Flumazenil is a white to off-white crystalline compound with an octanol-buffer partition coefficient of 14 to 1 at pH 7.4. It is insoluble in water but slightly soluble in acidic aqueous solutions. Flumazenil Injection, USP is available as a sterile parenteral dosage form for intravenous administration. Each mL contains 0.1 mg of flumazenil compounded with 1.8 mg of methylparaben, 0.2 mg of propylparaben, 0.9% sodium chloride, 0.01% edetate disodium, and 0.01% acetic acid; the pH is adjusted to approximately 3.8 to 4.3 with hydrochloric acid and/or, if necessary, sodium hydroxide.

**CLINICAL PHARMACOLOGY:**
Flumazenil, an imidazobenzodiazepine derivative, antagonizes the actions of benzodiazepines on the central nervous system. Flumazenil competitively inhibits the activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. Flumazenil is a weak partial agonist in some animal models of activity, but has little or no agonist activity in man. Flumazenil does not antagonize the central nervous system effects of drugs affecting GABA-ergic neurons by means other than the benzodiazepine receptor (including ethanol, barbiturates, or general anesthetics) and does not reverse the effects of opioids.

In animals pretreated with high doses of benzodiazepines over several weeks, flumazenil elicited symptoms of benzodiazepine withdrawal, including seizures. A similar effect was seen in adult human subjects.

**Pharmacodynamics**
Intravenous flumazenil has been shown to antagonize sedation, impairment of recall, psychomotor impairment and ventilatory depression produced by benzodiazepines in healthy human volunteers. The duration and degree of reversal of benzodiazepine effects are related to the dose and plasma concentrations of flumazenil as shown in the following data from a study in normal volunteers.

Generally, doses of approximately 0.1 mg to 0.2 mg (corresponding to peak plasma levels of 3 to 6 ng/mL) produce partial antagonism, whereas higher doses of 0.4 to 1 mg (peak plasma levels of 12 to 28 ng/mL) usually produce complete antagonism in patients who have received the usual sedatant doses of benzodiazepines. The onset of reversal is usually evident within 1 to 2 minutes after the injection is completed. Eighty percent response will be reached within 3 minutes, with the peak effect occurring at 6 to 10 minutes. The duration and degree of reversal are related to the plasma concentration of the sedating benzodiazepine as well as the dose of flumazenil given.

In healthy volunteers, flumazenil did not alter intracranial pressure when given alone and reversed the decrease in intracranial pressure seen after administration of midazolam.

**Elimination**
Elimination of radiolabeled drug is essentially complete within 72 hours, with 90% to 95% of the radioactivity appearing in urine and 5% to 10% in the feces. Clearance of flumazenil occurs primarily by hepatic metabolism and is dependent on hepatic blood flow. In pharmacokinetic studies of normal volunteers, total clearance was 1.5 mL/min/kg.

Pharmacokinetic parameters following a 5-minute infusion of a total of 1 mg of flumazenil mean (coefficient of variation, range):

- Cl\(_{\text{ave}}\) (ng/mL) 24 (38%, 11 to 43)
- AUC (ng·hr/mL) 15 (22%, 10 to 22)
- V\(_{\text{d}}\) (L/kg) 1 (24%, 0.8 to 1.6)
- Cl (L/hr/kg) 1 (20%, 0.7 to 1.4)
- Half-life (min) 54 (21%, 41 to 79)

**Food Effects**
Ingestion of food during an intravenous infusion of the drug results in a 50% increase in clearance, most likely due to the increased hepatic blood flow that accompanies a meal.

**Special Populations**

- **The Elderly**
The pharmacokinetics of flumazenil are not significantly altered in the elderly.
- **Gender**
The pharmacokinetics of flumazenil are not different in male and female subjects.

**Renal Failure** (creatinine clearance <10 mL/min) and Hemodialysis
The pharmacokinetics of flumazenil are not significantly affected.

**Patients With Liver Dysfunction**
For patients with moderate liver dysfunction, their mean total clearance is decreased to 40% to 60% and in patients with severe liver dysfunction, it is decreased to 25% of normal value, compared with age-matched healthy subjects. This results in a prolongation of the half-life to 1.3 hours in patients with moderate hepatic impairment and 2.4 hours in severely impaired patients. Caution should be exercised with initial and/or repeated dosing to patients with liver disease.

**Drug-Drug Interaction**
The pharmacokinetic profile of flumazenil is unaltered in the presence of benzodiazepine agonists and the kinetic profiles of those benzodiazepines studied (i.e., diazepam, flunitrazepam, lormetazepam, and midazolam) are unaltered by flumazenil. During the 4-hour steady-state and post infusion of ethanol, there were no pharmacokinetic interactions on ethanol mean plasma levels as compared to placebo when flumazenil doses were given intravenously (at 2.5 hours and 6 hours) nor were interactions of ethanol on the flumazenil elimination half-life found.

**Pharmacokinetics in Pediatric Patients**
The pharmacokinetics of flumazenil have been evaluated in 28 pediatric patients ranging in age from 1 to 17 years who had undergone minor surgical procedures. The average doses administered were 0.53 mg (0.044 mg/kg) in patients aged 1 to 5 years, 0.63 mg (0.020 mg/kg) in patients aged 6 to 12 years, and 0.8 mg (0.014 mg/kg) in patients aged 13 to 17 years. Compared to adults, the half-life was somewhat shorter and more variable in these patients with an averaging 40 minutes and generally ranging from 20 to 75 minutes. Clearance and volume of distribution, normalized for body weight, were in the same range as those seen in adults, although more variability was seen in the pediatric patients.

**CLINICAL TRIALS:**
Flumazenil has been administered in adults to reverse the effects of benzodiazepines in conscious sedation, general anesthesia, and the management of suspected benzodiazepine overdose. Limited information from uncontrolled studies in pediatric patients is available regarding the use of flumazenil to reverse the effects of benzodiazepines in conscious sedation only.

**Conscious Sedation in Adults**
Flumazenil was studied in four trials in 970 patients who received an average of 30 mg diazepam or 10 mg midazolam for sedation (with or without a narcotic) in conjunction with both inpatient and outpatient diagnostic or surgical procedures. Flumazenil was effective in reversing the sedating and psychomotor effects of the benzodiazepine; however, amnesia was less completely and less consistently reversed. In these studies, flumazenil was administered as an initial dose of 0.4 mg IV (two doses of 0.2 mg) with additional 0.2 mg doses as needed to achieve complete awakening, up to a maximum total dose of 1 mg.

Seventy-eight percent of patients receiving flumazenil responded by becoming completely alert. Of those patients, approximately half responded to doses of 0.4 mg to 0.6 mg, while the other half responded to doses of 0.8 mg to 1 mg. Adverse effects were infrequent in patients who received 1 mg of flumazenil or less, although injection site pain, agitation and anxiety did occur. Reversal of sedation was
not associated with any increase in the frequency of inadequate analgesia or increase in narcotic demand in comparison to the most patients remained alert. Throughout the 3-hour postprocedure observation period, resedation was observed to occur in 3% to 9% of the dose groups. In four patients who had received high doses of benzodiazepines (see PRECAUTIONS).

General Anesthesia in Adults
Flumazenil was studied in four trials in 644 patients who received midazolam as an induction and/or maintenance of anesthesia balanced and inhalational anesthesia. Midazolam was generally administered in doses ranging from 5 mg to 80 mg, alone and/or in combination with other agents, for induction, regional or local anesthetics, narcotics and/or inhalation anesthetics. Flumazenil was given as an initial dose and, in addition to 0.2 mg/kg, was needed to reach a complete response, up to a maximum of 3 mg in four trials of these doses were effective in reversing sedation and restoring psychomotor function, but did not completely restore memory and awareness. The dose of flumazenil as effective in the reversal of sedation in patients who had received multiple anesthetic agents in addition to midazolam.

Eighty-one percent of patients sedated with midazolam responded to flumazenil by becoming completely alert or just slightly drowsy. Of those patients, 63% responded to doses of 0.4 mg to 0.6 mg, while 64% responded to doses of 0.8 mg to 1 mg. Resedation in patients who responded to flumazenil occurred in 10% to 15% of patients studied and was dose related. In two large trials, nightly resedation was observed to occur in 3% to 5% of patients. Flumazenil re-administration was effective in the reversal of sedation in patients who had received multiple anesthetic agents in addition to midazolam.

Management of Suspected Benzodiazepine Overdose in Adults
Flumazenil was studied in two trials in 497 patients who were presumed to have taken an overdose of a benzodiazepine, either alone or in combination with a variety of other agents. In one trial, flumazenil was used in 10% of 15% of patients studied and was well tolerated. In another trial, nightly resedation was observed to occur in 3% to 5% of patients. Flumazenil re-administration was effective in the reversal of sedation in patients who had received multiple anesthetic agents in addition to midazolam.

Individualization of Dosage
General Principles

The serious adverse effects of flumazenil are related to the reversal of benzodiazepine effects. Using much more than the minimally effective dose of flumazenil is tolerated by most patients but may complicate the management of patients who are physically dependent on benzodiazepines or who are experiencing benzodiazepines for therapeutic effect (for example, maintenance of sedation in cyclic antidepressant poisoning, which increased the risk of seizures (see WARNINGS).

Anesthesia and Conscious Sedation in Adult Patients

Flumazenil is well tolerated at the recommended doses in individuals who have been taking benzodiazepines long enough to have some degree of tolerance. Patients who had been taking benzodiazepines prior to treatment with flumazenil, who were given flumazenil in doses over 1 mg, experienced withdrawal symptoms more frequently than those who received less than 1 mg. In patients who may have tolerance to benzodiazepines, as well as the need for larger than usual doses of benzodiazepines, slow titration rates of 0.1 mg/min and lower total doses may reduce the risk of emergence, confusion and agitation. In such cases, special care must be taken to monitor the patients for resedation because of the lower doses of flumazenil used.

Physically Dependent on Benzodiazepines

Flumazenil is known to precipitate withdrawal seizures in patients who are physically dependent on benzodiazepines, even if such dependence was established in a previous sedation or dose sedation in Intensive Care Unit (ICU) environments. The risk of either seizures or resedation in such cases is high and patients who are physically dependent on benzodiazepines before concluding that flumazenil should be used in such situations with caution, since the use of flumazenil in this situation has not been studied and no information is available on the dose and rate of titration. Flumazenil should be used in such patients only if the potential benefits of using the drug outweigh the risks of precipitating seizures. Physicians are directed to consult the literature for the most current information in this area.

Warning: Use of flumazenil in certain high-risk populations. Possible risk factors for seizures include marked hypnotic drug withdrawal, recent therapy with repeated doses of parenteral benzodiazepines, myoclonic or tonic-clonic activity prior to flumazenil administration in overdose cases, or concurrent use of anticonvulsant medications.

Flumazenil is not recommended in cases of serious cyclic antidepressant poisoning, as manifested by myoclonic or tonic-clonic activity (status epilepticus), dysrhythmia (wide QRS, ventricular dysrhythmia, heart block), anticholinergic signs (mydriasis, dry mouth, delirium, and cardiovascular collapse at presentation. In such cases flumazenil should be withheld and the patient should be allowed to remain sedated (with a ventilatory and respiratory support as needed) until the signs of antidepressant toxicity have subsided. Treatment with flumazenil has not been shown to benefit the serious sedation patient other than reversing sedation and should not be used in cases where seizures (from any cause) are likely.

Most convulsions associated with flumazenil administration require treatment with an anticonvulsant. Successfully managed with benzodiazepines, phenytoin or barbiturates. Because of the presence of flumazenil, higher than usual doses of benzodiazepines may be required.

Hyperventilation

Patients who have received flumazenil for the reversal of sedation (e.g., postoperative, delirium tremens, benzodiazepine overdose) should be monitored for the occurrence of hypoventilation or apparent respiratory depression (see WARNINGS) or other persistent or recurrent against effects for an adequate period of time after administration of flumazenil.

Resedation is least likely in cases where flumazenil is administered to reverse a low dose of a short-acting benzodiazepine (e.g., one mg or less). Flumazenil is mostly likely in cases where a large single or cumulative dose of a benzodiazepine or combination of benzodiazepines may be given. The use of large doses of benzodiazepines for sedation should be monitored for the occurrence of hypoventilation (see WARNINGS) or other persistent or recurrent against effects for an adequate period of time after administration of flumazenil. Flumazenil should be monitored for the occurrence of hypoventilation (see WARNINGS) or other persistent or recurrent against effects for an adequate period of time after administration of flumazenil. Flumazenil should be monitored for the occurrence of hypoventilation (see WARNINGS) or other persistent or recurrent against effects for an adequate period of time after administration of flumazenil.

The use of flumazenil to reverse the effects of benzodiazepines used for conscious sedation has been evaluated in one open-label clinical trial involving 107 pediatric patients between the ages of 1 year and 17 years. This study suggested that flumazenil may be safe and effective in children who have become fully awake following treatment with flumazenil may experience a recurrence of seizures, especially when younger than 1 year of age. Resedation was experienced in 7 of 60 patients who were given the initial dose of 1 mg or more of flumazenil. Physicians may wish to repeat the initial dose (up to 1 mg of flumazenil given at 0.2 mg/min) at 30 minutes and possibly again after an appropriate period of time. The dosage schedule, although not studied in clinical trials, was effective in preventing resedation in a pharmacodynamic study in patients in ICU.

The safety and effectiveness of repeated flumazenil administration in pediatric patients experiencing resedation have not been established. Use in the ICU

Flumazenil should be used with caution in the ICU because of the increased risk of unrecognized benzodiazepine dependence in such settings. Flumazenil may produce convulsions or seizures in some cases of benzodiazepine dependence (see Individualization of Dosage and WARNINGS).

Flumazenil was studied in 446 patients treated with flumazenil in these studies. In clinical studies, in clinical situations other than severe sedation or overdose, the available data are inconsistent and have not been adequately studied. The availability of flumazenil does not diminish the need for prompt detection of hyperventilation and the ability to effectively intervene by establishing intubation and ventilation.
The clearance of flumazenil is reduced to 40% to 60% on cardiovascular parameters when administered to less than 0.5 mg in studies reported in the clinical literature. Use to reverse benzodiazepines in cardiac patients induced alterations in ventilatory drive in healthy disease who experience serious respiratory depression due to benzodiazepines should be appropriate. The primary treatment of patients with serious lung disease who experience serious respiratory depression due to benzodiazepines should be appropriate. The primary treatment of patients with serious lung disease who experience serious respiratory depression due to benzodiazepines should be appropriate. The effects of nonbenzodiazepine agonists at benzodiazepine receptors, such as zopiclone, triazolopyridazines and others, are also blocked by flumazenil. The pharmacokinetics of benzodiazepines are unaltered in the presence of flumazenil and vice versa. There is no pharmacokinetic interaction between ethanol and flumazenil.

Use in Cardiovascular Disease Flumazenil does not increase the work of the heart when used to reverse benzodiazepines in cardiac patients when given at a rate of 0.1 mg/min in total doses of less than 10 mg. Studies reported in the literature. Flumazenil alone had no significant effects on cardiovascular parameters when administered to patients with stable ischemic heart disease.

Use in Liver Disease The clearance of flumazenil is reduced to 40% to 60% of normal in patients with severe hepatic dysfunction (see Pharmacokinetics). While the clearance of flumazenil only increased due to the increased frequency of benzodiazepine tolerance and dependence observed in these patient populations. Flumazenil is not recommended either as a treatment for benzodiazepine dependence or for the management of withdrawal benzodiazepine abstinence syndromes, as such use has not been studied.

The administration of flumazenil can precipitate benzodiazepine withdrawal in animals and man. This has been seen in healthy volunteers treated with therapeutic doses of oral lorazepam for up to 2 weeks who exhibited effects such as hot flushes, agitation and restlessness when treated with cumulative doses of up to 3 mg doses of flumazenil. Flumazenil is a mixed competitive antagonist of benzodiazepine withdrawal have occurred in some adult patients in clinical trials. Such patients had a short-lived syndrome characterized by dizziness, mild confusion, emotional lability, agitation (with signs and symptoms of anxiety), and was usually short-lived. When required (5 to 10 cases), these patients were successfully treated with higher doses of a barbiturate, a benzodiazepine, or other sedative drug.

Cardiovascular System

Body as a Whole

but they are included as alerting information for the

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Special Senses

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tration and/or reversal of benzodiazepine effects:

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aries unless otherwise marked.

diplopia) and paresthesia (sensation abnormal,

dysphoria, paranoia)

and emotional lability (crying abnormal, deperson-

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(sweating, flushing, hot flushes)

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