Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flumazenil 0.1 mg/ml solution for injection

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 with known effect: Sodium 3.7 mg / ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

concentrate for solution for infusion
clear colourless solution
pH 3.9 – 5.0

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Flumazenil is indicated in adults 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.

In intensive care situations

- For the specific reversal of the central effects of benzodiazepines, in order to restore spontaneous respiration.
- For diagnosis and treatment of intoxications or overdose with only or mainly benzodiazepines.

Paediatric population
Flumazenil is indicated for the reversal of conscious sedation induced with benzodiazepines in children > 1 year of age.

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 starting dose is 0.3 mg administered intravenously. 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, a second bolus injection of flumazenil may be administered. 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
Infants and toddlers, children and adolescents (from 1 to 17 years)
For the reversal of conscious sedation induced by benzodiazepines in children older than 1 year the recommended starting dose is 0.01 mg/kg (up to 0.2 mg), administered intravenously over a period of 15 seconds. If, after a waiting period of 45 seconds, the required level of consciousness is not obtained a follow-up injection of 0.01 mg/kg (up to 0.2 mg) may be administered and where necessary repeated at 60-second intervals (up to a maximum of 4 times) to a maximum dose of 0.05 mg/kg or 1 mg, depending on which is the lowest dose. The dose should be adjusted to the patient's response. There are no data on safety and efficacy of repeated flumazenil administration in children in case of resedation.

Newborn infants, infants and toddlers 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
In patients with impaired hepatic function, the elimination of flumazenil may be delayed (see section 4.4 and 5.2) and therefore careful titration of dosage is recommended. 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 medicinal 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 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).

4.4 Special warnings and precautions for use

- 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).
- Flumazenil specifically reverses benzodiazepines. Therefore if the patient does not wake up, another aetiology should be considered.
- 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 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.
- Postoperative pain must be taken into account.
- 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 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.

- 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 medicinal product contains approximately 3.7 mg sodium per ml of flumazenil solution for injection. This should be taken into consideration by patients on a controlled sodium diet.

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.
- 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.
- Use in children for other indications than reversal of conscious sedation is not recommemded as no controlled studies are available. The same applies for children below the age of 1 year.

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. 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 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of flumazenil in pregnant women.Animal studies do not indicate reproductive toxicity(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.
Emergency use of flumazenil during pregnancy is not contra-indicated.

Breastfeeding
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.
Emergency use of flumazenil during 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

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
Common: Allergic reactions

Psychiatric disorders
Common: Emotional lability, insomnia, somnolence.
Uncommon: Anxiety*, fear*
Unknown: Withdrawal symptoms (e.g., agitation, anxiety, emotional lability, confusion, sensory distortions, tension, hallucinations), 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
Common: Vertigo, headache, agitation*, tremor, dry mouth, hyperventilation, speech disorder, paresthesia.
Unknown: 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
Common: Diplopia, strabismus, lacrimation increased.

Ear and labyrinth disorders
Uncommon: Abnormal hearing.

Cardiac disorders
Uncommon: Palpitations*, tachycardia or bradycardia, extrasystole.

Vascular disorders
Common: Hypotension, orthostatic hypotension,
Not known: Flushing, transient increased blood pressure (on awakening).

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, cough, nasal congestion, chest pain.

Gastrointestinal disorders
Common: Nausea and vomiting during post-operative use, particularly if opiates have also been used, hiccup.

Skin and subcutaneous tissue disorders
Common: Sweating

General disorders and administration site conditions
Common: Fatigue, injection site pain.
Uncommon: Shivering

*: after rapid injection, not requiring treatment

Paediatric population
In general the undesirable effect profile in children is generally similar to that in adults. When using flumazenil for the reversal of conscious sedation abnormal crying, agitation and aggressive reactions have been reported.

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 at dosages of 100 mg i.v., no symptoms of overdose were observed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 (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
The half life of flumazenil in children over the age of one is a little shorter and varies more than in adults and amounts to an average of 40 minutes (in general varying from 20 to 75 minutes). The clearance and the distribution volume, corrected for body weight, are the same as in adults.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

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 solution 4% 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:
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

Do not store above 25°C.

6.5 Nature and contents of container

Carton boxes with 5 or 10 ampoules (colourless glass Type I) containing 5 ml solution for injection.
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 of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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, 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 MARKETING AUTHORISATION HOLDER

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Carl-Braun-Strasse 1
34212 Melsungen
Germany

8 MARKETING AUTHORISATION NUMBER

PA736/25/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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