B|BRAUN

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

FLUMAZENIL 5 ML B. BRAUN (0,5 mg/5 ml), solution for injection

FLUMAZENIL 10 ML B. BRAUN (1 mg/10 ml), solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 0,1 mg flumazenil.

FLUMAZENIL 5 ML B. BRAUN, solution for injection

1 ampoule with 5 mL contains 0,5 mg flumazenil.

FLUMAZENIL 10 ML B. BRAUN, solution for injection

1 ampoule with 10 mL contains 1 mg flumazenil.

Excipient with known effect: Sodium 3,7 mg/mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear colourless solution

pH 3.9 - 5.0

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adult patients

FLUMAZENIL B. BRAUN 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 B. BRAUN 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 B. BRAUN 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

If FLUMAZENIL B. BRAUN is drawn into a syringe or mixed with any of these solutions, it should be discarded after 24 hours. For optimum sterility, FLUMAZENIL B. BRAUN should remain in the ampoule until just before use. As with all parenteral medicines, FLUMAZENIL B. BRAUN should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

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

4.3. Contraindications

- Patients with known hypersensitivity to flumazenil or to any of the excipients of FLUMAZENIL B. BRAUN listed in section 6.1
- 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)
- Safety of FLUMAZENIL B. BRAUN during pregnancy and lactation has not been established (see section 4.6).

4.4. Special warnings and precautions for use

Flumazenil specifically reverses the effects of benzodiazepines. Therefore, if the patient does not wake up after Flumazenil administration, another aetiology should be considered.

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).

When used in anaesthesiology at the end of surgery, flumazenil should not be given until the effects of peripheral muscle relaxants have been fully reversed.

As the action of flumazenil 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.

FLUMAZENIL B. BRAUN may not fully reverse postoperative airway problems or ventilatory insufficiency induced by benzodiazepines. In addition, even if FLUMAZENIL B. BRAUN is initially effective, such problems may recur because the effects of FLUMAZENIL B. BRAUN wear off before the effects of many benzodiazepines.

In patients at increased risk the advantages of sedation by means of benzodiazepines should be weighed against the drawbacks of rapid awakening.
In some patients (e.g. with cardiac problems) maintenance of a certain level of sedation may be preferable to being fully awake.

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 week preceding flumazenil administration, rapid injection of doses equal or higher than 1 mg has led to withdrawal symptoms, including palpitations, agitation, anxiety, emotional lability as well as mild confusion and sensory distortions.

In patients suffering from pre-operative anxiety or having a history of chronic or episodic anxiety the dosage of flumazenil should be adjusted carefully.

After major surgery postoperative pain must be taken into account, 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 should be weighed against the risk of withdrawal symptoms. If withdrawal symptoms occur despite careful dosing an individually titrated dose of 5 mg diazepam or 5 mg midazolam should be given by slow intravenous injection.

The use of the antagonist is not recommended in patients with epilepsy, who have been treated with benzodiazepines for a prolonged period of time. Although flumazenil has some intrinsic anti-epileptic effects, the abrupt antagonising effect can cause convulsions in patients with epilepsy.

In patients with serious brain damage (and/or instable intracranial pressure) receiving flumazenil — to reverse the effects of benzodiazepines — an increased intracranial pressure may develop.

Elimination may be delayed in patients with hepatic impairment.

Particular caution is necessary when using flumazenil in cases of mixed-drug 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. Practitioners should individualise the dosage of FLUMAZENIL B. BRAUN and be prepared to manage seizures.

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 (up to 120 minutes) based on the dose and duration of effect of the benzodiazepine employed.

Because patients with underlying hepatic impairment may experience delayed effects as described above, an extended observation period may be required.

Flumazenil is not recommended for the treatment of benzodiazepine-dependence or for the treatment of long-term benzodiazepine-abstinence-syndromes.

Panic attacks have been reported after the use of flumazenil in patients with a history of panic disorder.

Due to the increased frequency of benzodiazepines tolerance and dependence in patients with alcoholism and other drug dependencies, flumazenil should be used with caution in this population.

This medicine contains 3,7 mg of sodium per mL.

4.5 Interaction with other medicines and other forms of interaction

Flumazenil reverses 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 antagonised by flumazenil. However, flumazenil 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.

Particular caution is necessary when using flumazenil 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.
No change in the pharmacokinetics of flumazenil has been observed in combination with the benzodiazepines midazolam, flunitrazepam and lormetazepam.

Flumazenil does not affect the pharmacokinetics of these benzodiazepines.

There is no pharmacokinetic interaction between ethanol and flumazenil.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of FLUMAZENIL B. BRAUN during pregnancy has not been established

Breastfeedinq

Safety of FLUMAZENIL B. BRAUN during breastfeeding has not been established. It is unknown whether flumazenil is excreted in human milk. For this reason, breast-feeding should be discontinued for 24 hours during treatment with flumazenil.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Patients who have received flumazenil to reverse the effects of benzodiazepine sedation should be warned not to drive, to operate machinery or to engage in other activities demanding physical or mental exertion for at least 24 hours, since the effect of the benzodiazepine may return.

4.8 Undesirable effects

Tabulated list of adverse reactions:

System organ class	
Immune system disorders	Frequency not known: Allergic reactions, including anaphylaxis may occur.
Psychiatric disorders	Frequent: insomnia, somnolence. Less frequent: Anxiety*, fear* Frequency not known: Withdrawal symptoms (e.g., agitation, anxiety, emotional lability, confusion, sensory distortions), 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 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*, tremor, dry mouth, hyperventilation, speech disorder, paraesthesia. Less frequent: Confusion (difficulty concentrating, delirium) Frequency not known: Seizures, particularly in patients known to suffer from epilepsy or severe hepatic impairment, mainly after long-

	term treatment with benzodiazepines or in case of mixed-drug overdose (see section 4.4).
Eye disorders	Frequent: Diplopia, strabismus, lacrimation increased.
Ear and labyrinth disorders	Less frequent: Abnormal hearing (transient hearing impairment, hyperacusis, tinnitus)
Cardiac disorders	Less frequent: Palpitations*, tachycardia or bradycardia, dysrhythmia (extrasystole, atrial, nodal, ventricular), hypertension
Vascular disorders	Frequent: Hypotension, orthostatic hypotension Frequency not known: Transient increased blood pressure (on awakening)
Respiratory, thoracic and mediastinal disorders	Frequent: Dyspnoea, cough, nasal congestion, chest pain.
Gastrointestinal disorders	Frequent: Nausea and vomiting during post-operative use, particularly if opiates have also been used, hiccup
Skin and subcutaneous tissue disorders	Frequent: Sweating Frequency not known: Flushing
General disorders and administration site conditions	Frequent: Fatigue, injection site pain. Less frequent: Shivering*, rigors

* after rapid injection, not requiring treatment

Reporting of suspected adverse reactions:

Reporting suspected adverse reaction after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://sahpra.org.za/Publications/Index/8.

4.9 Overdose

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

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

There is no specific antidote for overdose with Flumazenil. Treatment is symptomatic and supportive and should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Even at dosages of 100 mg i.v., no symptoms of overdose were observed.

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

Reversal with an excessively high dose of FLUMAZENIL B. BRAUN may produce anxiety, agitation, increased muscle tone, hyperaesthesia 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

Class of Medicine: A.34 Others

Pharmacotherapeutic group: Antidotes

ATC code: V03A B25

Mechanism of action:

Flumazenil, an imidazobenzodiazepine, is a benzodiazepine antagonist which, by competitive interaction, blocks the effects of substances acting via the benzodiazepine receptor. Neutralisation of paradoxal reactions of benzodiazepines has been reported.

Pharmacodynamic effects:

According to experiments in animals, the effects of substances, which are not acting via the benzodiazepine-receptor (like barbiturates, GABA-mimetics and adenosine-receptor agonists), are not blocked by flumazenil. Non-benzodiazepine-agonists, like cyclopyrrolones (zopiclone) and triazolopyridazines, are blocked by flumazenil. The hypnosedative effects of benzodiazepines are blocked rapidly (within 1-2 minutes) after intravenous administration.
Depending on the difference in elimination time between agonist and antagonist, the effect can recur after several hours. Flumazenil has possibly a slight agonistic, anticonvulsive effect.
Flumazenil caused withdrawal, including convulsions in animals receiving long-term flumazenil treatment.

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 is a lipophilic weak base. Flumazenil is bound for approximately 50 % to plasma proteins, from which two thirds are bound to albumin. Flumazenil is extensively divided over extra vascular space. During the distribution phase plasma concentration of flumazenil decreases with a half-life of 4-11 minutes. The distribution volume under steady-state conditions (Vss) is 0,9 — 1,1 l/kg.

Biotransformation:

Flumazenil is mainly eliminated through hepatic metabolism. The carboxylic acid metabolite was shown in plasma (in free form) and in urine (in free and conjugated form) to be the most important metabolite. In pharmacological tests this metabolite has proved to be inactive as benzodiazepine agonist or antagonist.

Elimination:

Almost no unchanged flumazenil is excreted in the urine. This indicates a complete metabolic degradation of the active substance in the body. Radiolabelled medicine is completely eliminated within 72 hours, with 90 to 95 % of the radioactivity appearing in the urine and 5 to 10 % in the faeces. Elimination is rapid, as is shown by the short half-life of 40 to 80 minutes. The total plasma clearance of flumazenil is 0,8 to 1,0 l/hour/kg and can almost completely be attributed to hepatic metabolism.

The pharmacokinetics of flumazenil is dose-proportional within the therapeutic dose-range and up to 100 mg.

The intake of food during the intravenous infusion of flumazenil results in an increase of 50 % of the clearance probably due to postprandial increase in liver perfusion.

Pharmacokinetics in special patient groups

Elderly

The pharmacokinetics of flumazenil in elderly is not different from that in young adults.

Patients with impaired hepatic function

In patients with a moderately to severely impaired liver function the half-life of flumazenil is increased (increase of 70 — 210 %) and the total clearance is lower (between 57 and 74 %) compared to normal healthy volunteers.

Patients with impaired renal function

Pharmacokinetics of flumazenil is not different in patients with impaired renal function or patients undergoing haemodialysis compared to normal healthy volunteers.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate

Glacial acetic acid

Sodium chloride

Sodium hydroxide solution 4% for pH adjustment

Water for injections

6.2 Incompatibilities

This medicine must not be mixed with other medicine except for those mentioned in section 6.6.

6.3 Shelf life

3 years at 25 °C.

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 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 at or below 25 °C.

Keep in original container until required for use.

6.5 Nature and contents of container

FLUMAZENIL 5 ML B. BRAUN

Carton boxes with 5 or 10 ampoules (colourless glass Type I) containing 5 mL solution for Injection.

FLUMAZENIL 10 ML B. BRAUN

Carton boxes with 5 or 10 ampoules (colourless glass Type I) containing 10 mL solution for injection.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused solution should be discarded.

FLUMAZENIL B. BRAUN is recommended for intravenous use only. It is compatible with 5 % glucose in water, lactated Ringer's and normal saline solutions.

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

Intravenous infusion solutions should be discarded after 24 hours.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION:

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8. REGISTRATION NUMBER(S):

FLUMAZENIL 5 ML B. BRAUN – 49/34/0215

FLUMAZENIL 10 ML B. BRAUN - 49/34/0216

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION:

10 August 2022

10. DATE OF REVISION OF THE TEXT

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