SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ANESED-R 0.5 mg/5 mL Solution For I.V. Injection

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Each ampoule contains 0.5 mg (0.1 mg/ml) flumazenil.

Excipients:

Sodium chloride: 9,3 mg/ml

See: section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Injectable solution for I.V. Injection

4. CLINICAL PARTICULARS

4.1 Therapeutical indications

Flumazenil is indicated for the complete or partial reversal of the central sedative effects of benzodiazepines. Therefore, it is used in anesthesia and intensive care in the following indications.

In anesthesia: termination of general anesthesia using benzodiazepines for induction and maintenance. Reversal of the sedative effects of benzodiazepines used in short diagnostic and therapeutic procedures in both inpatients and outpatients. In ICU and approach to loss of consciousness of unknown cause: Flumazenil is used to diagnose or determine the absence of benzodiazepine intoxications. In cases of overdose with benzodiazepines, it can also be used to specifically restore the central effects of benzodiazepines (spontaneous breathing and consciousness recovery to prevent unnecessary intubation or to allow intubation).

4.2 Posology and method of administration

Posology/Frequency and Duration of administration:

Unless otherwise recommended by the doctor;

Flumazenil should only be administered intravenously by an anesthesiologist or an experienced physician.

It is compatible with 5% dextrose in water and normal saline solutions. Flumazenil should be discarded after 24 hours being mixed with one of these solutions or drawn into the syringe.

The dose should be titrated according to the intended effect. Since the duration of action of some benzodiazepines may exceed the duration of action of flumazenil, additional doses may be required if sedation recurs after waking.

In anesthesia: The recommended starting dose is 0.2 mg in 15 sec administered introvenously. If the desired consciousness is not reached within 60 seconds, a second dose of 0.1 mg may be injected and, if necessary, repeated every 60 seconds, provided that the total dose does not exceed 1 mg.

Usually the dose administered is 0.3-0.6 mg, but individual requirements may vary depending on the patient characteristics, as well as the duration and dose of benzodiazepines administered.

In ICU and approach to loss of consciousness of unknown cause: The recommended initial dose is 0.3 mg administered i.v. If the desired consciousness is not reached within 60 seconds, flumazenil injections may be continued until the patient wakes up or the total dose reaches 2 mg. If drowsiness occurs again, flumazenil may contain one or more bolus i.v. or 0.1-0.4 mg i.v. infusion. The infusion rate should be adjusted individually for each patient according to the desired degree of alertness. If repeated doses of flumazenil do not improve significant effect on consciousness or respiration function, it should be considered an etiology associated with benzodiazepines.

In high-dose and / or long-term treatment with benzodiazepines in the intensive care unit, the dose of flumazenil should be adjusted very slowly for each patient and should not lead to withdrawal syndromes. If unexpected symptoms occur, diazepam or midazolam can be adjust as regard to patient's response by carefully titrated intravenously (see Special warnings and precautions for use).

Method of administration:

Flumazenil should only be administered intravenously by an anesthesiologist or an experienced physician.

Additional information on special populations:

Renal / Liver failure:

Be careful during exercised in the use of initial / repeat doses in patients with moderate or severe hepatic impairment.

Pediatric population:

Children older than one year: For the recovery of conscious sedation induced by benzodiazepines in children older than one year, the recommended starting dose is i.v. 0.01 mg / kg (up to 0.2 mg). If the desired level of consciousness cannot be achieved after an additional 45 seconds, additional injections of 0.01 mg / kg (up to 0.2 mg) may be given and, if necessary, the maximum total dose to 0.05 mg / kg or 1 mg (whichever is lower) can be

repeated at intervals of up to 60 seconds (maximum 4 times). The dose should be adjusted according to the patient's response.

Geriatric population:

No dosage adjustment is required (see 5.2 Pharmacokinetic properties: Characteristic characteristics of patients).

4.3. Contraindications

The use of flumazenil is contraindicated in patients with known hypersensitivity to flumazenil or any of the excipients contained in the drug or to benzodiazepine. flumazenil is contraindicated in patients receiving benzodiazepine to control potentially life-threatening conditions such as intracranial pressure control or status epilepticus.

The use of flumazenil is contraindicated in patients with symptoms of overdose cyclic antidepressants.

4.4 Special warnings and precautions for use

Seizures may occur during the use of flumazenil. Seizures are more common in patients taking benzodiazepine for long-term sedation or in cases of overdose in which patients exhibit signs of severe cyclic antidepressant overdose. Physicians should adjust flumazenil dose individually for each patient and be prepared to perform seizure treatment.

Risk of seizures:

The reversal of benzodiazepine effects is associated with the onset of seizures in certain high-risk populations. Possible risk factors for seizures include: simultaneous discontinuation of major sedative-hypnotic drug, recent treatment with repeated doses of parenteral benzodiazepines, myoclonic twitches or seizure activity or simultaneous cyclic antidepressant poisoning prior to administration of flumazenil in overdose cases.

Flumazenil is not recommended in cases of severe cyclic antidepressant poisoning manifested by motor anomalies (twitching, rigidity, focal seizures), dysrhythmia (broad QRS, ventricular dysrhythmia, heart block), anticholinergic symptoms (mydriasis, dry mucosa, hypoperistalsis), and cardiovascular collapse.

In such cases, flumazenil should be discontinued and the patient should be sedated (with ventilator and circulatory support if necessary) until symptoms of antidepressant toxicity disappear. flumazenil treatment has no known benefit other than reversing the effects of sedation in severely mixed overdose patients and should not be used in cases of being possibility of seizure (for any reason). Most of the convulsions associated with the administration of flumazenil require treatment and have been successfully treated with

benzodiazepines, phenytoin or barbiturates. Due to the presence of flumazenil, higher doses of benzodiazepine may be required.

Hypoventilation:

In order to reverse the effects of benzodiazepine (following conscious sedation or general anesthesia), patients receiving flumazenil should be monitored for a suitable period (up to 120 minutes) of resedation, respiratory depression or other benzodiazepine effects according to the dose and duration of action of benzodiazepine administered. This is because flumazenil has not been shown to be an effective treatment for the treatment of hypoventilation caused by benzodiazepine administration in patients. In healthy male volunteers, flumazenil is able to reverse the benzodiazepine-induced depression of hypercapnia and ventilatory responses to hypoxia following a single benzodiazepine administration. However, this type of depression may recur because the ventilator effects of typical doses of flumazenil (1 mg or less) are reduced without many benzodiazepine effects. After sedation using benzodiazepine in combination with an opioid, flumazenil has no consistent effects on the ventilator response and these effects have not been adequately investigated. The presence of flumazenil does not eliminate the need for rapid detection of hypoventilation and effective intervention to assist ventilation by opening an airway.

Overdose cases should be monitored for resedation until the patient is stable and the possibility of resedation is eliminated.

Return of Sedation

Flumazenil can be expected to increase the patient's wakefulness following sedation or anesthesia with benzodiazepines, but should not replace post-procedural follow-up for a sufficient period of time. The presence of flumazenil does not eliminate the risks associated with the use of high doses of benzodiazepine for sedation.

Patients should be followed up for a sufficient period of time following flumazenil administration for resedation, respiratory depression, or other sustained or recurrent agonist effects

If flumazenil is administered to reverse the effect of low-dose, short-acting benzodiazepine (<10 mg midazolam), the possibility of resedation is very low.

The risk of resedation is very high if benzodiazepine is administered in high single dose or cumulative doses during a long procedure with neuromuscular blocking agents and multiple anesthetic agents.

Significant resedation was observed in 1% to 3% of adult patients in clinical trials. In adult patients, in clinical situations that resedation should be prevented; doctors may want to repeat the initial dose (flumazenil up to 1 mg given at 0.2 mg / min) after 30 minutes and possibly 60 minutes. Although not studied in clinical trials, this dosing program was effective in preventing a resedation with normal volunteers.

The use of flumazenil to reverse the effects of benzodiazepines for conscious sedation was evaluated in an open-ended clinical trial involving 107 pediatric patients aged 1 to 17 years. This study suggests that pediatric patients who awaken completely after flumazenil administration may experience sedation recurrence, especially at younger ages (1-5 years). Seven out of 60 patients who had fully awakened after 10 minutes from the initiation of flumazenil had resedation. None of the patients returned to baseline sedation. The average time to recedation is 25 minutes (range: 19 to 50 minutes). The safety and efficacy of repeated flumazenil administration in pediatric patients experiencing resedation has not been demonstrated.

Intensive care unit (ICU) use:

Flumazenil should be used with caution in the ICU as the risk of undefined benzodiazepine dependence increases in environments such as the intensive care unit. Flumazenil may cause convulsions in patients with physical dependence on benzodiazepines.

Because of the risk associated with the above-mentioned side effects, Flumazenil is not recommended to diagnose benzodiazepine-induced sedation in the ICU. In addition, the prognostic significance of the patient's nonresponsiveness to flumazenil is unknown in patients who have been confused for metabolic disorder, traumatic injury, drugs other than benzodiazepine, or all other causes not associated with benzodiazepine receptor occupation.

Overdose:

Flumazenil was developed to be used in addition to airway support, respiratory aid, circulatory access and support, internal decontamination with lavage and coal, and not to replace adequate clinical assessment. Before flumazenil administration, necessary precautions should be taken to ensure airway safety, ventilation and intravenous access. After awakening, patients may attempt to pull endotracheal tubes and / or intravenous tubes as a result of confusion and agitation after awakening.

Head injury:

Flumazenil should be used with caution in patients with head injury, as it may cause accelerated convulsions and alter cerebral blood flow in patients receiving benzodiazepines.

However, if such complications occur, they should be used by physicians ready to remedy them.

Use with neuromuscular blocking agents:

Flumazenil should not be used until the effects of neuromuscular blockade are completely reversed.

Use in psychiatric patients:

Flumazenil has been reported to trigger a panic attack in patients with a history of panic disorder.

Pain at the injection site:

To minimize the possibility of pain or inflammation at the injection site; flumazenil should be administered by intravenous infusion flowing freely through a large vein. Local irritation may occur following extravasation into the perivascular tissues.

Respiratory diseases:

Appropriate ventilatory support should be used instead of flumazenil in patients with severe pulmonary disease and severe respiratory depression caused by benzodiazepine.

Flumazenil; in healthy volunteers, it can partially reverse the changes induced by benzodiazepine on the ventilator drive, but its clinical efficacy has not been demonstrated.

Use in cardiovascular diseases:

When Flumazenil was administered at rate of 0.1 mg / min in doses less than 0.5 mg in total to reverse the effects of benzodiazepines in cardiac patients, it did not cause an increase in heart function. Flumazenil alone has no significant effect on cardiovascular parameters when administered to stable ischemic heart patients.

Use in liver diseases:

Flumazenil clearance decreased to 40 to 60% of normal values in patients with mild to moderate hepatic impairment; 25% of normal values in patients with severe hepatic insufficiency. Although the dose of flumazenil used for the initial reversal of benzodiazepine effects is not affected, the size and frequency of the dose should be reduced in repeated use of the drug in liver diseases.

Use in drug and alcohol-dependent patients:

Flumazenil should be used with caution in patients with alcoholism and other drug addictions due to the increased frequency of benzodiazepine tolerance and dependence in this patient population. The use of Flumazenil for the treatment of benzodiazepine dependence or for the treatment of long-term benzodiazepine abstinence is not recommended as such use has not been studied. Administration of flumazenil can accelerate the withdrawal effects of

benzodiazepine in animals and humans. This was seen in healthy volunteers who were treated with oral lorazepam doses for up to 2 weeks and exhibited effects such as hot flashes, agitation, and tremors when treated with cumulative doses of flumazenil up to 3 mg.

Clinical studies have shown similar side effects in some adult patients suggesting that flumazenil accelerates the withdrawal effects of benzodiazepine. These patients had a short-term syndrome characterized by dizziness, mild confusion, emotional imbalance, agitation (with anxiety signs and symptoms), and mild sensory distortion. This response is dose-related; most commonly in doses greater than 1 mg, very rarely required treatment other than reinsurance and is usually short-term. When necessary, these patients (5 to 10 cases) were successfully treated with normal doses of barbiturate, benzodiazepine, and other sedative drugs.

Physicians should keep in mind that the administration of flumazenil may lead to dose-dependent withdrawal syndromes in patients with physical dependence on benzodiazepines and may complicate the treatment of withdrawal syndromes for alcohol, barbiturate and cross-tolerant sedatives.

The use of Flumazenil is not recommended in patients receiving long-term benzodiazepine therapy. Although Flumazenil has a mild anticonvulsion effect, it may suppress the protective effects of benzodiazepine agonists and cause an increase in convulsions.

Rapid injection of Flumazenil in patients who had been exposed to benzodiazepine at high doses or for a prolonged period in the week preceding the administration of Flumazenil; Sensory impairment, agitation, anxiety, mild confusion and emotional change were the symptoms of withdrawal syndrome.

This medicinal product contains less than 1 mmol (23 mg) of sodium per ampoule; that is, it does not contain sodium.

4.5 Interactions with other medical products and other forms of interaction

Flumazenil blocks the central effects of benzodiazepines by competitive interaction at the receptor level. The effects of zopiclone, triazolopyridazines and other non-benzodiazepine agonists on benzodiazepine receptors are also blocked by Flumazenil.

In the presence of Flumazenil, the pharmacokinetic properties of benzodiazepine agonists remain unchanged; but vice versa.

There is no pharmacokinetic interaction between ethanol and flumazenil.

Additional information on special populations:

There are no interaction studies.

Pediatric population:

There are no interaction studies.

4.6 Pregnancy and lactation

General recommendation

Pregnancy category: C

Women with childbearing potential/Contraception

Risk to humans is unknown.

Pregnancy

The safety of flumazenil in pregnant women has not been studied. Therefore, the benefits of drug therapy during pregnancy should be examined for possible risks to the fetus. Flumazenil should not be used during pregnancy unless necessary.

Lactation

Parenteral administration of flumazenil in nursing mothers is not contraindicated in emergencies.

The reproductive capability/Fertility

Studies on animals are insufficient in terms of effects on pregnancy, fetal development and birth. In vitro and animal studies with high doses of flumazenil showed no evidence of mutagenicity teratogenicity or degradation of fertility.

4.7 Effects on ability to drive and use machines

As the effect of benzodiazepine (eg sedation), which has already been swallowed or ingested, may occur, patients should be advised not to engage in hazardous work (such as operating a dangerous machine or driving a motor vehicle) that requires complete mental alertness during the first 24 hours after administration.

4.8 Undesirable effects

The side effects of flumazenil are listed below according to the classification and frequency of organs and systems. Frequency degrees are defined as follows:

Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10.000 and <1/1000), very rare (<1/10.000) and unknown (estimation based on the existing data is impossible).

Post-marketing experience:

Flumazenil is well tolerated in children and adults. Flumazenil was well tolerated, even in amounts exceeding the recommended dose.

Cardiovascular diseases:

Uncommon: Bradycardia, hypertension, ventricular tachycardia, chest pain, arrhythmia

Unknown: Temporary increase in heart rate (during awakening)

Endocrine diseases:

Common: Severe exacerbations

Psychiatric diseases:

Uncommon: Fear

Unknown: Panic attacks, withdrawal syndrome

Diseases of the nervous system:

Very common: dizziness, ataxia,

Common: Headache, Anxiety, irritability, unusual crying, extreme happiness, depression, agitation, dizziness, emotional variability, loss of self, increased tears, dysphoria, paranoia

Uncommon: Insomnia, confusion, generalized convulsions, speech disorders, fatigue

Eye diseases:

Common: Abnormal vision, blurred vision

Ear and internal ear diseases:

Uncommon: Abnormal hearing (transient hearing impairment, hyperacusia, tinnitus)

Cardiac disorders

Uncommon: Palpitations

Respiratory, chest disorders and mediastinal diseases:

Common: Dyspnea, hyperventilation

Gastrointestinal disorders

Very common: Nausea, vomiting

Common: Dry mouth, hiccup

Musculoskeletal disorders, connective tissue and bone diseases:

Common: Shivering, Fatigue, Paresthesia

General disorders and administration site diseases:

Common: Sweating, Pain at the injection site

Rare: Hypersensitivity reactions (including anaphylaxis)

Unknown: Cold feeling

After the rapid injection of Flumazenil, complaints such as anxiety, palpitation and fear were rarely observed. These undesirable effects usually do not require special treatment.

Convulsions have been reported in patients known to have epilepsy or severe hepatic impairment after long-term benzodiazepine treatment or in cases where a combination of several drugs is taken at high doses.

Toxic effects such as convulsion and cardiac dysrhythmia with cyclic antidepressants may be revealed during the reversal of the effects of benzodiazepines with flumazenil, in cases where a combination of several drugs is overdosed.

In patients who have been on benzodiazepine for a long time, rapid flumazenil injection may cause withdrawal symptoms, even if treatment has been discontinued a few weeks before the administration of flumazenil.

Flumazenil has been reported to induce panic attacks in patients with a history of panic disorder.

4.9. Overdose and therapy

There is very limited experience with acute overdose with flumazenil in humans. There is no specific antidote for overdose with flumazenil. Treatment of overdose with flumazenil should be based on general supportive measures in which vital signs are monitored and the patient's clinical condition is observed.

No overdose symptoms were observed when given in amounts exceeding the recommended dose. For withdrawal symptoms from agonists see *4.2 Posology and Method of Administration.*

5. PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic class: Benzodiazepine antagonist

ATC code: V03AB25

ANESED-R, an imidazobenzodiazepine derivative, is a benzodiazepine antagonist. It specifically blocks the effects of agents acting via benzodiazepine receptors on the central nervous system by competitive inhibition. In animal studies, the effects of compounds which are prone to benzodiazepine receptors have been blocked. In healthy volunteers, sedation, amnesia, and psychomotor disorder induced by benzodiazepine agonists were determined by i.v. It has been shown to be antagonized with ANESED-R. The hypnotic-sedative effects of benzodiazepine are reversed rapidly by intravenous injection of ANESED-R (within 1-2 minutes) and may slowly reappear in the next few hours, depending on the agonist and antagonist dose ratio and half-life. ANESED-R may exhibit a weak intrinsic agonistic effect, such as anticonvulsant activity. In animals given high doses of benzodiazepine for several weeks, ANESED-R caused withdrawal symptoms such as seizures. A similar effect was observed in adult humans.

5.2 Pharmacokinetic properties

General properties:

Absorption:

The pharmacokinetics of flumazenil are dose-proportional (up to 100 mg) within and above the therapeutic range (*See Distribution).*

Distribution:

Flumazenil, a weak lipophilic base, binds to plasma proteins in about 50%. Two-thirds of the portion that binds to plasma proteins binds to albumin. Flumazenil is widely distributed in the extravascular region. Plasma concentrations of flumazenil decrease in the dispersion phase with a half-life of 4-11 minutes. The dispersion volume is 0.9-1.1 l / kg in stable state.

Metabolism:

Flumazenil is extensively metabolized in the liver. Carboxylic acid metabolite is the main metabolite in plasma (free) and urine (free and glucuronide). In pharmacological tests, this major metabolite showed benzodiazepine agonist or antagonist activity.

Elimination:

Almost all of the flumazenil (99%) is excreted from the body by extra-renal ways. Considering that the drug is completely metabolized, there is no unchanged flumazenil in the urine. Elimination of the drug labeled with the radioactive substance is completed within 72 hours, of which 90-95% is in the urine and 5-10% is in the feces. Elimination is fast as shown by the half-life of 40-80 minutes. Total plasma clearance of flumazenil is 0.8-1.0 l / h / kg and can be attributed entirely to hepatic clearance.

Food intake during I.V. ANESED-R infusion probably results in a 50% increase in clearance due to high hepatic blood flow accompanying this period.

Characteristics of patients

The pharmacokinetics of ANESED-R are not significantly affected by sex, senility, hemodialysis or renal failure.

Liver Failure:

The elimination half-life of ANESED-R is longer in patients with impaired liver function and total body clearance is lower than in healthy individuals.

Pediatric population:

Elimination half-life in children over one year is usually more variable than in adults with an average of 40 minutes ranging from 20 to 75 minutes. When adjusted for body weight, the clearance and dispersion volume are as seen in adults.

5.3 Preclinical safety data

In vitro and animal studies using high doses of ANESED-R showed no evidence of mutagenicity or fertility disorder.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

EDTA

Glacial acetic acid

Sodium chloride

Water for injection

Sodium hydroxide (for pH adjustment)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at room temperature below 25 ° C.

ANESED-R should be used within 24 hours after drawing into the syringe or after mixing with normal saline or 5% dextrose, provided that it is stored at room temperature below 25 ° C (see Posology and method of administration).

For optimum sterility; The ANESED-R should be kept in the ampoule just before use.

6.5. Nature and contents of container

Type I, 5ml colorless glass ampoule, 5 pieces in the box.

6.6 Special precautions for and other handling

Unused products or waste materials must be disposed of in accordance with the “Regulation Related to the Control of Medical Wastes” and “Regulation Related to the Control of Packaging Materials and Packaging Waste”.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

2019/249

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

First licence date: 09.05.2019

Licence revision date:-

10. DATE OF REVISION OF THE TEXT