

Flumazenil Injection, USP

0.1 mg/mL

Benzodiazepine Antagonist

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form/Strength | Clinically Relevant Nonmedicinal Ingredients |
|-------------------------|---------------------------------------|---|
| Intravenous injection | Injectable Solution/ 0.1 mg per mL | For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section. |

INDICATIONS AND CLINICAL USE

Flumazenil Injection, USP is indicated for the complete or partial reversal of the central sedative effects of benzodiazepines. It may therefore be used in anesthesia and intensive care in the following situations:

- termination of general anesthesia induced and/or maintained with benzodiazepines;
- reversal of benzodiazepine sedation in short diagnostic and therapeutic procedures;
- for the diagnosis and/or management of deliberate or accidental benzodiazepine overdosage.

Pediatrics: No data available.

Geriatrics: No data available.

CONTRAINDICATIONS

Flumazenil Injection, USP is contraindicated:

- in patients with known hypersensitivity to flumazenil or to benzodiazepines;
- in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. The abrupt suppression of the protective effect of benzodiazepines may induce convulsions in epileptic patients;
- in patients who are showing signs of serious cyclic antidepressant overdose (see **WARNINGS AND PRECAUTIONS**);
- in patients who have been given a benzodiazepine for a potentially life-threatening condition (e.g., intracranial pressure).

WARNINGS AND PRECAUTIONS

- **In view of the short duration of action of flumazenil and the possible need for repeat doses, the patient should remain closely monitored until all possible central benzodiazepine effects have subsided.**
- **The immediate availability of oxygen, resuscitative equipment and skilled personnel for the maintenance of airway, ventilation and cardiac function should be ensured before the administration of any benzodiazepine or flumazenil.**

General

In high-risk patients, the advantages of counteracting benzodiazepine-related sedation should be weighed against the drawbacks of rapid awakening.

Postoperative pain must be taken into account. Following a major intervention, it may be preferable to maintain a moderate degree of sedation.

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

Resedation: Flumazenil is a competitive inhibitor of benzodiazepines at the receptor site and does not affect the pharmacokinetics of benzodiazepines. Thus, when the effect of flumazenil wears off, the patient returns to the point of residual sedation that would have been present at that time had flumazenil not been given. In patients administered large doses of long-acting benzodiazepines

or in critically ill patients, this could be deep sedation. In a U.S. clinical study in patients with benzodiazepine intoxication, 90/133 (67.7%) patients became resedated.

Therefore, flumazenil should be administered only when the continued observation of patients for recurrence of sedation can be assured.

Seizures: In patients treated for long periods of time and/or with high doses of benzodiazepines, flumazenil may trigger withdrawal symptoms (e.g., convulsions, agitation, anxiety, emotional lability as well as mild confusion and sensory distortions); rapid intravenous injections should therefore be avoided. 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.

Anxiety: The dosage of flumazenil should be adjusted carefully in patients suffering from preoperative anxiety or having a history of chronic or episodic anxiety. In anxious patients, particularly those with coronary heart disease, it is preferable to maintain a degree of sedation throughout the early postoperative period rather than bring about complete arousal.

Instructions to Patients Upon Discharge: Patients who have received flumazenil to reverse the effects of benzodiazepine sedation should be instructed, if possible in writing, not to drive, operate machinery or engage in any other physically or mentally demanding activity for 24 hours or until the effects of the benzodiazepine have subsided, since the effect of the benzodiazepine may return. Patients should also be warned not to take alcohol or drugs not prescribed by their physician, until the effects of the benzodiazepines have subsided.

Use in Patients with Increased Intracranial Pressure Receiving Benzodiazepines (e.g., head injury, brain tumour, intracranial hemorrhage): In patients with increased intracranial pressure, flumazenil may further increase intracranial pressure and decrease cerebral perfusion pressure, or precipitate convulsions. In such patients, flumazenil should be used with extreme caution and only by practitioners prepared to manage such complications, should they occur.

Multiple-drug Overdosage: Particular caution is necessary when using flumazenil in cases of multiple-drug overdosage, since the toxic effects (cardiac arrhythmias and/or convulsions) of other psychotropic drugs, especially cyclic antidepressants, may increase as the effects of benzodiazepines subside.

Patients should be evaluated for the signs and symptoms (autonomic, neurological or cardiovascular) of a cyclic antidepressant overdose. A diagnostic ECG can be used to confirm the presence of these agents; a QRS duration of 0.1 second or greater indicates a serious overdosage with cyclic antidepressants, which should be treated with appropriate measures. Depending on the extent of involvement of benzodiazepines in the multiple-drug overdose, this may or may not include flumazenil.

Use in the ICU: Flumazenil should be used with caution in the Intensive Care Unit because of the increased risk of unrecognized benzodiazepine dependence in such settings. Flumazenil may produce convulsions in patients physically dependent on benzodiazepines (see **WARNINGS AND PRECAUTIONS, General, Seizures**).

Respiratory

When used in anesthesiology at the end of surgery, flumazenil should not be given until the effects of neuromuscular blockade have been completely antagonized and careful monitoring of the respiratory depressant effect of opiate analgesics has been assured. After the benzodiazepine has been antagonized with flumazenil, any residual respiratory depressant effect of other agents, such as opiates, should be appropriately treated.

The ability of flumazenil to reverse benzodiazepine-induced respiratory depression is equivocal; in some studies, residual effects of benzodiazepines on respiration were still present despite reversal of sedation.

Cardiovascular

Flumazenil abruptly terminates the effects of benzodiazepines. As a result, sympathetic tone may be increased and thus, cardiac electrical instability enhanced. Consequently, caution is advised when administering flumazenil to patients with myocardial infarction or cardiac arrhythmias.

Hepatic/Renal

In patients with liver insufficiency, the elimination of flumazenil can be delayed (see **ACTION AND CLINICAL**

PHARMACOLOGY, Pharmacokinetics). No dosage adjustments are necessary in patients with renal impairment. Seizures have been reported in patients known to suffer from severe hepatic impairment, particularly after long-term treatment with benzodiazepines or in cases of mixed-drug overdose.

Special Populations

Pediatrics (< 18 years of age): The safety and effectiveness of flumazenil in children below the age of 18 have not been established.

Geriatrics: In the absence of data on the use of flumazenil in elderly patients, it should be borne in mind that this population is generally more sensitive to the effects of drugs and should be treated with due caution.

Pregnant Women: Although studies in animals have not shown evidence of embryotoxicity or teratogenicity, flumazenil should be used during pregnancy only, if in the opinion of the treating physician, the possible benefit to the patient outweighs the potential risks to the fetus.

Nursing Women: It is not known whether flumazenil is excreted in human milk. For this reason, breast-feeding should be interrupted for 24 hours when flumazenil is used during lactation.

ADVERSE REACTIONS

Flumazenil is generally well tolerated. In postoperative use, nausea and/or vomiting are observed, particularly if opiates have also been employed. Flushing has also been noted. If patients are awakened too rapidly, they may become agitated, anxious or fearful. Transient increases in blood pressure and heart rate may also occur.

Excessively and/or rapidly injected doses of flumazenil may induce benzodiazepine withdrawal symptoms such as anxiety attacks, tachycardia, dizziness, and sweating in patients on long-term benzodiazepine treatment.

Although clinical experience with flumazenil is limited, seizures and/or cardiac arrhythmias have been observed in patients who are physically dependent on benzodiazepines, and in multiple-drug overdose, particularly in the presence of tricyclic antidepressants.

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

The following table summarizes the adverse reactions which occurred with an incidence of >1%.

| Clinical Adverse Events > 1% | | | |
|------------------------------|---------------------------------|--|---|
| Organ System | Adverse Events | Frequency (%) | |
| | | General Anesthesia/Sedation n = 7,365 | Known or Suspected Benzodiazepine Overdose n = 764 |
| Central nervous system | Agitation | 0.2 | 5.8 |
| | Crying/Tears | 0.5 | 3.5 |
| | Headache | 0.5 | 1.6 |
| | Anxiety/Anxious | 0.3 | 1.4 |
| | Feeling Seizures/Convulsions | — | 1.3 |
| | Dizziness | 1.4 | 1.2 |
| Gastro-intestinal | Nausea | 4.3 | 2.2 |
| | Vomiting | 2.6 | 2.0 |
| Cardio-vascular | Hypertension | 0.1 | 1.4 |
| | Tachycardia | 0.1 | 1.2 |
| Miscellaneous | Shivering/Cold Sensation/Chills | 0.5 | 1.2 |

Other clinical adverse events which occurred with an incidence of <1% are as follows:

Cardiovascular: Ventricular premature beats, arrhythmia, palpitations, bradycardia, flush, hypotension;

Respiratory: Dyspnea, hypopnea, nasal congestion, cough, subjective suffocation;

CNS/Neuromuscular: Startle reaction, fear, nervousness, restlessness, excitation, aggressiveness, anger, euphoria, hallucinations, vertigo, confusion, tiredness/drowsiness, depression, involuntary/spontaneous movement, tremor, mouth movement, tetany;

Gastrointestinal: Salivation, dry mouth, hiccoughs;

Dermatological: Urticaria, pruritus;

Miscellaneous: Pain, allergic reaction, strabismus, sweating;

Local Tolerance: Slight to moderate pain at the site of injection occurred in 2.5% of patients and redness was observed in 1.3% of patients one hour after the administration of flumazenil.

DRUG INTERACTIONS

Flumazenil blocks the central effects of benzodiazepines by competitive interaction at the receptor level; the effects of non-benzodiazepines which act via the benzodiazepine receptor, such as zopiclone, triazolopyridazines and others, are also blocked. However, flumazenil does not reverse the effects of drugs that do not act via this route.

The pharmacokinetics of flumazenil are unaltered in the presence of benzodiazepines, and similarly, flumazenil does not affect the kinetics of benzodiazepines.

There is no pharmacokinetic interaction between ethanol and flumazenil.

DOSAGE AND ADMINISTRATION

Flumazenil should be administered intravenously by a physician with experience in anesthesiology.

The dose of flumazenil should always be individually titrated to the desired response to avoid abrupt awakening. Particular care is needed with patients who are physically dependent on benzodiazepines, patients who have ingested multiple drugs, and patients who are prone to anxiety. 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 (see **WARNINGS AND PRECAUTIONS**). If unexpected symptoms occur, diazepam or midazolam could be carefully titrated intravenously according to patient's response.

Flumazenil may be used concurrently with other resuscitative procedures.

Flumazenil Injection, USP may be diluted in a glass bottle to a final concentration of 0.05 mg/mL with 0.9% Sodium Chloride Injection, 0.45% Sodium Chloride and 2.5% Dextrose Injection, 5% Dextrose Injection, or Lactated Ringer's Injection (see **STORAGE AND STABILITY**).

Reversal of General Anesthesia/Sedation

The recommended initial dose is 0.2 mg administered intravenously over 15 seconds. If the desired level of consciousness is not obtained within 60 seconds, a further dose of 0.1 mg can be injected and repeated at 60-second intervals, up to a maximum total dose of 1 mg. The usual dose is between 0.3 and 0.6 mg.

Known or Suspected Benzodiazepine Overdose

For the reversal of excessive sedative effects of benzodiazepines in overdose cases, titrate flumazenil as described below, until the patient clearly responds or until the maximum recommended dose has been reached.

The recommended initial dose is 0.3 mg administered intravenously over 30 seconds, followed by a series of 0.3 mg injections, each administered over a 30-second period, at 60-second intervals. The maximum recommended dose is 2.0 mg.

If a significant improvement in the level of consciousness and respiratory function is not achieved after repeated injections of flumazenil, a non-benzodiazepine etiology must be assumed.

If drowsiness recurs, an intravenous infusion of 0.1 - 0.4 mg/hr may be useful. The rate of the infusion should be individually adjusted to the desired level of arousal.

OVERDOSAGE

Flumazenil, administered intravenously to healthy volunteers at a dosage of 100 mg, did not produce symptoms of overdosage.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Flumazenil, an imidazobenzodiazepine, is a benzodiazepine antagonist which blocks the central effects of agents that act via the benzodiazepine receptor, by competitive inhibition. The antagonism is specific, since in animal experiments the effects of compounds which have no affinity for the benzodiazepine receptor (e.g., barbiturates, meprobamate, ethanol, GABA-mimetics, and adenosine receptor agonists) were not affected by flumazenil.

Following the intravenous administration of radiolabelled flumazenil to human volunteers, the distribution of radioactivity corresponded closely to the distribution of benzodiazepine receptors as determined by positron emission tomography.

The hypnotic-sedative effects of benzodiazepines are rapidly reversed by flumazenil. However, the residual effects may reappear gradually within a few hours, depending on the dose of flumazenil, the time elapsed since the benzodiazepine agonist was given, and the dose and elimination half-life of the previously administered benzodiazepine. Flumazenil has shown some weak intrinsic agonistic (e.g., anticonvulsant) activity without therapeutic relevance.

Pharmacokinetics

In young male volunteers, the pharmacokinetics of intravenous flumazenil were linear over a dose range of 2 - 100 mg. Increasing doses of flumazenil were accompanied by a corresponding increase in the area under the plasma concentration-time curve (AUC: 37 ng/mL•hr at 2 mg and 1,906 ng/mL•hr at 100 mg), and maximum plasma concentration (C_{max} : 55 ng/mL at 2 mg and 3,332 ng/mL at 100 mg). However, elimination half-life, volume of distribution at steady state, and plasma clearance were independent of dose over the entire range studied. The mean elimination half-life of flumazenil following the administration of single intravenous doses to healthy subjects was approximately one hour.

The following table summarizes the ranges of mean pharmacokinetic parameters reported in a series of studies, after single intravenous doses of flumazenil.

| Subjects | Dose (mg) | Elimination Half-life ($t_{2\beta}$) (min) | Volume of Distribution at Steady State ($V_{d,ss}$) (L/kg) | Plasma Clearance (Cl_{pl}) (L/hr) |
|---|-----------|--|--|---------------------------------------|
| Male volunteers 23 - 26 years | 2 - 100 | 48 - 55 | 0.83 - 0.86 | 55 - 57 |
| Male volunteers 28 - 42 years | 2.5 | 42 - 72 | 0.63 | 41 |
| Volunteers 39 years | 2 | 46 | 0.62 | 74 |
| Cirrhosis - moderate 45 years | 2 | 76 | 0.68 | 29 |
| - severe 45 years | 2 | 142 | 0.85 | 19 |
| Volunteers 37 years | 1 | 51 | 0.91 | 60 |
| Chronic renal failure - without dialysis 36 years | 1 | 38 | 0.94 | 75 |
| - with dialysis 55 years | 1 | 43 | 1.07 | 75 |
| Age Volunteers: | | | | |
| Male: | | | | |
| 20 - 28 years | 2 | 54 | 0.87 | 56 |
| 65 - 77 years | 2 | 66 | 0.93 | 56 |
| Female: | | | | |
| 24 - 30 years | 2 | 48 | 0.96 | 66 |
| 63 - 67 years | 2 | 54 | 0.78 | 44 |

When administered together with the benzodiazepines, midazolam, flunitrazepam or lorazepam, the pharmacokinetic parameters of flumazenil were not affected. Similarly, the pharmacokinetics of benzodiazepines remained unaltered in the presence of the antagonist flumazenil.

Distribution: Plasma protein binding is rather low. Over a concentration range of 24 to 570 ng/mL, flumazenil was found to be 50% bound to human plasma proteins. Albumin accounts for approximately two-thirds of the plasma protein binding. The binding of flumazenil was not affected by a high concentration of diazepam (10 µg/mL), and flumazenil did not interfere with the binding of diazepam.

Metabolism/Excretion: Flumazenil undergoes rapid and extensive hepatic metabolism; less than 0.2% of the administered dose is eliminated unchanged in the urine. The major metabolites of flumazenil identified in the urine are the free acid and its glucuronide conjugate. In healthy volunteers, approximately 70% of an intravenous dose of flumazenil was excreted within the first two hours after dosing and another 16% during the next two hours. Elimination was essentially complete within 72 hours, with 90 to 95% of the total radioactivity appearing in the urine and 5 to 10% in the feces.

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.

Special Populations and Conditions

Geriatrics: There were no statistically significant differences between the distribution and elimination parameters of 12 elderly (8 males and 4 females) and 6 young (4 males and 2 females) healthy volunteers, following the administration of a 2 mg intravenous dose.

Hepatic Insufficiency: In patients with cirrhosis, the pharmacokinetics of flumazenil were altered, particularly in patients with severely impaired liver function. Elimination half-life was prolonged and plasma clearance markedly decreased. Since plasma protein binding is lower in cirrhotic patients than in healthy subjects, the levels of free drug are substantially increased, namely from 55% in controls to 64% and 79% in patients with moderate and severe liver dysfunction, respectively.

Renal Insufficiency: In patients with chronic stabilized renal failure (creatinine clearance < 10 mL/min) in the absence and presence of dialysis, the pharmacokinetics of flumazenil remained essentially unaltered.

STORAGE AND STABILITY

Flumazenil Injection, USP should be stored between 15 and 30°C.

Multiple-dose vial. Discard unused portion 28 days after initial puncture.

Stability and Storage of Diluted Solutions

Flumazenil Injection may be diluted in glass bottle to a final concentration of 0.05 mg/mL with 0.9% Sodium Chloride Injection, 0.45% Sodium Chloride and 2.5% Dextrose Injection, 5% Dextrose Injection, or Lactated Ringer's Injection. Infusion solutions containing flumazenil should be used within 24 hours, and unused portions discarded.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Flumazenil Injection, USP is a sterile aqueous solution for intravenous injection. Each mL of the colourless aqueous solution contains: 0.1 mg flumazenil, 1.8 mg methylparaben, 0.2 mg propylparaben, 0.1 mg disodium edetate, 9.0 mg sodium chloride and 0.1 mg acetic acid; sodium hydroxide and hydrochloric acid added to adjust pH to approximately 4, and Water for Injection.

Flumazenil Injection, USP is supplied in multiple-dose vials: Product Code:

C402405 5 mL fill in a 6.5 mL vial - packaged in trays of 10 vials

Vial stoppers do not contain natural rubber latex.

PHARMACEUTICAL PARTNERS OF CANADA INC.

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