NEW ZEALAND DATA SHEET

1 PRODUCT NAME (strength pharmaceutical form)

Flumazenil Kabi 0.1 mg/mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 0.1 mg flumazenil.

1 ampoule with 5 mL contains 0.5 mg flumazenil.

1 ampoule with 10 mL contains 1 mg flumazenil.

For the full list of excipients, see **section 6.1.**

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Flumazenil Kabi Injection is a colourless to almost colourless clear liquid. The active ingredient of flumazenil belongs to the chemical group of 1,2- imidazo benzodiazepines and is ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo- 4H-imidazo [1,5-a] [1,4] benzodiazepine -3- carboxylate (flumazenil). It has a molecular weight of 303.3.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Flumazenil Injection is indicated for reversal of the centrally sedative effects of benzodiazepines.

It should therefore be used in anaesthesia and intensive care in the following indications:

In anaesthesia

- Termination of general anaesthesia induced and maintained with benzodiazepines in inpatients.

- Reversal of benzodiazepine sedation in short diagnostic and therapeutic procedures in both inpatients and outpatients.

- Reversal of paradoxical reactions due to benzodiazepines.

In intensive care and in the management of unconsciousness of unknown origin

- For the diagnosis and/or management of benzodiazepine overdose due to self-poisoning or accidental overdose.

- As a diagnostic measure in unconsciousness of unknown origin to differentiate between involvement of benzodiazepines, other medicines or drugs or brain damage.

- Flumazenil Injection may also be used for specific reversal of the central effects of benzodiazepines in drug or medicine overdose (return to spontaneous respiration and consciousness in order to render intubation unnecessary or allow extubation).

4.2 Dose and method of administration

Flumazenil Injection is recommended for intravenous (IV) use only and should be administered by an anaesthesiologist or experienced physician.

For instructions on handling Flumazenil Injection, see Pharmaceutical Particulars.

Dosage should be titrated for the intended effect. Since the duration of action of some benzodiazepines may exceed that of Flumazenil Injection, repeated doses may be required if sedation recurs following awakening.

In anaesthesia

The recommended initial dose of Flumazenil Injection is 0.2 mg administered IV over 15 seconds. If the desired degree of consciousness is not obtained within 60 seconds, a second dose of 0.1 mg can be injected; this may be repeated at 60-second intervals where necessary, up to a total dose of 1 mg. The usual dose is 0.3-0.6 mg, but individual requirements may vary considerably, depending on the dose and duration of effect of the benzodiazepine administered and patient characteristics.

In intensive care and in the management of unconsciousness of unknown origin.

The recommended initial dose of Flumazenil Injection is 0.3 mg IV. If the desired level of consciousness is not obtained within 60 seconds, Flumazenil Injection may be injected repeatedly until the patient awakes or up to a total dose of 2 mg. If drowsiness recurs, Flumazenil Injection may be administered as one or more bolus IV doses as above, or as an IV infusion of 0.1-0.4 mg per hour. The rate of infusion should be individually adjusted to the desired level of arousal.

If a significant improvement in consciousness or respiratory function is not obtained after repeated doses of Flumazenil Injection, a non-benzodiazepine aetiology must be assumed.

In the intensive care unit, in patients treated with high doses of benzodiazepines and/or for long periods of time, the individually titrated injections of Flumazenil Injection, slowly administered, should not produce withdrawal syndromes. If unexpected symptoms occur, diazepam or midazolam could be carefully titrated intravenously according to patient response (see Warnings and Precautions).

Special dosage instructions

Children >1 year-of-age

For the reversal of conscious sedation induced with benzodiazepines in children above one year-of age, the recommended initial dose is 0.01 mg/kg (up to 0.2 mg) administered IV over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, further injections of 0.01 mg/kg (up to 0.2 mg) can be administered and repeated at 60 second intervals where necessary (up to a maximum of four additional times) to a maximum total dose of 0.05 mg/kg or 1 mg, whichever is lower. The dose should be individualised based on patient response. No data are available on the safety and efficacy of repeated administration of Flumazenil Injection to children for re-sedation.

Hepatic Impairment

Since Flumazenil Injection is primarily metabolised in the liver, careful titration of dosage is recommended in patients with impaired hepatic function.

4.3 Contraindications

- In patients with known hypersensitivity to the drug.
- Patients who have been given a benzodiazepine for control of a potentially life-threatening condition (e.g. control of intracranial pressure or status epilepticus).
- In mixed intoxications with benzodiazepines and cyclic 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 effects.

- contraindicated in patients with any hypersensitivity to the active ingredient or any of the excipients listed in Section 6.1).

4.4 Special warnings and precautions for use

Flumazenil blocks the effects of benzodiazepines in animals and can precipitate benzodiazepine withdrawal at high doses (refer to sections 5, 4.5 and 4.8). Flumazenil injection should be administered cautiously to patients with known or suspected benzodiazepine dependency or who have been treated with high doses of benzodiazepines for the weeks preceding the treatment. In such cases the reversal of benzodiazepine effects may precipitate withdrawal symptoms or convulsions. Titration of the dose may help to reduce this risk. In case of unexpected signs of withdrawal a slow intravenous injection of 5 mg diazepam or 5 mg midazolam should be given.

Flumazenil may remove the protective effect of benzodiazepines in multiple drug overdose. There have been several reports of tachyarrhythmia (the pathogenesis of which is unclear) following flumazenil administration in the presence of known arrhythmogenic drug overdose. Convulsions in epileptics previously treated with benzodiazepines may occur.

Consideration should be given to the possibility of resedation, respiratory depression or other residual benzodiazepine effects following the use of flumazenil. These patients should be monitored for an appropriate period based on the dose and duration of effect of the benzodiazepine employed.

The use of flumazenil in intensive care units for the interruption of long term/over sedation is not recommended because of a relative lack of clinical experience.

Flumazenil injection should not be used as a routine empirical means of assessing unconscious patients in settings where resuscitation equipment and expertise to deal with complications are not immediately to hand.

Patients with head injury (and/or unstable intracranial pressure) treated with flumazenil to reverse the effects of benzodiazepines may develop raised intracranial pressure. In addition, flumazenil may be capable of precipitating convulsions or altering cerebral blood flow in patients with head injury receiving benzodiazepines.

The use of flumazenil is not recommended in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Although flumazenil exerts a slight intrinsic anticonvulsant effect, its abrupt suppression of the protective effect of a benzodiazepine agonist can give rise to convulsions in epileptic patients.

When flumazenil is used with neuromuscular blocking agents, it should not be injected until the effects of neuromuscular blockade have been fully reversed.

Rapid injection of flumazenil should be avoided in patients with high dose and/or long-term exposure to benzodiazepines ending at any time within weeks preceding flumazenil administration as it may produce withdrawal symptoms, including agitation, anxiety, emotional lability as well as mild confusion and sensory distortions.

Flumazenil is not recommended either as a treatment for benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndromes.

When used in anaesthesiology at the end of the operation, flumazenil should not be injected before the effect of peripheral muscle relaxants has disappeared.

Paediatric population

An uncontrolled, single arm study has been conducted in children aged 1-17 years (n = 107) who were given weight based titration doses (see section 4.2) after undergoing various procedures (such as GI endoscopy and bronchoscopy) under midazolam. Agitation and aggressive reactions were seen in 3 % and 2 % of children respectively. The pharmacokinetic data from a subset of 27 children showed high variability in pharmacokinetic parameters, although the mean clearance was similar to that in historical control data in adults.

4.5 Interaction with other medicines and other forms of interaction

Flumazenil blocks the central effects of benzodiazepines by competitive interaction at the receptor level; the effects of nonbenzodiazepine agonists at benzodiazepine receptors, such as zopiclone, triazolopyridazines and others are also blocked by flumazenil. Interactions with other CNS depressant substances have not been observed.

The pharmacokinetics of benzodiazepines is unaltered in the presence of the antagonist flumazenil.

Particular caution is necessary when using flumazenil in cases of mixed drug overdose since the toxic effects (such as convulsions and cardiac dysrhythmias) of other drugs taken in overdose (especially cyclic antidepressants) may emerge with the reversal of the benzodiazepine effect by flumazenil.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B3

This category specifies drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of

an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

The safety of flumazenil in human pregnancy has not been established. Therefore the benefits of drug therapy during pregnancy should be weighed against risks to the foetus.

No evidence of teratogenicity was observed in pregnant rats or rabbits given oral doses of flumazenil up to 150 mg/kg/day throughout the period of organogenesis. These doses represented > 300 to 1700-fold the clinical exposure at the maximum recommended I.V. dose of 2 mg, based on AUC. In rabbits, embryotoxicity (increased resorptions) was observed at oral doses ≥ 50 mg/kg/day (>500 times the clinical exposure, based on AUC). The no-effect dose was 15 mg/kg/day (170 times the clinical exposure, based on AUC).

Because animal reproduction studies are not always predictive of human response, flumazenil should be used during pregnancy only if clearly needed.

Breastfeeding

Caution should be exercised when deciding to administer flumazenil to a breastfeeding woman because it is not known whether flumazenil is excreted in human milk.

Oral administration of flumazenil to pregnant rats at 125 mg/kg/day from late gestation through weaning was associated with decreased pup survival, increased pup liver weight and retarded physical development (delayed incisor eruption and ear opening). This dose represented > 300-fold the clinical exposure at the maximum recommended dose of 2 mg, based on AUC. The no-effect dose was 25 mg/kg/day (65 times the clinical exposure, based on available AUC data).

Fertility

Flumazenil did not affect fertility in female and male rats at oral doses up to 125 mg/kg/day (>300 times the clinical exposure at the maximum recommended i.v. dose of 2 mg, based on AUC).

4.7 Effects on ability to drive and use machines

Patients should be warned against engaging in hazardous activities requiring complete mental alertness (such as operating dangerous machinery or driving a motor vehicle) during the first 24 hours after administration since sedation and drowsiness may occur.

4.8 Undesirable effects

Flumazenil is well tolerated in adults and children. In adults, Flumazenil is well tolerated even at doses exceeding those recommended.

Hypersensitivity reactions, including anaphylaxis, have been observed.

Complaints such as feelings of anxiety, palpitations and fear have been infrequently observed after rapid injection of Flumazenil. These adverse effects usually do not necessitate special treatment.

Seizures have been reported in patients known to suffer from epilepsy or severe hepatic impairment, particularly after long-term treatment with benzodiazepines or in cases of mixed drug overdose.

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.

Withdrawal symptoms may occur following rapid injection of flumazenil in patients with long-term exposure to benzodiazepines ending at any time within the weeks preceding flumazenil administration.

Flumazenil has been reported to provoke panic attacks in patients with a history of panic disorders.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

There is very limited experience of acute overdose in humans with flumazenil.

Even when given at a dosage of 100 mg intravenously, no symptoms of overdosage were observed. For withdrawal symptoms attributable to the agonist, refer to section 4.4. For advice on the management of overdose please contact the National Poisons Centre for advice on management (in Australia call 13 11 26; in New Zealand call 0800 POISON (0800 764 766)).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Flumazenil, an imidazobenzodiazepine, is a benzodiazepine antagonist which specifically blocks the central effects of agents acting through the benzodiazepine receptor by competitive inhibition. In animal experiments the effects of compounds showing no affinity for the benzodiazepine receptor, e.g. barbiturates, ethanol, meprobamate, GABA mimetics, adenosine receptor agonists and other agents were not affected by flumazenil, but those of nonbenzodiazepine agonists of benzodiazepine receptors, such as cyclopyrrolones (e.g. zopiclone) and triazolopyridazines were blocked.

Flumazenil reverses the central sedative effects of benzodiazepines.

The hypnotic-sedative benzodiazepine effects are rapidly reversed by flumazenil after its intravenous injection (1 to 2 minutes) and may reappear gradually within the next few hours, depending on the half-life and dose ratio of the agonist and antagonist.

Flumazenil is well tolerated even in high doses.

Flumazenil may possess some weak intrinsic agonistic (e.g. anticonvulsant) activity.

In animals pre-treated with high doses of benzodiazepines over several weeks, flumazenil elicited signs of withdrawal, including seizure. A similar effect was seen in adult human subjects.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Flumazenil, a weak lipophilic base, is about 50% bound to plasma proteins. Albumin accounts for two thirds of the plasma protein binding. Flumazenil is extensively distributed in the extravascular space. The distribution phase of flumazenil is approximately 4 minutes.

The mean volume of distribution at steady state (Vss = 0.95 L/kg) is close to that of structurally related benzodiazepines and indicates tissue binding and/or partitioning of the drug.

Biotransformation

The carboxylic acid was identified in free and conjugated form as the main metabolite in human urine. In pharmacological tests, this main metabolite was inactive as a benzodiazepine agonist or antagonist.

Elimination

The average elimination half-life of flumazenil is 53 minutes.

Flumazenil is almost completely (99%) non-renally eliminated. Practically no unchanged flumazenil is excreted in the urine, suggesting complete metabolic degradation of the drug. Elimination of radiolabelled drug is essentially complete within 72 hours, with 90 to 95% of the radioactivity appearing in urine and 5 to 10% in the faeces. Elimination is rapid, as shown by a short elimination half-life of 40 to 80 minutes. The total plasma clearance of flumazenil is on average 1 L/min and can be attributed almost entirely to hepatic clearance. The low renal clearance rate suggests an effective reabsorption of the drug after glomerular filtration.

Ingestion of food during an intravenous infusion of flumazenil results in a 50% increase in clearance, most likely due to the increased hepatic blood flow that accompanies a meal.

When administered together with the benzodiazepines midazolam, flunitrazepam or lormetazepam, the basic pharmacokinetic parameters of flumazenil were not affected**.**

Pharmacokinetics in Special Populations

In patients with impaired liver function, the elimination half-life of flumazenil is longer and the total body clearance lower than in healthy subjects. In patients with moderate to severe hepatic impairment, clearance of flumazenil was found to be reduced by 57 to 74% and the elimination half-life prolonged up to 2-fold.

The pharmacokinetics of flumazenil are not significantly affected in the elderly, haemodialysis, or renal failure.

5.3 Preclinical safety data

Carcinogenesis

No long-term animal studies on the carcinogenic potential of flumazenil have been performed.

Mutagenesis

Flumazenil was not mutagenic in bacterial (*Salmonella typhimurium* or *Saccharomyces cerevisiae*) or mammalian (V79) cells *in vitro* nor clastogenic in human lymphocytes in vitro or rat micronuclei *in vivo*. Flumazenil caused a slight increase in unscheduled DNA synthesis in rat hepatocytes *in vitro* while no induction of DNA repair was observed in mouse germ cells *in vivo*.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate

Glacial acetic acid

Sodium chloride

Sodium hydroxide for pH adjustment

Water for injections

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in Section 6.6.

6.3 Shelf life

24 months

To reduce microbial contamination hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2° to 8°C for not more than 24 hours.

6.4 Special precautions for storage

Flumazenil Kabi Injection should be kept in a cool dry place where the temperature stays below 25 °C. For storage conditions after dilution of the medicine, see section 6.3

6.5 Nature and contents of container

Flumazenil Kabi 5 mL ampoules contain 0.5 mg flumazenil in 5 mL aqueous solution for intravenous (IV) administration. Flumazenil Kabi 10 mL ampoules contain 1 mg flumazenil in 10 mL aqueous solution for intravenous (IV) administration. Flumazenil Kabi is a colourless to almost-colourless, sterile, clear liquid stored in 5 mL and 10 mL glass ampoules. Flumazenil Kabi ampoules are supplied in packs of five or ten.

6.6 Special precautions for disposal and other handling.

Flumazenil Kabi Injection is for use in one patient only. Discard any remaining contents.

Flumazenil Kabi may be diluted in glucose 5% in water or 0.9% Sodium Chloride for infusion and may also be used concurrently with other resuscitative procedures.

7 MEDICINE SCHEDULE

New Zealand: Prescription Medicine

8 SPONSOR

Fresenius Kabi New Zealand Limited

60 Pavilion Drive

Airport Oaks, Auckland

New Zealand

Freecall: 0800 144 892

9) DATE OF FIRST APPROVAL

5th April 2019