PACKAGE LEAFLET: INFORMATION FOR THE USER

Flumazenil 0.1 mg/ml

solution for injection/infusion

flumazenil

Read all of this leaflet carefully before you start using this medicine
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. WHAT FLUMAZENIL IS AND WHAT IT IS USED FOR

Flumazenil is a counteragent (antidote) for the complete or partial reversal of the central sedative effects of benzodiazepines (specific group with sedative, sleep inducing, muscle relaxing and anxiolytic properties).
It may therefore be used in anaesthesia to wake you up after certain diagnostic tests or in intensive care if you have been held under sedative conditions. Flumazenil may also be used for treatment of intoxications or overdose with benzodiazepines as well as to revert any unexpected effects (paradoxical reactions) caused by them.
Flumazenil may be used to help find the reason for loss of consciousness in unconscious patients.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE FLUMAZENIL

Do not use Flumazenil
- if you are allergic to flumazenil or any of the other ingredients (listed in Section 6).
- if benzodiazepines have been given to you to control a life-threatening condition (e.g. pressure on the brain or a serious epileptic fit).
- if you have taken too much of a benzodiazepine with other medicines such as tricyclic and/or tetracyclic antidepressants (e.g. Imipramin, Clomipramin, Mirtazepine or Mianserin). Harmful effects of these other antidepressants may not be seen if benzodiazepines are also being used. If you have signs of overdose with other antidepressants, Flumazenil must not be used.

Warnings and precautions
Talk to your doctor or pharmacist before using Flumazenil
- the effects of flumazenil usually wear off more quickly than those of benzodiazepines. This means that the **relaxing effects** of the benzodiazepines **can come back**. You will be checked until the effects of flumazenil have worn off.
- if you have liver problems.
- if you have taken benzodiazepines for a long time flumazenil can cause **withdrawal symptoms** (see Section 4 for details).
- if you have **epilepsy** and have been taking benzodiazepines for a long period of time Flumazenil can cause **fits** (convulsions).
- if you have a **serious brain injury** (e.g. pressure on the brain or a serious epileptic fit) because Flumazenil can increase the pressure on the brain.
- if you are **dependent** (rely) **on benzodiazepines** or if you have **benzodiazepine withdrawal symptoms**. You should not use Flumazenil in these cases.
- if you have had panic or anxiety attacks in the past, Flumazenil can cause new attacks.
- if you are dependent (rely on) on alcohol or some other medicines. There is a risk of you becoming benzodiazepine tolerant (where you no longer get any benefit) or benzodiazepine dependent.
- children and infants should only receive Flumazenil to reverse **conscious sedation** (where they remain awake). Children should be closely observed for at least 2 hours after receiving Flumazenil.

Other medicines and Flumazenil
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Harmful effects of other medicines (especially tricyclic antidepressants like Imipramin) may worsen when the effects of benzodiazepines are treated with Flumazenil.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Because of insufficient experience during pregnancy Flumazenil should only be used if the advantage for you is higher than the potential risk for the unborn baby. The administration of flumazenil during pregnancy is not contraindicated in an emergency situation.

It is not known whether flumazenil is excreted in breast milk.
Therefore it is **recommended not to breast-feed 24 hours** after administration of Flumazenil.

Driving and using machines
After you have received Flumazenil the effects of benzodiazepines can come back. You must not drive a car, operate machinery or do strenuous activity for at least 24 hours after Flumazenil treatment.

Important information about some of the ingredients of Flumazenil
This medicinal product contains 3.7 mg sodium per ml (18.5 mg/5 ml ampoule size or 37 mg / 10 ml ampoule size) solution for injection.
To be taken into consideration if you are on a controlled sodium diet.

3. HOW TO USE FLUMAZENIL

Flumazenil is administered as an **intravenous** (into a vein) injection or may be diluted for **infusion** (injection over a longer period).

Flumazenil will be given by your anesthetist or an experienced physician. It may be used with other treatments given to revive (resuscitate) you.

The dose will be defined by your doctor according to the need. It depends from the circumstances and must be decided case by case. More details for healthcare professionals are given at the end of the package leaflet.

Anaesthesia
The recommended starting dose for adults 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 for adults 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.

Children under the age of 1 year
There is little information on the use of Flumazenil in children less than 1 year old. Children of less than 1 year old should only be given Flumazenil if the **benefits** are expected to be greater than the **risk.**

The following information is intended for medical or healthcare professionals only

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 chapter below).
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.

If no clear effect on awareness and respiration is obtained after repeated dosing with Flumazenil, the possibility should be considered that the intoxication is due to agents other than benzodiazepines.

If Flumazenil is used in anaesthesiology at the end of surgery, it should not be given until the effects of the muscle relaxants have been fully reversed.

Children who have been sedated with Midazolam should be closely observed for at least 2 hours after Flumazenil administration, in case repeated sedation or difficulty with breathing occurs. When other benzodiazepines have been used the monitoring time must be adjusted based on how long their effects last.

How to store Flumazenil
When Flumazenil is to be used as an infusion, it must be diluted prior to use.

Flumazenil should only be diluted with sodium chloride 9 mg/ml (0.9% w/v) solution or glucose 50 mg/ml (5% w/v). Compatibility between flumazenil and other solutions for injection has not been established.

From a microbiological perspective, the diluted Flumazenil should be used immediately, unless the method of dilution precludes the risk of microbial contamination. If not used immediately, the in-use storage times and conditions are the responsibility of the user.
Do not refrigerate.
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

Flumazenil must not be mixed with other medicinal products except for those mentioned above.

The recommended doses for Flumazenil

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.

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 10 micrograms/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.

If you have any further questions on the use of Flumazenil, ask your doctor.

Patients with hepatic (liver) impairment
In patients with impaired liver function, the dosing must be managed carefully.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The frequency of side effects is classified into the following categories:

Common (1 - 10 in 100 patients)
- feeling sick (nausea) or being sick (vomiting), especially if you have also had any opiate medicines

Uncommon (1 - 10 in 1,000 patients)
These effects are most likely to happen after rapid injection and do not require treatment:
- anxiety
- fear
- feeling your heartbeat (palpitations)

Unknown
- allergic reactions (hypersensitivity), including severe allergic reaction
- panic attacks (in people who have had panic attacks in the past)
- abnormal crying
- agitation
- being aggressive
- convulsions (seizures). These are more likely in people who already have epilepsy or severe liver problems or in people who have taken 'benzodiazepine' medicines for a long time or in case flumazenil is given after an overdose of more than one medicine
- transient high blood pressure on waking from the effects of benzodiazepines
- redness of the face and neck (flushing)
- chills (most likely to happen after rapid injection, do not require treatment)

If you have been treated with benzodiazepines for a long time or are given high doses of Flumazenil quickly, **withdrawal symptoms** can happen such as:
- agitation
- anxiety
- mood swings (emotional lability)
- confusion
- abnormal sensory perceptions (hearing voices, seeing things that aren't there, sensations on the skin)

Similar effects can be seen in children. When Flumazenil has been used in children abnormal crying, agitation and aggressive reactions have been reported.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in:
Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard
By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE FLUMAZENIL

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.

Do not store above 25°C.

This medicine is for single use only and should be used immediately after opening. If diluted, Flumazenil should not be refrigerated. 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.

Flumazenil should only be used if the solution is clear and free from particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Flumazenil contains

The active substance is flumazenil.

Each ml of solution for injection contains 0.1 mg flumazenil.
Each 5 ml ampoule contains 0.5 mg flumazenil.
Each 10 ml ampoule contains 1.0 mg flumazenil.

The **other ingredients** are:
- disodium edetate
- glacial acetic acid
- sodium chloride (3.7 mg per ml)
- hydrochloric acid 36% for pH adjustment
- sodium hydroxide for pH adjustment
- water for injections

What Flumazenil looks like and contents of the pack
Flumazenil is a clear and colourless solution for injection, or for dilution before infusion. Flumazenil comes in colourless glass ampoules.

Following pack sizes are available:
Carton boxes with 5 or 50 (10x5) ampoules containing 5 ml solution.
Carton boxes with 5 or 50 (10x5) ampoules containing 10 ml solution

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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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.

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.