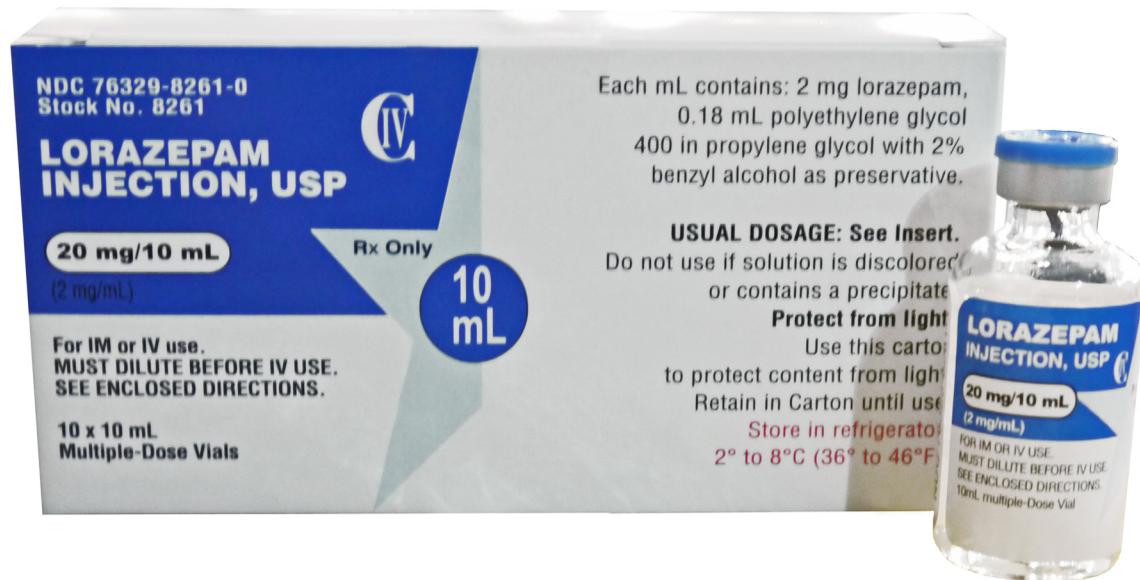


Lorazepam Injection, USP, C IV, 2mg/mL



- * For IM or IV use
- * Bar Coded
- * Latex Free
- * Store in refrigeration 2° to 8°C (36° to 46°F)

PRODUCT DESCRIPTION	NDC #	DELIVERY SYSTEM	UNIT SIZE	UNITS/BOX
Lorazepam Inj., USP, CIV	76329-8261-1	Multi Dose Vial	20 mg / 10 mL	10

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RX Only
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01-023-01

DESCRIPTION

Lorazepam a benzodiazepine with antianxiety, sedative, and anticonvulsant effects, is intended for the intramuscular or intravenous routes of administration. Each mL of sterile injection contains 2 mg of lorazepam, 0.18 mL polyethylene glycol 400 in propylene glycol with 2% benzyl alcohol as preservative.

Special Populations

Effect of Age

Pediatrics

Neonates (Birth to 1 month)

Following a single 0.05 mg/kg (n=4) or 0.1 mg/kg (n=6) intravenous dose of lorazepam, *mean total clearance normalized to body weight was reduced by 80% compared to normal adults*. Terminal half-life was prolonged 3-fold, and volume of distribution was decreased by 40% in neonates with asphyxia neonatorum compared to normal adults. All neonates were of \geq 37 weeks of gestational age.

Infants (1 month up to 2 years)

There is no information on the pharmacokinetic profile of lorazepam in infants in the age range of 1 month to 2 years.

Children (2 years up to 12 years)

Total (bound and unbound) lorazepam had a 50% higher mean volume of distribution (normalized to body-weight) and a 30% longer mean half-life in children with acute lymphocytic leukemia in complete remission (2 to 12 years, n=37) compared to normal adults (n=10). Unbound lorazepam clearance normalized to body-weight was comparable in children and adults.

Adolescents (12 years to 18 years)

Total (bound and unbound) lorazepam had a 50% higher mean volume of distribution (normalized to body-weight) and a mean half-life that was two fold greater in adolescents with acute lymphocytic leukemia in complete remission (12 to 18 years, n=13) compared to normal adults (n=10). Unbound lorazepam clearance normalized to body-weight was comparable in adolescents and adults.

Elderly

Following single intravenous doses of 1.5 to 3 mg of Lorazepam Injection, mean total body clearance of lorazepam decreased by 20% in 15 elderly subjects of 60 to 84 years of age compared to that in 15 younger subjects of 19 to 38 years of age. Consequently, no dosage adjustments appears to be necessary in elderly subjects based solely on their age.

Effect of Gender

Gender has no effect on the pharmacokinetics of lorazepam.

Effect of Race

Young Americans (n=15) and Japanese subjects (n=7) had very comparable mean total clearance value of 1 mL/min/kg. However, elderly Japanese subjects had a 20% lower mean total clearance than elderly Americans, 0.59 mL/min/kg vs 0.77 mL/min/kg, respectively.

Patients with Renal Insufficiency

Because the kidney is the primary route of elimination of lorazepam-glucuronide, renal impairment would be expected to compromise its clearance. This should have no direct effect on the glucuronidation (and inactivation) of lorazepam. There is a possibility that the enterohepatic circulation of lorazepam-glucuronide leads to a reduced efficiency of the net clearance of lorazepam in this population.

Six normal subjects, six patients with renal impairment (Cl_{cr} of 22-29 mL/min), and four patients on chronic maintenance hemodialysis were given single 1.5 to 3 mg intravenous doses of lorazepam. Mean volume of distribution and terminal half-life values of lorazepam were 40% and 25% higher, respectively, in renally impaired patients than in normal subjects. Both parameters were 75% higher in patients undergoing hemodialysis than in normal subjects. Overall, though, in this group of subjects the mean total clearance of lorazepam did not change. About 8% of the administered intravenous dose was removed as intact lorazepam during the 6-hour dialysis session.

The kinetics of lorazepam-glucuronide were markedly affected by renal dysfunction. The mean terminal half-life was prolonged by 55% and 125% in renally impaired patients and patients under hemodialysis, respectively, as compared to normal subjects. The mean metabolic clearance decreased by 75% and 90% in renally impaired patients and patients under hemodialysis, respectively, as compared with normal subjects. About 40% of the administered lorazepam intravenous dose was removed as glucuronide conjugate during the 6-hour dialysis session.

Hepatic Disease

Because cytochrome oxidation is not involved with the metabolism of lorazepam, liver disease would not be expected to have an effect on metabolic clearance. This prediction is supported by the observation that following a single 2 mg intravenous dose of lorazepam, cirrhotic male patients (n=13) and normal male subjects (n=11) exhibited no substantive difference in their ability to clear lorazepam.

Effect of Smoking

Administration of a single 2 mg intravenous dose of lorazepam showed that there was no difference in any of the pharmacokinetic parameters of lorazepam between cigarette smokers (n=10, mean=31 cigarettes per day) and nonsmoking subjects (n=10) who were matched for age, weight and gender.

INDICATIONS AND USAGE

Status Epilepticus

Lorazepam Injection, is indicated for the treatment of the status epilepticus.

Preanesthetic

Lorazepam Injection, is indicated in adult patients for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and a decreased ability to recall events related to the day of surgery. It is *most useful* in those patients who are anxious about their surgical procedure and who would prefer to have diminished recall of the events of the day of surgery (see **PRECAUTIONS: Information for Patients**).

CONTRAINDICATIONS

Lorazepam Injection is contraindicated in patients with a known sensitivity to benzodiazepines or its vehicle (polyethylene glycol, propylene glycol and benzyl alcohol), in patients with acute narrow-angle glaucoma, or in patients with sleep apnea syndrome. It is also contraindicated in patients with severe respiratory insufficiency, except in those patients requiring relief of anxiety and/or diminished recall of events while being mechanically ventilated. The use of lorazepam injection intra-arterially is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation (see **WARNINGS**).

WARNINGS

Use in Status Epilepticus

Management of Status Epilepticus

Status epilepticus is a potentially life-threatening condition associated with a high risk of permanent neurological impairment, if inadequately treated. The treatment of status, however, requires far more than the administration of an anticonvulsant agent. It involves observation and management of all parameters critical to maintaining vital function and the capacity to provide support of those functions as required. Ventilatory support must be readily available. The use of benzodiazepines, like Lorazepam Injection, is ordinarily only one step of a complex and sustained intervention which may require additional interventions (e.g., concomitant intravenous administration of phenytoin). Because status epilepticus may result from a correctable acute cause such as hypoglycemia, hyponatremia, or other metabolic or toxic derangement, such an abnormality must be immediately sought and corrected. Furthermore, patients who are susceptible to further seizure episodes should receive adequate maintenance antiepileptic therapy.

Any health care professional who intends to treat a patient with status epilepticus should be familiar with this package insert and the pertinent medical literature concerning current concepts for the treatment of status epilepticus. A comprehensive review of the considerations critical to the informed and prudent management of status epilepticus cannot be provided in drug product labeling. The archival medical literature contains many informative references on the management of status epilepticus, among them the report of the working group on status epilepticus of the Epilepsy Foundation of America "Treatment of Convulsive Status Epilepticus" (*JAMA* 1993; 270: 854-859). As noted in the report just cited, it may be useful to consult with a neurologist if a patient fails to respond (e.g., fails to regain consciousness).

For the treatment of status epilepticus, the usual recommended dose of Lorazepam Injection is 4 mg given slowly (2 mg/min) for patients 18 years and older. If seizures cease, no additional Lorazepam Injection is required. If seizures continue or recur after a 10- to 15-minute observation period, an additional 4 mg intravenous dose may be slowly administered. *Experience with further doses of lorazepam injection is very limited.* The usual precautions in treating status epilepticus should be employed. An intravenous infusion should be started, vital signs should be monitored, an unobstructed airway should be maintained, and artificial ventilation equipment should be available.

Respiratory Depression

The most important risk associated with the use of Lorazepam Injection in status epilepticus is respiratory depression. Accordingly, airway patency must be assured and respiration monitored closely. Ventilatory support should be given as required.

Excessive Sedation

Because of its prolonged duration of action, the prescriber should be alert to the possibility, especially when multiple doses have been given, that the sedative effects of lorazepam may add to the impairment of consciousness seen in the post-cital state.

Preanesthetic Use

AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. INTRAVENOUS LORAZEPAM AT ANY DOSE, WHEN GIVEN EITHER ALONE OR IN COMBINATION WITH OTHER DRUGS ADMINISTERED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY AND TO SUPPORT RESPIRATION/VENTILATION SHOULD BE AVAILABLE.

As is true of similar CNS-acting drugs, the decision as to when patients who have received injectable lorazepam, particularly on an outpatient basis, may again operate machinery, drive a motor vehicle, or engage in hazardous or other activities requiring attention and coordination must be individualized. It is recommended that no patient engage in such activities for a period of 24 to 48 hours or until the effects of the drug, such as drowsiness, have subsided, whichever is longer. Impairment of performance may persist for greater intervals because of extremes of age, concomitant use of other drugs, stress of surgery, or the general condition of the patient.

Clinical trials have shown that patients over the age of 50 years may have a more profound and prolonged sedation with intravenous lorazepam (see also **DOSEAGE AND ADMINISTRATION: Preanesthetic**).

DOSEAGE AND ADMINISTRATION: Preanesthetic

As with all central-nervous-system-depressant drugs, care should be exercised in patients given injectable lorazepam as premature ambulation may result in injury from falling.

There is no added beneficial effect from the addition of scopolamine to injectable lorazepam, and their combined effect may result in an increased incidence of sedation, hallucination and irrational behavior.

General (All Uses)

PRIOR TO INTRAVENOUS USE, LORAZEPAM INJECTION MUST BE DILUTED WITH AN EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSEAGE AND ADMINISTRATION). INTRAVENOUS INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CARE SHOULD BE TAKEN TO DETERMINE THAT ANY INJECTION WILL NOT BE INTRA-ARTERIAL AND THAT PERIVASCULAR EXTRAVASATION WILL NOT TAKE PLACE. IN THE EVENT THAT A PATIENT COMPLAINS OF PAIN DURING INTENDED INTRAVENOUS INJECTION OF LORAZEPAM INJECTION THE INJECTION SHOULD BE STOPPED IMMEDIATELY TO DETERMINE IF INTRA-ARTERIAL INJECTION OR PERIVASCULAR EXTRAVASATION HAS TAKEN PLACE.

Since the liver is the most likely site of conjugation of lorazepam and since excretion of conjugated lorazepam (glucuronide) is a renal function, this drug is not recommended for use in patients with hepatic and/or renal failure. Lorazepam should be used with caution in patients with mild-to-moderate hepatic or renal disease (see **DOSEAGE AND ADMINISTRATION**).

Pregnancy

LORAZEPAM INJECTION MAY CAUSE FETAL DAMAGE WHEN ADMINISTERED TO PREGNANT WOMEN. Ordinarily, Lorazepam Injection should not be used during pregnancy except in serious or life-threatening conditions where safer drugs cannot be used or are ineffective. Status epilepticus may represent such a serious and life-threatening condition.

An increased risk of congenital malformation associated with the use of minor tranquilizers (chloridiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy has been suggested in several studies. In humans, blood levels obtained from umbilical cord blood indicate placental transfer of lorazepam and lorazepam glucuronide.

Reproductive studies in animals were performed in mice, rats, and two strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull, and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all of these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg orally or 4 mg/kg intravenously and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

The possibility that a woman of childbearing potential may be pregnant at the time of therapy should be considered.

There are insufficient data regarding obstetrical safety of parenteral lorazepam, including use in cesarean section. Such use, therefore, is not recommended.

Endoscopic Procedures

There are insufficient data to support the use of lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observation time.

When lorazepam injection is used for peroral endoscopic procedures; adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS

General

The additive central-nervous-system effects of other drugs, such as phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine, and monamine-oxidase inhibitors, should be borne in mind when these other drugs are used concomitantly with or during the period of recovery from lorazepam injection. (See **CLINICAL PHARMACOLOGY** and **WARNINGS**).

Extreme caution must be used when administering lorazepam to elderly patients, very ill patients, or to patients with limited pulmonary reserve because of the possibility that hyperventilation and/or hypoxic cardiac arrest may occur. Resuscitative equipment for ventilatory support should be readily available (see **WARNINGS and DOSEAGE AND ADMINISTRATION**).

When lorazepam injection is used IV as the premedicant prior to regional or local anesthesia, the possibility of excessive sleepiness or drowsiness may interfere with patient cooperation in determining levels of anesthesia. This is most likely to occur when greater than 0.05 mg/kg is given and when narcotic analgesics are used concomitantly with the recommended dose. (See **ADVERSE REACTIONS**).

As with all benzodiazepines, paradoxical reactions may occur in rare instances and in an unpredictable fashion (see **ADVERSE REACTIONS**). In these instances, further use of the drug in these patients should be considered with caution.

There have been reports of possible propylene glycol toxicity (e.g., lactic acidosis, hypersmolarity, hypotension) and possible polyethylene glycol toxicity (e.g., acute tubular necrosis) during administration of Lorazepam Injection at higher than recommended doses. Symptoms may be more likely to develop in patients with renal impairment.

Information for Patients

Patients should be informed of the pharmacological effects of the drug, including sedation, relief of anxiety, and lack of recall, the duration of these effects (about 8 hours), and be apprised of the risks as well as the benefits of therapy.

Patients who receive lorazepam as a premedicant should be cautioned that driving a motor vehicle, operating machinery, or engaging in hazardous or other activities requiring attention and coordination, should be delayed for 24 to 48 hours following the injection or until the effects of the drug, such as drowsiness, have subsided, whichever is longer. Sedatives, tranquilizers and narcotic analgesics may produce a more prolonged and profound effect when administered along with injectable lorazepam. This effect may take the form of excessive sleepiness or drowsiness and, on rare occasions, interfere with recall and recognition of events of the day of surgery and the day after.

Patients should be advised that getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Since tolerance for CNS depressants will be diminished in the presence of lorazepam injection, these substances should either be avoided or taken in reduced dosage. Alcoholic beverages should not be consumed for at least 24 to 48 hours after receiving lorazepam injectable due to the additive effects on central-nervous-system depression seen with benzodiazepines in general. Elderly patients should be told that lorazepam may make them very sleepy for a period longer than six (6) to eight (8) hours following surgery.

Laboratory Tests

In clinical trials no laboratory test abnormalities were identified with either single or multiple doses of lorazepam. These tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus, and total proteins.

Drug Interactions

Lorazepam Injection, like other injectable benzodiazepines, produces additive depression of the central nervous system when administered with other CNS depressants such as ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors, and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam, an increased incidence of sedation, hallucinations and irrational behavior have been observed.

There have been rare reports of significant respiratory depression, stupor and/or hypotension with the concomitant use of loxapine and lorazepam.

Marked sedation, excessive salivation, axia, and, rarely, death have been reported with the concomitant use of clonazepam and lorazepam.

Apnea, coma, bradycardia, arrhythmias, heart arrest, and death have been reported with the concomitant use of haloperidol and lorazepam.

The risk of using lorazepam in combination with scopolamine, loxapine, clozapine, haloperidol, or other CNS-depressant drugs has not been systematically evaluated. Therefore, caution is advised if the concomitant administration of lorazepam and these drugs is required.

Concurrent administration of any of the following drugs with lorazepam had no effect on the pharmacokinetics of lorazepam: metoprolol, cimetidine, ranitidine, disulfiram, propranolol, metronidazole, and propoxyphene. No change in lorazepam injection dosage is necessary when concomitantly given with any of these drugs.

Lorazepam-Valproate Interaction

Concurrent administration of lorazepam (2 mg intravenously) with valproate (250 mg twice daily orally for 3 days) to 6 healthy male subjects resulted in decreased total clearance of lorazepam by 40% and decreased formulation rate of lorazepam glucuronide by 55%, as compared with lorazepam administered alone. Accordingly, lorazepam plasma concentrations were about two-fold higher for at least 12 hours post-dose administration during valproate treatment. Lorazepam dosage should be reduced to 50% of the normal adult dose when this drug combination is prescribed in patients (see also **DOSEAGE AND ADMINISTRATION**).

ADMINISTRATION:

Lorazepam-Oral Contraceptive Steroids Interaction

Coadministration of lorazepam (2 mg intravenously) with oral contraceptive steroids (norethindrone acetate 1 mg, and ethinyl estradiol 50 mcg, for at least 6 months) to healthy females (n=7) was associated with a 55% decrease in half-life, a 50% increase in the volume of distribution, thereby resulting in an almost 3.7-fold increase in total clearance of lorazepam as compared with control healthy females (n=8). It may be necessary to increase the dose of Lorazepam in female patients who are concomitantly taking oral contraceptives (see also **DOSEAGE AND ADMINISTRATION**).

Lorazepam-Probenecid Interaction

Concurrent administration of lorazepam (2 mg intravenously) with probenecid (500 mg orally every 6 hours) to 9 healthy volunteers resulted in a prolongation of lorazepam half-life by 130% and a decrease in its total clearance by 45%. No change in volume of distribution was noted during probenecid co-treatment. Lorazepam dosage needs to be reduced by 50% when coadministered with probenecid (see also **DOSEAGE AND ADMINISTRATION**).

Drug/Laboratory Test Interactions

No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, such as narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and a variety of tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. The results of a preimplantation study in rats, in which the oral lorazepam dose was 20 mg/kg, showed no impairment of fertility.

Pregnancy

Teratogenic Effects—Pregnancy Category D (See **WARNINGS**).

Labor and Delivery

There are insufficient data to support the use of lorazepam injection during labor and delivery, including cesarean section; therefore, its use in this clinical circumstance is not recommended.

Nursing Mothers

Lorazepam has been detected in human breast milk. Therefore, lorazepam should not be administered to nursing mothers because, like other benzodiazepines, the possibility exists that lorazepam may sedate or otherwise adversely affect the infant.

Pediatric Use

Status Epilepticus

The safety of lorazepam in pediatric patients with status epilepticus has not been systematically evaluated. Open-label studies described in the medical literature included 273 pediatric/adolescent patients; the age range was from a few hours old to 18 years of age. Paradoxical excitation was observed in 10% to 30% of the pediatric patients under 8 years of age and was characterized by tremors, agitation, euphoria, lorgorhea, and brief episodes of visual hallucinations. Paradoxical excitation in pediatric patients also has been reported with other benzodiazepines when used for status epilepticus, as an anesthesia, or for pre-chemotherapy treatment.

Pediatric patients (as well as adults) with atypical petit mal status epilepticus have developed brief tonic-clonic seizures shortly after lorazepam injection was given. This "paradoxical" effect was also reported for diazepam and clonazepam. Nevertheless, the development of seizures after treatment with benzodiazepines is probably rare, based on the incidence in the uncontrolled treatment of series reported (i.e., seizures were not observed for 112 pediatric patients and 18 adults or during approximately 400 doses).

Preanesthetic

There are insufficient data to support the efficacy of injectable lorazepam as a preanesthetic agent in patients less than 18 years of age.

General

Seizure activity and myoclonus have been reported to occur following administration of Lorazepam Injection, especially in very low birth weight neonates.

Pediatric patients may exhibit a sensitivity to benzyl alcohol, polyethylene glycol and propylene glycol, components of Lorazepam Injection (see also **CONTRAINDICATIONS**). The "gasping syndrome," characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine, has been associated with the administration of intravenous solutions containing the preservative benzyl alcohol in neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Central nervous system toxicity, including seizures and intraventricular hemorrhage, as well as unresponsiveness, tachypnea, tachycardia, and diaphoresis have been associated with propylene glycol toxicity. Although normal therapeutic doses of Lorazepam Injection contain very small amounts of these compounds, premature and low-birth-weight infants as well as pediatric patients receiving high dosages may be more susceptible to their effects.

Geriatric Use

Clinical studies of lorazepam generally were not adequate to determine whether subjects aged 65 and over respond differently than younger subjects, however, age over 65 years may be associated with a greater incidence of central nervous system depression and more respiratory depression (see **WARNINGS: Preanesthetic Use, PRECAUTIONS: General, and ADVERSE REACTIONS: Preanesthetic**).

Age does not appear to have significant effect on lorazepam kinetics (see **CLINICAL PHARMACOLOGY**).

Clinical circumstances, some of which may be more common in the elderly, such as hepatic or renal impairment, should be considered. Greater sensitivity (e.g., sedation) of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range (see **DOSEAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Status Epilepticus

The most important adverse clinical event caused by the use of Lorazepam Injection is respiratory depression (see **WARNINGS**).

The adverse clinical events most commonly observed with the use of Lorazepam Injection in clinical trials evaluating its use in status epilepticus were hypotension, somnolence, and respiratory failure.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Lorazepam is a controlled substance in Schedule IV.

Abuse and Physical and Psychological Dependence

As with other benzodiazepines, lorazepam injection has a potential for abuse and may lead to dependence. Physicians should be aware that repeated doses over a prolonged period of time may result in physical and psychological dependence and withdrawal symptoms, following abrupt discontinuance, similar in character to those noted with barbiturates and alcohol.

OVERDOSAGE

Symptoms

Overdosage of benzodiazepines is usually manifested by varying degrees of central-nervous-system depression, ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy. In more serious examples, symptoms may include ataxia, hypotonia, hypotension, hypnosis, stages one (1) to three (3) coma, and, very rarely, death.