ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLUMAZENIL MYLAN 0.1 mg/ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Flumazenil.....0.1 mg
For 1 ml of solution for injection

A 5 ml ampoule contains 0.5 mg of flumazenil.
A 10 ml ampoule contains 1 mg of flumazenil.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Flumazenil is indicated,

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 6 months:

- 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

Flumazenil must be administered by IV route.
Flumazenil may be administered in infusion, diluted in 5 % glucose, Ringer's lactate solution or 0.9 % NaCl solution.

It is recommended to use the titration method (see below).

1. In anaesthesiology

Flumazenil must be administered by an anaesthesiologist/intensive care physician.

a) In adults:
The recommended initial dose is of 0.2 mg, administered by IV route in 15 seconds. If the consciousness level desired is not obtained within 60 seconds, a second 0.1 mg dose may be injected. If necessary, this operation may be repeated at 60 second intervals, the maximum dose is 1 mg. The usual total dose is of 0.3 to 0.6 mg, depending on inter-individual variations that may be observed as a function of the dose and duration of action of the benzodiazepine administered and the characteristics of the patient.

b) In children over 6 months old:
The recommended initial dose is of 0.01 mg/kg (up to 0.2 mg per injection) administered by IV route in 15 seconds. If a satisfactory consciousness level is not obtained after waiting 45 additional seconds, other 0.01 mg/kg (up to 0.2 mg per injection) injections may be administered and repeated every minute, if necessary (up to 4 additional administrations), the maximum total dose is 0.05 mg/kg or 1 mg.

2. In intensive care

Flumazenil must be administered by an anaesthesiologist/intensive care physician.

a) In adults:
The recommended initial IV dose is of 0.3 mg. If the degree of consciousness desired is not obtained within 60 seconds, new injections of flumazenil of 0.2 or 0.3 mg may be performed, until obtaining signs of waking up or until attaining a maximum total dose of 2 mg. If the consciousness level of the patient and his/her respiratory function do not present a significant improvement after administration of this 2 mg total dose, it should admit that the clinical picture is not due to benzodiazepines.

If waking is obtained, and to maintain it, the administration of flumazenil in one or several IV injections of 0.3 mg or in IV infusion of 0.1 to 0.4 mg per hour may be continued. The infusion rate may be adjusted individually as a function of the degree of waking desired.

b) In children (including infants):
The recommended initial dose is of 0.01 mg/kg in slow intravenous injection every 2 minutes until obtaining signs of waking and followed, if necessary, of a continuous infusion with an hourly dose equal to the total loading dose.

3. In an emergency situation or in medical transport in adults and children over 6 years old.

Flumazenil must only be administered by experienced emergency and medical transport doctors.

The objective is to rectify the respiratory depression, also treated with the usual intensive care measures (the use of flumazenil in a hypoxia situation could increase the risk of convulsions and rhythm disorders).

a) In adults:
The recommended initial dose is of 0.2 mg, administered by IV route in 15 seconds. If the consciousness level desired is not obtained within 60 seconds, a second 0.1 mg dose may be injected. If necessary, this operation may be repeated at 60 second intervals, the maximum dose is 1 mg. The usual total dose is of 0.3 to 0.6 mg, depending on inter-individual variations that may be observed as a function of the dose and duration of action of the benzodiazepine administered and the characteristics of the patient.

b) In children over 6 years old:
The recommended initial dose is of 0.01 mg/kg (up to 0.2 mg per injection) administered by IV route in 15 seconds. If a satisfactory consciousness level is not obtained after waiting 45 additional seconds, other 0.01 mg/kg (up to 0.2 mg per injection) injections may be administered and repeated every minute, if necessary (up to 4 additional administrations), the maximum total dose is 0.05 mg/kg or 1 mg.

4.3. Contraindications

Flumazenil is contraindicated in patients with a known hypersensitivity or intolerance to this product (or to benzodiazepines and related substances) or to any ingredient of the product.

Flumazenil is contraindicated in patients who received benzodiazepines or related substances for a pathology that represents a vital risk (increase in intracranial pressure, epileptic seizure).

4.4. Warnings and special precautions for use

Warnings

Since flumazenil often has a shorter duration of action than benzodiazepines, a reappearance of sedation, respiratory depression or any other benzodiazepine residual effect could occur. Therefore, the patients must be monitored until the benzodiazepines effects disappear.

Flumazenil only opposes benzodiazepines, it is ineffective when the absence of waking is due to other products.

In the treatment of patients who received high doses of benzodiazepines and/or where treated in the long term, the benefit of the use of flumazenil must be carefully evaluated against the possible risk of triggering benzodiazepines withdrawal symptoms. In such cases, a rapid injection of high doses of flumazenil (more than 1 mg) could provoke the appearance of these symptoms. If in spite of careful adjustment of the doses, benzodiazepine withdrawal symptoms appear, this may be remedied by administering low doses of an injectable benzodiazepine.

In patients presenting a probable multidrug (especially with tricyclic antidepressants or other medicines that decrease the epileptogenic threshold) intentional or accidental overdose, the antagonism of the benzodiazepine effects by flumazenil could favour the appearance of seizures.

In these patients, a sudden removal of the benzodiazepine effect could also favour the occurrence of rhythm disorders (especially ventricular). The latter could be due to an increase in the sympathetic tonus and occur in particular in case of seizures and cardiovascular history and under heavy intensive care conditions.

Flumazenil will only be used after carrying out a directed interrogation of relations, a complete clinical examination as well as an electrocardiogram. It is not recommended to use flumazenil, in the presence of signs indicative of a multidrug intoxication (for example with tricyclic antidepressants) such as agitated or hypertonic coma, pyramidal or anticholinergic signs (mydriasis, tachycardia), electrical anomalies (lengthening of QT, broadening of QRS).

Flumazenil must not be used in case of hypothermia and/or collapse potentially associated with antidepressants.

The use of the antagonist is not recommended in epileptic patients who received a prolonged benzodiazepine treatment, or in patients who received benzodiazepines to control convulsions, a sudden suppression of the protective effect of benzodiazepines provoked could trigger convulsions.

Flumazenil must not be used for the treatment of benzodiazepine dependence syndrome, due to the risk of a withdrawal syndrome.

Precautions for use

In case of a concomitant use with curare, the neuromuscular blockage must be completely neutralised before administering flumazenil.

Due to a limited experience, flumazenil must be used with precaution:

- in children under 6 months, during reversal of conscious sedation in a hospital setting,
- in children under 6 years, during reversal of conscious sedation in a medical transport or emergency situation,
- in paediatrics, during treatment of an overdose and reversion of the sedative effect induces by the benzodiazepines used for the induction of a general anaesthesia,
- in intensive care of newborns.

In patients presenting a severe cranial trauma (and/or unstable intracranial pressure), flumazenil could favour an increase of the intracranial pressure.

This medicine contains 4.24 mg of sodium per ml of injectable solution: to be taken into account in persons who follow a strict low sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Not applicable

4.6 Pregnancy and lactation

Pregnancy

There are no reliable teratogenesis data in animals. In clinical practice, there is currently insufficient pertinent data to evaluate any possible malformation or foetotoxic effect of flumazenil when administered during pregnancy.

Therefore, the use of flumazenil during pregnancy is advised against except in emergency situations.

Breast-feeding:

Breast-feeding is not a contraindication to the administration of flumazenil in an emergency context. However the continuation of the breast-feeding must take into account the intoxication treated.

4.7 Effects on ability to drive and use machines

Even though intravenous administration of flumazenil does not cause somnolence, patients should be warned against any activity requiring constant attention, for example running machines or driving vehicles, within the 24 hours following the administration of this product, the effect of the benzodiazepines ingested or administered previously could reappear.

4.8 Undesirable effects

During administration in anaesthesiology: rare cases of nausea and/or vomiting.

The following has been occasionally reported: anxiety, palpitation and anguish. Usually, the undesirable effects mentioned did not require any special treatment.

Convulsions have been reported in some patients with a long term benzodiazepine treatment, in particular in epileptic subjects or in a multidrug overdose.

Withdrawal symptoms may appear after a fast injection of flumazenil in patients whose long term benzodiazepine treatment was stopped in the weeks preceding the administration of flumazenil.

Flumazenil may provoke panic attacks in patients who have already suffered from them.

4.9 Overdose

No sign of overdose has been observed, even when flumazenil is administered at doses higher than those recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic class: ANTIDOTES, ATC Code: V03AB25

Flumazenil, imidazo-benzodiazepine, is a benzodiazepine and related substances (zolpiden, zopiclone) antagonist: it specifically blocks by competitive inhibition the effects exerted on the central nervous system of substances that act on benzodiazepine receptors.
In animal experimentation, the effects produced by the substances that do not have an affinity for benzodiazepine receptors (for example, barbiturates, ethanol, meprobamate, GABA-mimetic substances and adenosine receptor agonists) were not modified by flumazenil; however, the effects exerted by non-benzodiazepine agonists of benzodiazepine receptors, such as cyclopyrrolones (for example zopiclone) and triazolopyrradazines were blocked.

The hypnotic and sedative effects of benzodiazepines are rapidly neutralised by flumazenil injected intravenously (1 to 2 minutes, for equimolar doses) and could reappear progressively within hours depending on the half life of the products and the existing ratio between the agonist and antagonist doses administered. Flumazenil is well tolerated, even at high doses and especially on a haemodynamic level.

Flumazenil can exert a low intrinsic agonist activity, for example anticonvulsive.

5.2 Pharmacokinetic properties

Distribution

Flumazenil is a weak lipophilic base, with a plasma protein binding ratio of approximately 50%. Albumin accounts for two thirds of the plasma proteins to which it binds.

Flumazenil is widely distributed in the extravascular space.

Plasma flumazenil concentrations decrease with a half-life of 4 to 11 minutes during the distribution phase.

Its mean distribution volume at the plateau concentration (Ves=0.95 l/kg) is close to that of benzodiazepines with a similar structure.

Metabolism

Flumazenil is largely metabolised by the liver. The main metabolite identified in plasma (as the free form) and in urine (as the conjugated form) is carboxylic acid.

This metabolite turned out to be inactive.

Elimination

Flumazenil metabolites are almost entirely (99%) eliminated by urinary route.

Less than 1% of the flumazenil dose injected is excreted as the unchanged form in urine, suggesting a complete metabolic degradation in the body.
Elimination is fast, as shown by the short elimination half-life of 40 to 80 minutes. The total plasma clearance of flumazenil is 0.8 to 1 l/h/kg and could be attributed to hepatic clearance.

The basic pharmacokinetics parameters of flumazenil were not modified during simultaneous administration of flumazenil with benzodiazepines, midozolam, flunitrazepam or lormetazepam.

Special clinical situations

The elimination half life of flumazenil in patients with hepatic failure is longer and the total clearance is smaller than in healthy subjects.

The flumazenil pharmacokinetics are not significantly affected by sex, age, chronic renal failure or in patients undergoing haemodialysis.
In children over 1 year, the elimination half-life is shorter and more variable than in adults. It is of 40 minutes on average and generally ranges between 20 and 75 minutes. The clearance and distribution volume with respect to body weight are within limits equivalent to those observed in adults.

There are no pharmacokinetic data on infants under 1 year.

5.3. Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid, disodium edetate, sodium chloride, sodium hydroxide, water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Before opening: To be stored at a temperature below +25°C.

After opening: The product must be used immediately.

From a microbiological viewpoint, if not used immediately, the time and storage conditions after opening and before use are the sole responsibility of the user and should not exceed 24 hours at a temperature comprised between +2°C and +8°C (refrigerated).

6.5 Nature and contents of container

5 ml in ampoule (type I colourless glass). Box of 1, 2, 5, 6, 10 or 25 ampoules.
10 ml in ampoule (type I colourless glass). Box of 1, 2, 5, 6, 10 or 25 ampoules.

6.6 Instructions for use, handling and disposal

Flumazenil may be administered by infusion, diluted in 5 % glucose, Ringer lactate solution or 0.9% NaCl solution.

7. Manufacturer:

Manufactured for MYLAN S.A.S, France
by Hamlen Pharmaceuticals GmbH, Germany

8. Registration holder:

Genmedix, 12 Beit Harishonim st., Emek Hefer

Israeli Drug License number: 138-66-31544-00

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