

The risks identified in the adult population with flumazenil use also apply to pediatric patients. Therefore, consult the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS** sections when using flumazenil in pediatric patients.

Geriatric Use

Of the total number of subjects in clinical studies of flumazenil, 248 were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

The pharmacokinetics of flumazenil have been studied in the elderly and are not significantly different from younger patients. Several studies of flumazenil in subjects over the age of 65 and one study in subjects over the age of 80 suggest that while the doses of benzodiazepine used to induce sedation should be reduced, ordinary doses of flumazenil may be used for reversal.

ADVERSE REACTIONS:

Serious Adverse Reactions

Deaths have occurred in patients who received flumazenil in a variety of clinical settings. The majority of deaths occurred in patients with serious underlying disease or in patients who had ingested large amounts of non-benzodiazepine drugs (usually cyclic antidepressants), as part of an overdose.

Serious adverse events have occurred in all clinical settings, and convulsions are the most common serious adverse events reported. Flumazenil administration has been associated with the onset of convulsions in patients with severe hepatic impairment and in patients who are relying on benzodiazepine effects to control seizures. are physically dependent on benzodiazepines, or who have ingested large doses of other drugs (mixed-drug overdose) (see **WARNINGS**).

Two of the 446 patients who received flumazenil in controlled clinical trials for the management of a benzodiazepine overdose had cardiac dysrhythmias (1 ventricular tachycardia, 1 junctional tachycardia).

Adverse Events in Clinical Studies

The following adverse reactions were considered to be related to flumazenil administration (both alone and for the reversal of benzodiazepine effects) and were reported in studies involving 1875 individuals who received flumazenil in controlled trials. Adverse events most frequently associated with flumazenil alone were limited to dizziness, injection site pain, increased sweating, headache, and abnormal or blurred vision (3% to 9%).

Body as a Whole: fatigue (asthenia, malaise), headache, injection site pain* and injection site reaction (thrombophlebitis, skin abnormality, rash)
Cardiovascular System: cutaneous vasodilation (sweating, flushing, hot flushes)
Digestive System: nausea and vomiting (11%)
Nervous System: agitation (anxiety, nervousness, dry mouth, tremor, palpitations, insomnia, dyspnea, hyperventilation)*, dizziness (vertigo, ataxia) (10%) and emotional lability (crying abnormal, depersonalization, euphoria, increased tears, depression, dysphoria, paranoia)
Special Senses: abnormal vision (visual field defect, diplopia) and paresthesia (sensation abnormal, hypoesthesia)

All adverse reactions occurred in 1% to 3% of cases unless otherwise marked.

*indicates reaction in 3% to 9% of cases.

Observed percentage reported if greater than 9%.

The following adverse events were observed infrequently (less than 1%) in the clinical studies, but were judged as probably related to flumazenil administration and/or reversal of benzodiazepine effects:

Nervous System: confusion (difficulty concentrating, delirium), convulsions (see **WARNINGS**) and somnolence (stupor)
Special Senses: abnormal hearing (transient hearing impairment, hyperacusis, tinnitus)

The following adverse events occurred with frequencies less than 1% in the clinical trials. Their relationship to flumazenil administration is unknown, but they are included as alerting information for the physician.

Body as a Whole: rigors, shivering
Cardiovascular System: arrhythmia (atrial, nodal, ventricular extrasystoles), bradycardia, tachycardia, hypertension and chest pain
Digestive System: hiccup
Nervous System: speech disorder (dysphonia, thick tongue)

Not included in this list is operative site pain that occurred with the same frequency in patients receiving placebo as in patients receiving flumazenil for reversal of sedation following a surgical procedure.

Additional Adverse Reactions Reported During Postmarketing Experience

The following events have been reported during postapproval use of flumazenil.

Nervous System: Fear, panic attacks in patients with a history of panic disorders.

Withdrawal symptoms may occur following rapid injection of flumazenil in patients with long-term exposure to benzodiazepines.

DRUG ABUSE AND DEPENDENCE:

Flumazenil acts as a benzodiazepine antagonist, blocks the effects of benzodiazepines in animals and man, antagonizes benzodiazepine reinforcement in animal models, produces dysphoria in normal subjects, and has had no reported abuse in foreign marketing.

Although flumazenil has a benzodiazepine-like structure it does not act as a benzodiazepine agonist in man and is not a controlled substance.

OVERDOSAGE:

Large intravenous doses (exceeding those recommended) of flumazenil, when administered to healthy normal volunteers in the absence of a benzodiazepine agonist, produced no serious adverse reactions, severe signs or symptoms, or clinically significant laboratory test abnormalities. In clinical studies, most adverse reactions to flumazenil were an extension of the pharmacologic effects of the drug in reversing benzodiazepine effects.

Reversal with an excessively high dose of flumazenil may produce anxiety, agitation, increased muscle tone, hyperesthesia and possibly convulsions. Convulsions have been treated with barbiturates, benzodiazepines and phenytoin, generally with prompt resolution of the seizures (see **WARNINGS**).

DOSAGE AND ADMINISTRATION:

Flumazenil Injection, USP is recommended for intravenous use only. It is compatible with 5% dextrose in water, lactated Ringer’s and normal saline solutions. If Flumazenil Injection, USP is drawn into a syringe or mixed with any of these solutions, it should be discarded after 24 hours. For optimum sterility, Flumazenil Injection, USP should remain in the vial until just before use. As with all parenteral drug products, Flumazenil Injection, USP should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To minimize the likelihood of pain at the injection site, Flumazenil Injection, USP should be administered through a freely running intravenous infusion into a large vein.

Reversal of Conscious Sedation

Adult Patients

For the reversal of the sedative effects of benzodiazepines administered for conscious sedation, the recommended initial dose of Flumazenil Injection, USP is 0.2 mg (2 mL) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, a further dose of 0.2 mg (2 mL) can be injected and repeated at 60-second intervals where necessary (up to a maximum of 4 additional times) to a maximum total dose of 1 mg (10 mL). The dosage should be individualized based on the patient’s response, with most patients responding to doses of 0.6 mg to 1 mg (see ***Individualization of Dosage***).

In the event of resedation, repeated doses may be administered at 20-minute intervals as needed. For repeat treatment, no more than 1 mg (given as 0.2 mg/min) should be administered at any one time, and no more than 3 mg should be given in any one hour.

It is recommended that Flumazenil Injection, USP be administered as the series of small injections described (not as a single bolus injection) to allow the practitioner to control the reversal of sedation to the approximate endpoint desired and to minimize the possibility of adverse effects (see ***Individualization of Dosage***).

Pediatric Patients

For the reversal of the sedative effects of benzodiazepines administered for conscious sedation in pediatric patients greater than 1 year of age, the recommended initial dose is 0.01 mg/kg (up to 0.2 mg) administered intravenously 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 4 additional times) to a maximum total dose of 0.05 mg/kg or 1 mg, whichever is lower. The dose should be individualized based on the patient’s response. The mean total dose administered in the pediatric clinical trial of flumazenil was 0.65 mg (range: 0.08 mg to 1 mg). Approximately one-half of patients required the maximum of five injections.

Resedation occurred in 7 of 60 patients who were fully alert 10 minutes after the start of Flumazenil Injection, USP administration (see **PRECAUTIONS, Pediatric Use**). The safety and efficacy of repeated flumazenil administration in pediatric patients experiencing resedation have not been established.

It is recommended that Flumazenil Injection, USP be administered as the series of small injections

described (not as a single bolus injection) to allow the practitioner to control the reversal of sedation to the approximate endpoint desired and to minimize the possibility of adverse effects (see ***Individualization of Dosage***).

The safety and efficacy of Flumazenil Injection, USP in the reversal of conscious sedation in pediatric patients below the age of 1 year have not been established.

Reversal of General Anesthesia in Adult Patients

For the reversal of the sedative effects of benzodiazepines administered for general anesthesia, the recommended initial dose of Flumazenil Injection, USP is 0.2 mg (2 mL) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, a further dose of 0.2 mg (2 mL) can be injected and repeated at 60-second intervals where necessary (up to a maximum of 4 additional times) to a maximum total dose of 1 mg (10 mL). The dosage should be individualized based on the patient’s response, with most patients responding to doses of 0.6 mg to 1 mg (see ***Individualization of Dosage***).

In the event of resedation, repeated doses may be administered at 20-minute intervals as needed. For repeat treatment, no more than 1 mg (given as 0.2 mg/min) should be administered at any one time, and no more than 3 mg should be given in any one hour.

It is recommended that Flumazenil Injection, USP be administered as the series of small injections described (not as a single bolus injection) to allow the practitioner to control the reversal of sedation to the approximate endpoint desired and to minimize the possibility of adverse effects (see ***Individualization of Dosage***).

Management of Suspected Benzodiazepine Overdose in Adult Patients

For initial management of a known or suspected benzodiazepine overdose, the recommended initial dose of Flumazenil Injection, USP is 0.2 mg (2 mL) administered intravenously over 30 seconds. If the desired level of consciousness is not obtained after waiting 30 seconds, a further dose of 0.3 mg (3 mL) can be administered over another 30 seconds. Further doses of 0.5 mg (5 mL) can be administered over 30 seconds at 1-minute intervals up to a cumulative dose of 3 mg.

Do not rush the administration of Flumazenil Injection, USP. Patients should have a secure airway and intravenous access before administration of the drug and be awakened gradually (see **PRECAUTIONS**).

Most patients with a benzodiazepine overdose will respond to a cumulative dose of 1 mg to 3 mg of Flumazenil Injection, USP, and doses beyond 3 mg do not reliably produce additional effects. On rare occasions, patients with a partial response at 3 mg may require additional titration up to a total dose of 5 mg (administered slowly in the same manner).

If a patient has not responded 5 minutes after receiving a cumulative dose of 5 mg of Flumazenil Injection, USP, the major cause of sedation is likely not to be due to benzodiazepines, and additional Flumazenil Injection, USP is likely to have no effect.

In the event of resedation, repeated doses may be given at 20-minute intervals if needed. For repeat treatment, no more than 1 mg (given as 0.5 mg/min) should be given at any one time and no more than 3 mg should be given in any one hour.

Safety and Handling

Flumazenil Injection, USP is supplied in sealed dosage forms and poses no known risk to the healthcare provider. Routine care should be taken to avoid aerosol generation when preparing syringes for injection, and spilled medication should be rinsed from the skin with cool water.

HOW SUPPLIED:


Product NDC

No.	No.	
402405	63323-424-05	Flumazenil Injection, USP 0.5 mg per 5 mL (0.1 mg per mL), in a 5 mL multiple dose vial, packaged in trays of 10.

402410	63323-424-10	Flumazenil Injection, USP 1 mg per 10 mL (0.1 mg per mL), in a 10 mL multiple dose vial, packaged individually.
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The container closure is not made with natural rubber latex.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].


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