Certified Translation from the German Language

PACKAGE LEAFLET: INFORMATION FOR THE USER

Flumazenil Inresa 0.5 mg IV, solution for injection

Active substance: flumazenil

Read all of this leaflet carefully before you use this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What *Flumazenil Inresa 0.5 mg IV* is and what it is used for
2. Before you use *Flumazenil Inresa 0.5 mg IV*
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4. Possible side effects
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1. WHAT *Flumazenil Inresa 0.5 mg IV* IS AND WHAT IT IS USED FOR

Flumazenil Inresa 0.5 mg IV contains the active substance flumazenil. Flumazenil belongs to a group of medicines known as benzodiazepine antagonists.

Flumazenil is used to reverse the effects of a group of medicines known as benzodiazepines, which are used to cause deep sleep. By reversing the effects of benzodiazepines, it allows the patient to become conscious so that they can breathe unaided.

Flumazenil can be used to partly or completely reverse the sedative effect of benzodiazepines during general anaesthesia after medical tests and operations in hospital. It is used in intensive care patients to bring about unaided breathing. It is also used to diagnose and treat benzodiazepine poisoning or overdose.

2. BEFORE YOU USE *Flumazenil Inresa 0.5 mg IV*

Do not use *Flumazenil Inresa 0.5 mg IV*
- if you are allergic (hypersensitive) to flumazenil or any of the other ingredients of *Flumazenil Inresa 0.5 mg IV*.
- if you are receiving benzodiazepines to control potentially life-threatening conditions (e.g. to control pressure in the skull cavity [intracranial pressure] or an acute status epilepticus where epileptic fits increasingly occur.
- if you have taken or been given too much of benzodiazepines (medicines for anxiety and tension, sleep disorders) together with tricyclic and/or tetracyclic antidepressants (medicines for depression), the toxic properties of antidepressants may be masked by the benzodiazepine effect,

which protects against harmful influences.
- if you have taken or been given too much of tricyclic and/or tetracyclic antidepressants and are experiencing effects on the nervous and cardiovascular system (anticholinergic, neurological or cardiovascular symptoms of severe intoxication), Flumazenil Inresa must not be used to reverse the benzodiazepine effects.

Take special care with *Flumazenil Inresa 0.5 mg IV*
- if sedation was brought on by other medicines than benzodiazepines. Flumazenil will not usually have an effect because it is meant to reverse the effects of benzodiazepines only.
- when Flumazenil Inresa is used in cases of combined drug intoxication (poisoning with various substances), as the toxic effects (such as seizures and heart rhythm disorders) of other medicines taken at an overdose (especially cyclic antidepressants) may be enhanced due to the reversal of the benzodiazepine effect by Flumazenil Inresa.
- in children below the age of 1 year. Flumazenil should only be given to children below the age of 1 year if considered absolutely necessary (e.g. in case of accidental intake of benzodiazepine tablets).
- if you have a severe head injury. Flumazenil can cause increased pressure on the brain.
- if you are anxious about the operation or suffer from general anxiety. Flumazenil should be given with care.
- if you are treated with flumazenil because you took too much of several medicines at once. Flumazenil may worsen some of the side effects that can occur.
- if you suffer from epilepsy and you have received benzodiazepines for longer periods. Flumazenil can cause seizures.
- if you have a history of alcohol or drug abuse.
- if you are on a controlled sodium diet.
- if you have received benzodiazepines for long periods. Flumazenil can cause withdrawal symptoms. If, despite careful dosing, withdrawal symptoms occur, your doctor may consider treatment with low doses of benzodiazepines.
- if you suffer from liver disease. Your doctor may need to adjust the dose of flumazenil.

If any of the above apply to you, or if you are not sure, contact your doctor or nurse before you have *Flumazenil Inresa 0.5 mg/ml*.

Flumazenil is not recommended for the treatment of benzodiazepine dependence or for the treatment of benzodiazepine withdrawal symptoms.

Children
Use in children is not recommended for indications other than the reversal of intentionally induced sedation, as no controlled studies are available. The same applies to use in children below 1 year of age.

Elderly patients
As no data are available on the use of Flumazenil Inresa in elderly patients, it should be remembered that this patient group is generally more sensitive to the effects of medicinal products. Elderly patients should therefore be treated with the necessary caution.

Other medicines and *Flumazenil Inresa 0.5 mg IV*
Please tell your doctor or pharmacist if you are taking/using or have recently taken/used any other medicines, including medicines obtained without a prescription.
This is especially important for the following medicines as they may interact with Flumazenil Inresa:
- medicines working in the same way as benzodiazepines, e.g. zopiclone (a type of sleeping pill) and triazolopyridazine. Flumazenil may decrease the effects of these medicines.
- antidepressants or other treatments for mental illness (such as amitriptyline, imipramine or dosulepin)

It may still be all right for you to be given flumazenil; your doctor will decide what is suitable for you.

Pregnancy, breast-feeding and fertility

Ask your doctor or pharmacist for advice before taking/using any medicine.

Pregnancy
During pregnancy and especially in the first 3 months, *Flumazenil Inresa 0.5 mg IV* should be used only after careful benefit/risk assessment by the treating doctor.

Breast-feeding
It is not known whether flumazenil, the active substance of *Flumazenil Inresa 0.5 mg IV*, passes into breast milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be stopped during treatment with flumazenil for 24 hours after parenteral administration in acute cases.

Fertility
No data on effects and potentially harmful effects of flumazenil on fertility are available.

Driving and using machines
If you have been given Flumazenil Inresa to reverse the suppressant (sedative) effects of benzodiazepines, you must not drive, use machines or perform any other activities requiring physical or mental alertness for at least 24 hours, as the benzodiazepine effect may return.

Important information about some of the ingredients of *Flumazenil Inresa 0.5 mg IV*
Flumazenil Inresa 0.5 mg IV contains sodium, but less than 1 mmol (23 mg) sodium per ampoule, i.e. essentially "sodium-free".

3. HOW TO USE *Flumazenil Inresa 0.5 mg IV*

Flumazenil Inresa 0.5 mg IV must be administered by an anaesthetist or experienced doctor.

Method of administration: For intravenous use

Flumazenil can be used at the same time as other resuscitation procedures.

Dosage
Flumazenil is given intravenously (into a vein) by an anaesthetist or experienced doctor.

Adults

Anaesthesia
The recommended starting dose (initial dose) is 0.2 mg intravenously and should be administered over a period of 15 seconds. If the desired level of consciousness is not reached within 60 seconds, a further dose of 0.1 mg can be injected. This procedure can be repeated as needed at 60-second intervals up to a maximum dose of 1.0 mg. The usual required dose is between 0.3 and 0.6 mg, but may also be outside this range depending on the patient's condition and the benzodiazepine used.

Intensive care medicine
The recommended initial dose is 0.2 mg intravenously and should be administered over a period of 15 seconds. If the desired level of consciousness is not reached within 60 seconds, a further dose of 0.1 mg can be injected. This procedure can be repeated as needed at 60-second intervals, until the patient awakens or up to a total dose of 2.0 mg.

If drowsiness returns, an infusion of 0.1 – 0.4 mg/hour may be appropriate.
The infusion rate should be individually adjusted until the desired level of consciousness is reached.
If there is no significant effect on consciousness and respiration after repeated administration, it should be considered that poisoning (intoxication) is not due to benzodiazepines.

Infusions should be stopped every 6 hours to determine whether sedation returns.

In order to avoid withdrawal symptoms in intensive care patients treated with high-dose benzodiazepines over a prolonged period, the Flumazenil Inresa dose must be individually titrated and the injection must be administered slowly (see section 4 "Possible side effects").

Patients with a liver disorder may need a lower dose.

Children over 1 year of age
To reverse benzodiazepine-induced sedation in children older than 1 year of age, the recommended starting dose (initial dose) is 0.01 mg/kg (up to 0.2 mg), which is to be administered intravenously over a period of 15 seconds. If the desired level of consciousness is not reached within 45 seconds, a further dose of 0.01 mg/kg (up to 0.2 mg) can be injected. This procedure can be repeated as needed at 60-second intervals (up to a maximum of 4 additional doses), until a maximum total dose of 0.05 mg/kg or 1 mg is reached, whichever is the lower dose. The dose should be individually determined in relation to the patient's response. No data are available on the safety and efficacy of repeated administration of Flumazenil Inresa among children in the case of repeat sedation.

Children below 1 year of age
There are no sufficient data for the use of Flumazenil Inresa in children below 1 year of age. For this reason, Flumazenil Inresa may only be used in children below 1 year of age if the potential benefit outweighs the possible risks.

Patients with impaired kidney and liver function
As the metabolism and hence excretion [elimination] of Flumazenil Inresa may be delayed in patients with impaired liver function, the dose should be carefully titrated. No dose adjustments are needed for patients with impaired kidney function.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

If you are administered more Flumazenil Inresa 0.5 mg IV than you need
Even at doses of 100 mg Flumazenil Inresa into a vein, no symptoms of overdose have been observed. Withdrawal symptoms due to medicines that contain benzodiazepine are reported in section "4. Possible side effects".

4. POSSIBLE SIDE EFFECTS

Like all medicines, *Flumazenil Inresa 0.5 mg IV* can cause side effects, although not everybody gets them.

The following frequency data are used for evaluating side effects:

very common:	more than 1 in 10 patients treated
common:	less than 1 in 10, but more than 1 in 100 patients treated
uncommon:	less than 1 in 100 but more than 1 in 1,000 patients treated
rare:	less than 1 in 1,000 but more than 1 in 10,000 patients treated
very rare:	less than 1 in 10,000 patients treated, including isolated cases
Not known:	cannot be estimated from the available data

The following side effects have been reported after use of Flumazenil Inresa:

Very common (more than 10 in 100 patients treated)
- nausea (during anaesthesia)

Common (1 to 10 in 100 patients treated)
- allergic reactions
- states of anxiety*, affective lability, insomnia, excessive tiredness
- dizziness, headache, agitation*, tremor, dry mouth, hyperventilation, speech disorders, abnormal sensations (paraesthesia)
- diplopia (double vision), strabismus (squinting), increased tear flow
- pounding heart*
- skin redness, hypotension (low blood pressure), orthostatic hypotension (dizziness on standing), temporarily increased blood pressure (during recovery)
- vomiting (during anaesthesia), hiccough, nausea, vomiting during postoperative use, especially if opiates have also been used
- sweating
- exhaustion, pain at the injection site

Uncommon (1 to 10 in 1,000 patients treated)
- anxiety, fear after rapid injection, generally not requiring treatment
- seizures (in patients suffering from epilepsy or severe liver failure, mainly after prolonged treatment with benzodiazepines or multiple drug abuse)
- hearing disorders
- tachycardia or bradycardia (rapid or slow heart rate), extrasystoles, pounding heart (irregular heart beat) after rapid injection, generally not requiring treatment
- dyspnoea (breathlessness), cough, blocked nose, chest pain
- tremor

Not known (frequency cannot be estimated from the available data)
- withdrawal symptoms (e.g. agitation, anxiety, emotional lability, confusion, abnormal sensations) after rapid injection of doses of 1 mg or more in patients with high-dose or long-term benzodiazepine exposure ending within a few weeks before flumazenil administration (see section 4.4), panic attacks (in patients with a history of panic reactions), abnormal crying, agitation, aggressive reactions (the adverse reaction profile in children is generally comparable with that in adults. When flumazenil was used to reverse conscious sedation, abnormal crying, agitation and aggressive reactions have been reported).
- seizures, especially in patients with known epilepsy or severe liver dysfunction, mainly after long-term treatment with benzodiazepines or in the case of overdose with several substances (see section 4.4)
- temporarily increased blood pressure (during recovery)
- flushing
- chills after rapid injection, generally not requiring treatment.

*After rapid injection; no treatment required.

All medicines can produce allergic reactions, but serious allergic reactions are very rare. **Tell your treating doctor straight away if you experience wheezing, breathing problems, swelling of the eyelids, face or lips, skin rash or itching (especially all over your body).**

In patients receiving prolonged treatment with benzodiazepines, Flumazenil Inresa can cause withdrawal phenomena. The symptoms are: tension, excitation, states of anxiety, confusion, hallucinations, tremor and seizures.

In general, the side effect profile in children does not differ greatly from that in adults. After the use of

Flumazenil Inresa to reverse sedation, abnormal crying, excitation and aggressiveness have been reported.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Bundesinstitut für Arzneimittel und Medizinprodukte[1], Abt. Pharmakovigilanz[2], Kurt-Georg-Kiesinger-Allee 3, D-53175, Bonn, website: http://www.bfarm.de. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE *Flumazenil Inresa 0.5 mg IV*

This medicinal product does not require any special storage conditions.

Do not use Flumazenil Inresa 0.5 mg IV after the expiry date which is stated on the ampoule label and box. The expiry date refers to the last day of that month.

Shelf life after first opening:
After first opening, the medicines should be used immediately.

Shelf life of the diluted solution:
The chemical and physical stability of the ready-to-use preparation has been demonstrated for 24 hours at 2-8°C and for 8 hours at 25°C.
From a microbiological point of view, this medicine should be used immediately. If the ready-to-use preparation is not used immediately, storage times and conditions are the responsibility of the user. Unless dilution has taken place in controlled and aseptic conditions, it should be stored for no longer than 24 hours at 2 to 8°C.

This medicine is intended for single use only and any unused solution should be discarded.

Flumazenil Inresa 0.5 mg IV may only be used if the solution is clear and practically free from particles.

Keep out of the reach and sight of children.

6. FURTHER INFORMATION

What *Flumazenil Inresa 0.5 mg IV* contains:
The active substance is flumazenil.
1 mL contains 0.1 mg flumazenil

One 5 mL ampoule contains 0.5 mg Flumazenil Inresa.

The other ingredients are: sodium edetate (Ph.Eur.), acetic acid 99%, sodium chloride, sodium hydroxide, water for injections.

What *Flumazenil Inresa 0.5 mg IV* looks like and contents of the pack
Flumazenil Inresa 0.5 mg IV is a solution for injection.
The solution is clear and colourless.

1 The German Federal Institute for Drugs and Medical Devices

2 Department of Pharmacovigilance

The following packs are available:

Boxes containing 5 ampoules (glass type I), each with 5 mL solution for injection

Marketing Authorisation Holder and Manufacturer:
Inresa Arzneimittel GmbH
Obere Hardtstr. 18
79114 Freiburg
Tel.: +49 (0)761 47 50 47

This leaflet was last revised in September 2016.

The following information is intended for medical or healthcare professionals only:

Warnings and precautions
The patient should be monitored over an appropriate period of time (ECG, pulse measurement, oximetry, level of patient consciousness and other vital functions, such as heart rate, breathing and blood pressure).
Flumazenil specifically reverses the effect of benzodiazepines. An alternative aetiology should therefore be considered if the patient does not awaken.
When used in anaesthesiology at the end of a surgical procedure, flumazenil should not be administered until the effects of peripheral muscle relaxants have completely worn off.
As the effect of flumazenil is usually shorter than that of benzodiazepines and sedation may therefore return, the patient should continue to be closely monitored. This should preferably take place in an intensive care unit until the effect of flumazenil can be assumed to have worn off.
In patients at risk, the benefits of benzodiazepine sedation should be weighed against the drawbacks of rapid emergence. In certain patients, maintaining a certain level of sedation may be preferable to a fully awake state (e.g. if they have cardiovascular problems).
Rapid injection of high-dose flumazenil (more than 1 mg) should be avoided in patients receiving chronic benzodiazepine treatment, as withdrawal symptoms such as palpitations, agitation, anxiety, emotional lability, as well as mild confusion and abnormal sensations (paraesthesia), may occur. The flumazenil dosage should be carefully adjusted in patients who are anxious during the pre-surgery phase, or if they are known to suffer from chronic or temporary states of anxiety.
Pain after the operation must also be taken into account.
In patients receiving high-dose benzodiazepine treatment over a prolonged period, the benefits of treatment with 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 as a slow intravenous injection.
As sedation and depressed breathing may possibly return, children previously sedated with midazolam should be observed for at least 2 hours after being given flumazenil. If other benzodiazepines have been used for sedation, the observation period must be adjusted according to the expected duration of effect.
Until sufficient data become available, flumazenil must not be used in children aged 1 year or less, unless the risks for the patient (especially in the event of an accidental overdose) have been weighed against the benefits of treatment.
The use of this antagonist is not recommended in patients with epilepsy receiving prolonged benzodiazepine treatment. Although flumazenil has certain intrinsic anti-epileptic effects, the abrupt antagonistic effect may trigger seizures in patients with epilepsy.
In patients with serious brain damage (and/or unstable intracranial pressure) who are receiving flumazenil to reverse the effects of benzodiazepines, raised intracranial pressure may develop.
Patients receiving flumazenil to reverse the effect of benzodiazepines must be monitored for an appropriate period (depending on the dose and duration of effect of the administered benzodiazepine) for re-sedation, depressed breathing or other residual benzodiazepine effects.
Flumazenil is not recommended either for the treatment of benzodiazepine dependence or for the management of protracted benzodiazepine withdrawal syndrome.

In patients with a history of anxiety disorders, panic attacks have been reported to occur after flumazenil use.
Due to the increased frequency of benzodiazepine tolerance and dependence in patients with alcohol or drug addiction, flumazenil should only be used with caution in this patient group.

Instructions for handling:
This medicinal product is intended for single use only and any unused solution must be discarded.

This medicinal product must be visually inspected. It may only be used if the solution is clear and practically free from particles.

When using *Flumazenil Inresa 0.5 mg IV* as an infusion, the medicine must be diluted prior to infusion.

Flumazenil Inresa 0.5 mg IV is compatible with glucose 5% in water, Ringer's lactate solution or isotonic sodium chloride solution. Solutions for infusion for intravenous use must be stored at 2-8°C and discarded after 24 hours.