1 PRODUCT NAME

Flumazenil 0.1mg/mL

Flumazenil 0.5 mg per 5 mL, solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Flumazenil 0.5 mg per 5 mL.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection.

Benzodiazepine antagonist.

Flumazenil ampoules contain 0.5 mg flumazenil in 5 mL aqueous solution for intravenous (IV) administration. Flumazenil is a colourless to almost-colourless, sterile, clear liquid stored in 5 mL glass ampoules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Flumazenil is indicated for reversal of the centrally sedative effects of benzodiazepines. It should therefore be used in anaesthesia and intensive care in the following indications:

In anaesthesia

- Termination of general anaesthesia induced and maintained with benzodiazepines in inpatients.
- Reversal of benzodiazepine sedation in short diagnostic and therapeutic procedures in both inpatients and outpatients.
- Reversal of paradoxical reactions due to benzodiazepines.

In intensive care and in the management of unconsciousness of unknown origin

- For the diagnosis and/or management of benzodiazepine overdose due to self-poisoning or accidental overdose.
- As a diagnostic measure in unconsciousness of unknown origin to differentiate between involvement of benzodiazepines, other medicines or drugs or brain damage.
- Flumazenil may also be used for specific reversal of the central effects of benzodiazepines in drug or medicine overdose (return to spontaneous respiration and consciousness in order to render intubation unnecessary or allow extubation).

4.2 Dose and method of administration

Flumazenil is recommended for intravenous (IV) use only and should be administered by an anaesthesiologist or experienced physician.

For instructions on handling flumazenil, see section 6 Pharmaceutical Particulars.

Dosage should be titrated for the intended effect. Since the duration of action of some benzodiazepines may exceed that of flumazenil, repeated doses may be required if sedation recurs following awakening.

In anaesthesia
The recommended initial dose of flumazenil is 0.2 mg administered IV over 15 seconds. If the desired degree of consciousness is not obtained within 60 seconds, a second dose of 0.1 mg can be injected; this may be repeated at 60-second intervals where necessary, up to a total dose of 1 mg. The usual dose is 0.3-0.6 mg, but individual requirements may vary considerably, depending on the dose and duration of effect of the benzodiazepine administered and patient characteristics.

In intensive care and in the management of unconsciousness of unknown origin
The recommended initial dose of flumazenil is 0.3 mg IV. If the desired level of consciousness is not obtained within 60 seconds, flumazenil may be injected repeatedly until the patient awakes or up to a total dose of 2 mg. If drowsiness recurs, flumazenil may be administered as one or more bolus IV doses as above, or as an IV infusion of 0.1-0.4 mg per hour. The rate of infusion should be individually adjusted to the desired level of arousal.

If a significant improvement in consciousness or respiratory function is not obtained after repeated doses of flumazenil, a non-benzodiazepine aetiology must be assumed.

In the intensive care unit, in patients treated with high doses of benzodiazepines and/or for long periods of time, the individually titrated injections of flumazenil, slowly administered, should not produce withdrawal syndromes. If unexpected symptoms occur, diazepam or midazolam could be carefully titrated intravenously according to patient response (see section 4.4Warnings and Precautions).

Special dosage instructions
Children >1 year-of-age
For the reversal of conscious sedation induced with benzodiazepines in children above one year-of-age, the recommended initial dose is 0.01 mg/kg (up to 0.2 mg) administered IV over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, further injections of 0.01 mg/kg (up to 0.2 mg) can be administered and repeated at 60 second intervals where necessary (up to a maximum of four additional times) to a maximum total dose of 0.05 mg/kg or 1 mg, whichever is lower. The dose should be individualised based on patient response. No data are available on the safety and efficacy of repeated administration of flumazenil to children for re-sedation.

Hepatic Impairment
Since flumazenil is primarily metabolised in the liver, careful titration of dosage is recommended in patients with impaired hepatic function.

4.3 Contraindications

Flumazenil is contraindicated in patients with known hypersensitivity to the medicine.

Flumazenil is contraindicated in patients who have been given a benzodiazepine for control of a potentially life-threatening condition (e.g. control of intracranial pressure or status epilepticus).

4.4 Special warnings and precautions for use

General

Particular caution is necessary when using flumazenil in cases of mixed-substance overdose since the toxic effects (such as convulsions and cardiac dysrhythmias) of other medicines taken in overdose (especially cyclic antidepressants) may emerge with the reversal of benzodiazepine effects by flumazenil.

The use of flumazenil is not recommended in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Although flumazenil exerts a slight intrinsic anticonvulsant effect, its abrupt suppression of the protective effect of a benzodiazepine agonist can give rise to convulsions in epileptic patients.

Patients who have received flumazenil for the reversal of benzodiazepine effects should be monitored for resedation, respiratory depression or other residual benzodiazepine effects for an appropriate period based on the dose and duration of effect of the benzodiazepine employed. As patients with underlying hepatic impairment may experience delayed benzodiazepine effects, an extended observation period may be required.

When flumazenil is used with neuromuscular-blocking agents, it should not be injected until the effects of neuromuscular blockade have been fully reversed.

Flumazenil should be used with caution in patients with head injury as it may be capable of precipitating convulsions or altering cerebral blood flow in patients receiving benzodiazepines.

Rapid injection of flumazenil should be avoided in patients with high dose and/or long-term exposure to benzodiazepines ending at any time within the weeks preceding flumazenil administration as it may produce withdrawal symptoms, including agitation, anxiety, emotional lability as well as mild confusion and sensory distortions (see section 4.2 Dosage and Administration).

Flumazenil is not recommended either as a treatment for benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndromes.

Flumazenil should be used with caution for the reversal of conscious sedation in children below the age of one year, for the management of overdose in children, for resuscitation of the newborn and for reversal of the sedative effects of benzodiazepines used for induction of general anaesthesia in children, as experience is limited (see section 4.2 Dosage and Administration).

4.5 Interaction with other medicines and other forms of interaction

Flumazenil blocks the central effects of benzodiazepines by competitive interaction at the receptor level. The effects of non-benzodiazepine agonists at benzodiazepine receptors, such as zopiclone, triazolopyridazines and others, are also blocked by flumazenil.

The pharmacokinetics of benzodiazepine agonists are unaltered in the presence of flumazenil and vice versa.

There is no pharmacokinetic interaction between ethanol and flumazenil.

4.6 Fertility, pregnancy and lactation

Pregnancy
Although *in-vitro* and animal studies using high doses of flumazenil have not shown evidence of mutagenicity, teratogenicity or impairment of fertility, the safety of flumazenil in human pregnancy has not been established. Therefore, the benefits of medication during pregnancy should be weighed against possible risks to the foetus.

Breast-feeding
Parenteral administration of flumazenil in emergencies is not contraindicated during lactation.

Fertility
No data available.

4.7 Effects on ability to drive and use machines

Patients should be warned against engaging in hazardous activities requiring complete mental alertness (such as operating dangerous machinery or driving a motor vehicle) during the first 24 hours after administration, since the effect of the originally ingested or administered benzodiazepine (for example, sedation) may occur.

4.8 Undesirable effects

Post-Marketing
Flumazenil is well tolerated in adults and children. In adults, flumazenil is well tolerated even at doses exceeding those recommended.

Hypersensitivity reactions, including anaphylaxis, have been observed.

Complaints such as feelings of anxiety, palpitations and fear have been infrequently observed after rapid injection of flumazenil. These adverse effects usually do not necessitate special treatment.

Seizures have been reported in patients known to suffer from epilepsy or severe hepatic impairment, particularly after long-term treatment with benzodiazepines or in cases of mixed-substance overdose.

In cases of mixed-substance overdose, particularly with cyclic antidepressants, toxic effects (such as convulsions and cardiac dysrhythmias) may emerge with the reversal of benzodiazepine effects by flumazenil.

Withdrawal symptoms may occur following rapid injection of flumazenil in patients with long-term exposure to benzodiazepines ending at any time within the weeks preceding flumazenil administration.

Flumazenil has been reported to provoke panic attacks in patients with a history of panic disorders.

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

4.9 Overdose

There is very limited experience of acute overdose in humans with flumazenil.

There is no specific antidote for overdose with flumazenil. Treatment of an overdose with flumazenil should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

Even when given at doses exceeding those recommended, no symptoms of overdosage were observed. For withdrawal symptoms attributable to the agonist, see section 4.2 Dosage and Administration.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products, Antidotes.
ATC code: V03AB25

Mechanism of action
Flumazenil, an imidazobenzodiazepine derivative, is a benzodiazepine antagonist. It competitively inhibits agents that act via benzodiazepine receptors, specifically blocking their central nervous effects. In animal experiments, the effects of compounds showing affinity for benzodiazepine receptors were blocked. In healthy volunteers, IV flumazenil has been shown to antagonise the sedation, amnesia and psychomotor impairment produced by benzodiazepine agonists. Hypnotic-sedative benzodiazepine effects are rapidly reversed by flumazenil after IV injection (1-2 minutes) and may then reappear gradually within the next few hours depending on the half-life and dose ratio of the agonist and antagonist.

Flumazenil may possess some weak intrinsic agonistic (e.g. anticonvulsant) activity.

In animals pre-treated with high doses of benzodiazepines over several weeks**,** flumazenil elicited symptoms of benzodiazepine withdrawal, including seizures. A similar effect was seen in adult human subjects.

5.2 Pharmacokinetic properties

Absorption
The pharmacokinetics of flumazenil are dose-proportional within and above the therapeutic range (up to 100 mg).

Distribution
Flumazenil, a weak lipophilic base, is about 50% bound to plasma proteins. Albumin accounts for two-thirds of plasma protein binding. Flumazenil is extensively distributed in the extravascular space. Plasma concentrations of flumazenil decrease with a half-life of 4-11 minutes during the distribution phase. The volume of distribution at steady state is 0.9-1.1 L/kg.

Metabolism
Flumazenil is extensively metabolised in the liver. The carboxylic acid metabolite is the main metabolite in plasma (free form) and urine (free form and its glucuronide). This main metabolite shows no benzodiazepine agonist or antagonist activity in pharmacological tests.

Elimination
Flumazenil is almost completely (99%) eliminated by non-renal routes. Practically no unchanged flumazenil is excreted in the urine, suggesting complete metabolic degradation of the medicine. Elimination of radiolabelled substance is essentially complete within 72 hours, with 90-95% of the radioactivity appearing in urine and 5-10% in the faeces. Elimination is rapid, as shown by a short elimination half-life of 40-80 minutes. The total plasma clearance of flumazenil is 0.8-1.0 L/hr/kg and can be attributed almost entirely to hepatic clearance.

Ingestion of food during an intravenous infusion of flumazenil results in a 50% increase in clearance, most likely due to the increased hepatic blood flow that accompanies a meal.

Pharmacokinetics in special populations
In patients with impaired liver function, the elimination half-life of flumazenil is longer (1.3 hours in moderate impairment and 2.4 hours in severely impaired patients) and the total body clearance is lower than in healthy subjects. The pharmacokinetics of flumazenil are not significantly affected in the elderly, by gender, haemodialysis or renal failure.

The elimination half-life in children over one year of age is more variable than in adults, averaging 40 minutes and generally ranging from 20-75 minutes. Clearance and volume of distribution, normalised for body weight, are in the same range as is seen in adults.

5.3 Preclinical safety data
Late prenatal as well as per- and postnatal exposure to flumazenil induced both behavioural alterations and an increase of hippocampal benzodiazepine receptor density in the rat offspring. The effect of these findings is not considered relevant if the product is used for a very short time as instructed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Disodium edetate
Glacial acetic acid
Sodium chloride
Sodium hydroxide (for pH-adjustment)
Sterile 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.

Shelf life after first opening
After first opening the medicinal product should be used immediately.

Shelf life after dilution
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 conditions.

6.4 Special precautions for storage

Store below 25°C.

Do not freeze. Keep the ampoules in the outer carton in order to protect from light.

For storage conditions after dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

Box of 5 x 5 mL or 10 x 5 mL ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product is for single use only and any unused solution should be discarded.

Please inspect the medicinal product visually. It should only be used if the solution is clear and practically free from particles.

When flumazenil is to be used in infusion, it must be diluted prior to infusion.

Flumazenil should only be diluted with sodium chloride 9 mg/ml (0.9%) solution, dextrose 50 mg/ml (5%) solution or sodium chloride 4.5 mg/ml (0.45%) + dextrose 25 mg/ml (2.5%) solution (10, 20, 50 ml Flumazenil 0.1 mg/ml in 500 ml solution). Compatibility between flumazenil and other solutions for injection has not been established.

Intravenous infusion solutions should be discarded after 24 hours.

Any unused medicine should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Max Health Ltd, PO Box 65 231, Mairangi Bay, Auckland 0754

Ph:(09) 815 2664.

9 DATE OF FIRST APPROVAL

24 September 2015

10 DATE OF REVISION OF THE TEXT

19 December 2017

SUMMARY TABLE OF CHANGES

Date of Revision	Section Changed	Summary of new information
19 December 2017	All	Updated to SPC format.