NEW ZEALAND DATA SHEET

1 FLUMAZENIL-BAXTER (0.1mg/mL, solution for injection)

Flumazenil-Baxter 0.5mg/5mL solution for injection.
Flumazenil-Baxter 1.0mg/10mL solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Flumazenil-Baxter, solution for infusion contains 0.1mg flumazenil per mL.

One 5mL ampoule contains 0.5mg flumazenil.
One 10mL ampoule contains 1.0mg flumazenil.

Each 1mL of **Flumazenil-Baxter** solution for injection contains approximately 3.5mg of sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Flumazenil-Baxter is a clear, colourless to almost-colourless, sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Flumazenil-Baxter 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-Baxter** 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

Dosage

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

For instructions on handling **Flumazenil-Baxter**, see section 6.6.

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

In anaesthesia

The recommended initial dose of **Flumazenil-Baxter** is 0.2mg administered IV over 15 seconds. If the desired degree of consciousness is not obtained within 60 seconds, a second dose of 0.1mg can be injected; this may be repeated at 60-second intervals where necessary, up to a total dose of 1mg. The usual dose is 0.3 - 0.6mg, 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-Baxter** is 0.3mg IV. If the desired level of consciousness is not obtained within 60 seconds, **Flumazenil-Baxter** may be injected repeatedly until the patient awakes or up to a total dose of 2mg. If drowsiness recurs, **Flumazenil-Baxter** may be administered as one or more bolus IV doses as above, or as an IV infusion of 0.1 - 0.4mg 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-Baxter**, 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-Baxter**, slowly administered, should not produce withdrawal syndromes. If unexpected symptoms occur, diazepam or midazolam could be carefully titrated intravenously according to patient response (see section 4.4).

Special dosage instructions

Children under the age of 1 year

There are insufficient data on the use of flumazenil in children younger than 1 year. Therefore, **Flumazenil-Baxter** should only be administered in children younger than 1 year if the potential benefits to the patient outweigh the possible risk.

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 0.01mg/kg (up to 0.2mg) administered IV over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, further injections of 0.01mg/kg (up to 0.2mg) 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 0.05mg/kg or 1mg, 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 to children for re-sedation.

Patients with renal and hepatic impairment

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

4.3 Contraindications

Flumazenil-Baxter is contraindicated in patients with known hypersensitivity to this medicine, the active substance or to any of the excipients listed in section 6.1.

Flumazenil-Baxter is contraindicated in 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-Baxter** should not be used to reverse benzodiazepine effects.

4.4 Special warnings and precautions for use

General

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

Mixed substance overdose

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

Epileptic patients

The use of **Flumazenil-Baxter** 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.

Reversal of benzodiazepine effects

Patients who have received **Flumazenil-Baxter** 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. As patients with underlying hepatic impairment may experience delayed benzodiazepine effects, an extended observation period may be required.

Concomitant use with neuromuscular blocking agents

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

Patients with head injury

Flumazenil-Baxter should be used with caution in patients with head injury as it may be capable of precipitating convulsions or altering cerebral blood flow in patients receiving benzodiazepines.

Patients with long term benzodiazepine exposure

Rapid injection of **Flumazenil-Baxter** should be avoided in patients with high dose and/or long-term exposure to benzodiazepines ending at any time within the weeks preceding **Flumazenil-Baxter** administration as it may produce withdrawal symptoms, including agitation, anxiety, emotional lability as well as mild confusion and sensory distortions (see section 4.2).

Paediatric patients

Flumazenil-Baxter should be used with caution for the reversal of conscious sedation in children below the age of one year, for the management of overdose in children, for resuscitation of the newborn and for reversal of the sedative effects of benzodiazepines used for induction of general anaesthesia in children, as experience is limited (see section 4.2).

Patients with hepatic impairment
See section 4.2/Special dosage instructions.

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 - 74% and the elimination half-life prolonged up to 2-fold.

Elderly
The pharmacokinetics of flumazenil are not significantly affected in the elderly.

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 non-benzodiazepine agonists at benzodiazepine receptors, such as zopiclone, triazolopyridazines and others, are also blocked by flumazenil. Interactions with other centrally acting (CNS) substances have not been observed.

The pharmacokinetics of benzodiazepine agonists are unaltered in the presence of flumazenil and vice versa.

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 medicinal products taken in overdose (especially tricyclic antidepressants) may emerge with the reversal of the benzodiazepine effect by flumazenil.

There is no pharmacokinetic interaction between ethanol and flumazenil.

4.6 Fertility, pregnancy and lactation

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

Pregnancy - Pregnancy category B3
Although *in vitro* and animal studies using high doses of flumazenil have not shown evidence of mutagenicity, teratogenicity or impairment of fertility, the safety of flumazenil in human pregnancy has not been established.

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

Because animal reproduction studies are not always predictive of human responses, the benefits of flumazenil during pregnancy should be weighed against the possible risks to the foetus.

Breast-feeding
It is not known whether flumazenil passes into breast milk. In emergency situations, however, the parenteral administration of **Flumazenil-Baxter** to a patient who is breastfeeding is not contraindicated.

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 the effect of the originally ingested or administered benzodiazepine (for example, sedation) may occur.

4.8 Undesirable effects

Summary of the safety profile

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.

Tabulated list of adverse reactions

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 (< /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 1mg 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 in cases of 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	Dyspnea, cough, nasal congestion.
Gastrointestinal disorders	
Common	Nausea, vomiting: during post-operative 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.
Not known	Chills*.
*: following rapid injection, generally did not require treatment.	

Description of selected adverse reactions

In cases of mixed-substance 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 **a**dministration.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Other special populations

Epileptic patients

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-substance overdose.

Patients with a history of panic disorders/anxiety

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

Reporting of suspected adverse reactions

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

4.9 Overdose

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

There is no specific antidote for overdose with flumazenil. Treatment of an overdose with flumazenil should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

Even when given at doses exceeding those recommended, no symptoms of overdosage were observed. For withdrawal symptoms, attributable to the agonist, see section 4.2.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Antidotes (benzodiazepine antagonist).

ATC code

V03AB25.

Mechanism of action

Flumazenil, an imidazobenzodiazepine derivative, is a benzodiazepine antagonist. It competitively inhibits agents that act via benzodiazepine receptors, specifically blocking their central nervous effects. In animal experiments, the effects of compounds showing affinity for benzodiazepine receptors were blocked. In healthy volunteers, IV flumazenil has been shown to antagonise the sedation, amnesia and psychomotor impairment produced by benzodiazepine agonists. Hypnotic-sedative benzodiazepine effects are rapidly reversed by flumazenil after IV injection (1 - 2 minutes) and may then reappear gradually within the next few hours depending on the half-life and dose ratio of the agonist and antagonist.

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 symptoms of benzodiazepine withdrawal, including seizures. A similar effect was seen in adult human subjects.

Physicochemical properties

Flumazenil is a white or almost white crystalline powder. It is very slightly soluble in water, freely soluble in methylene chloride and sparingly soluble in methanol.

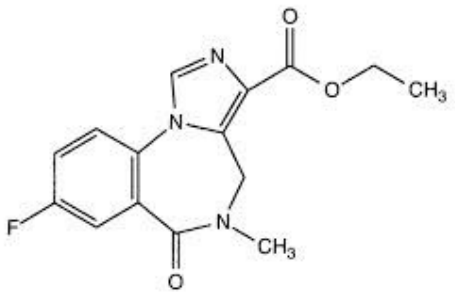
Chemical Name

Ethyl 8-fluoro-5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo [1,5-α][1,4]benzodiazepine-3-carboxylate.

Empirical formula

$C_{15}H_{14}FN_3O_3$

Chemical structure



Molecular weight
303.3.

CAS number
78755-81-4.

5.2 Pharmacokinetic properties

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

Distribution
Flumazenil, a weak lipophilic base, is about 50% bound to plasma proteins. Albumin accounts for two- thirds of plasma protein binding. Flumazenil is extensively distributed in the extravascular space. Plasma concentrations of flumazenil decrease with a half-life of 4 - 11 minutes during the distribution phase. The volume of distribution at steady state is 0.9 - 1.1L/kg.

Metabolism/biotransformation
Flumazenil is extensively metabolised in the liver. The carboxylic acid metabolite is the main metabolite in plasma (free form) and urine (free form and its glucuronide). This main metabolite shows no benzodiazepine agonist or antagonist activity in pharmacological tests.

Elimination
Flumazenil is almost completely (99%) eliminated by non-renal routes. Practically no unchanged flumazenil is excreted in the urine, suggesting complete metabolic degradation of the medicine. Elimination of radiolabelled substance is essentially complete within 72 hours, with 90 - 95% of the radioactivity appearing in urine and 5 - 10% in the faeces. Elimination is rapid, as shown by a short elimination half-life of 40 - 80 minutes. The total plasma clearance of flumazenil is 0.8 - 1.0L/hr/kg and can be attributed almost entirely to hepatic clearance.

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.

Pharmacokinetics in special populations
Patients with impaired hepatic function
In patients with impaired liver function, the elimination half-life of flumazenil is longer (1.3 hours in moderate impairment and 2.4 hours in severely impaired patients) and the total body clearance is lower than in healthy subjects. The pharmacokinetics of flumazenil are not significantly affected in the elderly, by gender, haemodialysis or renal failure.

Paediatric population
The elimination half-life in children over one year of age is more variable than in adults, averaging 40 minutes and generally ranging from 20 - 75 minutes. Clearance and volume of distribution, normalised for body weight, are in the same range as is seen in adults.

5.3 Preclinical safety data
In vitro and animal studies using high doses of flumazenil have not shown evidence of mutagenicity, teratogenicity or impairment of fertility.

Genotoxicity
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*.

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Disodium edetate
Glacial acetic acid
Sodium chloride
Sodium hydroxide (to adjust pH to approx. 4)
Water for injection.

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except for those mentioned in section 6.6.

6.3 Shelf life
36 months. This medicine should not be used after the expiry date (EXP) shown on the pack.

Intravenous infusion solutions or syringes filled with a **Flumazenil-Baxter** solution should be discarded after 24 hours.

Also, see section 6.6.

6.4 Special precautions for storage
Store at or below 25°C. Protect from light. Do not freeze.

6.5 Nature and contents of container
Flumazenil-Baxter 0.1mg/mL solution for intravenous injection, is available in the following pack sizes:

- **0.5mg/5mL**: Carton boxes with 5 or 10 ampoules (glass Type I) containing 5mL solution for injection.
- **1mg/10mL**: Carton boxes with 5 or 10 ampoules (glass Type I) containing 10mL solution for injection.

Not all pack sizes may be available.

6.6 Special precautions for disposal and other handling

Contains no antimicrobial preservative. This medicinal product is for single use, in one patient 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 form particles.

When **Flumazenil-Baxter** is to be used in infusion, it must be diluted prior to infusion.
Flumazenil-Baxter should only be diluted with:
Normal saline Sodium Chloride 9mg/mL (0.9 %) solution,
Dextrose 50mg/mL (5 %) solution, or
Lactated Ringer's solution.

Compatibility between flumazenil and other solutions for injection has not been established. Intravenous infusion solutions or syringes filled with a **Flumazenil-Baxter** solution should be discarded after 24 hours, see section 4.2.

For optimum sterility, **Flumazenil-Baxter** should remain in the ampoule until just before use.

From a microbiological point of view the diluted solution should be used immediately. If the diluted product is not used immediately, the user/administrator is responsible for the terms of use employed and storage conditions for administration.

7 MEDICINE SCHEDULE

Prescription only medicine.

8 SPONSOR

Flumazenil-Baxter is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

Flumazenil-Baxter is distributed in Australia by:
Baxter Healthcare Pty Ltd [ABN: 43 000 392 781]
1 Baxter Drive
Old Toongabbie, NSW 2146.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
3 December 2015.

10 DATE OF REVISION OF THE TEXT

29 April 2020.

SUMMARY TABLE OF CHANGES

Section	Summary of new information
6.4	Storage condition change to: Store at or below 25°C.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.