PROFESSIONAL INFORMATION

SCHEDULING STATUS S5

1 NAME OF THE MEDICINE

FLUMAZENIL 0,5 mg/5 mL FRESENIUS

FLUMAZENIL 1,0 mg/10 mL FRESENIUS

Solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of ampoule solution contains 0,1 mg flumazenil

Each 5 mL ampoule contains 0,5 mg flumazenil

Each 10 mL ampoule contains 1,0 mg flumazenil

Excipient(s) with known effect

FLUMAZENIL FRESENIUS contains approximately 3,7 mg sodium per mL of flumazenil solution for injection/infusion (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/ infusion

Clear and colourless solution, free from visible particles

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult patients

FLUMAZENIL FRESENIUS is indicated for the reversal of the sedative effects of benzodiazepines in cases where general anaesthesia has been induced and/or maintained with benzodiazepines, where sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures, and for the management of benzodiazepine overdose.

4.2 Posology and method of administration

Posology

Reversal of general anaesthesia in adult patients

For the reversal of the sedative effects of benzodiazepines administered for general anaesthesia, the recommended initial dose of FLUMAZENIL FRESENIUS is 0,2 mg (2 mL) administered intravenously over 15 seconds.

If the desired level of consciousness is not obtained after waiting an additional 45 seconds, a further dose of 0,2 mg (2 mL) can be injected and repeated at 60-second intervals where necessary (up to a maximum of 4 additional times) to a maximum total dose of 1 mg (10 mL). The dosage should be individualised based on the patient's response, with most patients responding to doses of 0,6 mg to 1 mg.

In the event of re-sedation, repeated doses may be administered at 20-minute intervals as needed. For repeat treatment, no more than 1 mg (given as 0,2 mg/min) should be administered at any one time, and no more than 3 mg should be given in any one hour.

It is recommended that FLUMAZENIL FRESENIUS be administered as the series of small injections described (not as a single bolus injection) to allow the practitioner to control the

reversal of sedation to the approximate endpoint desired and to minimise the possibility of adverse effects. See section 4.4.

Method of administration

FLUMAZENIL FRESENIUS is recommended for intravenously administration only.

To minimise the likelihood of pain at the injection site, FLUMAZENIL FRESENIUS should be administered through a freely running intravenous infusion into a large vein.

For instructions on dilution of the medicine before administration, see section 6.6. If FLUMAZENIL FRESENIUS is drawn into a syringe or mixed with any of the solutions, it should be discarded after 24 hours.

It may be used concomitantly with other resuscitative measures.

FLUMAZENIL FRESENIUS should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

4.3 Contraindications

- Hypersensitivity to flumazenil or to any of the excipients of FLUMAZENIL FRESENIUS listed in section 6.1.
- Patients receiving benzodiazepines for control of a potentially life-threatening condition (e.g. control of intracranial pressure or status epilepticus).

Safety of FLUMAZENIL FRESENIUS during pregnancy and lactation has not been established. See section 4.6.

4.4 Special warnings and precautions for use

Patients who have received FLUMAZENIL FRESENIUS for the reversal of benzodiazepine effects (after conscious sedation or general anaesthesia) should be monitored for re-sedation, respiratory depression, or other residual benzodiazepine

effects for an appropriate period (up to 120 minutes) based on the dose and duration of effect of the benzodiazepine employed. Because patients with hepatic impairment may experience delayed effects as described above, an extended observation period may be required.

- Seizures have been reported, especially in patients known to suffer from epilepsy or severe hepatic impairment, particularly after long-term treatment with benzodiazepines or in the cases of mixed-medicine overdose. The use of FLUMAZENIL FRESENIUS is not recommended in epileptic patients who have been on benzodiazepine treatment for a prolonged period.

  Although FLUMAZENIL FRESENIUS 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.

  Particular caution is necessary when using FLUMAZENIL FRESENIUS in cases of mixed-medicine overdose. In particular in the case of an intoxication with benzodiazepines and cyclic antidepressants, certain toxic effects such as convulsions and cardiac dysrhythmias, which are caused by these antidepressants, but which emerge less readily on concomitant administration with benzodiazepines, are exacerbated on administration of FLUMAZENIL FRESENIUS. Practitioners should individualise the dosage of FLUMENAZIL FRESENIUS and be prepared to manage seizures.
- Rapid injection of FLUMAZENIL FRESENIUS should be avoided. In patients with high dose and/or long-term exposure to benzodiazepines ending at any time within the weeks preceding FLUMAZENIL FRESENIUS administration, rapid injection of doses equal to or higher than 1 000 micrograms has led to withdrawal symptoms, including palpitations, agitation, anxiety, emotional lability as well as mild confusion and sensory distortions.

- Panic attacks have been reported after the use of flumazenil as in FLUMAZENIL FRESENIUS in patients with a history of panic disorder.
- FLUMAZENIL FRESENIUS may not fully reverse postoperative airway problems or ventilatory insufficiency induced by benzodiazepines. In addition, even if FLUMAZENIL FRESENIUS is initially effective, such problems may recur because the effects of FLUMAZENIL FRESENIUS wear off before the effects of many benzodiazepines.
- FLUMAZENIL FRESENIUS should be used with caution in patients with head injury as it may be capable of precipitating convulsions or altering blood flow in patients receiving benzodiazepines.
- In patients with severe brain injury (and/or instable intracranial pressure), receiving flumazenil as in FLUMAZENIL FRESENIUS (to reverse the effects of benzodiazepines), an increased intracranial pressure may develop.
- FLUMAZENIL FRESENIUS is not recommended either as a treatment for benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndromes, as such use has not been studied.
- Elimination may be delayed in patients with hepatic impairment.
- The patient should be monitored for an adequate period of time based on the dose and duration of effect of the benzodiazepine employed (ECG, pulse, oximetry, patient alertness and other vital signs such as heart rate, respiratory rate and blood pressure).
- The antagonistic effect of flumazenil as in FLUMAZENIL FRESENIUS is specific to benzodiazepines; an effect is therefore not to be expected if the 'non-awakening' is caused by other substances.
- When used in anaesthesiology at the end of surgery, FLUMAZENIL FRESENIUS should not be given until the effects of peripheral muscle relaxants have been fully reversed.

- As the action of flumazenil as in FLUMAZENIL FRESENIUS is usually shorter than that of benzodiazepines and sedation may possibly recur, the patient should remain closely monitored, preferably in the intensive care unit, until the effect of flumazenil has presumably worn off.
- In high-risk patients, the benefits of benzodiazepine-induced sedation should be weighed against the risks of rapid awakening. In patients (e.g. with cardiac problems) maintenance of a certain level of sedation may be preferable to being fully awake.
- In patients suffering from pre-operative anxiety or having a history of chronic or episodic anxiety the dosage of FLUMAZENIL FRESENIUS should be adjusted carefully.
- After major surgery, postoperative pain must be considered and it may be preferable to keep the patient lightly sedated.
- In patients treated for long periods with high doses of benzodiazepines, the advantages of the use of flumazenil as in FLUMAZENIL FRESENIUS should be weighed against the risk of withdrawal symptoms. If withdrawal symptoms occur despite careful dosing, individually titrated low doses of benzodiazepines (diazepam or midazolam) should be given by slow intravenous injection.
- Due to the increased frequency of benzodiazepines tolerance and dependence in patients with alcoholism and other medicine dependencies, flumazenil should be used with caution in its population.

Sodium content

FLUMAZENIL FRESENIUS contains approximately 3,7 mg sodium per mL of flumazenil solution for injection.

Each 5 mL ampoule of the product contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium-free'.

Each 10 mL ampoule of the product contains 37 mg sodium, equivalent to 2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Flumazenil as in FLUMAZENIL FRESENIUS blocks the central effects of benzodiazepines by means of competitive interaction at receptor level. The effects of non-benzodiazepine agonists acting via the benzodiazepine receptor, such as zopiclone, triazolopyridazine and others, are also blocked by FLUMAZENIL FRESENIUS. However, FLUMAZENIL FRESENIUS does not block the effect of medicines that do not operate via this route. Interaction with other central nervous system depressants has not been observed.

Caution is necessary when using FLUMAZENIL FRESENIUS in cases of accidental overdose since the toxic effects of other psychotropic medicines (especially tricyclic antidepressants) taken concurrently may increase with the subsidence of the benzodiazepine effect.

The pharmacokinetics of flumazenil as in FLUMAZENIL FRESENIUS are unaltered in combination with the benzodiazepines midazolam, flunitrazepam and lormetazepam.

The pharmacokinetics of benzodiazepines are unaltered in the presence of the antagonist FLUMAZENIL FRESENIUS.

There is no pharmacokinetic interaction between ethanol and FLUMAZENIL FRESENIUS.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of FLUMAZENIL FRESENIUS during pregnancy has not been established.

Breastfeeding

Safety of FLUMAZENIL FRESENIUS during breastfeeding has not been established.

It is not known whether flumazenil is excreted in human milk. Therefore, breastfeeding should be interrupted for 24 hours when FLUMAZENIL FRESENIUS is used during lactation.

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

Tabulated summary of adverse reactions

Immune systems disorders	
Frequent:	Allergic reactions
Less frequent:	Severe hypersensitivity reactions, including anaphylaxis.
Psychiatric disorders	
Frequent:	Anxiety following rapid injection, emotional lability, insomnia, somnolence
Less frequent:	Fear
Frequency unknown:	Withdrawal symptoms (e.g., agitation, anxiety, confusion, sensory distortions, tachycardia, dizziness, sweating), following rapid injection of doses of 1 mg or more in patients with high dose and/or long-term exposure to benzodiazepines ending at any time within the weeks preceding FLUMAZENIL

	FRESENIUS administration (see section 4.4), panic attacks (in patients with a history of panic reactions), abnormal crying, agitation, aggressive reactions.
Nervous system disorders	
Frequent:	Vertigo, headache, agitation following rapid injection, tremor, dry mouth, hyperventilation, speech disorder, paraesthesia
Less frequent:	Convulsions in patients suffering epilepsy or severe hepatic insufficiency, mainly after long-term treatment with benzodiazepines or multiple medicines abuse – see section 4.4).
Eye disorders	
Frequent:	Abnormal vision (diplopia, visual field defects), strabismus, increased lacrimation
Ear and labyrinth disorders	
Less frequent:	Abnormal hearing (transient hearing impairment, hyperacusis, tinnitus)
Cardiac disorders	
Frequent:	Palpitations following rapid injection.
Less frequent:	Tachycardia, bradycardia, dysrhythmia (atrial, nodal, ventricular, extrasystoles), chest pain
Vascular disorders	
Frequent:	Flushing, hypotension, orthostatic hypotension, transient increased blood pressure (on awakening)
Less frequent:	Hypertension

Respiratory, thoracic and mediastinal disorders	
Less frequent:	Dyspnoea, cough, nasal congestion, chest pain
Gastrointestinal disorders	
Frequent:	Nausea (during anaesthesia), vomiting (during anaesthesia), hiccup
Skin and subcutaneous tissue disorders	
Frequent:	Sweating
General disorders and administration site conditions	
Frequent:	Injection site pain
Less frequent:	Shivering, rigors
Frequency unknown:	Fatigue (asthenia, malaise), injection site pain, injection site reaction (thrombophlebitis, skin abnormality, rash)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

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

For withdrawal symptoms attributable to agonists, the intravenous use of other benzodiazepines is indicated.

There is no specific antidote for overdose with FLUMAZENIL FRESENIUS. Treatment of an overdose is symptomatic and supportive.

Reversal with an excessively high dose of FLUMAZENIL FRESENIUS may produce anxiety, agitation, increased muscle tone, hyperesthesia and possibly convulsions. Convulsions have been treated with barbiturates, benzodiazepines and phenytoin, generally with prompt resolution of the seizures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category A: 34 - Others.

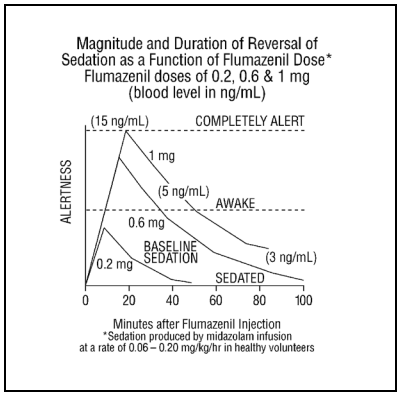
Pharmacotherapeutic group: All other therapeutic products, Antidotes.

ATC code: V03A B25

Flumazenil, an imidazobenzodiazepine derivative, is a benzodiazepine antagonist. It competitively inhibits medicines that act via benzodiazepine receptors, specifically blocking their central nervous effects. It antagonises the sedation, amnesia and psychomotor impairment produced by benzodiazepine agonists.

Hypnotic-sedative benzodiazepine effects may reappear gradually, 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 vitro*. Flumazenil may elicit symptoms of benzodiazepine withdrawal, including seizures.

The duration and degree of reversal of sedative benzodiazepine effects are related to the dose and plasma concentrations of flumazenil as shown in the following data from a study in normal volunteers.



Generally, doses of approximately 0,1 mg to 0,2 mg (corresponding to peak plasma levels of 3 to 6 ng/mL) produce partial antagonism, whereas higher doses of 0,4 to 1 mg (peak plasma levels of 12 to 28 ng/mL) usually produce complete antagonism in patients who have received the usual sedating doses of benzodiazepines. The onset of reversal is usually evident within 1 to 2 minutes after the injection is completed. Eighty percent response will be reached within 3 minutes, with the peak effect occurring at 6 to 10 minutes. The duration and degree of reversal are related to the plasma concentration of the sedating benzodiazepine as well as the dose of flumazenil given.

5.2 Pharmacokinetic properties

Distribution

Flumazenil, a weak lipophilic base, is about 50 % bound to plasma proteins. Albumin accounts for two thirds of the plasma protein binding. FLUMAZENIL FRESENIUS is extensively distributed in the extravascular space. Plasma concentrations of FLUMAZENIL FRESENIUS 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.

Biotransformation

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 nonrenal routes. Elimination is rapid, as shown by a short elimination half-life of 40 – 80 minutes (mean 53 minutes). The total plasma clearance is on average 0,8 – 1,0 L/hr/kg and can be attributed almost entirely to hepatic clearance. Practically no unchanged flumazenil is excreted in the urine, suggesting complete metabolic degradation of the medicine. Elimination of radiolabelled medicine is essentially complete within 72 hours, with 90 – 95 % of the radioactivity appearing in the urine and 5 - 10 % in the faeces.

Linearity/non-linearity

The pharmacokinetics of flumazenil is dose–proportional within, and above, the therapeutic range (up to 100 mg).

Special populations

In patients with impaired liver function, the elimination half-life of flumazenil is longer, and the total body clearance lower, than in healthy persons.

The pharmacokinetics of flumazenil is not significantly affected in the elderly, by gender, renal failure, or haemodialysis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate

Acetic acid (99 %)

Sodium chloride

Sodium hydroxide 1N (for pH-adjustment)

Water for injection

6.2 Incompatibilities

FLUMAZENIL FRESENIUS must not be mixed with other medicines except for those mentioned in section 6.6.

6.3 Shelf life

3 years

Shelf life after first opening

After first opening the medicine 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 microbial point of view the product should be used immediately once diluted. 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 at or 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

Flumazenil Fresenius 0,5 mg/5 mL: Carton boxes with 5 or 10 clear colourless neutral Type I glass ampoules containing 5 mL solution.

Flumazenil Fresenius 1,0 mg/10 mL: Carton boxes with 5 or 10 clear colourless neutral Type I glass ampoules containing 10 mL solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

FLUMAZENIL FRESENIUS is for single use only and any unused solution should be discarded.

When FLUMAZENIL FRESENIUS is to be used in infusion, it must be diluted prior to infusion. For optimum sterility, FLUMAZENIL FRESENIUS should remain in the ampoule until just before use.

Please inspect the medicine visually. It should only be used if the solution is clear and practically free from particles prior to administration.

It is compatible with dextrose 5 %, sodium chloride 0,9 %, Ringer's lactate or sodium chloride 0,45 % + dextrose 2,5 % solutions. No preparations other than those recommended should be added to the ampoule contents or mixed with the infusion solution.

If FLUMAZENIL FRESENIUS is drawn into a syringe or mixed with any of the solutions, it should be discarded after 24 hours.

Compatibility between flumazenil and other solutions for injection has not been established.

Intravenous infusion solutions should be discarded after 24 hours.

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

FRESENIUS KABI SOUTH AFRICA (PTY) LTD

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House, Extension 7

Midrand, Gauteng

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SOUTH AFRICA

Telephone number: +27 (0)11 545 0000

8. REGISTRATION NUMBER(S)

Flumazenil 0,5 mg/5 ml Fresenius: 46/34/0063

Flumazenil 1,0 mg/10 ml Fresenius: 46/34/0064

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 12 July 2022

10. DATE OF REVISION OF THE TEXT