SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Flumazenil Kabi 0.1 mg/ml

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.

Excipients with known effect:
Each 10 ml ampoule contains 37 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Benzodiazepine antagonist for reversal of benzodiazepine anesthesia, as well as for patients with Benzodiazepine intoxication.

In a hospital setting:
In anaesthesiology to neutralise the sedative effects of benzodiazepines on the central nervous system in adults and children **older than 1 year**:

- reversal of sedative effect during general anaesthesia induced and maintained by benzodiazepines,
- reversal of conscious sedation induced by benzodiazepines in short operations with a diagnostic or therapeutic objective.

In intensive care to neutralise the sedative effects of benzodiazepines on the central nervous system and treat a coma of unknown aetiology, in adults and children (including newborns) if the semiology is compatible with the hypothesis of a benzodiazepine or related substance-induced coma:

- diagnosis and/or treatment of intentional or accidental benzodiazepine overdose,
- aetiological diagnosis of an unexplained coma in order to differentiate what is caused by a benzodiazepine from another cause (pharmacological or neurological).
- specific cancellation of the effects on the central nervous system by excessive benzodiazepine doses (re-establishment of spontaneous ventilation to avoid intubation or interrupt ventilatory assistance).

In an emergency situation or medical transport, in adults and children older than 6 years:

- reversal of benzodiazepine-induced conscious sedation in case of respiratory depression or apnoea.

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 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, a second bolus injection may be administered.
An intravenous infusion of 0.1 – 0.4 mg/h has also been shown to be useful. The dosage and 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 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.

Patients with hepatic impairment

Since flumazenil is primarily metabolized in the liver, careful titration of dosage is recommended in patients with impaired hepatic function.

Patients with renal impairment

No dosage adjustments are required in patients with renal impairment.

Paediatric population

Children above 1 year of age

For the reversal of conscious sedation induced by 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 10 micrograms/kg may be administered (up to 200 micrograms) and repeated at 60 second intervals where necessary (a maximum of 4 times) to a maximum total dose of 50 micrograms/kg or 1 mg, whichever is lower. The dose should be individualised 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 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.

Method of administration

Flumazenil should be administered intravenously by an anaesthetist or experienced physician.
Flumazenil may be administered as infusion (see 6.6).
Flumazenil may be used concomitantly with other resuscitative measures.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance 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).

- 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

Use in children for other indications than reversal of conscious sedation is not recommended as no controlled studies are available.

- 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 high dose and/or chronic treatment with benzodiazepines at any time within the weeks 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. 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 carefully 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.
- 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.

- 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.
- 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.
- 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.
- 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.
- Elimination may be delayed in patients with hepatic impairment.
- Each 5 ml ampoule contains less than 1 mmol sodium (or 23 mg), that is to say essentially ‘sodium-free’.
- Each 10 ml ampoule contains 1.61 mmol sodium (or 37 mg), equivalent to 1.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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.

There is no pharmacokinetic interaction between ethanol and flumazenil.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

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

Fertility
Studies in animals have not shown evidence of embryo toxicity or teratogenicity (see section 5.3).

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 following convention has been used for the classification of the adverse reactions:

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.
Not known	Hypersensitivity reactions, including anaphylaxis
Psychiatric disorders	
Common	Anxiety*, emotional lability, insomnia, somnolence.
Uncommon	Fear
Not known	Withdrawal symptoms (see below); 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.
Uncommon	Convulsions (in patients suffering from epilepsy or severe hepatic insufficiency, mainly after long-term treatment with benzodiazepines or mixed drug overdose (see section 4.4)).

Ear and labyrinth disorders	
Uncommon	Abnormal hearing.
Eye disorders	
Common	Diplopia, strabismus, lacrimation increased.
Cardiac disorders	
Common	Palpitations*.
Uncommon	Tachycardia or bradycardia, extrasystole.
Vascular disorders	
Common	Flushing, hypotension, orthostatic hypotension, transient increased blood pressure (on awakening).
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, cough, nasal congestion, chest pain.
Gastrointestinal disorders	
Very common	Nausea (during postoperative use).
Common	Vomiting (during postoperative use), 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

Following rapid injection of doses of 1 mg or more or in patients treated for long periods and/or high dose with benzodiazepines flumazenil can induce withdrawal symptoms. The symptoms are: tension, agitation, anxiety, emotional lability as well as confusion and sensory distortions, hallucinations, tremor and convulsions.

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.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il
and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com.

4.9 Overdose
There is very limited experience of acute overdose in humans with Flumazenil. However, even when administered intravenously at doses of 100 mg, no symptoms of overdose attributable to flumazenil have been observed.

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.

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.

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.

Pharmacokinetic/pharmacodynamic relationship(s)

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
Sodium chloride
1N Sodium hydroxide solution
Disodium edetate
Acetic acid (99%)
Water for injections
Nitrogen (as inert gas)

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

The expiry date of the product is indicated on the packaging materials.

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

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

Not all pack sizes may be marketed.

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

7. MANUFACTURER

Fresenius Kabi Austria GmBH
Hafnerstrasse 36, A-8055 Graz, Austria

8. REGISTRATION HOLDER

Neopharm (Israel) 1996 Ltd.
Hashiloach 6, POB 7063 Petach Tiqva 4917001

9. MARKETING AUTHORISATION NUMBER

177-37-37182-99

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Flumazenil Kabi sol for inf SPC vr 02A