Flumazenil

Brand names	Romazicon, generic
Medication error potential	Look-alike, sound-alike drug names. Flumazenil and the influenza virus vaccine have been confused.[1]
Contraindications and warnings	**U.S. boxed warning:** Flumazenil has been associated with seizures.[2] These occur most frequently when flumazenil is given to a person who has chronically received a benzodiazepine or in association with a tricyclic antidepressant overdose.[2] Practitioners should individualize the dosage of flumazenil and be prepared to manage seizures.[2] (See Rare Adverse Effects in the Comments section.) **Contraindications:** In those with a known hypersensitivity to flumazenil or benzodiazepines and in those receiving a benzodiazepine for control of a life-threatening condition (e.g., intracranial pressure [ICP] or status epilepticus). Flumazenil should not be used in those with symptoms of serious tricyclic antidepressant overdose.[2] (See Other in the Comments section.) **Other warnings:** The use of flumazenil is not recommended in patients with epilepsy who have received benzodiazepine therapy for a prolonged period. It should be used cautiously in the ICU setting because of the increased risk of unrecognized benzodiazepine dependence. Administration to diagnose benzodiazepine-induced sedation in the ICU is not recommended due to the risk of adverse events. Flumazenil should not be used until the effects of neuromuscular blockade have been fully reversed. Use cautiously in cases of mixed drug overdose because their toxic effects (e.g., convulsions and cardiac dysrhythmias) may emerge.[2]
Infusion-related cautions	To minimize pain or local inflammation, infuse through a freely running IV into a large vein.[2] Extravasation may cause local irritation.[2] (See Appendix E for information on extravasation)
Dosage	The safety and effectiveness of flumazenil has not been established in patients <1 year of age.[2] Because flumazenil has been associated with seizures, emergency resuscitative equipment and drugs should be immediately available to manage seizures. The dose should be individualized based on patient response. **Reversal of** **Benzodiazepine-induced anesthesia or conscious sedation (>1 year of age):** *Flumazenil should not be used until the effects of neuromuscular blockade have been fully reversed.*[2] 0.01 mg/kg (up to 0.2 mg) over 15 seconds.[2-10] If the desired clinical response is not achieved within 45 seconds, give 0.01 mg/kg (up to 0.2 mg) and repeated at 60-second intervals to a maximum total dose of 0.05 mg/kg or 1 mg, whichever is smaller.[2,8] The mean total dose in clinical trials was 0.65 mg (range: 0.08–1 mg).[2] About 50% of patients require 5 doses.[2,8] Some patients who regain complete consciousness may develop resedation.[2] (See Other in the Comments and Resedation section.) A single, large dose of 0.1–0.2 mg has been used successfully.[3,11,12] Conversely, one study used smaller doses (0.002 mg/kg).[13] Another study used a loading dose of 10 mcg/kg followed by 5 mcg/kg/min until the patient awoke or until a maximum of 1 mg had been infused.[6] **Benzodiazepine overdose or ingestion:** *Use cautiously in cases of mixed drug overdose because their toxic effects (e.g., convulsions and cardiac dysrhythmias) may emerge.*[2] 0.01 mg/kg (maximum 0.2 mg/dose); if no effect in 1–2 minutes repeat dose q 2 min until patient responds or a total cumulative dose of 0.05 mg/kg or 1 mg is given. A single dose of 0.2 mg (0.017 mg/kg) was used in a 12-kg child.[14] Initial doses have been followed by continuous infusions to prevent resedation.[16] Infusions as large as 5 mcg/kg/min (0.3 mg/kg/hr) have been used.[6]

Dosage *(cont.)*	**Prenatal benzodiazepine exposure:** A 1820-g premature male was born to a mother who had been given repeat doses of diazepam for preeclampsia seizures. The infants was hypotonic without spontaneous respiration and was given a loading dose of 10 mcg/kg of flumazenil. Within 30 seconds, facial and limb movements were noted and spontaneous respiration occurred. A flumazenil infusion was started at 10 mcg/kg/hr. The flumazenil dose was decreased to 5 mcg/kg/hr on day 2 to 3.8 mcg/kg/hr on day 3 and discontinued on day 5.[17] 0.02 mg/kg followed by 0.8 mcg/kg/min (0.05 mg/kg/hr) for 6 hours.[18] **Diagnostic potential** **Coma of unknown origin:** Several reports in *adults* have noted the successful use of flumazenil in this situation.[19-21] Patients who responded were able to provide information regarding their ingestion within about 10 minutes, which resulted in a 30% decrease in gastric lavage, urinary catheterization, and intubation.[20] **Diagnose of benzodiazepine-induced sedation in the ICU:** Not recommended due to the risk of adverse events.[2] The prognostic significance of a patient's failure to respond in cases confounded by metabolic disorder, traumatic injury, drugs other than benzodiazepines, or any other reasons not associated with benzodiazepine receptor occupancy is unknown.[2]
Dosage adjustment in organ dysfunction	No adjustment in renal dysfunction.[22] Flumazenil clearance is reduced to 40% to 60% in mild-to-moderate hepatic disease and to 25% in severe hepatic dysfunction. The initial dose should *not* be reduced, but repeat doses should be reduced or the interval prolonged in hepatic dysfunction.[2]
Maximum dosage	0.2 mg/dose up to a cumulative dose of 1 mg in infants and children.[2,11] Seventy-five percent of *adults* respond to a cumulative dose of 1–3 mg. Doses above 3 mg do not produce additional effects and no more than 3 mg should be given in any 1 hour.[2]
Additives	Contains 1.8 mg methylparabens, 0.2 mg propylparabens/mL, edetate disodium 0.01%, and acetic acid 0.01%.[23] (See Appendix C for specific information about parabens potential for toxicity.)
Suitable diluents	D5W, LR, or NS[2,23]
Maximum concentration	0.1 mg/mL (commercially available)[2]
Preparation and delivery	*Parenteral products should be visually inspected for particulate matter and discoloration before use. Refer to appropriate references for more information on compatibility with other drugs and solutions; compatibility following Y-site delivery, and suggested storage and extended stability.*[23] **Stability:** Store at room temperature (20°C to 25°C).[2,23] Should be used within 24 hours following removal from original vial, whether admixed in an infusion solution or simply drawn into a syringe.[23]
IV push	0.1 mg/mL over 15 seconds (conscious sedation) to 30 seconds (general anesthesia).[2,23] Not to exceed 0.2 mg/min.[2]
Intermittent infusion	Not administered by this method
Continuous infusion	Loading dose (0.01 mg/kg) followed by 5–10 mcg/kg/hr until the patient awoke (or until a maximum of 1 mg had been infused) has been given to prevent/minimize resedation. However, the final concentration and solution type were not provided.[6,15,17]