1 Name of the medicinal product

Flumazenil 0.1 mg/ml solution for injection / infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 0.1 mg flumazenil.

1 ampoule with 5 ml contains 0.5 mg flumazenil.
1 ampoule with 10 ml contains 1 mg flumazenil.

Excipient: Sodium 3.73 mg / ml.

For a full list of excipients, see section 6.1.

3 Pharmaceutical form

- Solution for injection/infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Flumazenil is indicated for the complete or partial reversal of the central sedative effects of benzodiazepines. It may therefore be used in anaesthesia and in the intensive care in the following situations:

In anaesthesia
- Termination of hypnosedative effects in general anaesthesia induced and/or maintained with benzodiazepines in hospitalized patients.
- Reversal of benzodiazepine sedation in short-term diagnostic and therapeutic procedures in ambulatory patients and hospitalized patients.
- Reversal of paradoxical reactions due to benzodiazepines.
- For the reversal of conscious sedation induced with benzodiazepines in children >1 year of age.

In intensive care situations
- For the specific reversal of the central effects of benzodiazepines, in order to restore spontaneous respiration.
- For treatment of intoxications or overdose with only or mainly benzodiazepines.
- As a diagnostic measure in unconsciousness of unknown origin to differentiate between involvement of benzodiazepines, other medicines or drugs or brain damage.

4.2 Posology and method of administration

Posology

Adults:
Anaesthesia
The recommended starting dose is 0.2 mg administered intravenously over 15 seconds. If the required level of consciousness is not obtained within 60 seconds, a further dose of 0.1 mg can be injected and repeated at 60-second intervals, up to a maximum dose of 1.0 mg. The usual dose required lies between 0.3 and 0.6 mg, but may deviate depending on the patient's characteristics and the benzodiazepine used.

Intensive Care
The recommended initial dose of Flumazenil is 0.3 mg i.v. If the required level of consciousness is not obtained within 60 seconds, a further dose of 0.1 mg can be injected and repeated at 60-second intervals, up to a total dose of 2 mg or until the patient awakes.
If drowsiness recurs, an intravenous infusion of 0.1 – 0.4 mg/h may be useful.
The rate of infusion should be adjusted individually to achieve the desired level of consciousness.

If no clear effect on awareness and respiration is obtained after repeated dosing, it should be considered that the intoxication is not due to benzodiazepines.

Infusion should be discontinued every 6 hours to verify whether resedation occurs.

To avoid withdrawal symptoms in patients treated for a long period of time with high doses of benzodiazepines in the intensive care unit, the dosage of flumazenil has to be titrated individually and the injection has to be administered slowly (see section 4.4).

Elderly
In the absence of data on the use of flumazenil in elderly patients, it should be noted that this population is generally more sensitive to the effects of medicinal products and should be treated with due caution.

Paediatric population

Children above 1 year of age

For the reversal of conscious sedation induced with benzodiazepines in children >1 year of age, the recommended initial dose is 10 micrograms/kg (up to 200 micrograms) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, further injection of 10micrograms/kg may be administered (up to 200micrograms) and repeated at 60 second intervals where necessary (a maximum of 4 times) to maximum total dose of 50 micrograms/kg or 1mg, whichever is lower. The dose should be individualised based on the patient's response. No data available on the safety and efficacy of repeated administration of flumazenil to children for re-sedation.
Children under the age of 1 year
There are insufficient data on the use of flumazenil in children under 1 year.
Therefore flumazenil should only be administered in children under 1 year if the potential benefits to the patient outweigh the possible risk.

Patients with renal or hepatic impairment
Since flumazenil is primarily metabolized in the liver, careful titration of dosage is recommended in patients with impaired hepatic function. No dosage adjustments are required in patients with renal impairment.

Method of administration

Flumazenil should be administered intravenously by an anaesthetist or experienced physician.
Flumazenil may be administered as injection or as infusion (For instructions on dilution of the product before administration, see section 6.6).
Flumazenil may be used concomitantly with other resuscitative measures.
This medicinal product is for single use only. It should be inspected visually prior to use and should only be used if the solution is clear and practically free from particles.

4.3 Contraindications

- Hypersensitivity to flumazenil or to any of the excipients.

- Patients receiving benzodiazepines for the treatment of a potentially life-threatening condition (e.g. increased of intracranial pressure or status epilepticus).

- In mixed intoxications with benzodiazepines and tricyclic and/or tetracyclic antidepressants, the toxicity of the antidepressants can be masked by protective benzodiazepine effects.
In the presence of autonomic (anticholinergic), neurological (motor abnormalities) or cardiovascular symptoms of severe intoxication with tricyclics/tetracyclics, Flumazenil should not be used to reverse benzodiazepine effect.

4.4 Special warnings and precautions for use

Warnings:
- The patient should be monitored for an adequate period of time (ECG, pulse, oximetry, patient alertness and other vital signs such as heart rate, respiratory rate and blood pressure).
- The antagonistic effect of Flumazenil 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 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.
- In patients at increased risk the advantages of sedation by means of benzodiazepines should be weighed against the drawbacks of rapid awakening. In patients (e.g. with cardiac problems) maintenance of a certain level of sedation may be preferable to being fully awake.
- Rapid injection of high doses (more than 1 mg) flumazenil should be avoided in patients who receive chronic treatment with benzodiazepines as this may cause withdrawal symptoms.
- 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 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 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.
- 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 arrhythmias, which are caused by these antidepressants but which emerge less readily on concomitant administration with benzodiazepines, are exacerbated on administration of flumazenil.
- 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. 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.

Precautions

- 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.
- 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.

Paediatric population

- Because of the potential for resedation and respiratory depression children previously sedated with midazolam should be monitored at least 2 hours after flumazenil administration. In case of other sedating benzodiazepines, the monitoring time must be adjusted according to their expected duration.
- Use in children for other indications than reversal of conscious sedation is not recommended as no controlled studies are available. The same applies for children below the age of 1 year.
- Until sufficient data are available flumazenil should not be used in children of 1 year or younger unless the risks for the patient (especially in case of accidental overdose) have been weighed against the advantages of the therapy.

This medicinal product contains approximately 3.73 mg sodium per ml of flumazenil solution for injection. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products 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 medicinal products that do not operate via this route. Interaction with other central nervous system depressants has not been observed. The pharmacokinetics of benzodiazepines are not influenced by the antagonist Flumazenil. Particular caution is necessary when using flumazenil in cases of accidental overdose since the toxic effects of other psychotropic

medicinal products (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 Pregnancy and lactation

Although studies in animals have not shown evidence of embryo toxicity or teratogenicity, the possible risk to humans caused by flumazenil during pregnancy has not been determined (see section 5.3). Therefore, flumazenil should only be used during pregnancy if the possible benefit to the patient outweighs the potential risks for the foetus.
It is not known whether flumazenil is excreted in human milk. For this reason, breast-feeding should be interrupted for 24 hours when flumazenil is used during lactation.
Emergency use of flumazenil during pregnancy and lactation is not contra-indicated.

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

The adverse events below have been reported. Adverse events usually subside rapidly without the need for special treatment.
Frequency categories are defined using the following convention:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000), not known (cannot be estimated from the available data)

Immune systems disorders		
	Hypersensivity reactions, including anaphylaxis	Unknown
Psychiatric disorders	.	
	Anxiety, fear, following rapid injection, generally did not require treatment	Uncommon
	Withdrawal symptoms (e.g.,	Unknown

	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 (the side effect profile in children is generally similar to that in adults. When Flumazenil has been used for the reversal of conscious sedation, abnormal crying, agitation and aggressive reactions have been reported).	
Nervous system disorders		
	Seizures: particularly in patients known to suffer from epilepsy or severe hepatic impairment, mainly after long-term treatment with benzodiazepines or in cases of mixed-drug overdose (see section 4.4).	Unknown
Cardiac disorders		
	Palpitations, following rapid injection, generally did not require treatment.	Uncommon
Vascular disorders	Transient increased blood pressure (on awakening).	Unknown
Gastrointestinal disorders		
	Nausea, vomiting; during post-operative use, particularly if opiates have also been used.	Common
Skin and subcutaneous tissue disorders		
	Flushing	Unknown
General disorders and administration site conditions		
	Chills, following rapid injection, generally did not require treatment	Unknown

Paediatric population
In general the undesirable effect profile in children does not differ much from that in adults. When using flumazenil for the reversal of conscious sedation abnormal crying, agitation and aggressive reactions have been reported.

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 via the national reporting system listed in Appendix V

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 should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.
Even when administered intravenously at doses of 100 mg, no symptoms of overdose attributable to flumazenil have been observed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidotes.
ATC code: V03A B25

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.

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 (zopiclon) 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.

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 4-15 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 medicinal product 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.

Paediatric population
In children above one year old, the half life elimination is shorter and the variability is higher than in adults, approximately of 40 min with a range of 20 to 75 min. Clearance and volume of distribution, by kg of body weight are the same than 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
Hydrochloric acid 36% for pH adjustment
Sodium hydroxide for pH adjustment
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:
Do not refrigerate
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Carton boxes with 5 or 50 (10x5) ampoules (colourless glass Type I) containing 5 ml solution for injection.
Carton boxes with 5 or 50 (10x5) 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.

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 or dextrose 50 mg/ml (5 %) solution. Compatibility between flumazenil and other solutions for injection has not been established.

Intravenous infusion solutions should be discarded after 24 hours.

7 MARKETING AUTHORISATION HOLDER

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