Summary of product characteristics

Flumazenil-hameln 0.1 mg/ml Injection

DESCRIPTION

Clear and colourless solution, free from visible particle

After dilution:

Clear and colourless solution

CONTENTS

Each ml contains 0.1 mg flumazenil.
One 5 ml ampoule contains 0.5 mg flumazenil.
One 10 ml ampoule contains 1 mg flumazenil.

Excipients

Disodium edetate, glacial acetic acid, sodium chloride, 1N sodium hydroxide solution, water for injections

PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products, 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 (such as barbiturates, GABA-mimetics and adenosine-receptor agonists), are not blocked by flumazenil. Non-benzodiazepine agonists like cyclopyrolones (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 effects 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.

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 extravascular 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 (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. Radiolabeled 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 due to 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.
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.

Children

In children above one year of age, the half life elimination is shorter and the variability is higher than in adults, approximately of 40 minutes (with a range of 20 to 75 minutes). Clearance and volume of distribution, by kg of body weight are the same as in adults.

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.

INDICATIONS

Flumazenil-hameln 0.1 mg/ml Injection is indicated for the complete or partial reversal of the central sedative effects of benzodiazepines. It may therefore be used in anaesthesia and in intensive care in the following situations:

In anaesthesia

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

In intensive care situations

- For diagnosis and treatment of intoxications or overdose with only or mainly benzodiazepines. (see special warnings and precautions for use)
- For the specific reversal of the central effects of benzodiazepines, in order to restore spontaneous respiration.

DOSAGE & ADMINISTRATION

Flumazenil-hameln 0.1 mg/ml Injection is to be administered intravenously by an anaesthetist or a doctor with experience in anesthesiology. Flumazenil-hameln 0.1 mg/ml Injection may be administered as an infusion. for instructions on dilution of the medicinal product before administration, (see special precautions for disposal and other handling)

Flumazenil-hameln 0.1 mg/ml Injection may also be used concomitantly with other resuscitative measures.

<u>Adults</u>

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 is 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 dosage and rate of infusion should be adjusted individually to achieve the desired level of consciousness.
If a significant improvement in consciousness and respiratory function is not obtained after repeated doses of flumazenil, a non-benzodiazepine aetiology must be assumed.
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 special warnings and precautions for use)

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.

Patients with renal or hepatic impairment
Since flumazenil is primarily metabolised 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.

Children above 1 year of age
For the reversal of conscious sedation induced by benzodiazepines in children > than 1 year, the recommended initial dose is 0.01 mg/kg (up to 0.2 mg) administered intravenously over 15 seconds. If, after waiting an additional 45 seconds, the required level of consciousness is not obtained, further injection of 0.01 mg/kg (up to 0.2 mg) may be administered where necessary, repeated at 60-second intervals (a maximum of 4 times) to a maximum dose of 0.05 mg/kg or 1 mg whichever is lower. The dose should be individualized based on the patient's response. No data are 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 younger than 1 year. Therefore flumazenil should only be administered in children younger than 1 year if the potential benefits to the patient outweigh the possible risk.

CONTRAINDICATIONS
- Hypersensitivity to flumazenil or to any of the excipients (see excipients).
- Patients receiving benzodiazepines for control of a potentially life-threatening condition (e.g. control of intracranial pressure or status epilepticus).

WARNINGS & PRECAUTIONS
- Elimination may be delayed in patients with hepatic impairment.

- 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 the benzodiazepine has presumably worn off.
- In high risk patient, 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.

- Rapid injection of high doses 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, rapid injection of doses equal to 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 episode 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, individually titrated doses of benzodiazepines (diazepam or 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.
- 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.
- In patients with severe brain injury (and/or instable intracranial pressure) receiving flumazenil – to reverse the effects of benzodiazepines- an increased intracranial pressure may develop.
- Due to the increased frequency of benzodiazepine tolerance and dependence in patients with alcoholism and other drug dependencies, flumazenil should be used with caution in this population.
- 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 arhythmias) 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.
- Use in children for indications other than reversal of conscious sedation is not recommended, as no controlled studies are available. Until sufficient data are available, Flumazenil also should only be administered to children below the age of 1 year if the risks to the patient (especially in case of accidental overdose) have been weighed up against the benefits of the treatment.
- 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.
- This medicinal product contains approximately 3.7 mg sodium per ml of flumazenil solution for injection/infusion.
    - 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.

<u>Important incompatibilities</u>

This medicinal product must not be mixed with other medicinal products except for those mentioned in section “Dosage & Administration”.

<u>Effects on ability to drive and use machines</u>

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.

INTERACTION WITH OTHER MEDICINES

Flumazenil reverses the central effects of benzodiazepines by means of competitive interaction at the 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 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 when used in combination with benzodiazepines such as midazolam, flunitrazepam and lormetazepam. Flumazenil does not affect the pharmacokinetics of these benzodiazepines. There is no pharmacokinetic interaction between ethanol and flumazenil.

PREGNANCY & LACTATION

Pregnancy

Flumazenil should only be used during pregnancy if the possible benefit to the patient outweighs the potential risks for the foetus.

Lactation

It is not known whether flumazenil is excreted in breast milk. For this reason, breast-feeding should be interrupted for 24 hours when flumazenil is used during lactation. Emergency use of flumazenil during lactation is not contra-indicated.

Fertility

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 preclinical safety data).

ADVERSE REACTIONS

Any side-effects associated with Flumazenil usually subside rapidly without the need for special treatment.

Immune systems disorders	Allergic reactions Severe hypersensitivity reactions (including anaphylaxis)	Common (≥1%, <10%) Rare (≥1/10,000 to<1/1,000)
Psychiatric disorders	Anxiety*, emotional liability, insomnia, somnolence. Fear	Common (≥1%, <10%) Uncommon (≥0.1%, <1%)
Nervous system disorders	Vertigo, headache, agitation*, tremor, dry mouth, hyperventilation, speech disorder, paraesthesia	Common (≥1%, <10%)

	Convulsions (in patients suffering epilepsy or severe hepatic insufficiency, mainly after long-term treatment with benzodiazepines or multiple medicinal products abuse) (see warnings and precautions)	Uncommon (≥0.1%, <1%)
Ear disorders	Abnormal hearing	Uncommon (≥0.1%, <1%)
Eye disorders	Diplopia, strabismus, lacrimation increased	Common (≥1%, <10%)
Cardiac disorders	Palpitations*	Common (≥1%, <10%)
	Tachycardia or bradycardia, extrasystole	Uncommon (≥0.1%, <1%)
Vascular disorders	Flushing, hypotension, orthostatic hypotension, transient increased blood pressure (on awakening)	Common (≥1%, <10%)
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough, nasal congestion, chest pain	Uncommon (≥0.1%, <1%)
Gastrointestinal disorders	Nausea (during anaesthesia)	Very common (≥10%)
	Vomiting (during anaesthesia), hiccup	Common (≥1%, <10%)
Skin and subcutaneous tissue disorders	Sweating	Common (≥1%, <10%)
General disorders and administration site conditions	Injection site pain	Common (≥1%, <10%)
	Shivering	Uncommon (≥0.1%, <1%)
	Severe hypersensitivity reactions (including anaphylaxis)	Rare (≥1/10,000 to<1/1,000)

* following rapid injection, not requiring treatment

Unknown: Withdrawal symptoms. (e.g agitation, anxiety, emotional lability,confusion, sensory distortions, tachycardia, dizziness, sweating), folloeing 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 admistration (see warnings and precautions); 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.

SYMPTOMS & TREATMENTS OF OVERDOSAGE

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.

STORAGE CONDITIONS & PHARMACEUTICAL PRECAUTIONS

Do not store above 30°C. Do not freeze. Any unused solution from opened ampoules should be discarded.
Keep out of reach of children. Jauhi daripada kanak-kanak.

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 and 2-8°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, the 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 reconstitution/dilution has taken place in controlled and validated aseptic conditions.
This medicinal product is for single use only and any unused solution should be discarded. Prior to use, please inspect the medicinal product visually. It should only be used if the solution is clear and practically free from particles.

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 product or waste material should be disposed of in accordance with local requirements.

PACKING / PACK SIZES

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

MANUFACTURED BY

Siegfried Hameln Gmbh
Langes Feld 13
31789 Hameln
Germany

Revision date: 27 Oct 2022