizole survived with sequelae instead of dying compared with patients with a similar pH treated with ethanol.

Due to the limited number of subjects in the fomepizole group, analysis of these patients was more susceptible to the effects of outliers. For instance, one patient in the group of fomepizole-treated patients who died was admitted with a pH of 7.13. However, the diagnosis of this patient was delayed and treatment was not commenced until 6 hours post-admission, at which time the patient was already severely acidotic (pH 6.8) and in a coma. When this outlier is excluded from the analysis, the difference between the ethanol and fomepizole treated groups would be significant ($p = 0.038$).

The study also investigated the CNS-depressive effects of ethanol treatment using data from the Estonian outbreak. As these patients were part of the same outbreak, the influence of bias due to differences in treatment quality is diminished. The authors reported that the CNS-depressive effect of ethanol may interfere with treatment and the need for mechanical ventilation and could potentially influence patient outcome. Patients who became comatose after the initiation of treatment with ethanol appeared to have a poorer outcome than those who remained conscious throughout treatment (6/25 compared with 0/39 patients who died). Despite a higher degree of hyperventilation on admission, patients treated with ethanol still died. It is suggested that the removal of their respiratory drive after addition of a CNS depressant may be associated with a poorer outcome. The suggestion that the CNS depression caused by ethanol affects outcome is supported by a study which found methanol co-ingestions with opioids were associated with a poorer outcome (Hassanian-Moghaddam et al., 2007). As a result, ethanol should be used with caution in patients who have co-ingested CNS depressant drugs or who present with severe poisoning and an established acidosis and associated CNS depression (Barceloux et al., 2002).

Paasma et al. noted limitations in their study, mostly due to the inherent nature of using retrospective data. They also state that the association found between the ability to hyperventilate when severely acidotic to a better outcome should ideally be confirmed in a prospective randomised trial. However, this observation was based on well-established theories which show the more hyperventilation, the better the correction of metabolic acidosis and that ethanol is a CNS depressant. An additional limitation was the possible variations in time from admission to treatment initiation and the available treatment modalities other than the choice of antidote. Delays in treatment were found in both ethanol and fomepizole groups, although the previously mentioned outlier in the fomepizole group had more impact on data analysis due to the smaller number of subjects in this group. The same treatment modalities were found across all countries included in this study, including buffer and haemodialysis. The authors note that the limited number of subjects in the fomepizole group, especially for patients discharged with sequelae and who died, gave insufficient power to allow statistical analysis to find differences in outcomes.

10.5.3 Practical Considerations

Whilst there have been suggestions that ethanol and fomepizole are equally effective treatments for ethylene glycol and methanol poisoning given optimal treatment (Paasma et al., 2012), there are many practical disadvantages of ethanol treatment which can affect its efficacy. In their retrospective analysis of ethanol and fomepizole use in methanol outbreaks, Paasma et al. (2012) concluded that although their results do not demonstrate fomepizole is superior to ethanol given optimal treatment, providing optimal treatment is a major challenge with ethanol use. For instance, maintaining a constant serum

concentration between 100-150 mg/dL, necessary for ethanol treatment, is difficult (Hantson et al., 2002). In addition, the CNS depressant effects of ethanol may interfere with treatment and affect the need for mechanical ventilation, and therefore patient outcome (Paasma et al., 2012). These have important implications for management of ethylene glycol and methanol poisoning, e.g. ethanol should be used with caution in patients who have co-ingested CNS depressant drugs. The practical disadvantages of ethanol treatment are particularly relevant to poisoning epidemics in economically disadvantaged countries where haemodialysis facilities and blood monitoring required for ethanol treatment are not readily available.

Fomepizole, with a much simpler, validated treatment regimen offers many practical advantages, especially in situations where frequent laboratory monitoring or continuous intravenous infusion is not feasible. Unlike ethanol, monitoring of plasma fomepizole concentration is unnecessary as fomepizole is relatively safe and has a wide therapeutic index.

The plasma concentration of fomepizole necessary to inhibit alcohol dehydrogenase is approximately 0.8 μg/mL (10 μmol/L) based on preclinical animal studies (Brent et al., 1999; Brent et al., 2001; McMartin et al., 1975; McMartin et al., 1980). In the META Study Group clinical trial for ethylene glycol poisoning using the AACT/EAPCCT recommended dosing regimen, plasma fomepizole concentration during therapy ranged from 15-30 μg/mL (183-366 μmol/L), 18-38 times the minimum therapeutic concentration (Brent et al., 1999). Despite these high plasma fomepizole concentrations, very few adverse effects were reported with the use of this dosing regimen.

In addition, therapeutic concentrations of fomepizole are easily maintained above the minimum therapeutic concentration using the AACT/EAPCCT dosing regimen. Brent et al. (2001) measured the plasma concentrations of fomepizole during therapy and found that 98% of measurements met or exceeded the minimum therapeutic concentration of 0.8 μg/mL (10 μmol/L). By contrast, maintaining serum concentrations of ethanol between the recommended range of 100-150 mg/dL is difficult and requires frequent blood monitoring (see Section 11.4.2).

A comparison of fomepizole and ethanol treatments is summarised in Appendix Table 1.

10.6 Fomepizole Use in Epidemics

The increasing use of fomepizole in outbreaks of toxic alcohol and glycol poisoning has been reported in recent years. Hovda et al. (2005c) described the successful use of fomepizole in a methanol outbreak in Norway, with many practical advantages of fomepizole over ethanol. Such advantages include its ease of administration and the lack of therapeutic drug monitoring required. In addition, fomepizole has been donated during epidemics of methanol and diethylene glycol poisoning in developing countries. In the 2006 outbreak of methanol poisoning in Nicaragua, Jazz Pharmaceuticals donated 1200 vials of fomepizole, the equivalent of 300 courses of treatment (PAHO, 2006). Later that year, another donation by Jazz Pharmaceuticals was made during an outbreak of diethylene glycol poisoning in Panama (PR Newswire, 2006). Furthermore, 103 boxes of fomepizole were recently donated by the Norwegian NBC Centre, EUSA Pharma, Swedish Orphan Biovitrum, and the Norwegian Medicinal Depot during an outbreak of methanol poisoning in the Czech Republic (Cameron, 2012; Pelclova, personal communication 2012).

Fomepizole treatment offers many practical advantages and may obviate the need for haemodialysis in patients admitted without significant metabolic acidosis, renal failure (ethylene glycol) or visual deficits (methanol). These are particularly relevant to epidemics of toxic alcohol and glycol poisoning in

developing countries where haemodialysis is not widely available and blood monitoring facilities may not exist. The number of patients is often high and the capacities for treatment overwhelmed. Given that the time from ingestion to treatment of intoxicated patients is crucial in determining patient outcome, fomepizole treatment, which (unlike ethanol therapy) does not require intensive care unit hospitalisation or blood monitoring every two hours, can be useful for severely intoxicated patients who require hospital transfer to haemodialysis facilities.

Although the efficacy of fomepizole has not been shown to be superior to ethanol given optimal treatment, providing such optimal treatment is a challenge, as noted by Paasma et al. (2012). In addition, the reported ability of fomepizole to reduce and reverse visual impairments may make it a more suitable antidote for methanol poisoning. As stated by Brahmi et al. (2007) for the methanol outbreak in Tunisia, "government authorities should be encouraged to include fomepizole in the list of necessary antidotes". The Czech Ministry of Health made this a reality after their recent outbreak in September 2012.

11. Summary of Comparative Evidence on Safety

11.1 Estimate of Total Patient Exposure to Date

Patients treated with fomepizole reported within our literature searches were tallied, and approximately 1250 were found. However, the total patient exposure is unknown.

11.2 Description of Adverse Effects/Reactions

The majority of adverse effects associated with fomepizole treatment described in clinical trials, case series, and case reports have been mild and transient.

The best evidence for this outcome is provided by:

- 2 randomised controlled trials in healthy subjects (Jacobsen et al., 1988; Jacobsen et al., 1990), which were limited by incomplete blinding of the subjects due to inability to completely mask the taste of fomepizole.
- 2 prospective observational clinical studies (Brent et al., 1999; Brent et al., 2001), which had adequate protocols with respect to the recognition and attribution of adverse effects, but did not include control groups, and were rated of low-moderate quality with respect to the outcome of adverse effects when rated using the GRADE approach.
- a retrospective study (Lepik et al., 2009), with a well-designed protocol for assessing adverse effects of fomepizole treatment, using validated tools to score and classify the severity of each sign or symptom and the seriousness of the event, and experienced toxicologists to assess association of each adverse event with fomepizole.

These studies consistently reported that fomepizole was well tolerated at therapeutic doses and was associated with few serious adverse effects. No adverse effects necessitated discontinuation of therapy, despite fomepizole concentrations being in excess of therapeutic concentrations in one study (Jacobsen et al., 1988). This is supported by case reports and other studies that were excluded from the quality assessment for this outcome because of insufficient information on their method for assessing association with fomepizole, and severity.

The following sections give an account of the adverse reactions reported across a range of sources.

11.2.1 Central Nervous System (CNS) Effects

The most frequently reported adverse effects following fomepizole administration are dizziness and headache (>10%) (SPC, 2011).

In a single dose study in healthy volunteers (Jacobsen et al., 1988), "slight to moderate dizziness" was reported up to two hours after dosing by 3 out of 4 subjects given 50 mg/kg fomepizole, and all four individuals in the 100 mg/kg group, but not by any of the subjects given 10 and 20 mg/kg fomepizole. In addition the subjects in the highest dose group experienced a sensation of inebriation accompanied by mild vertigo, mild pulsating headache, and mild visual and speech disturbances. These symptoms were short lived in two subjects, but lasted for up to 30 hours in one subject with a positive Romberg test and vertical nystagmus.

Mild transient dizziness, headache, and light-headedness were also reported in 7 of 15 subjects (47%) in a multiple dosing study of fomepizole in healthy volunteers (Jacobsen et al., 1990). Headache reported by two subjects in a prospective study was also considered as possibly related to fomepizole (Brent et al., 1999).

Other CNS side effects possibly related to fomepizole reported in two prospective studies included agitation, anxiety, and a "strange" feeling in patients with methanol poisoning (Brent et al., 2001), as well as seizure in 2 of 19 patients with ethylene glycol poisoning. The patients with seizures were a 57 year old man who had a generalised seizure 15 minutes after his first dose which was given during an evolving myocardial infarction that had begun before admission, and a 33 year old man who had a 45-60 second seizure 15 minutes after his first dose, but did not experience any further seizures after subsequent fomepizole doses (Brent et al., 1999). The authors state that the clinical courses suggest the seizures were unrelated to fomepizole.

In the retrospective study of adverse drug events with fomepizole, the only CNS symptom attributed to fomepizole was a transient resedation of an intubated patient (Glasgow Coma Scale score decrease from 13 to 6) after incorrect administration of an excessive dose of 24 mg/kg of fomepizole during a 5 hour period post dialysis. This event occurred 17 hours after the start of fomepizole, when the patient was otherwise improving clinically (Lepik, 2009). CNS depression is not associated with therapeutic doses of fomepizole.

Nystagmus, which resolved within one hour, was reported in a 6 year old girl treated with fomepizole for ethylene glycol poisoning. It is unclear whether this effect was related to fomepizole, as it developed two hours after administration, and the patient had multiple metabolic abnormalities and had received other medications (cefotaxime, pyridoxine, thiamine). The patient was discharged without sequelae (Benitez et al., 2000).

11.2.2 Cardiovascular Effects

Bradycardia and hypotension with fomepizole infusion during haemodialysis in a 59 year old man was judged to be a serious adverse event by WHO criteria (Lepik et al., 2008; Lepik et al., 2009; Lepik et al., 2011). The patient presented to hospital 10 hours after ethylene glycol ingestion, and treatment began 7.5 hours after admission. Severe bradycardia (29/min) and hypotension (69 mmHg systolic) occurred immediately following a 30 minute intravenous infusion of the first fomepizole dose (19 mg/kg), but rapidly corrected with 1 mg atropine. After the second dose (10 mg/kg), transient bradycardia (48/min) and hypotension (89/57 mmHg) recurred immediately. These symptoms cannot be attributed to fomepizole with any certainty, however the close temporal relationship with fomepizole administration, the dose-related symptom intensity, and the recurrence of symptoms suggest a causal relationship. A

post-dialysis fomepizole dose was well tolerated, suggesting haemodialysis, acidosis and a high initial fomepizole dose may have enhanced patient susceptibility.

Bradycardia after treatment with fomepizole for ethylene glycol poisoning was reported in a 35 year old man who developed transient bradycardia (heart rate 50-60 beats per minute) 2.5 hours after his first dose, and in a 20 year old man 16 hours after his last dose (heart rate 60 beats per minute) (Brent et al., 1999). These were probably idiosyncratic reactions to fomepizole.

Transient tachycardia has been seen once following intravenous fomepizole for treatment of methanol poisoning (Brent et al., 2001). The only cardiac effect reported in the placebo-controlled multiple dose study (Jacobsen et al., 1990) was a mild, sporadic, and transient elevation in blood pressure which was judged to have no apparent relation to the administration of fomepizole (Jacobsen et al., 1990).

11.2.3 Gastrointestinal and Metabolic Effects

Slight to moderate nausea and diarrhoea were reported in healthy volunteer studies (Jacobsen et al., 1988; Jacobsen et al., 1990).

Minor gastrointestinal side effects including nausea, vomiting and abdominal pain were reported in 3 of 42 patients treated with fomepizole (Lepik et al., 2009).

Mild transient increases in liver function tests were associated with multiple doses of fomepizole in a healthy volunteer study, but were not dose-related and did not appear to be mediated by a hypersensitivity reaction (Jacobsen et al., 1990). No liver function abnormalities were reported in prospective observational studies of ethylene glycol poisoning (Brent et al., 1999) and methanol poisoning (Brent et al., 2001), nor in the retrospective study of adverse effects of fomepizole (Lepik et al., 2009). However, a slight increase in serum transaminase activity was seen in 2 patients treated with fomepizole for ethylene glycol poisoning that may have reflected rhabdomyolysis as opposed to hepatic effects (Baud et al., 1986-7).

A transient episode of hypoglycaemia was reported in a 22 month old treated with 3 doses of fomepizole without haemodialysis. The reason for this episode was unclear (Caravati et al., 2004).

11.2.4 Dermatological Effects

Dermatological side effects include rash and application-site reactions (Brent et al., 2001), a burning skin sensation (Mégarbane et al., 2001) and a generalised cutaneous eruption (Borron et al. (1999). A skin rash with pruritus possibly related to drug administration was noticed on the second day of treatment with a daily dose of 20 mg/kg oral fomepizole, but disappeared when fomepizole treatment was stopped (Baud et al., 1986-7).

11.2.5 Haematological Effects

Lymphangitis and mild transient eosinophilia were reported in a patient who received 16 doses of fomepizole (Mégarbane et al., 2001). Transient eosinophilia has also been reported in patients treated for ethylene glycol poisoning (Borron et al., 1999).

11.2.6 Other Effects

One patient treated for methanol poisoning developed hiccups which were possibly related to fomepizole (Brent et al., 2001).

Table 7. Adverse Drug Events Reported with Fomepizole. Adverse events from studies were classified as 'very common' (>10%) or 'common' (1-10%) according to the EUSA Pharma SPC.

	Number of Reports				EUSA Pharma SPC, 2011
	Healthy Volunteer Studies (Jacobsen et al., 1988; Jacobsen et al., 1990; Maraffa et al., 2008)	Prospective Studies (Brent et al., 1999; Brent et al., 2001; Borron et al., 1999)	Fomepizole Adverse Effects study (Lepik et al., 2009)	Retrospective Study (Mégarbane et al., 2001)	
Total n Volunteers/Patients	40	41	42	14	
Gastrointestinal					
Nausea/vomiting/abdominal pain	3		3	1	common
Dyspepsia		1			common
Diarrhoea	7				common
Metallic taste	10				
CNS					
Coma			1		
Seizure		2			common
Dizziness	16				very common
Vertigo	1				common
Lightheadedness	7				
Nystagmus	1				common
Speech disturbance	1				common
Visual disturbance	1				common
Headache	11	2		1	very common
Anxiety		1			common
Feeling of drunkenness	1				
Agitation		2			common
Positive Romberg's test	1				
Cardiovascular					
Tachycardia		1			common
Bradycardia		2	1		common
Hypotension			1		
Hypertension	5				common
Phlebitis		1			
Metabolic					
Fever				2	
Elevated triglycerides	4				
Transient rise in transaminase	6				common
Dermatological					
Rash		1			common
Pruritus					common
Generalised skin eruption		1			
Burning skin sensation				1	
Injection site reactions		1			common
Venous inflammation		2			common
Haematological					
Eosinophilia		2		1	common
Anaemia					common
Lymphangitis				1	
Other					
Increase in uric acid	1				
Hiccups		1			common
Rise in blood creatinine phosphokinase					common

11.3 Identification of Variation in Safety due to Health Systems and Patient Factors

11.3.1 Paediatrics

The pharmacokinetic properties of fomepizole have not been determined in the paediatric population. However, therapeutic plasma concentrations have been achieved in paediatric patients following the same weight-adjusted dosing regimen used in adult patients. As in adults, there appear to be no severe adverse effects and most patients recover without sequelae (Boyer et al., 2001; Caravati et al., 2004). There has been a report of nystagmus in a 6 year old girl with ethylene glycol poisoning, however it was unclear whether this effect was related to fomepizole administration (Benitez et al., 2000). Infants with serum concentrations as high as 384 mg/dL ethylene glycol (Baum et al., 2000) and 350 mg/dL methanol (Brown et al., 2001) have been treated successfully with fomepizole.

11.3.2 Pregnancy and Breast Feeding

Fomepizole is classified as a Pregnancy Category C drug (see Section 8.3). The only controlled animal study regarding pregnancy performed to date is a recently published study by Gracia et al. (2012) revealing elevated concentrations of fomepizole in the foetus following maternal admission. This should protect the foetus against the toxic alcohol metabolites, but the long-term effects of fomepizole itself on the foetus need further research. There is, however, some evidence that excessive doses of fomepizole can cause foetal harm. Intraperitoneal administration of a dose 6.5 times the loading therapeutic dose in mice at day 11 of pregnancy induced embryotoxic and teratogenic effects (SPC, 2011).

The potential risk of reproductive toxicity in humans is unknown. In a case of a pregnant woman treated with fomepizole for methanol poisoning on two separate occasions at 11 weeks and 16 weeks gestation no neonatal adverse effects were recorded however post-natal outcome was not recorded (Velez, 2003).

There is no data on the extent to which fomepizole is excreted in human breast milk and patients are advised to stop breastfeeding temporarily during treatment.

The need for treatment should be made on a case by case basis. The potential life-threatening toxicity of methanol or ethylene glycol exposure is likely to outweigh the risks of fomepizole therapy. Alternative therapy with ethanol could be used, however this is associated with the risk of foetal alcohol syndrome (Barceloux et al., 2002) and as such treatment with fomepizole may be preferred.

11.3.3 Haemodialysis

Patients may require haemodialysis in conjunction with fomepizole treatment due to severe acid-base derangement. Haemodialysis is an invasive technique associated with various adverse effects such as an increased risk of bleeding, infection, thrombosis, hypovolemia, hypotension, and electrolyte abnormalities and is associated with worse outcomes in extreme age groups e.g. paediatrics (Caravati et al., 2004).

11.3.4 Other Factors

Other safety considerations during fomepizole treatment are:

- Elderly patients: there is insufficient data to determine whether the pharmacokinetics of fomepizole differ in the older population.
- Pre-existing renal insufficiency: the two primary metabolites of fomepizole (4-hydroxymethylpyrazole and 4-carboxypyrazole) are excreted renally. Urinary 4-carboxypyrazole was measured as 65.9 ± 4.5% and 65.1 ± 2.0% of the fomepizole dose after IV and oral doses, respectively (McMartin et al., 2012). Pharmacokinetic and related safety studies of fomepizole in patients with renal impairment have not been performed, however those with severe poisoning

often present/develop acute kidney injury and therefore by extrapolation it is likely that safety is similar in those with chronic renal failure.

- Impaired liver function: Careful monitoring of hepatic transaminases is recommended in individuals with impaired liver function (SPC, 2011). Pharmacokinetic and related safety studies of fomepizole in patients with pre-existing liver failure have not been performed.
- Contraindications: fomepizole should not be administered to patients with a known hypersensitivity to fomepizole or to other pyrazoles.
- Special warnings and precautions for use: minor transient hypersensitivity reactions such as rash and hypereosinophilia have been reported in a few patients, and these should be monitored. In the unlikely event of a major hypersensitivity reaction and in the absence of another established cause, fomepizole infusion should be discontinued immediately and alternative treatment used.
- Drug-drug interaction: Concurrent use of ethanol and fomepizole is usually not recommended for safety reasons as it reduces the elimination rate for both substances. However, the clinical efficacy of fomepizole does not appear to be impaired by this combination (SPC, 2011).

11.4 Summary of Comparative Safety against Comparators

11.4.1 Adverse Effects of Ethanol

A comprehensive search of ethanol-related adverse effects was not performed for this paper. However, an evaluation of the safety and ease of titrating ethanol infusions for the treatment of methanol or ethylene glycol ingestion suggests that adverse events occur frequently with ethanol infusions (Wedge et al., 2012). Of 49 patients, 45 (92%) experienced at least one adverse event, the most common being agitation requiring chemical or physical restraints in 35 cases (71%). Others included tachycardia in 16 patients (33%), vomiting in 11 (22%), and a decreased level of consciousness requiring intubation in 10 (20%). 9 patients (18%) had hypotension requiring vasopressor support, 5 (10%) had phlebitis, and seizures occurred in 3 (6%).

The adverse effects outlined below are a summary of those reported in case series, case reports, and reviews within our literature searches:

Central Nervous System (CNS) Effects

Ethanol may exacerbate the CNS depressant effects of ethylene glycol and methanol. For example, patients are more susceptible to developing drowsiness and coma with ethanol treatment the more severely poisoned they are (Paasma et al., 2012). There is an increased risk of these side effects in patients who have ingested other substances with CNS depressant activity.

A number of CNS adverse events associated with ethanol therapy are also clinical signs and symptoms of ethanol intoxication, such as:

- inebriation
- depression of cortical function
- emotional liability
- poor coordination
- loss of judgement, visual impairment
- slurred speech
- drowsiness (Roy et al., 2003)
- headache (Lepik et al., 2009)
- behavioural disorders

- withdrawal symptoms (Thanacoody et al., 2012)
- agitation
- seizures (Lepik et al., 2009)

Respiratory Effects

Aspiration or respiratory depression requiring mechanical ventilation due to CNS depression (Paasma et al., 2012).

Cardiovascular Effects

- circulatory problems exacerbated by the CNS depressant effects of ethanol
- phlebitis (Wedge et al., 2012)
- hypotension (Wedge et al., 2012)
- tachycardia (Wedge et al., 2012)

Gastrointestinal Effects

- nausea, vomiting, abdominal pain (Lepik et al., 2009; Wedge et al., 2012)
- pancreatic injury may be complicated by prolonged ethanol administration (Hantson and Mahieu, 2000)

Metabolic Effects

Although hypoglycaemia is often considered a significant adverse effect of ethanol, it is infrequently reported in patients treated with ethanol for methanol or ethylene glycol poisoning. In a retrospective chart review of paediatric patients, Roy et al. defined hypoglycaemia as at least one serum glucose concentration <2.78 mmol/L (<50 mg/dL) or at least one serum glucose concentration between 2.78 and 3.61 mmol/L (50 and 65 mg/dL) with the presence of symptoms compatible with hypoglycaemia (e.g. diaphoresis, sudden altered behaviour, or somnolence) (Roy et al., 2001). No patients had symptoms compatible with hypoglycaemia, however 8 of 50 (16%) had at least one serum glucose concentration between 2.78-3.61 mmol/L. Other studies found no evidence of hypoglycaemia in adult patients (Lister et al., 2005; Wedge et al., 2012). This is probably explained by the administration of ethanol in a dextrose solution.

Renal Effects

Polyuria of minor clinical importance has been observed in ethanol-treated patients (Lepik et al., 2009).

Effects in Pregnancy

The use of alcohol during the first trimester has been associated with foetal alcohol syndrome and is therefore not advised (Barceloux et al., 2002), but should be evaluated against the negative effect of ethanol during pregnancy.

11.4.2 Comparative Safety of Fomepizole and Ethanol

Adverse Effects

Lepik et al. (2009) conducted a retrospective cohort study of adverse events associated with ethanol and fomepizole in 172 patients aged 13 and above who had received at least 1 dose of antidote for suspected methanol or ethylene glycol poisoning. Results are summarised in Table 8 below. Toxicologists identified at least 1 adverse drug event in 74 of 130 (57%) ethanol-treated cases compared with 5 of 42 (12%) fomepizole-treated cases.

Table 8. Incidence, Rate and Event Detail of Ethanol- and Fomepizole-Related Adverse Drug Events (Lepik et al., 2009)

	Ethanol 130 cases No. (% of cases; 95% CI)	**Fomepizole 42 cases No. (% of cases; 95% CI)**
Incidence of Antidote-Related Adverse Drug Events		
Any adverse drug event	74 (57; 48-65)	5(12; 2-22)
Severe adverse drug event	26 (20; 13-27)	2(5; 0-11)
Serious adverse drug event	11(8; 4-13)	1(2; 0-7)
Adverse Drug Event Rate Per Person-Day of Antidote Treatment	Rate per person-day(95% CI)	
Any adverse drug event	0.93(0.87-0.98)	0.13(0.02-0.24)
Severe adverse drug event	0.20(0.13-0.27)	0.05(0-0.12)
Serious adverse drug event	0.07 (0.03-0.11)	0.03(0-0.07)
Event Detail: Antidote Adverse Drug Events by Organ System	No. (% of cases; 95% CI)	
Cardiovascular, any	7(5; 2-9)	1(2; 0-7)
Severe (pulse rate <40 or ≥180 beats/min, MAP <50 or ≥160 mmHg, symptomatic dysrhythmia, cardiac arrest)	4(3; 0-6)	1(2; 0-7)
CNS, any	63(48; 40-57)	1(2; 0-7)
Severe CNS depression (GCS score 3-8 [coma])	14(11; 5-16)	1(2; 0-7)
Severe CNS excitation (violent, combative, multiple seizures)	10(8; 3-12)	0
Hepatic (elevated hepatic enzyme levels, INR, bilirubin)	0	0
Hypoglycaemia (blood or serum glucose level <72 mg/dL [<4.0 mmol/L]	5 (4; 1-7)	0
Phlebitis at antidote intravenous site	5(4; 1-7)	0
Gastrointestinal (nausea, vomiting, abdominal pain)	12 (9; 4-14)	3 (7; 0-15)

Severe adverse drug events occurred in 26 of 130 (20%) ethanol-treated patients compared with only 2 of 42 (5%) fomepizole-treated patients.

CNS effects were reported in 63 of 130 (48%) ethanol-treated cases, accounting for the majority of adverse events in this treatment group. These included 14 cases of ethanol induced coma, and 10 cases of severe CNS excitation such as violent, combative behaviour and multiple seizures.

CNS symptoms were only observed in 1 of 42 (2%) fomepizole-treated cases, and involved transient resedation of an intubated patient following incorrect administration of a 24 mg/kg dose during a 5 hour period post dialysis, when the patient was otherwise improving clinically.

The patient treated with fomepizole who developed severe cardiovascular side effects (bradycardia and hypotension) following drug administration is described in more detail by Lepik et al. (2008) and in Section 11.2.2.

Analysis of the results showed the adverse drug event rates per treatment day for ethanol and fomepizole were 0.93 and 0.13, respectively, with an adjusted hazard ratio of 0.16 (95% confidence interval 0.06-0.40). There was a 6-fold reduction in adverse event rate in the fomepizole treatment group in comparison to the ethanol group, suggesting ethanol is associated with a higher incidence of adverse drug events.

There have been two reports of paediatric patients who experienced adverse events following ethanol administration that resolved when the antidote was changed to fomepizole. In one case, a 13 year old girl became promptly obtunded and required intubation following ethanol administration. This resolved after substitution with fomepizole (Boyer et al., 2001). In a similar case a three year old boy treated with ethanol for methanol poisoning, irritability and aggressive behaviour resolved when treatment was changed to fomepizole (DeBrabander et al., 2005).

The findings from the study and case reports listed above suggest that the choice of antidote can have a substantial effect on patient safety. Ethanol therapy appears to be associated with more frequent adverse events. Using fomepizole as the first line treatment for suspected methanol or ethylene glycol poisonings may therefore reduce antidote-related adverse effects.

Administration and Monitoring

It is recommended that ethanol treatment is given intravenously and that concentrations are maintained at a therapeutic concentration of 100-150 mg/dL (see Appendix 2). To facilitate this, frequent blood ethanol concentrations are required every 1-2 hours due to individual differences in ethanol metabolism and elimination, and variations in concentration during haemodialysis (Hantson et al., 2002). Doses must subsequently be adjusted according to these concentrations.

Even with appropriate doses of ethanol, intoxication and obtundation may occur (Boyer et al., 2001). It is therefore recommended that patients treated with ethanol are monitored in a high-dependency environment in order to observe for signs of CNS and respiratory depression, hypoglycaemia (particularly in paediatric poisoning (Roy et al., 2003)), and electrolyte disturbances which may occur due to large infusion volumes (Hantson et al., 2002).

In contrast, 12 hourly dosing with fomepizole is less labour intensive and as therapeutic concentrations are achieved (Mégarbane, 2010) there is no need to monitor serum concentrations. This is of particular relevance in cases where frequent ethanol monitoring is not practical or possible, and where high dependency facilities for patients are unavailable. Other benefits of fomepizole therapy compared to ethanol are that is it less irritant to veins during administration (Barceloux et al., 2002) and patients, particularly those who present early, rarely require critical care support due to the mild and transient adverse events associated with it.

Early, Unconfirmed Diagnosis

False positive clinical diagnosis of suspected toxic alcohol poisoning can result in patient harm. Given its safety compared to ethanol, fomepizole permits a margin of diagnostic error. This means that recommendations for early antidote administration can be followed because fomepizole can be given without waiting for laboratory confirmation of diagnosis, avoiding a potentially deleterious delay and allowing treatment to be initiated on the basis of patient history, metabolic acidosis, elevated serum formate/glycolate and/or an elevated osmolal gap. This may be useful in circumstances where hospitals have no immediate access to a laboratory that can measure serum methanol or ethylene glycol concentrations (Sivilotti et al., 2009).

Medication Errors

Treatment with intravenous ethanol requires frequent monitoring of blood concentrations and changes to infusion rates to maintain therapeutic levels. It is therefore inherently subject to medication errors and adverse reactions. In a retrospective chart analysis of 26 consecutive patients with methanol poisoning the mean number of changes to an ethanol infusion rate per patient was 12, and one individual required 31 changes. 22 patients (85%) experienced at least one episode within the subtherapeutic range (blood ethanol <100 mg/dL), and supratherapeutic concentrations (>200 mg/dL) were observed in eight patients (30%) (Hovda et al., 2008). Wedge et al. (2012) reported in 49 patients who required a median number of 6 ethanol concentration measurements per treatment course, only 27% were within the therapeutic range and 47% were below. Patients were more likely to experience adverse events during time intervals when ethanol concentrations were outside of the target range (crude odds ratio 2.2; 95% confidence interval 1.1-4). These studies suggest that optimal ethanol therapy

is difficult to achieve, which may have harmful effects on patients due to both undertreatment of the toxic alcohol poisoning and/or an increased risk of ethanol related adverse effects. However, they offer no comparison of medication errors between ethanol and fomepizole treatment.

Lepik et al. (2011) conducted a study to describe and compare the frequency, type, causes, and outcome of ethanol and fomepizole-related medication errors. They reviewed data from 10 hospitals in British Columbia, and identified patients ≥13 years admitted between January 1996 and December 2005 with ethylene glycol or methanol poisoning who received one or more antidote dose. There was a total of 305 individual medication errors that occurred in 113 of 145 (78%) ethanol-treated cases, and 36 in 20 of 44 (45%) fomepizole-treated cases. Medication errors leading to harmful clinical effects were identified in 3 of 44 (7%) fomepizole-treated cases compared to in 28 of 145 (19%) ethanol-treated cases (p=0.06). Harmful effects were attributed to antidote toxicity (23 ethanol-related, two fomepizole-related), or to methanol or ethylene glycol toxicity. Those attributed to the antidotes include CNS effects (e.g. agitation, combative behaviour, coma), cardiovascular effects (e.g. hypotension, bradycardia), and other effects (e.g. hypoglycaemia). One fomepizole-treated patient developed transient hypotension and bradycardia following an excessive fomepizole dose (Lepik et al., 2008), and another developed CNS depression associated with a prescribing error (Lepik et al., 2009). Further analysis showed that a significantly lower proportion of fomepizole-treated cases experienced antidote related medication errors (p=0.0001). Effects attributed to methanol or ethylene glycol poisoning include metabolic acidosis and end-organ injury (e.g. acute renal failure, permanent visual impairment), which occurred in 11 ethanol-treated patients and one fomepizole-treated patient.

One of the causes contributing to medication errors was prescribing errors related to an inadequate or excessive antidote dose. These accounted for errors in 50 of 145 (34%) ethanol-treated cases, and 8 of 44 (18%) fomepizole-treated cases (p=0.04). The highest recorded serum ethanol concentration was 5 fold higher than the therapeutic concentration. Other identifiable causes were a delay in initiation of antidote therapy or inappropriate treatment duration, which occurred in 22 of 145 (15%) ethanol versus 1 of 44 (2%) fomepizole-treated cases. These medication errors occurred in a significantly higher proportion of ethanol-treated cases (p=0.02).

Fomepizole therapy therefore appears to be associated with fewer prescription and administration errors compared to ethanol. In addition to this, there is a reduced probability of harmful clinical effects when error does occur in fomepizole-treated patients.

Haemodialysis

The indications for haemodialysis are discussed in Section 9.3.2. Several of the studies in Sections 10.3.2 and 10.3.3 provide data to suggest that in some cases ethylene glycol and methanol poisoning can be successfully treated by fomepizole without the concurrent use of haemodialysis. In contrast, haemodialysis is recommended for patients treated with ethanol to reduce the period of stay in an intensive care unit and to reduce the period of risk for toxicity and potential complications of ethanol treatment (Palatnick et al., 1995).

This has implications for comparative safety of the two antidotes since haemodialysis is an invasive technique with risks of adverse events. Furthermore ethanol therapy is associated with various adverse effects which may complicate haemodialysis. For example, behavioural disorders may be problematic when haemodialysis has to be performed in an uncooperative patient. This has been well described in a report of uncontrollable agitation during catheter insertion, which lead to an arterial tear and resulted in shock and cardiac arrest (Lepik et al., 2009).

Fomepizole offers significant advantages over ethanol in cases where it can eliminate the need for haemodialysis because the procedure introduces new risks to patient safety, is costly, and may not be easily accessible. The problems of availability and cost of haemodialysis are noted in Sections 9.3.2 and 12 respectively.

12. Summary of Available Data on Comparative Cost and Cost-Effectiveness within the Pharmacological Class or Therapeutic Group

Pricing information was obtained directly from companies and is summarised in Table 9 below.

Table 9. Range of Costs of Fomepizole by Company. Prices were calculated per 100 mg and per 70 kg patient treated with 3.5 doses for ethylene glycol poisoning (Brent et al., 1999) and 4 doses for methanol poisoning (Brent et al., 2001). These were based on the prices quoted by the companies converted into Euros/USD based on exchange rates on 21 November 2012 (XE, 2012).

Manufacturer	Price as Quoted by Company	Price per 100 mg Fomepizole	Price per 70 kg Patient EG/Methanol
L'Agence Générale des Equipements et Produits de Santé (AGEPS)	$110.23 (€86.19) per vial of 20 mL containing 5 mg/mL	$110.23 (€86.19)	$3086.38 (€2413.32) / $3472.18 (€2714.99)
X-Gen Pharmaceuticals	$1312 (€1025.01) average wholesale price per vial of 1.5 mL containing 1 g/ml	$87.47 (€68.33)	$2449.16 (€1913.35)/ $2755.31 (€2152.52)
Mylan	$725 (€566.46) per vial of 1.5 mL containing 1 g/mL	$48.33 (€37.76)	$1353.24 (€1057.39) / $1522.40 (€1189.56)
Distributor / Wholesaler	**Price as Quoted by Company**	**Price per 100 mg Fomepizole**	**Price per Patient EG/Methanol**
Paladin Labs	$4553.62 (€3557.58) for 4 vials of 1.5 mL containing 1 g/mL each	$75.89 (€59.29)	$2125.02 (€1660.20) / $2390.65 (€1867.73)
EUSA Pharma	$920.75 - $946.25 (€720 - €740) per pack of 5 vials of 20 mL containing 5 mg/mL each. Exceptions: Sweden: $907.49 (€709.63); Denmark: $759.88 (€594.13); Finland: $914.26 (€715.00); Republic of Ireland: $639.31 (€500); Norway: $854.12 (€668)	$184.15- $189.25 (€144 - €148) Exceptions: Sweden: $181.50 (€141.93); Denmark: $151.98 (€118.83); Finland: $182.85 (€143); Republic of Ireland: $127.86 (€100); Norway: $170.82 (€133.6)	$5156.18 - $5298.99 (€4032 – €4144)/ $5800.71 - $5961.37 (€4536 – €4662) Exceptions: Sweden: $5081.96 (€3974.04)/ $5717.21 (€4470.80); Denmark: $4255.32 (€3327.24)/ $4787.23 (€3743.15); Finland: $5119.88 (€4004)/ $5759.86 (€4504.50); Republic of Ireland: $3580.11 (€2800)/ $4027.63 (€3150); Norway: $4783.04 (€3740.80)/ $5380.92 (€4208.40)
Durbin PLC	$580.69 (€453.64) per pack of 5 vials of 20 mL containing 5 mg/mL each	$116.14 (€90.73)	$3251.86 (€2540.38)/ $3658.35 (€2857.93)
Morris & Dickson	$900 (€703.05) average wholesale price per vial of 1.5 mL containing 1 g/mL	$60 (€46.87)	$1680 / $1890 (€1312.36 - €1476.40)

Cannarozzi et al. (2010) calculated the costs of fomepizole monotherapy versus fomepizole treatment accompanied by haemodialysis in ethylene glycol-poisoned patients. Prices were based on fees charged

at a US tertiary care academic hospital, and patients were evaluated based on their weight and their initial serum concentration of ethylene glycol. Fomepizole monotherapy was less expensive in patients weighing up to 75 kg with initial ethylene glycol concentrations below 500 mg/dL. Cost analysis of patients weighing between 75 and 100 kg with initial ethylene glycol concentrations up to 300 mg/dL showed that treatment with fomepizole alone is more cost-effective than combined treatment with haemodialysis. However, they found that fomepizole monotherapy is more expensive in patients weighing >100 kg with initial ethylene glycol levels >75 mg/dL.

Table 10. Range of Costs of Ethanol by Country. Prices were calculated per 70 kg patient (non-alcoholic or alcoholic) treated for three days with six hours dialysis (see Appendix 2), and converted to USD based on exchange rates on 21 November 2012 (XE, 2012).

Country	% Ethanol in Solution	Price per Vial (Vial Size)	Price per 70kg Patient	
			Non-Alcoholic	Alcoholic
France	Approx. 25%	$3.02 (€2.36) (20mL)	$319.98 (€249.68)	$659.58 (€514.67)
Norway	70%	$165.35 (€129) (50mL)	$2498.63 (€1949.70)	$5150.45 (€4018.92)
Sweden	99.5%	$118.31 (€92.3) (10x10mL)	$628.87 (€490.71)	$1296.29 (€1011.50)

Although the cost of ethanol appears to be lower than that of fomepizole (with the exception of Norway), the economics of antidote use are far more complex than drug acquisition cost alone. Any comparison between antidotes should include other relevant factors such as costs of hospitalisation/day, ICU cost/day, and laboratory tests (Sivilotti et al., 2009).

Ethanol therapy is a complex process requiring frequent laboratory measurements of the serum ethanol concentration every 1-2 hours in order to maintain therapeutic concentrations by dose adjustments (Barceloux et al., 1999). Other factors that may affect the cost of treating patients with ethanol are related to its side effects. Increased nursing care is required for inebriated patients, and admission to an ICU may be necessary to observe for signs of severe CNS and respiratory depression (Mégarbane, 2010). Healthcare costs for ICU admission are high: Dasta et al. (2005) calculated costs ranged from $3184 to $10794 (€2486.95 to €8430.96) in 2002. Patients in the developing world may be more affected by these problems if there are limited facilities for hospital monitoring and treatment.

In contrast, the 12 hour dosing schedule of fomepizole is less complicated, less labour intensive, and does not require frequent blood monitoring. The good adverse effect profile of fomepizole may also yield cost savings due to decreased time in the ICU. In addition to this, fomepizole therapy may reduce costs by eliminating the need for haemodialysis in certain patients (Barceloux et al., 1999). The suggested shelf life of fomepizole is 3 years, however some manufacturers may replace expired products at no extra charge, which may make it more economical to stock this antidote (Mégarbane et al., 2005).

No formal cost-effectiveness studies have been performed, however Barceloux et al. (1999) considered all factors involved in the antidotal treatment of patients, and suggested the cost of ethanol therapy may be equal to or greater than the cost of using fomepizole alone in patients who are stable. Pharmacoeconomic considerations that differ between healthcare systems and countries must also be considered when evaluating cost-effectiveness. For example, Anseeuw et al. (2008) found that fomepizole treatment was three times more expensive than ethanol treatment in the Belgian healthcare system. In contrast, Boyer et al. (2001) collected data from the Unites States indicating substantial cost

savings can be made from fomepizole monotherapy in patients with ethylene glycol poisoning, regardless of the increase in ethylene glycol elimination half-life.

Table 11. Cost comparison of ethanol therapy in an ICU versus fomepizole therapy on the general medical floor (Boyer et al., 2001). Prices were converted into Euros based on exchange rates on 21 November 2012 (XE, 2012).

Intensive Care Unit	General Medical Floor
Bed cost $8034 (€6274.99)	Bed cost $3864 (€3018.07)
Laboratory - hourly ethanol level $2000 (€1562.11) Daily ethylene glycol level $660 (€515.50)	Laboratory - daily ethylene glycol level $660 (€515.50)
Therapy - ventilation, oxygen $3558 (€2779.06) Ethanol drip $27 (€21.09)	Therapy - fomepizole $5000 (€3903.56)
Consults (for dialysis) $200 (€156.18)	Consults $0 (€0)
Dialysis $1244 (€971.44)	Dialysis $0 (€0)
Total cost $15723 (€12278.15)	Total cost $9524 (€7435.50)

According to Boyer et al. (2001), the cost comparison depicted in Table 11 indicates that fomepizole has the potential to reduce costs by at least 40%. Several additional costs associated with intensive care monitoring were omitted from the table, such as portable chest radiographs and serial arterial blood gas measurements. Increased nursing costs for haemodialysis and intensive care are also not included, therefore cost savings of fomepizole monotherapy may be even more significant, particularly in early presenting patients not requiring ICU care. However, the most severely ill patients, particularly those presenting late with an established metabolic acidosis would need ICU facilities regardless of antidote used, and so this factor may be less important in this cohort.

There is a danger that distorted cost estimates may deter antidote deployment to healthcare facilities with limited laboratory equipment and access to haemodialysis, where fomepizole availability is particularly important (Sivilotti et al., 2009).

13. Summary of Regulatory Status of the Medicine

Fomepizole was granted Orphan Drug status by the United States FDA in 1997 and approved for the treatment of ethylene glycol poisoning in 1997 and methanol poisoning in 2000. Generic fomepizole is available in the United States. It was also approved for use in ethylene glycol poisoning by the European Medicines Agency in 2001 and therefore has marketing authorisation in all member states of EU. In addition, fomepizole is licensed in Canada, Switzerland, Iceland, Norway, Croatia, Macedonia, Serbia, Bosnia-Herzegovina, Montenegro, Kosovo, Hungary, the Czech Republic, Turkey, Korea, Taiwan, China, Hong-Kong, Singapore, Malaysia, India, Pakistan, Thailand, Philippines, Indonesia and Japan.

14. Availability of Pharmacopoeial Standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

Fomepizole is included in the French Pharmacopoeia (Bédry, 2008)

15. Proposed Text for the WHO Model Formulary

Fomepizole

Injection: 5 mg/mL (sulphate) in 20 mL ampoule or 1000 mg/mL (base) in 1.5 mL ampoule

Uses

Treatment of acute toxic alcohol and glycol poisoning.

Contraindications

Hypersensitivity to fomepizole or other pyrazoles.

Precautions

The rate of elimination of ethanol is reduced by approximately 40% by fomepizole therapeutic doses. Ethanol decreases the rate of elimination of fomepizole by approximately 50%.

Dose

Adult Dose:

All intravenous doses should be administered as slow intravenous infusion for 30 minutes. The doses stated below can also be given orally.

Loading dose: 15 mg/kg IV diluted to a final volume of 250 mL saline or dextrose over 30 minutes.

Maintenance doses: 10 mg/kg IV diluted to a final volume of 250 mL saline or dextrose over 30 minutes every 12 hours (starting at 12 hours after the loading dose is given) for a maximum of 4 doses; followed by 15 mg/kg IV diluted to a final volume of 250 mL saline or dextrose over 30 minutes every 12 hours thereafter.

Fomepizole Dosing during Haemodialysis:

A loading dose of 15 mg/kg is infused over 30 to 45 minutes, followed by 10 mg/kg every 4 hours up to 48 hours, then 15 mg/kg after (Barceloux et al., 1999; Barceloux et al., 2002).

Duration of Treatment:

Fomepizole should be continued until:

ethylene glycol or methanol concentration is undetectable

OR

ethylene glycol or methanol concentration is <20 mg/dL AND acidosis has resolved

Doses in Children:

The limited data available suggests that the fomepizole dosing regimen used in adults would be efficacious and well tolerated in children (Boyer et al., 2001; Brent, 2010; Detaille et al., 2004).

Doses in Pregnancy:

As for adults above. Use with care in this population.

Adverse Effects

Fomepizole is generally well tolerated with few adverse effects.

During clinical trials the most commonly reported features were nausea, dizziness and headaches. Less common features included vomiting, diarrhoea, tachycardia, hypotension, vertigo, nystagmus, slurred speech, skin rashes, eosinophilia and transient rise in liver transaminases. These effects occurred at doses much greater than the therapeutic dose.

Pain and inflammation may occur at the injection site.

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Appendix

1. Search Terms Used in Literature Searches

MEDLINE

"fomepizole"[Supplementary Concept] OR "fomepizole"[All Fields] – 20/08/12

("methanol"[MeSH Terms] OR "methanol"[All Fields]) AND ("ethylene glycol"[MeSH Terms] OR ("ethylene"[All Fields] AND "glycol"[All Fields]) OR "ethylene glycol"[All Fields]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields]) – 23/08/12

("diethylene glycol"[Supplementary Concept] OR "diethylene glycol"[All Fields]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields]) – 23/08/12

("diethylene glycol"[Supplementary Concept] OR "diethylene glycol"[All Fields]) AND ("poisoning"[Subheading] OR "poisoning"[All Fields] OR "poisoning"[MeSH Terms]) – 23/08/12

("ethylene glycol"[MeSH Terms] OR ("ethylene"[All Fields] AND "glycol"[All Fields]) OR "ethylene glycol"[All Fields]) AND ("poisoning"[Subheading] OR "poisoning"[All Fields] OR "poisoning"[MeSH Terms]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields]) – 24/08/12

("methanol"[MeSH Terms] OR "methanol"[All Fields]) AND ("poisoning"[Subheading] OR "poisoning"[All Fields] OR "poisoning"[MeSH Terms]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields]) – 24/08/12

("Methanol/antagonists and inhibitors"[Mesh] OR "Methanol/poisoning"[Mesh] OR "Methanol/toxicity"[Mesh]) AND (Clinical Trial[ptyp] OR Randomised Controlled Trial[ptyp] OR Controlled Clinical Trial[ptyp] OR Case Reports[ptyp]) – 28/08/12

("Ethylene Glycol/antagonists and inhibitors"[Mesh] OR "Ethylene Glycol/poisoning"[Mesh] OR "Ethylene Glycol/toxicity"[Mesh]) AND (Clinical Trial[ptyp] OR Randomised Controlled Trial[ptyp] OR Comparative Study[ptyp]) – 29/08/12

("Ethylene Glycol/antagonists and inhibitors"[Mesh] OR "Ethylene Glycol/poisoning"[Mesh] OR "Ethylene Glycol/toxicity"[Mesh]) AND Case Reports[ptyp]) – 29/08/12

("fomepizole"[Supplementary Concept] OR "fomepizole"[All Fields] OR "4 methylpyrazole"[All Fields]) AND ("ethylene glycol"[MeSH Terms] OR ("ethylene"[All Fields] AND "glycol"[All Fields]) OR "ethylene glycol"[All Fields]) – 29/08/12

("fomepizole"[Supplementary Concept] OR "fomepizole"[All Fields] OR "4 methylpyrazole"[All Fields]) AND ("methanol"[MeSH Terms] OR "methanol"[All Fields]) – 29/08/12

("fomepizole"[Supplementary Concept] OR "fomepizole"[All Fields]) AND ("diethylene glycol"[Supplementary Concept] OR "diethylene glycol"[All Fields]) – 29/08/12

("Methanol/antagonists and inhibitors"[Mesh] OR "Methanol/poisoning"[Mesh] OR "Methanol/toxicity"[Mesh]) AND Comparative Study[ptyp]) – 29/08/12

("fomepizole"[Supplementary Concept] OR "fomepizole"[All Fields] OR "4 methylpyrazole"[All Fields]) AND ("diethylene glycol"[Supplementary Concept] OR "diethylene glycol"[All Fields]) – 30/08/12

EMBASE

([4 methylpyrazole/] OR [fomepizole.mp]) AND [ethylene glycol/]

([4 methylpyrazole/] OR [fomepizole.mp]) AND [methanol poisoning/]

/ = subject heading; .mp = text word

2. Ethanol Dosing Regimen (MICROMEDEX)

Ethanol – Intravenous and Oral Guidelines (MICROMEDEX, 2012)

American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning (Barceloux et al., 1999) and Methanol Poisoning (Barceloux et al., 2002).

Dose	Amount Absolute Ethanol	Volume 10% IV Solution	Volume 43% Oral Solution
Loading*	600 mg/kg	7.6 mL/kg	1.8 mL/kg
Non-Drinker			
maintenance	66 mg/kg/hr	0.83 mL/kg/hr	0.2 mL/kg/hr
dialysis	169 mg/kg/hr	2.13 mL/kg/hr	0.5 mL/kg/hr
Chronic Drinker			
maintenance	154 mg/kg/hr	1.96 mL/kg/hr	0.46 mL/kg/hr
dialysis	257 mg/kg/hr	3.26 mL/kg/hr	0.77 mL/kg/hr
*Independent of drinker status; initial ethanol serum concentration assumed to be zero			

Ethanol can be given intravenously, orally, by nasogastric tube. Intravenous solutions should always be administered slowly to avoid alcoholic intoxication, vertigo, flushing, disorientation, sedation, local pain, and vein irritation.

The objective is to reach a serum ethanol level of 100-150 mg/dL by giving a loading dose over 30 minutes. The maintenance infusion should be started concurrently with the loading dose. Usual maintenance infusions are approximately 100 mg/kg/hr. Chronic alcoholics generally require higher doses, while non-drinkers may require less. During ethanol treatment, serum ethanol levels must be maintained at 100-150 mg/dL. To achieve this ethanol levels must be checked every 1-2 hours as ethanol metabolism varies greatly between patients.

Plasma ethylene glycol and methanol levels should be monitored every 12 to 24 hours and the infusion should be continued until ethylene glycol or methanol serum levels are undetectable or <10 mg/dL, and acidosis (pH and blood gases), clinical findings, electrolyte abnormalities (bicarbonate) serum amylase and osmolal gap have resolved. This may take up to 5 days.

Health facilities initiating this treatment must therefore have the appropriate analytical techniques and skills to provide the monitoring required.

Abbreviations Used in the Tables

EG = ethylene glycol
HD = haemodialysis
ICU = intensive care unit
IQR = interquartile range
IV = intravenous

Table 1. Comparison of Fomepizole with Ethanol

	Fomepizole	Ethanol
Route of Administration	IV. Can also be given orally.	IV. Can also be given orally.
Dose	Loading dose of 15 mg/kg followed by 10 mg/kg every 12 hr for 48 h by IV. Dose then increased to 15 mg/kg every 12 hr until EG concentration is undetectable or >20 mg/dL and the patient is asymptomatic with a normal arterial pH. During haemodialysis, the frequency of dosing is increased to every 4 hrs.	Loading dose of 600 mg/kg of absolute ethanol (1.8 mL/kg 43% oral solution, 7.6 mL/kg 10% IV solution). Standard maintenance dose varies between non-drinkers (66 mg/kg/hr) and ethanol abusers (154 mg/kg/hr). The serum ethanol concentration should be monitored every 1-2 hrs in order to ensure that the serum concentration remains in the recommended therapeutic range of 100-150 mg/dL. See Appendix 2.
Contraindications	Patients with known hypersensitivity reactions to fomepizole or other pyrazole compounds (none have been reported so far)	Use with caution in patients who have recently ingested disulfiram or drugs that produce CNS depression Ethanol may cause orthostatic hypotension in patients who use vasodilator drugs
Side Effects and Adverse Drug Reactions	Mild and transient effects See **Section 11** for details	Clinical signs and symptoms of ethanol intoxication e.g. inebriation, depression of cortical function, emotional liability, poor coordination, loss of judgement, visual impairment, slurred speech Hypoglycaemia, especially in paediatric patients and malnourished patients Pancreatitis Severe CNS depression, including loss of breathing reflexes requiring intratracheal intubation in order to protect against aspiration and respiratory depression Local phlebitis Further adverse effects are listed in **Section 11**
Mechanism of Action	Inhibits alcohol dehydrogenase	Preferential substrate for alcohol dehydrogenase

	Fomepizole	Ethanol
Advantages	Validated efficacy and longer duration of action Ease of administration Predictable pharmacokinetics Standardised and simpler dosing regimen Obviates need for haemodialysis in certain cases, an adjunct therapy that is often unavailable in many facilities and costly Requires less laboratory support than that used to monitor ethanol administration Does not require therapeutic drug monitoring of fomepizole concentrations Few reported significant adverse effects Fewer medication errors Does not cause CNS depression Does not require stay in an intensive care unit itself – implications for reducing cost Safe transfer between hospitals if necessary e.g. for dialysis facilities	Low acquisition cost in most countries (see Table 9) Available in most clinical settings Long-term clinical experience
Limitations	High acquisition cost Not available in all clinical settings Lack of familiarity with its reconstitution and dosing schedules	Erratic pharmacokinetics Lower affinity for alcohol dehydrogenase than fomepizole Requires stay in an intensive care unit during treatment Transfer between hospitals may be more complicated Requires frequent blood monitoring of ethanol concentration Complicated dosing regimen (see *Appendix 2*) Adverse reactions are common Medication errors are more likely to occur Causes intoxication at therapeutic concentrations – inebriated patients are difficult to manage and may be a safety issue for staff Labour intensive – requirements for supportive care Frequently requires central venous access Not approved by the FDA for these indications

Table 2. Prospective Studies in Efficacy of Fomepizole Treatment – Summary of Clinical Data

Ref.	Study Design	Inclusion Criteria	Subjects	Intervention	Admission Values	Clinical Course and Outcomes
Brent et al. (1999) and Sivilotti et al. (2000)	Phase III multi-centre prospective study of EG poisoning	Consecutive patients admitted Nov 1995 – Aug 1997, aged >12 yrs old with confirmed/possible EG poisoning i.e. one of 3 sets of characteristics • plasma EG conc >20 mg/dL • suspected ingestion of EG and 3 of 4 specific lab findings (arterial pH below 7.3, serum bicarbonate conc <20 mmol/L, serum osmolar gap >10 mOsm/kgH_2O and oxaluria) • suspected ingestion of EG within the preceding hour and serum serum osmolar gap >10 mOsm/kgH_2O Excluding patients given ethanol in hospital	19 patients Mean age 41 yrs (range 19-73 yrs)	All patients administered with loading dose of IV fomepizole 15 mg/kg, then 10 mg/kg every 12 hrs for 48 hrs, then 15 mg/kg every 12 hrs Mean 3.5 doses (range 1-7) over mean of 17.8 hrs (range 5-58 hrs) 17 patients received haemodialysis ***End Point:*** Treatment discontinued when serum EG concentration <20 mg/dL	Mean EG concentration 123 mg/dL, range 24-446 mg/dL Mean pH 7.24, range 6.93-7.47 Mean serum bicarbonate 12.9 mmol/L, range 4-28 mmol/L Mean serum creatinine 1.5 mg/dL, range 0.6-3.3 mg/dL Mean serum glycolate 89.7 mg/dL, range 0-264.4 mg/dL Time from ingestion of EG to treatment with fomepizole mean 11.4 hrs, range 6.6-20.8 hrs 9 admitted with renal injury ***Co-Ingestants (no. of patients):*** Ethanol (12) – 4 had concentrations >100 mg/dL, doxepin (1), cyclobenzaprine (1), cocaine (1), gasoline (1)	18 survived, 1 died from cardiogenic shock 22 hrs after admission – admitted with arterial pH of 7.05 and had an acute myocardial infarction before enrolment Clinical improvement correlated with the normalisation of acid–base status No patients had spontaneous deteriorations in mental status or hypoglycaemia after initiation of therapy Renal function decreased during therapy in 9 patients – these patients presented later, had high serum creatinine concentrations, markedly elevated plasma glycolate concentrations (≥97.7 mg/dL) and more severe acidosis at enrolment No patients had cranial neuropathy Serum glycolate concentrations decreased progressively in all the patients and arterial pH values and serum bicarbonate concentrations increased progressively None of the 10 patients with normal serum creatinine concentrations at enrolment had renal injury during treatment; all 10 had plasma glycolate concentrations ≤76.8 mg/dL

Ref.	Study Design	Inclusion Criteria	Subjects	Intervention	Admission Values	Clinical Course and Outcomes
Brent et al. (2001)	Phase III multi-centre prospective study of methanol poisoning	Consecutive patients, admitted Nov 1995 – Aug 1997, aged >12 yrs old with confirmed/ possible methanol poisoning and serum methanol conc. >20 mg/dL, or a history/strong suspicion of methanol poisoning and at least 2 of the following: • arterial pH <7.3, • serum bicarbonate conc <20 mmol/L, or • serum osmolality gap of >10 mOsm per kg of water Excluding patients given ethanol in hospital	11 patients Mean age 40 yrs (range 18-61 yrs)	All patients administered with loading dose of IV fomepizole 15 mg/kg, then 10 mg/kg every 12 hrs for 48 hrs, then 15 mg/kg every 12 hrs All patients received supplemental folate Mean 4 doses (range 1-10) over mean of 30 hrs (range 0.5-60 hrs) 7 patients received haemodialysis ***End Point:*** Treatment discontinued when serum methanol concentration <20 mg/dL	Mean methanol concentration 170.41 mg/dL Mean pH 7.26, range 6.90-7.46 Mean plasma formate 11.7 mmol/L, range 0-43.10 mmol/L Time from ingestion of methanol to treatment with fomepizole range 3.3-26.4 hrs (unknown in 3 patients) 3 patients received ethanol at referring hospitals before enrolment 7 patients had visual abnormalities on admission ***Co-Ingestants:*** Ethanol – 3 had concentrations >100 mg/dL, carisoprodol (4)	9 survived, 2 died from anoxic brain injury as a result of methanol poisoning – both were comatose and had severe acidosis at enrolment Plasma formate concentrations fell and metabolic abnormalities resolved in all patients Measurements of plasma formate concentration indicated the production of formate from methanol had been inhibited After the institution of fomepizole therapy improvements in mental status and visual symptoms and signs were observed No patient had hypoglycaemia No surviving patient had any detectable visual deficits related to methanol poisoning at the end of the trial
Hovda et al. (2005a)	Prospective observational study	Mild to moderate metabolic acidosis upon admission and no visual disturbances after rapid and full correction of metabolic acidosis in the ED	8 patients Median age 50 yrs (range 35-70 yrs)	Fomepizole given as a bolus dose of 15 mg/kg IV, then 10 mg/kg IV every 12 hrs 3 patients received dialysis after 14, 23, and 32 hrs Bicarbonate	Median pH 7.27 (range 7.12-7.50) Median base deficit 15 mmol/L (range 5-22 mmol/L) Median serum methanol 20.4 mmol/L (65 mg/dL) (range 8.4-140.6 mmol/L)	7 patients discharged without sequelae, 1 patient discharged with persistent slight visual impairment The mean plasma half-life ($T_{1/2}$) of methanol during fomepizole treatment was 52 hrs (range 22-87); the higher the serum methanol, the longer the $T_{1/2}$. Mean half-life of serum formate was 2.6 hrs, when methanol metabolism was assumed blocked by fomepizole and no folinic acid was given Concluded: methanol –poisoned patients with moderate metabolic acidosis and methanol levels up to 19 mmol/L (60 mg/L) may safely be treated with bicarbonate and fomepizole only without dialysis

Ref.	Study Design	Inclusion Criteria	Subjects	Intervention	Admission Values	Clinical Course and Outcomes
Hovda et al. (2005b)	Prospective observational case series	Patients with suspected or clinical features of methanol poisoning treated with fomepizole and HD	7 patients	Fomepizole and haemodialysis (average 7 hrs range 5-8) 4 patients dialysed early after diagnosis, 3 dialysed next day	Median pH 6.9 (range 6.6-7.5) and median base deficit 20.4 mmol/L (range 5.1-30.0) Median serum methanol 76.3 mmol/L (range 15.6-140.6) Serum formate 13.6 mmol/L (range 3.3-21)	Medan half-life of methanol during fomepizole treatment before dialysis was 71.2 hrs (range 69.3-77); compared to 2.5 hrs (range 1.7-3.3 during dialysis. The median half-life of formate during dialysis was 1.7hrs (range 1.5-1.9) 4 patients discharged without sequelae, (including all 3 dialysed day after admission); 2 discharged with permanent visual and cerebral sequelae (1 died a year later), 1 patient died
Hovda et al. (2005c)	Prospective observational study	Patients admitted with methanol poisoning, between 2002-2004; confirmed by serum methanol analysis	51 patients Median age 53 yrs	Buffer to correct acidosis within first hours Ethanol (15 patients), fomepizole (36 patients), haemodialysis (37 patients) Fomepizole given as bolus dose of 15 mg/kg IV then 10 mg/kg IV every 12 hrs. From 5th dose and on 15 mg/kg was given to compensate for increased metabolism. During dialysis 10 mg/kg given every 4 hrs	Median serum methanol 25.0 mmol/L (80 mg/dL) (range 3.1-147.0 mmol/L) Medan pH 7.20 (6.50-7.50) Median base deficit 22 mmol/L (range 0-31) 39 (7%) symptomatic on admission, 24 % comatose, 8 (16%) with respiratory arrest, 28 (55%) with visual disturbances	37 survived without sequelae (37%), 5 discharged with sequelae (10%), 9 died in hospital (18%) Respiratory arrest, coma and severe metabolic acidosis (pH <6.90) base deficit >28 mmol/L) on admissions were strong predictors of poor outcome Early admission and ability of respiratory compensation (hyperventilation) of metabolic acidosis was associated with survival

Table 3. Retrospective Case Series in Efficacy of Fomepizole Treatment – Summary of Clinical Data

Ref.	Inclusion Criteria	Subjects	Intervention (number of patients in brackets)	Admission Values	Clinical Course and Outcomes
Borron et al. (1999)	Consecutive patients with EG concentration ≥20 mg/dL	11 patients	Fomepizole administered by oral route (4), intravenous (6) and both (1) every 12 hrs Median 3 doses (IQR 1-8) Median loading dose 800 mg (IQR 675-838 mg) Haemodialysis (3) – because of renal insufficiency (2), and very high plasma ethylene glycol concentration (831 mg/dL) (1) ***End Point:*** Fomepizole was given until plasma ethylene glycol concentrations became undetectable	Median plasma EG concentration 81 mg/dL (IQR 50-277 mg/dL) Median serum creatinine concentrations 76.0 µmol/L (IQR 61.0–126.4 µmol/L) Median arterial pH 7.31 (IQR 7.12–7.37) Median serum bicarbonate concentrations 18.0 mmol/L (6.3–20.5 mmol/L) Median plasma ethanol concentrations 0.07 g/L (IQR 0.00–0.65 g/L) 4 had renal injury on admission ***Co-Ingestants:*** Ethanol (4)	10 survived, 1 died within a few hours of admission with severe multi-organ failure The 7 patients with normal renal function had no subsequent deterioration of serum creatinine concentration during fomepizole therapy
Caravati et al. (2004)	Patients < 18yrs old admitted between 1999-2002 with EG poisoning (peak serum EG conc >50 mg/dL) Excluded patients who were discharged from emergency dept, or had received HD	6 patients Age range 22 months-14 yrs	Ethanol only (1) Fomepizole only (2) each given 3 doses Leading dose of ethanol (700-800 mg/kg) followed by fomepizole therapy: (3) given 4, 6, and 7 doses respectively until ethylene glycol concentration <10 mg/dL Mean time to initiation of antidote therapy was 4.1±3.7 hrs after exposure HD (0) Intravenous fluid and supplemental bicarbonate within 24 hrs (2)	Initial serum ethylene glycol range 62-394 mg/dL (mean 174 mg/dL) Lowest measured individual serum bicarbonates ranged from 4-17 mmol/L Normal creatinine 3 patients had oxalate crystalluria	Metabolic acidosis resolved within 24 hrs Mean length of stay in intensive care was 21 hrs and on the ward was 33.7 hrs One episode of hypoglycaemia occurred in a 22 month-old All patients discharged without evidence of renal insufficiency or other major complications Elimination half-life of ethylene glycol during treatment appears to be in the range of 10-15 hrs

Ref.	Inclusion Criteria	Subjects	Intervention (number of patients in brackets)	Admission Values	Clinical Course and Outcomes
Green (2007)	Adults ≥17 yrs who had IV ethanol or fomepizole ordered after emergency dept registration, or were admitted to ICU with detectable serum conc of either EG or methanol, or a clinical history and an arterial blood gas consistent with toxic alcohol ingestion	14 patients with methanol poisoning and 6 patients with ethylene glycol poisoning Age range 18-62 yrs	Fomepizole alone (5) Ethanol alone (8) Combined ethanol and fomepizole (7) HD (19)	Serum methanol range 8.79-826.92 mg/dL Serum ethylene glycol range 8.70-416.15 mg/dL	All patients discharged without sequelae Total hospital stay for methanol poisoning, average 3 days (range 1-8); for ethylene glycol poisoning average 5 days, range 1-17)
Hovda et al. (2011)	N/A	1 subject	Fomepizole 99 times Ethanol 60 times Combination of both 6 times	Median pH 7.31 (6.87-7.49) Median pCO_2 32 mmHg (9-50) Median HCO_3^- 15 mEq/L (4-26) Median base deficit 10 mEq/L (-4 to 27) Median serum creatinine 0.74 mg/dL (0.45-1.51) Median osmolar gap 81 mOsm/kgH_2O (25-132) Median serum EG 250 mg/dL (25-700)	Frequent use of fomepizole was not associated with any detectable side effects
Levine et al. (2012)	Patients >15 yrs old with known or suspected poisoning with EG (peak serum EG >20 mg/dL) admitted June 2002-March 2010, excluding patients who received HD	40 patients Median age 42 yrs (range 16-80 yrs)	All patients received fomepizole as per package insert with loading dose of 15 mg/kg Thiamine and pyridoxine	Peak serum ethylene glycol median 127 mg/dL (IQR 84–225.8 mg/dL, range 40-635 mg/dL) Initial serum creatinine median 0.97 mg/dL (0.50-1.54 mg/dL) Median pH 7.37 (7.29-7.43) Serum anion gap median 15 mEq/L (4-29 mEq/L)	Peak serum creatinine median 1.0 mg/dL (0.6-2.1) Mean serum ethylene glycol elimination half-life was 14.2 hrs (SD=3.7 hrs; 95% confidence interval 13.1-15.3 hrs) 1 patient developed mild transient renal insufficiency All patients were discharged without sequelae

Ref.	Inclusion Criteria	Subjects	Intervention (number of patients in brackets)	Admission Values	Clinical Course and Outcomes
Mégarbane et al. (2001)	Patients admitted to ITU between 1987-1999, with history of methanol exposure given at least 1 dose of fomepizole	14 patients Median age 46 yrs (range 18-58)	Gastric lavage (1), activated charcoal (3) Fomepizole orally (4) or IV, (10). Loading dose 15 mg/kg followed by 10 mg/kg every 12hrs until plasma methanol undetectable Median number of doses 2 (1-16) Median cumulative delivered dose 1250 mg (500-6000, approx 20.2 mg/kg (8.3-88.2) Haemodialysis (4) Ethanol initial therapy (3) stopped due to significant side effects Sodium bicarbonate (2) folinic acid (7), thiamine and pyridoxine (8) Peritoneal dialysis (1) following 3 doses of fomepizole when serum methanol < 20 mg/dL	Median plasma methanol 50 mg/dL (4-146) Median arterial pH 7.34 (7.11-7.21) serum bicarbonate 17.5 mmol/L (3.0-25.0) Anion gap 22.1 mmol/L (11.8-42.2), serum creatinine 84 µmol/L (50-128) Median plasma ethanol concentration 195 mg/dL (12-530) (due to ingestion of ethanol (8) or ethanol initial therapy (3) Toxicology screen negative for psychotropic medications and ethylene glycol	Median ICU stay 5 days (2-20) Low pH resolved with 5-12 hrs and low bicarbonate resolved within 4-34 hrs. elevated anion gaps resolved within 3-62 hrs Fomepizole well tolerated 4 patients discharged with visual disturbances, 13 patients discharged without sequelae 4 patients with methanol >50mg/dL recovered completely without haemodialysis
Paasma et al. (2012)	Patients admitted to hospital alive with methanol poisoning confirmed by positive serum methanol analysis and had a blood acid-base status drawn on admission. Excluding those given treatments before admission that could interfere with the analysis	203 patients Median age 44 yrs (range 3-77)	**Fomepizole** Survived (22) Survived with sequelae (4) Died (6) **Ethanol** Survived (99) Survived with sequelae (30) Died (42)	**Survived** median serum methanol 31 mmol/L (1-179) median pH 7.24 (6.52-7.57) median bicarbonate 10 (2.0-37.8) median serum creatinine 79(35-212) median pCO_2 3.2 (1.0-7.5) **Survived with Sequelae** median serum methanol 65 mmol/L (18-158) median pH 7.15 (6.60-7.46) median bicarbonate 7 (1.0-26.0) median serum creatinine 99 (40-186) median pCO_2 2.9 (1.2-6.8) **Died** median serum methanol 59 mmol/L (8-199) median pH 6.73 (6.34-7.29) median bicarbonate 4.2 (1.0-11.0) median serum creatinine 124 (545-380) median pCO_2 4.3 (1.3-15.9)	Survived 121 Survived with neurological sequelae (34) Died (48) pH <7.00 found to be the strongest risk factor for poor outcome, along with coma (Glasgow Coma Scale <8), and inadequate ventilation (pCO_2 ≥3.1 kPa in spite of a pH <7.00) Not possible to directly compare outcomes from ethanol and fomepizole due to limited number of patients in the fomepizole group, however, data suggests a trend towards better outcome In spite of severe metabolic acidosis shown by low pH, more patients who were given fomepizole survived with sequelae instead of dying than patients with similar pH treated with ethanol

Table 4. Clinical Studies and Case Series in Safety of Fomepizole Treatment

Ref.	Study Design	Subjects	No. with Adverse Effects	Dose of Fomepizole	Adverse effects Reported
Jacobsen et al. (1988)	Phase I clinical trial. Placebo-controlled, double blind study of safety in healthy human subjects after single, ascending doses	22 healthy volunteers All male Groups 1-3: fomepizole (4) and placebo (2) Group 4: fomepizole (3) and placebo (1)	3/4 drug subjects in Group 3 (75%) 3/3 drug subjects in Group 4 (100%)	Group 1: 10 mg/kg Group 2: 20 mg/kg Group 3: 50 mg/kg Group 4: 100 mg/kg	Group 3: Moderate dizziness ("feeling drunk") and mild nausea in 3 of 4 drug subjects Group 4: Mild to moderate dizziness, mild speech and visual disturbances, "feeling of drunkenness", mild to moderate nausea, loss of appetite, mild vertigo, mild headache. Effects lasted for up to 30 hrs in one subject with a positive Romberg's test and vertical nystagmus
Jacobsen et al. (1990)	Phase I clinical trial. Placebo-controlled, double blind study of safety in healthy human subjects after multiple, sequential, ascending dose	21 healthy volunteers All male 3 groups of 7 Each group employed 5 subjects on fomepizole and 2 on placebo	Subjective side effects were reported in 3/6 (50%) placebos and in 7/15 (47%) drug subjects	Group 1: loading dose of 10 mg/kg followed by supplemental doses of 3 mg/kg every 12 hrs up to 96 hrs Group 2: loading dose of 15 mg/kg plus 5 mg/kg every 12 hrs up to 96 hrs Group 3: loading dose of 10 mg/kg plus 5 mg/kg every 12 hrs up to 36 hrs, then 10mg/kg every 12 hrs up to 96 hrs, followed in sequential order	Mild and transient dizziness, lightheadedness, diarrhoea, headache reported in placebo and drug subjects. No apparent drug relation to the side effects reported No significant changes in objective clinical parameters (e.g. pulse rate, body temperature, respiratory rate) in any subject at any time during the study Mild, sporadic and transient elevation in blood pressure unrelated to fomepizole administration in 5/15 drug subjects and 3/6 placebos Mild increase in one or both serum transaminase (SGOT and SGPT) values in 6/15 (40%) drug subjects Elevated cholesterol and triglyceride levels in both drug and placebo subjects
Brent et al. (1999)	Phase III multi-centre prospective study of EG poisoning	19 patients 2 female 17 male	6/19 (32%)	All patients – loading dose of IV fomepizole (1 g/mL) 15 mg/kg, then 10 mg/kg every 12 hrs for 48 hrs, then 15 mg/kg every 12 hrs until serum EG concentration was <20 mg/dL Mean 3.5 doses (range 1-7)	No AEs either definitely or probably related to fomepizole were reported Bradycardia, seizure and headache were reported, but their clinical courses suggest they were unrelated to fomepizole; additionally these side effects were not described in phase I studies

Ref.	Study Design	Subjects	No. with Adverse Effects	Dose of Fomepizole	Adverse effects Reported
Brent et al. (2001)	Phase III multi-centre prospective study of methanol poisoning	11 patients 2 female 9 male	6/11 (55%)	All patients – loading dose of IV fomepizole (1 g/mL) 15 mg/kg, then 10 mg/kg every 12 hrs up to 48 hrs, then 15 mg/kg every 12 hrs until serum methanol concentration was <20 mg/dL Mean 4 doses (range 1-10)	6 patients reported adverse effects possibly related to fomepizole: phlebitis (1), dyspepsia (1), anxiety (1), agitation (2), hiccups (1), a reaction at the infusion site (1), transient tachycardia (1), transient rash (1), and a “strange” feeling (1)
Borron et al. (1999)	Case series	38 patients	1 (definitely related), 1 (probably related), 4 (possibly related)	Median number of doses per patient was 3 (IQR 1-8)	Pain or inflammation at site of injection (2), transient eosinophilia (2), generalised cutaneous eruption (1)
Marraffa et al. (2008)	Prospective randomised crossover trial	10 healthy volunteers 7 female 3 male	3/10 (30%)	5 volunteers received 15 mg/kg fomepizole orally 5 volunteers received 15 mg/kg IV fomepizole	3 subjects complained of headache and dizziness All 10 subjects complained of an unpleasant, metallic taste after both routes of administration

Table 5. Comparison of Safety between Fomepizole and Ethanol Treatment

Ref.	Study Design	Subjects	No. with Adverse Reactions	Comparative Data
Lepik et al. (1999)	Retrospective case series	172 patients Aged ≥ 13 yrs Hospitalised between 1996 and 2005 for methanol or EG poisoning 130 ethanol treated 42 fomepizole treated	At least one adverse drug event in 74/130 (57%) ethanol treated and 5/42 (12%) fomepizole treated	CNS symptoms accounted for most AEs (48% ethanol treated, 2% fomepizole treated) Severe AEs occurred in 26/130 (20%) ethanol treated (coma, extreme agitation, cardiovascular) and 2/42 (5%) fomepizole treated (coma, cardiovascular) Serious (life-threatening) AEs occurred in 11/130 (8%) ethanol treated (respiratory depression, hypotension) and 1/42 (2%) fomepizole treated (hypotension, bradycardia) cases Given observational study limitations, results suggest lower occurrence of adverse drug events with fomepizole than ethanol
Lepik et al. (2011)	Retrospective case series	189 patients Aged ≥13 yrs Hospitalised between 1996-2005 for methanol or EG poisoning 145 ethanol treated 44 fomepizole treated	At least one medication error in 113/145 (78%) ethanol treated and 20/44 (45%) fomepizole treated	Medication errors were more frequent in ethanol treated compared to fomepizole treated cases (p=0.0001) Ethanol related errors mostly involved excessive dose, inadequate monitoring and inappropriate antidote duration Harmful errors occurred in 19% of ethanol and 7% of fomepizole treated cases, and were largely due to excessive antidote dose or delayed antidote initiation

Table 6. Assessment of Quality of Evidence

6.1 Summary of Clinical Studies

Author	Aim	Study Design	Population	No. Given Fomepizole/ No. in Study	Other Treatment
	Prospective Studies				
Brent et al., 1999	To evaluate fomepizole in treatment of EG poisoning	Prospective, multicentre, open label observational study (META trial)	Consecutive patients admitted between Nov 1995 – Aug 1997, aged >12 yrs old with confirmed/possible EG poisoning according to one of 3 sets of characteristics 1. plasma EG conc >20 mg/dL 2. suspected ingestion of EG and 3 of 4 specific lab findings (arterial pH below 7.3, serum bicarbonate conc <20 mmol/L, serum osmolar gap >10 mOsm/kgH_2O and oxaluria) 3. suspected ingestion of EG within the preceding hour and serum serum osmolar gap >10 mOsm/kgH_2O. Excluding patients given ethanol in hospital.	19/19	HD
Sivilotti et al., 2000	To characterise the elimination kinetics of EG; To demonstrate the efficacy of ADH inhibition caused by fomepizole; To identify a minimal effective inhibitor concentration; To analyse the effects of renal function and HD on EG elimination.	Prospective, multicentre, open label observational study (META trial)	Consecutive patients admitted between Nov 1995 – Aug 1997, aged >12 yrs old with confirmed/possible EG poisoning and one plasma EG conc >20 mg/dL (as in Brent et al., 1999)	19/23	HD
Brent et al., 2001	To evaluate fomepizole in treatment of methanol poisoning	Prospective observational study, multicentre, (META trial)	Consecutive patients, admitted Nov 1995 – Aug 1997, aged >12 yrs old with confirmed/ possible methanol poisoning and serum methanol conc. >20 mg/dL, or a history/strong suspicion of methanol poisoning and at least 2 of the following 3 findings: 1 arterial pH <7.3, 2 serum bicarbonate conc <20 mmol/L, or 3 serum osmolality gap of > 10 mOsm per kg of water. Excluding patients given ethanol in hospital	11/11	HD

Author	Aim	Study Design	Population	No. Given Fomepizole/ No. in Study	Other Treatment
Borron et al., 1999	To assess fomepizole in treatment of uncomplicated EG poisoning	Observational case series	Consecutive patients presenting with clinical features of EG poisoning	38/38 11 given >1 dose .	HD
Hovda et al., 2005a	To study methanol and formate kinetics without influence of dialysis	Prospective observational study of hospitalised patients in Norway Selected from population in Hovda et al., 2005c	Patients treated with fomepizole and bicarbonate without HD, with mild to moderate metabolic acidosis on admission, no visual disturbances after rapid and full correction of metabolic acidosis in emergency department.	8/8	
Hovda, et al., 2005b	To evaluate the role of HD in methanol-poisoned patients treated with fomepizole and HD; To find a possible new indication for HD based on patient's initial clinical status	Prospective case series Patients selected from population in Hovda, et al., 2005c	Patients with suspected or clinical features of methanol poisoning treated with fomepizole and HD	7/7	HD
Hovda et al. 2005c	To study epidemiology, clinical features, treatment and prognostic signs in a methanol poisoning outbreak	Prospective observational study of hospitalised patients in Norway retrospectively divided into groups according to outcome (This population included in Paasma et al., 2012)	Patients admitted with methanol poisoning, between 2002-2004; confirmed by serum methanol analysis	36/59	Ethanol HD
	Retrospective Studies				
Mégarbane et al., 2001	To assess efficacy and safety of fomepizole in treatment of methanol-poisoned patients and their requirements for HD	Retrospective, case review	Patients admitted to ITU between 1987-1999, with history of methanol exposure given at least 1 dose of fomepizole	14/14	HD
Caravati, et al., 2004	To describe clinical course, length of stay and outcome in children with EG poisoning	Retrospective case review	Patients < 18yrs old admitted between 1999-2002 with EG poisoning (peak serum EG conc >50 mg/dL). Excluded patients who • were discharged from emergency dept, • received HD	5/6	ethanol
Green, 2007	To describe presentation, management and clinical course of toxic alcohol ingestions at a tertiary care centre after introduction of fomepizole to the hospital formulary	Retrospective case review	Adults ≥17 years who had IV ethanol or fomepizole ordered after emergency dept registration, or were admitted to ICU with detectable serum conc of either EG or methanol or a clinical history and an arterial blood gas consistent with toxic alcohol ingestion.	12/20 confirmed ingestions	Ethanol HD

Author	Aim	Study Design	Population	No. Given Fomepizole/ No. in Study	Other Treatment
Lepik et al., 2009	To investigate incidence of fomepizole and ethanol-related adverse drug events (AEs) in setting of EG and methanol poisoning To evaluate time of AE onset after antidote initiation To test hypothesis that fomepizole is less likely to result in a AE than ethanol AE includes medication errors.	Retrospective case review in 10 hospitals including tertiary care, secondary care, non-teaching regional hospitals and primary care community hospitals. Same population in Lepik et al., 2011.	Patients ≥13 yrs old admitted with suspected EG or methanol poisoning and given ≥1 dose of ethanol or fomepizole.	44/174	Ethanol HD
Lepik et al., 2011	To describe and compare frequency, type and outcome of ethanol and fomepizole-related medication errors and identify the types of errors and underlying causes associated with harm.	Retrospective case review 10 hospitals including tertiary care, secondary care, non-teaching regional hospitals and primary care community hospitals Same population in Lepik et al., 2009.	Patients ≥13 yrs old admitted with suspected EG or methanol poisoning and given ≥1 dose of ethanol or fomepizole.	44/174	Ethanol HD
Paasma et al., 2012	To develop a prediction model for outcome of methanol poisoned patients To determine whether CNS depression effects of ethanol are related to outcome To determine whether fomepizole is superior to ethanol in methanol poisoning	Retrospective case review from hospitals in Norway, Estonia, Tunisia, Teheran, Mashad Includes population from Norway in Hovda et al., 2005c	Patients admitted to hospital alive with methanol poisoning confirmed by positive serum methanol analysis. Excluding those given treatments before admission that could interfere with the analysis	32/219 with positive serum methanol	Ethanol, HD
Levine et al., 2012	To determine elimination ½ life of EG when fomepizole used alone with no HD To determine mortality and development of renal failure	Retrospective case review	Patients >15 yrs old with known or suspected poisoning with EG (peak serum EG >20 mg/dL) admitted June 2002-March 2010	40/85	

6.2 Summary of Healthy Volunteer Studies

Author	Aim	Study Design	Dose regimen	No. given fomepizole/No. in study
Jacobsen et al., 1988	To evaluate safety and pharmacokinetics of fomepizole in volunteers	Placebo-controlled, double-blind, single dose, randomised, sequential ascending dose study	Double blind allocation into 4 groups of 6 subjects each. Within each group 4 subjects randomly allocated to oral fomepizole and 2 to placebo. Group 1 10 mg/kg Group 2 20 mg/kg Group 3 50 mg/kg Group 4 100 mg/kg (only 4 subjects completed)	15/22
Jacobsen et al., 1990	To study tolerance of fomepizole in healthy volunteers To evaluate effect of fomepizole on ethanol elimination	Placebo controlled, double-blind, multiple dose, sequential ascending dose study	Double blind allocation into 3 groups of 7 subjects each. Within each group 5 subjects randomly allocated to oral fomepizole and 2 to placebo. Group 1 loading dose 10 mg/kg, then 3 mg/kg every 12 h to 96 h (total dose 34 mg/kg); and ethanol 0.5 mg/kg Group 2: loading dose 15 mg/kg plus 5 mg/kg every 12 h to 96 h (total dose 55 mg/kg) Group 3: loading dose 10 mg/kg, then 5 mg/kg very 12 h up to 36 h then 10 mg/kg every 12 h to 96 h (total dose 75 mg/kg)	15/21
Marraffa et al., 2008	To describe the comparative pharmacokinetic profiles of fomepizole after both oral and intravenous therapeutic doses in healthy volunteers	Prospective, randomised, crossover trial	15 mg/kg iv or 15 mg/kg orally	10/10
McMartin et al., 2012	To determine kinetics and metabolism after single oral and iv doses and multiple oral doses in healthy volunteers	Double-blind, single-dose crossover study Double-blind randomised multiple dose study	**Single dose study** 7 mg/kg iv plus oral placebo, 7 mg/kg fomepizole orally plus IV placebo **Multiple dose study** 3 groups of 7 subjects each. Within each group random allocation 5 subjects to fomepizole and 2 to placebo. Group 1. oral lading dose of 10 mg/kg then 3 mg/kg very 12 hr up to 96 h Group 2 oral doses of 15 mg/kg plus 5 mg/kg every 12 h to 96 h Group 3 oral doses of 15 mg/kg plus10 mg/kg every 12 h up to 36h, then 10 mg/kg up to 96 h	Single-dose study = 10 Multiple dose study = 21

6.3 Limitations of Clinical Studies

Author	Study design	Method for data collection standardisation and validation	No. given fomepizole/ No. in study	Exposure measures flawed?	Outcome measures flawed/not validated/ incompletely reported?	Accurate measure of all prognostic factors?	Incomplete follow-up?	Comment
Brent et al., 1999	Prospective, multicentre, open label observational study (META trial)	Data entry verified by a 2nd person.	19/19	No; exposure confirmed with lab analysis	No	Yes	No. All patients followed up for at least 24h after completion of treatment, and patients with high serum creatinine followed up until values were normal	All patients had toxicology screen
Silvoltti et al., 2000	Prospective, multicentre, open label observational study (META trial)	Data entry verified by a 2nd person.	19/23	No; exposure confirmed with lab analysis	No	Yes	No. All patients followed up for at least 24h after completion of treatment, and patients with residual effects followed up until effects resolved	All patients had toxicology screen
Brent et al., 2001	Prospective observational study, multicentre, (META trial)	Data entry verified by a 2nd person.	11 /11	No; exposure confirmed with lab analysis	No	Yes;	No. All patients followed up for at least 24h after completion of treatment, and patients with residual effects followed up until effects resolved	All patients had toxicology screen
Borron et al., 1999	Observational case series	Not stated	11/38	Unclear	Unclear how relationship of AEs to fomepizole was decided	Yes except no details of routine lab test methods .	Unclear: follow up period not stated	Protocol not described. Fomepizole and EG metabolites not measured; unclear whether patients had toxicology screen.
Hovda et al.2005c	Prospective observational study of hospitalised patients	Not stated	36/59	Based on clinical findings and plasma concentrations	Unclear whether AEs fully reported	Yes except no details of routine lab test methods	Followed up until discharge; Death 1 year after discharge recorded for patient discharged with sequelae.	Fomepizole and methanol metabolites not measured; unclear whether patients had toxicology screen; Some given ethanol before fomepizole
Hovda et al. 2005a	Prospective observational study	Not stated	8/8	No – Based on clinical findings and plasma concentrations	No-	Yes; samples analysed twice	Unclear; half-life of methanol was long so could not observe for 3 x the half-life	Limited number of representative data points in a few patients, but data are within the time-span of metabolic inhibition by the antidote. Long discussion on confounders
Hovda et al. 2005b	Prospective case series	Not stated	7/7	No – Based on clinical findings and plasma concentrations	No	Yes; samples analysed twice	No; followed up until discharge; death 1 year after discharge recorded for patient discharged with sequelae.	

Author	Study design	Method for data collection standardisation and validation	No. given fomepizole/ No. in study	Exposure measures flawed?	Outcome measures flawed/not validated/ incompletely reported?	Accurate measure of all prognostic factors?	Incomplete follow-up?	Comment
Mégarbane et al., 2001	Retrospective, case review	Not stated	14/14	No Based on clinical findings and plasma concentrations	Inconsistent ophthalmology referrals may have missed eye abnormalities	Unclear – retrospective study	Unclear; followed up until discharge from hospital; inconsistent ophthalmology referrals; possibility of late onset effects not known.	Protocol not described Methanol metabolites not measured in most patients, instead used anion gap as surrogate marker; patients had toxicology screen
Caravati et al., 2004	Retrospective case review	Identified from ICD coding on medical records. Standard pre-printed data collection forms Included patients who had received ethanol loading dose before fomepizole	5/6	No exposure confirmed with lab analysis No details of method used	No	Unclear – retrospective study	Unclear; followed up until discharge but "renal injury might have occurred after discharge". Inpatient stay 31-83 h.	Fomepizole and EG metabolites not measured; small number of patients; 1 patient treated with ethanol only; no toxicology screen but maybe unnecessary in paediatric patients.
Green, 2007	Retrospective case review	Identified by manual search of pharmacy database, ICU records and HD records. Data collection not validated/checked	12/20	No	No	Unclear – retrospective study	Unclear; followed up until discharge from hospital; possibility of late onset effects not known.	Protocol not described. Fomepizole and methanol metabolites not measured "no conclusion can be made about role of fomepizole and/or alcohol in the outcome" Patients probably did not have toxicology screen

Author	Study design	Method for data collection standardisation and validation	No. given fomepizole/ No. in study	Exposure measures flawed?	Outcome measures flawed/not validated/ incompletely reported?	Accurate measure of all prognostic factors?	Incomplete follow-up?	Comment
Lepik et al., 2009	Retrospective case review	2 trained abstractors independently reviewed each chart, using standardized data collection forms Rigorously developed method for identifying and classifying AEs. Included medication errors.	44/174	Patients selected if given antidotes, not on the basis of laboratory data	No	Unclear – retrospective study	Unclear; reviewed charts up to recovery or death; possibility of late onset effects not known.	12/41 had co-ingestants. " The panel review and analytical methods cannot conclusively delineate the role of antidote, coingestants, other treatments, effects of toxic alcohol poisoning and other medical conditions in the occurrence of apparent drug events."
Lepik et al., 2011	Retrospective case review	2 trained abstractors independently reviewed each chart, using standardized data collection forms Rigorously developed method for identifying and classifying AEs, and rigorously developed error definitions, and method for identifying differences from accepted practice for use of ethanol and fomepizole	44/174	Patients selected if given antidotes, not on basis of laboratory data	No, but the estimated frequency of medication error may have been influenced by local factors and may not be generalisable elsewhere or to a more recent time period.	Unclear – retrospective study	Unclear; reviewed charts up to recovery or death; possibility of late onset effects not known.	Consensus agreement may be influenced by personal bias, Information less complete for ethanol than fomepizole but underestimation of ethanol-related errors would not have changed study conclusion.

Author	Study design	Method for data collection standardisation and validation	No. given fomepizole/ No. in study	Exposure measures flawed?	Outcome measures flawed/not validated/ incompletely reported?	Accurate measure of all prognostic factors?	Incomplete follow-up?	Comment
Paasma et al., 2012	Multicentre retrospective case review	Not stated	32/219 with positive serum methanol	No; exposure confirmed with lab analysis and lab methods described	No	Unclear – retrospective study	Unclear; followed up until discharge from hospital; possibility of late onset effects not known.	Methanol metabolites not measured. Fomepizole used on only one site so limited in number and gave insufficient power to statistical analysis to find differences with respect to outcome."
Levine et al., 2012	Retrospective case review	To eliminate abstractor and interpretation bias, data limited to continuous variables or clear categorical variables. Data collectors trained, data independently checked for accuracy and 10% records reviewed	40/85	No; exposure confirmed with lab analysis	No	Unclear – retrospective study	Unclear; followed up until discharge from hospital; possibility of late onset effects not known.	Calculation of half life more likely to be accurate because not interrupted by HD Fomepizole and EG metabolites not measured. Unclear whether patients had toxicology screens

6.4 Limitations of Healthy Volunteer Studies

Author	Study design	Randomisation	Allocation concealment	Blinding	Loss to FU	Other
Jacobsen et al., 1988	Placebo controlled, Double blind allocation into 4 groups Within each group subjects randomly allocated to oral fomepizole or placebo	Method unclear	Method unclear	Described as double blind Taste disguised, subjects dosed alone and not allowed to comment on taste with subjects or testers. Blind efficacy evaluation performed because of unpleasant taste; evaluated when study was complete. At higher doses all subjects guessed correctly whether they had drug or placebo **Moderate risk of bias**	Study stopped early; 1 subject in highest dose group did not complete the study	Side effects monitored by self-report and observation by testers. Subjects were asked to rate severity. At the end of the study subjects were asked about specific side effects
Jacobsen et al., 1990	Placebo controlled, allocation into 3 groups; within each group subjects randomly allocated to oral fomepizole or placebo	Method unclear	Method unclear	Described as double blind Taste disguised, subjects dosed alone and not allowed to comment on taste with subjects or testers Blind efficacy evaluation performed because of unpleasant taste; evaluated when study was complete. 73% of drug subjects guessed correctly that they had received drug compared to 50% correct among placebos **Moderate risk of bias**		Side effects monitored by self-report and observation by testers. Subjects were asked to rate severity. At the end of the study, subjects completed a side-effects checklist.
Marraffa et al., 2008	Prospective, randomised, crossover trial	Random number table	none	Not blinded Drug given in fruit juice; no other flavour masking	none	Not designed to evaluate safety. Side effects reported, but subjects not blinded and no placebo comparator group.
McMartin et al., 2012	Double-blind, single-dose crossover study Double-blind randomised multiple dose study. Random allocation to groups and within each group random allocation to fomepizole and to placebo.	**Single dose study** Route of administration randomised by coin flip among subjects. **Multiple dose study** Random number generator	Unclear	Double blind Test medication administered by blinded investigators; Taste of oral drug disguised (placebo contained the same)	none	

6.5 Outcomes Reported in Clinical Studies and Healthy Volunteer Studies

Ref	Study design	Survived/ died	Long-term disability	Decrease in EG/Me serum concentration	Increase in elimination half-life ME/ EG	Inhibition of metabolite production	Effect on renal function	Adverse events related to fomepizole	Hospital days	Cost
Brent et al., 1999	Prospective, observational study (META trial)	Y		Y	Y	Y	Y	Y		
Sivilotti et al., 2000	Prospective, observational study (META trial)	Y		Y	Y		Y			
Brent et al., 2001	Prospective observational study (META trial)	Y		Y	Y	Y		Y		
Borron et al., 1999	Observational study	Y		Y			Y	Y		
Hovda et al. 2005c	Prospective observational study	Y	Y	Y	Y					Y
Hovda et al., 2005a	Prospective observational study	Y	Y	Y	Y	Y				
Hovda, et al., 2005b	Prospective observational study	Y	Y	Y	Y	Y				
Mégarbane et al., 2001	Retrospective, case review,	Y	Y	Y	Y		Y	Y	Y	
Caravati, et al., 2004	Retrospective case review	Y	Y	Y			Y		Y	
Green, 2007	Retrospective case review	Y		Y					Y	
Lepik et al., 2009	Retrospective case review	Y					Y	Y		
Lepik et al., 2011	Retrospective case review						Y	Y		
Paasma et al., 2012	Retrospective case review	Y	Y	Y			Y			
Levine et al., 2012	Retrospective case review	Y		Y	Y		Y			
Jacobsen et al., 1988	Placebo controlled, double-blind, single dose, randomised, sequential ascending dose study	n/a	n/a	n/a	n/a	n/a	Y	Y	n/a	
Jacobsen et al., 1990	Placebo controlled, double-blind, multiple dose, sequential ascending dose study	n/a	n/a	n/a	n/a	n/a	Y	Y	n/a	
Marraffa et al., 2008	Prospective, randomised, cross over trial	n/a	n/a	n/a	n/a	n/a		Y	n/a	
McMartin et al., 2012	Double-blind, single-dose crossover study and a double-blind randomised multiple dose study	n/a	n/a	n/a	n/a	n/a			n/a	

6.6 Outcome: Fomepizole Treatment Influenced Survival of Patients with Ethylene Glycol or Methanol Poisoning

6.6.1 Quality Assessment

Number of studies (number patients given fomepizole)	Limitations	Inconsistency	Quality of evidence	Comment	References
6(85) Prospective observational studies	No comparison group	No		Moderate	Brent et al., 1999; Silvoltti et al., 2000; Brent et al.,2001; Hovda et al., 2005a; Hovda et al., 2005b; Hovda et al., 2005c
5 (91) Retrospective studies	No comparison group; not clear whether follow-up complete; because possibility of late onset sequelae not clear	No	Low	Low	Caravati et al., 2004; Levine et al., 2012; Megarbane et al.,2001; Paasma et al.,2012

6.6.2 Summary of Findings for Mortality and Morbidity Following Treatment with Fomepizole

				Patients given fomepizole			
Author	**Study design**	**No. given fomepizole/ No. in study**	**Other treatment**	**Survived without sequelae**	**Survived with sequelae**	**Died**	**Confidence that mortality and morbidity are an estimate of the true effect**
	Ethylene glycol						
Brent et al., 1999	Prospective, multicentre, open label observational study (META trial)	19/19	HD	18	0	1	High
Sivilotti et al., 2000	Prospective, multicentre, open label observational study (META trial)	19/23	HD	18	0	1	High
Borron et al.,1999	Observational case series	11 given >1 dose/38	HD	10		1	Consistent with other studies, but not enough detail; follow-up period not stated. **Exclude from quality assessment for this outcome**.
Caravati et al., 2004	Retrospective case review	5/6 children	Ethanol	5	0	0	Moderate - Unclear whether follow-up complete but consistent with other studies
Levine et al., 2012	Retrospective case review,	40/85		40	0	0	Moderate - Unclear whether follow-up complete but consistent with other studies
	Methanol						
Brent et al.,2001	Prospective observational study, (META trial)	11/11	HD	9	None related to Methanol	2	High
Hovda et al., 2005c	Prospective observational study	36/59	Ethanol HD	29	Visual – 5 CNS – 3	7	High
Hovda et al.,2005ax	Prospective observational study	8/8		7	1 slight visual sequelae	0	Included in total in Hovda 2005c

				Patients given fomepizole			
Author	**Study design**	**No. given fomepizole/ No. in study**	**Other treatment**	**Survived without sequelae**	**Survived with sequelae**	**Died**	**Confidence that mortality and morbidity are an estimate of the true effect**
Hovda et al.,2005b	Prospective case series	7/7	HD	4	2 with visual sequelae and CNS sequelae	1	Included in total in Hovda 2005c
Mégarbane et al., 2001	Retrospective, case review	14/14	HD	10	4	0	Moderate: inconsistent ophthalmology referrals; unclear whether follow-up complete but consistent with other studies
Paasma et al.,2012	Retrospective case review	32/219 with positive serum methanol	Ethanol	22	4	6	Moderate: Unclear whether follow-up complete but consistent with other studies
	Ethylene glycol & methanol						
Green, 2007	Retrospective case review	12/20 confirmed ingestions	Ethanol HD	12	n/a	0	Low: unclear whether follow-up complete and whether data is complete **Exclude from quality assessment for this outcome**

6.7 Outcome: Fomepizole Treatment Associated with an Inhibition of Ethylene Glycol Metabolism until Ethylene Glycol Concentrations were <20mg/dL

6.7.1 Quality Assessment

Number of studies (number patients given fomepizole)	**Limitations**	**Inconsistency**	**Quality of evidence**	**comment**	**References**
1 (17) prospective observational studies	Yes no comparison group; small number of patients	No	Moderate	Data from the META trial. Upgrade from low because several samples taken	Brent et al., 1999

6.7.2 Summary of Findings for Inhibition of Ethylene Glycol Metabolism until Ethylene Glycol Concentrations were <20mg/dL during Fomepizole Treatment

Study	**Design**	**No Patients given fomepizole/no in study**	**Patients given fomepizole & HD**	**Patients given ethanol**	**Metabolites measured?**	**Fomepizole Concentration measured?**	**Confidence that inhibition of EG metabolism was associated with fomepizole**
Brent et al., 1999	Prospective, multicentre, observational study (META trial)	19 /19 with EG >20 mg/dl	17/19	Plasma ethanol detectable in 12 patients, concs >100 mg/dL in 4 patients	Y Urinary oxalate and plasma glycolate	Y	Moderate

6.8 Outcome: Fomepizole Treatment Associated with an Inhibition of Methanol Metabolism until Methanol Concentrations were <20 mg/dL

6.8.1 Quality Assessment

Number of studies (number patients given fomepizole)	Limitations	Inconsistency	Indirectness	Publication bias	Quality of evidence	Comment	References
3 prospective studies (26)	Yes no comparison group	No	No	Unlikely	Low	Some patients given HD which would have removed some of the metabolites;	Brent et al., 2001, Hovda et al., 2005a, b

6.8.2 Summary of Findings for Inhibition of Methanol Metabolism until Methanol Concentrations were <20 mg/dL during Fomepizole Treatment

Study	Design	No. patients given fomepizole/ no in study	Patients given fomepizole & HD	Patients given ethanol as well as fomepizole	Metabolites measured?	Fomepizole concentration measured?	Analytical method for formate	>1 decreasing methanol measurement?	Confidence that inhibition of methanol metabolism was associated with fomepizole
Brent et al., 2001	Prospective multicentre, observational study (META trial)	11/11	7	N	Y	Y	Gas chromatography	Y	High; fall in plasma formic acid concentration occurred after fomepizole therapy started. Plasma fomepizole measurements monitored and within therapeutic range. Some patients given HD which would have removed some of the metabolites.
Hovda et al. 2005b	Prospective observational study	7/7	7/7	2 before transfer	Y	N	Enzymatically using Cobas Mira analyser (Roche diagnostics)	Y	Some patients given HD which would have removed some of the metabolites.
Hovda, et al., 2005a	Prospective observational study	8/8	0	4 (before referral)	Y	n	Enzymatically using Cobas Mira analyser (Roche diagnostics)	Y	High – no HD given. Includes only patients with mild to moderate metabolic acidosis on admission and no visual disturbances after full correction of metabolic acidosis in AE

6.9 Outcome: Adverse Effects Associated with Treatment with Fomepizole for Toxic Alcohol Poisoning

6.9.1 Quality Assessment

Number of studies (number patients given fomepizole)	Limitations	Inconsistency	Quality of evidence	Comment	References
2 RCTs (30)	Incomplete blinding of subjects	No	Moderate		Jacobsen et al., 1988 Jacobsen et al., 1990
2 prospective observational studies (30)	No comparison group,	No	Moderate		Brent et al., 1999; Brent et al., 2001
1 retrospective case series (42)	No comparison group	No	Low	Upgrade from very low because expert assessment of association of AEs with fomepizole	Mégarbane et al., 2001; Lepik et al., 2009

6.9.2 Summary of Findings for Adverse Effects of Fomepizole Treatment

Ref	EG or Me?	Study design	How were AEs identified?	No. individuals given fomepizole	Were patients given ethanol?	Results Numbers in brackets are numbers of patients	Confidence that AEs correctly attributed to fomepizole
Jacobsen et al., 1988	n/a	Placebo controlled, double-blind, single dose, randomised, sequential ascending dose study	Self-report and observation by testing personnel. At study end, subjects were asked to complete a checklist	15	No	Well tolerated. 10 and 20 mg/kg dose: no side effects 50 mg/kg dose: slight to moderate dizziness (3), nausea (2) 100 mg/kg dose: mild to moderate dizziness lasting 4 hours (3), mild speech and visual disturbances (1), a sensation of inebriation, mild vertigo, mild pulsating headache, vertical nystagmus, nausea lasted for up to 30 hours (1) positive Romberg test (2) Increase in serum uric acid (1)	Moderate because unable to completely mask taste of fomepizole so subjects not completely blinded.
Jacobsen et al., 1990	n/a	Placebo controlled, double-blind, multiple dose, sequential ascending dose study	Self-report and observation by testing personnel. At study end, subjects were asked to complete a checklist	15	No	Well tolerated; Mild transient dizziness, headache, lightheadedness and diarrhoea (7) Mild, transient rise in blood pressure (5) apparently not related to fomepizole. No significant changes in objective clinical parameters Mild transient elevation in serum transaminase, increase in either SGPT or SGPT and SGOT levels (6) unrelated to dose; raised serum triglyceride levels (3), raised serum cholesterol (1).	Moderate because unable to completely mask taste of fomepizole so subjects not completely blinded

Ref	EG or Me?	Study design	How were AEs identified?	No. individuals given fomepizole	Were patients given ethanol?	Results Numbers in brackets are numbers of patients	Confidence that AEs correctly attributed to fomepizole
Brent et al., 1999	EG	Prospective, multicentre, observational study (META trial)	Local investigator determined dates of onset and resolution, severity and relation to fomepizole.	19	Not given ethanol in treatment but some patients had self-administered before admission	No side effects rated definitely or probably related to fomepizole. Bradycardia (2) seizure (2) and headache (2) rated possibly related but clinical course suggested they were not related	Moderate
Brent et al., 2001	Me	Prospective observational study, multicentre, (META trial)	Local investigator determined dates of onset and resolution, and severity relation to fomepizole.	11	Not given ethanol in treatment but some patients had self-administered before admission	AEs in 6 patients possibly related to fomepizole. None definitely or probably related to fomepizole. Phlebitis (1), dyspepsia (1) anxiety (1) agitation (2) hiccups (1) reaction at the injection site (1) transient rash (1) transient tachycardia (1)	Moderate
Lepik et al., 2009	EG and Me	Retrospective case review across diverse clinical settings	Used standardised, validated poisons severity score categories to classify severity of each sign or symptom. Antidote related symptoms were classified by poisoning severity score and WHO criteria for seriousness of event. The association of AE with antidote was independently assessed by experienced medical toxicologists who then met to reach consensus. A blinded reviewer was also undertaken to evaluate bias. If patients had received both fomepizole and ethanol they were excluded if reviewers could not decide which antidote was responsible.	44	Some	5 patients with AEs; minor gastrointestinal (3), transient coma (1), bradycardia and hypotension in 1 patient classified as serious by WHO (see main text)	High

Ref	EG or Me?	Study design	How were AEs identified?	No. individuals given fomepizole	Were patients given ethanol?	Results Numbers in brackets are numbers of patients	Confidence that AEs correctly attributed to fomepizole
Mégarbane et al., 2001	Me	Retrospective case review	Not stated	14	Ethanol given to some patients but not to any of the patients reporting AEs. One patient with an AE had self-administered ethanol	Well tolerated, even with up to 8 days administration. Lymphaginitis(1), mild eosinophilia (1): fever (2), nausea (1), headache (1)	Moderate; method for determining attribution of AEs not stated, but expert assessment by clinical toxicologists, and patients had toxicology screen for co-ingestants.
Borron et al., 1999	EG	Observational case series	Not stated	11	No but self-administered in some cases	Pain at injection site (2), transient eosinophilia (2), generalised cutaneous eruption (1). Possibly related (2), Probably related (1), definitely related (1)	Low; method for determining attribution of AEs not state but consistent with other studies; unclear whether there were co-ingestants. **Exclude from quality assessment for this outcome**
Marraffa et al., 2008	n/a	Prospective, randomised, cross over trial	Not stated. AE reporting was not the aim of the study.	10	No	Well tolerated; headache (3), dizziness (3), metallic taste (10) Vital signs stable for entire study period	Low; subjects not blinded, method for determining attribution of AEs not stated. **Exclude from quality assessment for this outcome**