

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Flumazenil 0.1 mg/ml 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.

For a full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

solution for injection  
concentrate for solution for infusion

clear colourless solution

### 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 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 intoxication or overdose with only or mainly benzodiazepines

#### 4.2 Posology and method of administration

Flumazenil should be administered intravenously by an anaesthetist or experienced physician.  
Flumazenil may be administered as an infusion (see 6.6).

Flumazenil may be used concomitantly with other resuscitative measures.

#### 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 0.2 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 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 re-sedation 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 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.

#### 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 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

In patients with impaired hepatic function, the elimination of flumazenil may be delayed (see section 5.2) and therefore careful titration of dosage is recommended. No dosage adjustments are required in patients with renal impairment.

### 4.3 Contraindications

- Hypersensitivity to flumazenil or to any of the excipients.
- Patients receiving benzodiazepines for control of a potentially life-threatening condition (e.g. control 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 the benzodiazepine effect.

### 4.4 Special warnings and special precautions for use

Use in children for indications other 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.

- 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 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 preoperative 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.
- Because of the potential for re-sedation and respiratory depression, children previously sedated with midazolam should be monitored for 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.
- 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 unstable intracranial pressure) receiving flumazenil – to reverse the effects of benzodiazepines – an increased intracranial pressure may develop.
- 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 benzodiazepine 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.

#### **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 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 in combination with the benzodiazepines midazolam, flunitrazepam and lormetazepam. Flumazenil does not affect the pharmacokinetics of these benzodiazepines.

#### **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 contraindicated.

#### **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

Immune systems disorders	Allergic reactions.	Common ( $\geq 1\%$ , $< 10\%$ )
Psychiatric disorders	Anxiety*, emotional lability, insomnia, somnolence.	Common ( $\geq 1\%$ , $< 10\%$ )
Nervous system disorders	Vertigo, headache, agitation*, tremor, dry mouth, hyperventilation, speech disorder, paresthesia.	Common ( $\geq 1\%$ , $< 10\%$ )
	Convulsions (in patients suffering epilepsy or severe hepatic insufficiency, mainly after long-term treatment with benzodiazepines or multiple medicinal product abuse).	Uncommon ( $\geq 0.1\%$ , $< 1\%$ )
Ear disorders	Abnormal hearing.	Uncommon ( $\geq 0.1\%$ , $< 1\%$ )
Eye disorders	Diplopia, strabismus, lacrimation increased.	Common ( $\geq 1\%$ , $< 10\%$ )
Cardiac disorders	Palpitations*.	Common ( $\geq 1\%$ , $< 10\%$ )
	Tachycardia or bradycardia, extrasystole.	Uncommon ( $\geq 0.1\%$ , $< 1\%$ )
Vascular disorders	Flushing, hypotension, orthostatic hypotension, transient increased blood pressure (on awakening).	Common ( $\geq 1\%$ , $< 10\%$ )
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough, nasal congestion, chest pain.	Uncommon ( $\geq 0.1\%$ , $< 1\%$ )
Gastrointestinal disorders	Nausea (during anaesthesia).	Very common ( $\geq 10\%$ )
	Vomiting (during anaesthesia), hiccup.	Common ( $\geq 1\%$ , $< 10\%$ )
Skin and subcutaneous tissue disorders	Sweating.	Common ( $\geq 1\%$ , $< 10\%$ )
General disorders and administration site conditions	Fatigue, injection site pain.	Common ( $\geq 1\%$ , $< 10\%$ )
	Shivering.	Uncommon ( $\geq 0.1\%$ , $< 1\%$ )

\*: after rapid injection, not requiring treatment

In patients treated for long periods with benzodiazepines flumazenil can induce withdrawal symptoms. The symptoms are: tension, agitation, anxiety, confusion, hallucinations, tremor and convulsions.

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.

## 4.9 Overdose

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 paradoxical 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 (zopiclone) and triazolopyridazines, are blocked by flumazenil. The hypnotic 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 benzodiazepine withdrawal symptoms, including convulsions, in animals receiving long-term flumazenil treatment.

### 5.2 Pharmacokinetic properties

#### Distribution

Flumazenil is a lipophilic weak base. Flumazenil is bound by approximately 50 % to plasma proteins, from which two thirds are bound to albumin. Flumazenil is extensively distributed across the 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 ( $V_{ss}$ ) is 0.9 – 1.1 L/kg.

#### Metabolism

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 a 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 are 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 the elderly are 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*

The pharmacokinetics of flumazenil are not different in patients with impaired renal function or patients undergoing haemodialysis compared to normal healthy volunteers.

##### *Children*

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**

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 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 (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.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

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.

### **7. MARKETING AUTHORISATION HOLDER**

hameln pharma plus gmbh  
Langes Feld 13  
31789 Hameln  
Germany

### **8. MARKETING AUTHORISATION NUMBER**

PL 25215/0001

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

17/02/2006

**10. DATE OF REVISION OF THE TEXT**

October 2007