

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

DBL™ Flumazenil Injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ampoules contain 0.1 mg/mL flumazenil in aqueous solution (for intravenous administration) and also the following ingredients: disodium edetate, acetic acid, sodium chloride, sodium hydroxide in water for injections adjusted to pH 4.0. DBL Flumazenil Injection is available as 0.5 mg/5 mL and 1 mg/10 mL ampoules.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

DBL Flumazenil Injection is a colourless to almost colourless clear liquid, adjusted to pH 4.0.

Solution for injection.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

DBL Flumazenil Injection is indicated for use in hospitalised patients for the reversal of acute benzodiazepine effects (overdose or therapeutic). Hospitalised patients are patients admitted to hospital, inpatient care and under continued professional observation while under the influence of flumazenil. Not to be used in outpatients or short stay patients. Not to be used as a diagnostic.

### 4.2 Dose and method of administration

DBL Flumazenil Injection should be administered intravenously by an anaesthetist or experienced physician.

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

The use of DBL Flumazenil Injection should be balanced against the risk of precipitating withdrawal symptoms (see section 4.4). The desirability of retaining a degree of sedation in the early postoperative period should be considered.

DBL Flumazenil Injection may be diluted in glucose 5% in water or 0.9% NaCl for infusion and may also be used concurrently with other resuscitative procedures. In order to reduce microbial contamination hazards, infusion should be commenced as soon as practicable after

preparation. Infusion should be completed within 24 hours of preparation and any residue discarded.

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

### **Reversal of benzodiazepine effects at therapeutic doses (anaesthesia or sedation)**

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

### **Children > 1 year of age (see section 4.4)**

The recommended initial dose is 0.01 mg/kg (or up to 0.2 mg, whichever is lower) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting for 60 seconds, further injections of 0.01 mg/kg (or up to 0.2 mg, whichever is lower) can be administered and repeated at 60 second intervals where necessary to a maximum total dose of 0.05 mg/kg or 1 mg, whichever is lower. The dose should be individualised based on the patient's response. The patients should be observed for at least 2 hours after treatment with flumazenil. No data are available on the safety and efficacy of repeated administration of flumazenil to children for re-sedation.

When using flumazenil, consideration should be given to the potential impact of rapid reversal of sedation and anxiolysis, and the risk of precipitating withdrawal symptoms. The safety and efficacy of flumazenil for reversal of prolonged sedation, such as in an intensive care unit, has not been studied.

### **Reversal of benzodiazepine effects at overdose, known or suspected**

The recommended initial intravenous dose is 0.3 mg. If the desired degree of consciousness is not obtained within 60 seconds, flumazenil may be injected repeatedly until the patient awakes or up to a total dose of 2 mg. If drowsiness recurs, an intravenous infusion of 0.1 to 0.4 mg/hour has been shown to be useful. The rate of the infusion should be individually adjusted up to the desired level of arousal.

If a significant improvement in consciousness or respiratory function is not obtained after repeated doses of flumazenil, 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, 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).

## **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 is contraindicated in patients with known hypersensitivity to the drug.

Flumazenil 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 should not be used to reverse benzodiazepine effects.

## **4.4 Special warnings and precautions for use**

Flumazenil blocks the effects of benzodiazepines in animals and can precipitate benzodiazepine withdrawal at high doses (also see section 5.1 and section 4.8).

Flumazenil 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 re-sedation, 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. As patients with underlying hepatic impairment may experience delayed benzodiazepine effects, an extended observation period may be required.

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 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 to 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 % 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.

Flumazenil 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).

## **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 are unaltered in the presence of the antagonist 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 drugs taken in overdose (especially cyclic 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**

Animal studies using high doses of flumazenil have not shown evidence of impairment of fertility.

### **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 fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal 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 fetus.

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 intravenous dose of 2 mg, based on AUC. In rabbits, embryotoxicity (increased resorptions) was observed at oral doses  $\geq$  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.

### **Lactation**

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).

Parenteral administration of flumazenil in emergencies is not contraindicated during lactation.

## 4.7 Effects on ability to drive and use machinery

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 was systemically and locally well tolerated. Nausea and/or vomiting were reported in clinical trials with flumazenil. This occurred more frequently when flumazenil was given as a single high dose to reverse anaesthesia and when opioids and other anaesthetic agents were used as a component of the anaesthesia. These reactions occurred rarely in volunteer studies or when benzodiazepines alone were used for sedation.

Hypersensitivity reactions, including anaphylaxis, have been observed.

Infrequently reported adverse events included dizziness, vertigo, anxiety, palpitation, fearfulness, depressed mood, and tearfulness with or without agitation. These may be related to reversal of the anaesthetic.

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 of suspected adverse reactions

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.

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 a dosage of 100 mg intravenously, no symptoms of overdose were observed. For withdrawal symptoms attributable to the agonist, see under section 4.4.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

#### **Mechanism of action**

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 ( $V_{ss} = 0.95$  L/kg) is close to that of structurally related benzodiazepines and indicates tissue binding and/or partitioning of the drug.

## **Biotransformation**

Flumazenil is extensively metabolised in the liver. 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%) nonrenally 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 (1.3 hours in moderate impairment and 2.4 hours in severely impaired patients) 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 is not significantly affected in the elderly, hemodialysis, or renal failure.

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 to 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**

### **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.

## **Reproductive and developmental toxicity**

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).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

- Disodium edetate
- Acetic acid
- Sodium chloride
- Sodium hydroxide
- Water for injections

### **6.2 Incompatibilities**

This medicine must not be mixed with other medicines except those mentioned below.

DBL Flumazenil Injection may be diluted in glucose 5% in water or 0.9% NaCl for infusion and may also be used concurrently with other resuscitative procedures. Infusion should be completed within 24 hours of preparation and any residue discarded.

### **6.3 Shelf life**

24 months from date of manufacture.

### **6.4 Special precautions for storage**

Store below 25°C.

### **6.5 Nature and contents of container**

DBL Flumazenil Injection 0.5 mg/5 mL 5 x 5 mL ampoules (glass)

DBL Flumazenil Injection 1 mg/10 mL 5 x 10 mL ampoules (glass)

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

## 7. MEDICINE SCHEDULE

Prescription Medicine

## 8. SPONSOR

Pfizer New Zealand Limited

P O Box 3998

Auckland 1140, New Zealand

Toll Free Number: 0800 736 363

## 9. DATE OF FIRST APPROVAL

15 March 2007

## 10. DATE OF REVISION OF THE TEXT

27 July 2020

### Summary table of changes

Section changed	Summary of new information
2, 4.2, 4.6, 5.2, 6.1, 6.2, 6.5, 8	Minor editorial changes. Includes correction to text, input of sub-headings and text appropriate to Medsafe Data Sheet template requirements. Deletion of information not required.
4.2	Include recommendation regarding dose titration and expand text regarding individual requirements.  Include information regarding use in children for re-sedation.  Expanded text included under reversal of benzodiazepine effects at overdose.  Include sub-section and recommendations for patients with hepatic impairment.
4.4	Include recommendations for patients with hepatic impairment.  Caution included regarding use in children below the age of one year.
4.5	Expanded text included and information on interaction with ethanol.

4.6	Information relating to fertility and animal studies updated. Expanded information regarding administration during lactation.
4.8	Hypersensitivity reactions, including anaphylaxis included.
4.9	Expanded text regarding overdose included.
5.2	Expanded text regarding metabolism and elimination half-life.
6.2	Text included regarding mixing with other medicines.