Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fomepizole SERB 5 mg/mL, concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 8 mg of fomepizole sulphate equivalent to 5 mg fomepizole.

An ampoule of 20 ml contains 160 mg fomepizole sulphate, equivalent to 100 mg fomepizole;

Excipient(s) with known effect: An ampoule of 20 ml contains 2,4 mmol sodium

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Fomepizole SERB is a clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fomepizole SERBis an antidote used in the treatment of acute ethylene glycol poisoning.

4.2 Posology and method of administration

Posology

The treatment should begin whenever ethylene glycol poisoning is suspected, as early as possible after its ingestion, even in the absence of signs of toxicity.
In the absence of ethylene glycol assay, ethylene glycol poisoning should be suspected on the following criteria:
- patient's history ;
- osmolar gap $\geq$ 20 mOsm/kg H_20 ;
- metabolic acidosis with anion gap > 16 mmol/l (presence of high levels of glycolates) ;
- calcium oxalate crystals in the urine.

An assay for plasma ethylene glycol should be performed at admission,but this determination should not delay start of treatment with fomepizole. Plasma ethylene glycol levels should be monitored every 12 to 24 hours**.**

Dosage depends on plasma ethylene glycol concentration and renal function:
- patients with normal renal or mild to moderate impaired renal function as assessed by serum creatinine (100 to 265 mmol/l) in whom hemodialysis is not required :
Administration should be performed by slow intravenous infusion, over 30 to 45 minutes, given as follows: infusion of a loading dose of 15 mg/kg followed by doses every 12 hours until ethylene glycol levels has been reduced below 0.2 g/l (3.2 mmol/l).

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

The number of maintenance doses and the dose after 48 hours will depend on initial concentration and the time course of the ethylene glycol levels.
Generally, 4 to 5 maintenance doses are recommended for initial ethylene glycol levels between 3 to 6 g/l (48 to 96 mmol/l) and 1 to 3 maintenance doses are recommended for initial ethylene glycol levels between 0.35 to 1.5 g/l (5.6 to 24 mmol/l).

-patients with severe impaired renal function as assessed by serum creatinine (> 265 mmol/l)
Hemodialysis is indicated in combination with fomepizole.
A loading dose of 15 mg/kg is infused over 30 to 45 minutes, followed by 1 mg/kg/hour continuous infusion for the entire duration of the hemodialysis.

The dosage of fomepizole during continuous venovenous hemodiafiltration, another mode of extracorporal elimination, is not known.

Hemodialysis and fomepizole sulphate administration should be discontinued when the metabolic acidosis is corrected and plasma ethylene glycol levels have been reduced below 0. 2 g/l (3.2 mmol/l).

- Hemodialysis should also be initiated under at least one of the following features in combination with fomepizole :
- arterial pH < 7.10 ;
- drop in arterial pH > 0.05 resulting in a pH outside the normal range despite bicarbonate infusion ;
- inability to maintain arterial pH > 7.30 despite bicarbonate therapy ;
- decrease in serum bicarbonate concentration of more than 5 mmol/ldespite bicarbonate therapy ;
- rise in serum creatinine by > 90 mmol/l (1 mg/dl).

elderly patients :
Clinical experience in elderly patients is limited. The regimen has to be adjusted to the renal function (see above).

children :
There is no available data regarding the pharmacokinetics of fomepizole in children. Clinical experienceis limited and based on similar weight-adjusted doses.

patients with impaired liver function :
No clinical data are available.

Method of administration
Fomepizole SERB 5mg/mL, concentrate for solution for infusion, is to be diluted before use (see section 6.6). The diluted solution should be administered by slow intravenous infusion.

4.3 Contraindications

Hypersensitivity to the active substance or to other pyrazoles or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Previous treatment of ethylene glycol poisoning with ethanol does not preclude the use of fomepizole. Nevertheless, the combination of ethanol and fomepizole is usually not recommended**.** (See section 4.5.)

Minor hypersensitivityreactions have been reported in a few patients (rash, hypereosinophilia). These symptoms should be monitored.

Management should be modified in case of a major hypersensitivity reaction (angioedema, bronchospasms, anaphylactic shock). In these cases, the fomepizole sulphate infusion should be immediately discontinued in the absence of another established cause; symptomatic treatment should startand fomepizole sulphate should not be re-administered to the patient. Treatment by ethanol should be started and hemodialysis considered

Ethylene glycol poisoning in its severe forms is expressed by metabolic acidosis (anion gap > 16 mmol/l), convulsive coma and renal failure.

Treatment of ethylene glycol intoxication involves prevention of the metabolism of ethylene glycol to its toxic metabolites, correction of metabolic acidosis, sufficient hydration (oral or venous if applicable) to prevent the risks of dehydration and hypernatremia and to increase urine clearance of ethylene glycol, and if necessary, removal of toxic metabolites with hemodialysis. Monitoring requires frequent measurements of plasma ethylene glycol, blood gas, pH, electrolytes, serum creatinine, urine analysis and presence of urinary oxalate crystals.

Evaluation of hepatic transaminases and blood cell counts before and one month after treatment is recommended**.**

Pre-existing impaired liver functionrequires careful monitoring of hepatic transaminases.

Fomepizole SERB 5 mg/mL, concentrate for solution for infusion, should not be given undiluted. The diluted concentrate should not be given by bolus injection.

This medicinal product contains 55 mg (2.4 mmol) sodium per ampoule, equivalent to 2.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Fomepizole is recommended to be diluted in a glucose solution for patients on a controlled sodium diet (see section 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

Combination with ethanol:

Concurrent use of alcohol and fomepizole reduces the elimination rate for both substances. Although the clinical efficacy of fomepizole seems not impaired, for safety reason, the concomitant use of fomepizole with alcohol is not-recommended (See section 4.4 Special warnings and precaution for use).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no clinical data from the use of fomepizole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
Fomepizole should not be used during pregnancy unless clearly necessary.

Breastfeeding
There is no information on the excretion of fomepizole in human milk. It is advised to discontinue breastfeeding temporarily during treatment with Fomepizole SERB.

Fertility
No fertility studies have been performed.

4.7 Effects on ability to drive and use machines

The possible risks of dizziness and vertigo related to the treatment should be pointed out.

It is not advisable to drive or use machines during the first few days after treatment is discontinued.

4.8 Undesirable effects

Blood and lymphatic system disorders:	
Common:	Eosinophilia, anaemia
Psychiatric disorders:	
Common:	Anxiety, agitation
Nervous system disorders:	
Very common:	Dizziness, headache
Common:	Vertigo, convulsion, nystagmus, speech disorder
Eye disorders:	
Common:	Visual impairment
Cardiac disorders:	

Common:	Bradycardia, tachycardia
Vascular disorders:	
Common:	Increased blood pressure
Gastrointestinal disorders:	
Common:	Nausea, vomiting, diarrhoea, dyspepsia, hiccups
Hepatobiliary disorders:	
Common:	Increased transaminases
Skin and subcutaneous tissue disorders:	
Common:	Pruritus, rash
Musculoskeletal and connective tissue disorders:	
Common:	Increased blood creatine phosphokinase
General disorders and administration site conditions:	
Common:	Injection site reaction, injection site inflammation

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions : HPRA Pharmacovigilance, Earlsfort Terrace , IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517 - Website: www.hpra.ie; Email: medsafety@hpra.ie

4.9 Overdose

Dizziness, drunkenness, nausea, vertigo, headaches, nystagmus and speech disturbances have been observed for doses of 50 to 100 mg/kg in healthy volunteers.
In case of a substantial overdose, as fomepizole sulphate is dialysable, hemodialysis could be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidote
ATC code: VO 3 AB34
Fomepizole is a competitive inhibitor of alcohol dehydrogenase (ADH). ADH catalyses the first stage of the metabolism of ethylene glycol in the liver. Fomepizole treatment blocks the formation of the toxic metabolites of ethylene glycol and prolongs its plasma half-life. Ethylene glycol is thus eliminated unchanged in urine and induces osmotic polyuria.
The spontaneous 4-hour plasma half-life of ethylene glycol is extended to 10-16 hours with fomepizole.
The efficacy of fomepizole in the treatment of ethylene glycol poisoning has been shown in dogs and monkeys, with loading doses of 20 and 50 mg/kg, respectively.
In healthy volunteers, pharmacological effects of fomepizole have been shown indirectly, by the demonstration of a metabolic interaction with ethanol, which is also metabolised by ADH. Doses of fomepizole ranging from 7 to 20 mg/kg are efficient both orally or intravenously.

5.2 Pharmacokinetic properties

Fomepizole has a volume of distribution of approximately 0.7 l/kg. The elimination of fomepizole is non-linear and is saturable for doses ranging from 7 to 20 mg/kg. Upon repeated administration, fomepizole induces its own metabolism.
Fomepizole is almost entirely eliminated by metabolism. The principal metabolite, 4-carboxypyrazole does not have any inhibitory effect on human ADH in vitro.
The enzymes involved in the metabolism of fomepizole have not been identified. In preclinical studies, fomepizole has been shown to be both an inhibitor and an inducer of CYP450 isoenzymes. Corresponding studies have not been performed in human and the potential to affect the pharmacokinetics of drugs metabolised by CYP450 cannot be predicted.
Fomepizole and its metabolites are excreted in urine. Only 2 to 3 % of fomepizole administered is excreted unchanged in the urine.
Fomepizole is dialysable. The extraction ratio is about 0.75, and the hourly extraction ranges between 0.41 and 1.15 mg/kg/h.

5.3 Preclinical safety data

Toxicity studies in animals have not demonstrated fomepizole to have any particular toxicity.

Fomepizole sulphate has shown no sign of mutagenicity or clastogenicity.

Its carcinogenic potential and its reproductive toxicity have not been studied.

With respect to reproductive toxicology no conventional studies were performed. It is known from literature that fomepizole administered intraperitoneally to mice once at day 11 of pregnancy at a dose (mg/kg/day) of 6.5 times the loading therapeutic dose induced embryotoxic (increased rate of fetal resorption) and teratogenic (increased number of anterior limb malformations) effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride.
Water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except for those mentioned in section 6.6.

6.3 Shelf life

3 years.

After dilution (see section 6.4): 24 hours.

6.4 Special precautions for storage

Do not freeze.

After dilution (see section 6.6) : chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in–use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic condition.

6.5 Nature and contents of container

20 ml in One-Point Cut (OPC) ampoule (type I colourless glass); box of 5.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Only clear and colourless solution without visible particles should be used.

For single use only. Any unused product must be discarded.

FOMEPIZOLE EUSA Pharma 5 mg/mL, concentrate for solution for infusion, is to be diluted before use. Preparation of solution for infusion must take place in aseptic conditions.

The concentrate should be diluted with 0.9 % sodium chloride solution or 5 % glucose solution for intravenous use.

In patient with normal renal function:
Each single dose will be diluted with 100 to 250 ml of the above solutions and infused over 30 to 45 minutes as outlined in section 4.2.

In patient with impaired renal function:
For continuous infusion in patient undergoing haemodialysis, the concentrate may exceptionally be diluted in a reduced volume of the above solutions, in order to avoid fluid overload.

6.6 Special precautions for disposal and other handling

Only clear and colourless solution without visible particles should be used.

For single use only. Any unused product must be discarded.

Fomepizole SERB 5 mg/ml, concentrate for solution for infusion, is to be diluted before use. Preparation of solution for infusion must take place in aseptic conditions.

The concentrate should be diluted with 0.9 % sodium chloride solution or 5 % glucose solution for intravenous use.

In patient with normal renal function :
Each single dose will be diluted with 100 to 250 ml of the above solutions and infused over 30 to 45 minutes as outlined in section 4.2.

In patient with impaired renal function :
For continuous infusion in patient undergoing hemodialysis, the concentrate may exceptionally be diluted in a reduced volume of the above solutions, in order to avoid fluid overload.

7 MARKETING AUTHORISATION HOLDER

SERB S.A.,
Avenue Louise 480
1050 Brussels
Belgium

8 MARKETING AUTHORISATION NUMBER

PA20595/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11/10/2002
Date of latest renewal: 21/09/2010

10 DATE OF REVISION OF THE TEXT

October 2019