Product Name: **FLUMAZENIL**	Territory: **MY**	Colour: ● **BLACK** ● **Die Cut**	1. Draft 04.03.2020, 08:30		Variable Data:
Type of Packaging: **PIL**	Dosage: **5x5ml / 5x10ml**				
Material number: **M080387/00 MY**	2-D-Matrix Code **M080387/00 MY**				
Pharma-Code (Laetus) **-**	EAN Code:				
Dimension: **180 x 588 mm**	Font: Arial Smallest Size: 8 Pt.		Operator: **Roberto Grill**		

PACKAGE INSERT – INSTRUCTIONS FOR USE – READ CAREFULLY!

Product Name
Flumazenil Kabi 0.1 mg/ml solution for injection

Name and strength of active ingredients
Each ml contains 0.1 mg flumazenil.
1 ampoule with 5 ml contains 0.5 mg flumazenil.

Product description
Solution for injection
Concentrate for solution for infusion
Clear colourless solution

Pharmacodynamics/Pharmacokinetics
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.

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 4-11 minutes. The distribution volume under steady-state conditions (Vss) is 0.9 – 1.1 L/kg.

Metabolism
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.

Pharmacokinetics in special patient groups
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.

Indications
Flumazenil 0.1mg/ml injection is indicated for the complete or partial reversal of the central sedative effects of benzodiazepines. It may therefore be used in anaesthesia and in intensive care in the following situations:

In anaesthesia
- Termination of hypnosedative effects in general anaesthesia induced and/or maintained with benzodiazepines in hospitalized patients.
- Reversal of benzodiazepine sedation in short-term diagnostic and therapeutic procedures in ambulatory patients and hospitalized patients.

In intensive care situations:
- For diagnosis of intoxication with benzodiazepines or to rule out such intoxication.
- As a diagnostic measure in unconsciousness unknown origin to differentiate between involvement of benzodiazepines, other drugs or brain damage.
- For specific reversal of the central effects of benzodiazepines in drug overdose (return to spontaneous respiration and consciousness in order to render intubation unnecessary or allow extubation).

Recommended dosage
Adults :

Anaesthesia
The recomended starting dose is 0.2mg administered intravenously over 15 seconds. If the required level of consciousness is not obtained within 60 seconds, a further dose of 0.1mg can be injected and repeated at 60-second intervals, up to a maximum dose of 1.0mg. The usual dose required lies between 0.3mg and 0.6mg, but may vary depending on the patient's characteristics, the dose and duration of effect of benzodiazepine used.

Intensive Care
The recommended starting dose is 0.3mg administered intravenously. If the required level of consciousness is not obtained within 60 seconds, a further dose can be injected and repeated at 60-seconds intervals, up to a total dose of 2mg or until the patient awakes. If drowsiness recurs, an intravenous infusion of 0.1-0.4mg/h may be useful. The rate of infusion should be adjusted individually to achieve the desired level of consciousness.
If a significant improvement in consciousness and respiratory function is not obtained after repeated doses of flumazenil, a non-benzodiazepine aetilogy, must be assumed.
To avoid withdrawal symptoms in patient 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. If the symptoms of overstimulation arise during the use of flumazenil, then diazepam or midazolam may be administered by slow intravenous injection.

Children above 1 year of age
For the reversal of conscious sedation induced by benzodiazepines for children older than 1 year, the starting dose is 0.01mg/kg (up to 0.2mg) administered intravenously over a period of 15 seconds. If after an additional waiting period of 45 seconds, the required level of consciousness is not obtained, a follow-up injection of 0.01mg/kg (up to 0.2mg) may be administered and if necessary, repeated at 60 seconds interval (up to maximum of 4 times) to a maximum dose of 0.05mg/kg or 1mg, depending on which is the lowest dose. The dose may be adjusted according to the patient's response.

Route of Administration
Flumazenil should be administered intravenously by an anaesthetist or experienced physician.
Flumazenil may be administered as infusion (see section: Storage Conditions).
Flumazenil may be used concomitantly with other resuscitative measures.
For instructions on dilution of the medicinal product before administration, see section Storage Conditions

Contraindications
Hypersensitivity to flumazenil or to any of the excipients listed in section Composition.

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.

Warnings and precautions
Use in children for other indications than reversal of conscious sedation is not recommended as no controlled studies are available. The same applies for children below the age of 1 year.
- Until sufficient data are available, flumazenil should only be administered to children below the age of 1 year if the risks to the patient (especially in case of accidental overdose) have been weighed up against the benefits of the treatment.
- Elimination may be delayed in patients with hepatic impairment.
- The antagonistic effect of flumazenil is specific to benzodiazepines; an effect is therefore not to be expected if the 'non-awakening' is caused by other substances. If flumazenil is administered for anaesthesiology at the end of the operation, the effect of the peripheral muscle relaxants must first have disappeared. Because flumazenil generally has a shorter duration of action than the benzodiazepines and therefore sedation can re-occur, the clinical state of the patient must be monitored, preferably in the intensive care unit, until the effect of flumazenil is eliminated.
- In high-risk patients the benefits of a benzodiazepine-induced sedation should be weighed up against the risks of rapid return to consciousness. In patients (e.g. with cardiac problems), maintenance of a certain degree of sedation during the early post-operative period may be preferable to complete consciousness
- Rapid injection of flumazenil should be avoided. In patients with high dose and/or long-term exposure to benzodiazepines ending at any time within the weeks preceding Flumazenil administration, rapid injection of doses equal to 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 who are anxious during the pre-operative phase or patients who are known to suffer from chronic or transient anxiety, the dosage of flumazenil should be adjusted carefully.
- However, after major surgery, the post operative pain should be considered and it may be preferable to keep the patient lightly sedated.
- For patients who have been treated chronically with high doses of benzodiazepines, the advantages of the use of flumazenil should be carefully weighed up against the risk of withdrawal symptoms; if, despite careful dosing, withdrawal symptoms occur, treatment with low doses of benzodiazepines, titrated intravenously according to the patient's response, may be considered if necessary.
- 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 exerts a slight intrinsic anti convulsant effect, the abrupt suppression of the protective effect of a benzodiazepine agonist can induce convulsions in epileptic patients.
- In patients with serious brain injury (and/or instable intracranial pressure) who are being treated with flumazenil – to antagonise the effects of benzodiazepines – increased intracranial pressure may develop.
- 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.
- 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 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.
- Flumazenil is not recommended for the treatment of benzodiazepine dependence or for the treatment of protracted 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 its population.
- This medicinal product contains approximately 3.7 mg sodium per ml of flumazenil solution for injection. This should be taken into consideration by patients on a controlled sodium diet.

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.

Interactions with other medicaments
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.

Statement on usage during pregnancy and lactation
There are insufficient data on use in human pregnancy for an assessment of possible harmful effects and efficacy in the foetus. Caution is therefore required. To date, there is no evidence of harmful effects in animal studies. The efficacy in the foetus has not been investigated in animal studies.
It is not known whether flumazenil passes into breast milk. In emergency situations, however, the parenteral administration of flumazenil to a patient who is breastfeeding is not contraindicated.

Adverse Effects/Undesirable Effects
The adverse events listed below have been reported. Adverse events usually subside rapidly without the need for special treatment.
Frequency categories are defined using the following convention: 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.
Psychiatric disorders	
Uncommon	Anxiety*, fear*
Not known	Withdrawal symptoms (e.g., agitation, anxiety, emotional lability, confusion, sensory distortions), following rapid injection of doses of 1 mg or more in patients with high-dose and/or long-term exposure to benzodiazepines ending at any time within the weeks preceding flumazenil administration (see section 4.4),; panic attacks (in patients with a history of panic reactions); abnormal crying, agitation, aggressive reactions (the side effect profile in children is generally similar to that in adults. When flumazenil has been used for the reversal of conscious sedation, abnormal crying, agitation and aggressive reactions have been reported).
Nervous system disorders	
Common	Vertigo, headache, agitation*, tremor.
Not known	Seizures: particularly in patients known to suffer from epilepsy or severe hepatic impairment, mainly after long-term treatment with benzodiazepines or mixed-drug abuse).
Eye disorders	
Common	Diplopia, strabismus, lacrimation increased.
Cardiac disorders	
Uncommon	Palpitations* tachycardia or bradycardia, extrasystole.
Vascular disorders	
Common	hypotension, orthostatic hypotension
Not known	Transient increased blood pressure (on awakening).
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, cough, nasal congestion.
Gastrointestinal disorders	
Common	Nausea, vomiting: during postoperative use, particularly if opiates have also been used..
Skin and subcutaneous tissue disorders	
Common	Sweating.
Not known	Flushing.
General disorders and administration site conditions	
Common	Fatigue, injection site pain.
Uncommon	Chills*.

*: following rapid injection, generally did not require treatment

Overdose and treatment
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.

Incompatibilities
This medicinal product must not be mixed with other medicinal products except for those mentioned in section Storage conditions.

Storage conditions
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 medicinal product is for single use only.
Do not use this medicine if the solution is not clear and free from particles.
Any unused solution should be discarded in accordance with local requirements.
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.

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.

Instruction for use and 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.

Dosage forms and packaging available
Carton boxes with 5 ampoules (glass Type I) containing 5 ml solution for injection.

Name and Address of Manufacturer/Product Owner
Manufactured by:
Fresenius Kabi Austria GmbH
A-8055 Graz, Austria

on behalf of:
Fresenius Kabi Deutschland GmbH
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FRESENIUS KABI