FLUMAZENIL

**Therapeutics**

**Brands**
- Romazicon
- Anexate
- Lanexat

*see index for additional brand names*

**Generic?** Yes

**Class**
- Benzodiazepine receptor antagonist

**Commonly Prescribed for** (bold for FDA approved)
- Reversal of sedative effects of benzodiazepines after general anesthesia has been induced and/or maintained with benzodiazepines
- Reversal of sedative effects of benzodiazepines after sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures
- Management of benzodiazepine overdose
- Reversal of conscious sedation induced with benzodiazepines (pediatric patients)

**How the Drug Works**
- Blocks benzodiazepine receptors at GABA-A ligand-gated chloride channel complex, preventing benzodiazepines from binding there

**How Long Until It Works**
- Onset of action 1–2 minutes; peak effect 6–10 minutes

**If It Works**
- Reverses sedation and psychomotor retardation rapidly, but may not restore memory completely
- Patients treated for benzodiazepine overdose may experience CNS excitation
- Patients who receive flumazenil to reverse benzodiazepine effects should be monitored for up to 2 hours for resedation, respiratory depression, or other lingering benzodiazepine effects
- Flumazenil has not been shown to treat hypoventilation due to benzodiazepine treatment

**If It Doesn’t Work**
- Sedation is most likely not due to a benzodiazepine, and treatment with flumazenil should be discontinued and other causes of sedation investigated

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- None – flumazenil is basically used as a monotherapy antidote to reverse the actions of benzodiazepines

**Tests**
- None for healthy individuals

**Side Effects**

**How Drug Causes Side Effects**
- Blocks benzodiazepine receptors at GABA-A ligand-gated chloride channel complex, preventing benzodiazepines from binding there

**Notable Side Effects**
- May precipitate benzodiazepine withdrawal in patients dependent upon or tolerant to benzodiazepines
- Dizziness, injection site pain, sweating, headache, blurred vision

**Life-Threatening or Dangerous Side Effects**
- Seizures
- Death (majority occurred in patients with severe underlying disease or who overdosed with non-benzodiazepines)
- Cardiac dysrhythmia

**Weight Gain**
- Reported but not expected

**Sedation**
- Reported but not expected
- Patients may experience resedation if the effects of flumazenil wear off before the effects of the benzodiazepine
**FLUMAZENIL (continued)**

### What to Do About Side Effects
- Monitor patient
- Restrict ambulation because of dizziness, blurred vision, and possibility of resedation

### Best Augmenting Agents for Side Effects
- None – augmenting agents are not appropriate to treat side effects associated with flumazenil use

### Pharmacokinetics
- Terminal half-life 41–79 minutes

### Drug Interactions
- Food increases its clearance

### Other Warnings/Precautions
- Flumazenil may induce seizures, particularly in patients tolerant to or dependent on benzodiazepines, or who have overdosed on cyclic antidepressants, received recent/repeated doses of parenteral benzodiazepines, or have jerking or convulsion during overdose
- Patients dependent on benzodiazepines or receiving benzodiazepines to suppress seizures in cyclic antidepressant overdose should receive the minimally effective dose of flumazenil
- Use with caution in patients with head injury
- Greater risk of resedation if administered to a patient who took a long-acting benzodiazepine or a large dose of a short-acting benzodiazepine
- Flumazenil may induce panic attacks in patients with panic disorder
- Use with caution in cases of mixed overdose because toxic effects of other drugs used in overdose (e.g., convulsions) may appear when the effects of the benzodiazepine are reversed

### Do Not Use
- Should not be used until after effects of neuromuscular blockers have been reversed
- If benzodiazepine was prescribed to control a life-threatening condition (e.g., status epilepticus, intracranial pressure)
- If there is a high risk of seizure
- If patient exhibits signs of serious cyclic antidepressant overdose
- If there is a proven allergy to flumazenil or benzodiazepines

### DOSING AND USE

#### Usual Dosage Range
- 0.4–1 mg generally causes complete antagonism of therapeutic doses of benzodiazepines
- 1–3 mg generally reverses benzodiazepine overdose

#### Dosage Forms
- Intravenous 0.1 mg/mL – 5 mL multiple-use vial, 10 mL multiple-use vial

#### How to Dose
- Conscious sedation, general anesthesia: 0.2 mg (2 mL) over 15 seconds; can administer 0.2 mg again after 45 seconds; can administer 0.2 mg each additional 60 seconds; maximum 1 mg
- Benzodiazepine overdose: 0.2 mg over 30 seconds; can administer 0.3 mg over next 30 seconds; can administer 0.5 mg over 30 seconds after 1 minute; maximum 5 mg

#### Dosing Tips
- May need to administer follow-up doses to reverse actions of benzodiazepines that have a longer half-life than flumazenil (i.e., longer than 1 hour)

#### Overdose
- Anxiety, agitation, increased muscle tone, hyperesthesia, convulsions

#### Long-Term Use
- Not a long-term treatment

#### Habit Forming
- No

#### How to Stop
- N/A

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### FLUMAZENIL

**Labeling Rule (PLLR or final rule)** applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001.

Controlled studies have not been conducted in pregnant women. Not recommended to treat the effects of benzodiazepines during labor and delivery because the effects on the infant have not been studied.

**Breast Feeding**
- Unknown if flumazenil is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk.
- If treatment with flumazenil is necessary, it should be administered with caution.

### SPECIAL POPULATIONS

#### Renal Impairment
- Dosage adjustment may not be necessary.

#### Hepatic Impairment
- Prolongation of half-life
- Moderate: clearance reduced by half
- Severe: clearance reduced by three-quarters

#### Cardiac Impairment
- Dosage adjustment may not be necessary.

#### Elderly
- Dosage adjustment may not be necessary.

#### Children and Adolescents
- More variability of pharmacokinetics than in adults.
- Safety and efficacy established for reversal of conscious sedation for children over age 1.
- Initial 0.01 mg/kg (up to 0.2 mg) over 15 seconds; same dosing pattern as adults; maximum 0.05 mg/kg or 1 mg.
- Safety and efficacy for reversal of benzodiazepine overdose, general anesthesia induction or resuscitation of a newborn have not been established, but anecdotal data suggest similar safety and efficacy as for conscious sedation.

#### Pregnancy
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation

### THE ART OF PSYCHOPHARMACOLOGY

#### Potential Advantages
- To reverse a low dose of a short-acting benzodiazepine.

#### Potential Disadvantages
- May be too short-acting.

#### Primary Target Symptoms
- Effects of benzodiazepines
- Sedative effects
- Recall and psychomotor impairments
- Ventilatory depression

#### Pearls
- Can precipitate benzodiazepine withdrawal seizures
- Can wear off before the benzodiazepine is reversing
- Can precipitate anxiety or panic in conscious patients with anxiety disorders.
Suggested Reading


