CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74496

DRAFT FINAL PRINTED LABELING

J-3291B

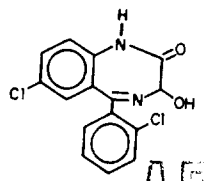
ELKINS-SINN

LORAZEPAM INJECTION, USP

CIV

DESCRIPTION

Lorazepam Injection, USP, a benzodiazepine with antianxiety and sedative effects, is intended for the intramuscular or intravenous routes of administration. It has the chemical formula (±)-7-Chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one, and the C.A.S. No. is [846-49-1]. The structural formula is:



SEP 28 1998

APPROVED

$C_{15}H_{10}Cl_2N_2O_2$ MW 321.16

Lorazepam is a nearly white powder almost insoluble in water. Each mL of the sterile injection contains lorazepam, USP 2 mg or 4 mg, polyethylene glycol 400 0.18 mL and benzyl alcohol 0.02 mL in propylene glycol.

CLINICAL PHARMACOLOGY

Lorazepam interacts with the γ-aminobutyric acid (GABA)-benzodiazepine receptor complex, which is widespread in the brain of humans as well as other species. This interaction is presumed to be responsible for lorazepam's mechanism of action. Lorazepam exhibits relatively high and specific affinity for its recognition site but does not displace GABA. Attachment to the specific binding site enhances the affinity of GABA for its receptor site on the same receptor complex. The pharmacodynamic consequences of benzodiazepine agonist actions include antianxiety effects and sedation. The intensity of action is directly related to the degree of benzodiazepine receptor occupancy.

EFFECTS IN PRE-OPERATIVE PATIENTS

Intravenous or intramuscular administration of the recommended dose of 2 mg to 4 mg of Lorazepam Injection to adult patients is followed by dose-related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to the day of surgery in the majority of patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that the majority of patients are able to respond to simple instructions whether they give the appearance of being awake or asleep. The lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing; using props designed to enhance recall. The majority of patients under these reinforced conditions had difficulty recalling perioperative events or recognizing props from before surgery. The lack of recall and recognition was optimum within 2 hours following intramuscular administration and 15 to 20 minutes after intravenous injection.

The intended effects of the recommended adult dose of Lorazepam Injection usually last 6 to 8 hours. In rare instances and where patients received greater than the recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness and enhanced sensitivity to CNS-depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

PHYSIOLOGIC EFFECTS IN HEALTHY ADULTS

Studies in healthy adult volunteers reveal that intravenous lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to the respiratory stimulating effect of carbon dioxide and does not enhance the respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction has been observed in rare instances where the patient received greater than the recommended dose and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of Lorazepam Injection do not greatly affect the circulatory system in the supine position or employing a 70-degree tilt test. Doses of 8 to 10 mg of intravenous lorazepam (2 to 21/2 times the maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received Lorazepam Injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following administration of 4 mg of intramuscular lorazepam and four (4) hours following administration of 2 mg intramuscularly with considerable subject variation. Similar findings were noted with pentobarbital, 150 and 75 mg. Although this study showed that both lorazepam and pentobarbital interfered with eye-hand coordination, the data are insufficient to predict when it would be safe to operate a motor vehicle or engage in a hazardous occupation or sport.

PHARMACOKINETICS AND METABOLISM

Absorption

Intravenous

A 4-mg dose provides an initial concentration of approximately 70 ng/mL.

Intramuscular

Following intramuscular administration, lorazepam is completely and rapidly absorbed reaching peak concentrations within 3 hours. A 4-mg dose provides a C_{max} of approximately 48 ng/mL. Following administration of 1.5-5.0 mg of lorazepam IM, the amount of lorazepam delivered to the circulation is proportional to the dose administered.

Distribution/Metabolism/Elimination

At clinically relevant concentrations, lorazepam is 91±2% bound to plasma proteins, its volume of distribution is approximately 1.3 L/kg. Unbound lorazepam penetrates the blood/brain barrier freely by passive diffusion, a fact confirmed by CSF sampling. Following parenteral administration, the terminal half-life and total clearance averaged 14±5 hours and 1.1±0.4 mL/min/kg, respectively.

Lorazepam is extensively conjugated to the 3-O-phenolic glucuronide in the liver and is known to undergo enterohepatic recirculation. Lorazepam-glucuronide is an inactive metabolite and is eliminated mainly by the kidneys.

Following a single 2-mg oral dose of ^{14}C-lorazepam to 8 healthy subjects, 88±4% of the administered dose was recovered in urine and 7±2% was recovered in feces. The percent of administered dose recovered in urine as lorazepam-glucuronide was 74±4%. Only 0.3% of the dose was recovered as unchanged lorazepam, and the remainder of the radioactivity represented minor metabolites.

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 ≥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 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 (2-12 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 (12-18 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 1.5-3 mg of Lorazepam Injection, mean total body clearance of lorazepam decreased by 20% in 15 elderly subjects of 60-84 years of age compared to that in 15 younger subjects of 19-38 years of age. Consequently, no dosage adjustment 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 1.0 mL/min/kg. However, elderly Japanese subjects had a 20% lower mean total clearance than elderly Americans, 0.59 mL/min/kg versus 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±9 mL/min), and four patients on chronic maintenance hemodialysis were given single 1.5 to 3.0 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 to 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

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) and in patients with acute narrow-angle glaucoma. The use of Lorazepam Injection intra-arterially is contraindicated because, as with other injectable benzodiazepines, such use may produce arteriospasm resulting in gangrene which may require amputation (see WARNINGS).

WARNINGS

PREANESTHETIC USE

PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. INTRAVENOUS LORAZEPAM, WHEN GIVEN ALONE IN GREATER THAN THE RECOMMENDED DOSE OR AT THE RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING THE ADMINISTRATION OF 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, patients receiving injectable lorazepam should not operate machinery or engage in hazardous occupations or drive a motor vehicle for a period of 24 to 48 hours. 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. Ordinarily, an initial dose of 2 mg may be adequate unless a greater degree of lack of recall is desired.

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 DOSAGE 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.

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*. This does not preclude use of the drug in patients with mild-to-moderate hepatic or renal disease (see DOSAGE AND ADMINISTRATION).

PREGNANCY

LORAZEPAM 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.

An increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, 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.

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

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 ran-

formly 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.

ENDOSCOPIC PROCEDURES

There are insufficient data to support the use of Lorazepam Injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations.

Pharyngeal reflexes are not impaired when Lorazepam Injection is used for peroral endoscopic procedures; therefore, 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 monoamine-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 care must be used in administering Lorazepam Injection to elderly patients, very ill patients and to patients with limited pulmonary reserve because of the possibility that underventilation and/or hypoxic cardiac arrest may occur. Resuscitative equipment for ventilatory support should be readily available (see WARNINGS and DOSAGE 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 to determine 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).

INFORMATION FOR PATIENTS

As appropriate, the patient should be informed of the pharmacological effects of the drug, such as sedation, relief of anxiety and lack of recall, and the duration of these effects (about 8 hours), so that they may adequately perceive the risks as well as the benefits to be derived from its use.

Patients who receive Lorazepam Injection as a premedicant should be cautioned that driving an automobile or operating hazardous machinery or engaging in a hazardous sport should be delayed for 24 to 48 hours following the injection. 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.

Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving Lorazepam Injection. 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 Injection may make them very sleepy for a period longer than 6 to 8 hours following surgery.

LABORATORY TESTS

In clinical trials, no laboratory test abnormalities were identified with either single or multiple doses of Lorazepam Injection. 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 depression of the central nervous system when administered with 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 has been observed.

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 formation 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 DOSAGE AND ADMINISTRATION).

Lorazepam–Oral Contraceptive Steroids Interaction

Coadministration of lorazepam (2 mg intravenously) with oral contraceptive steroids (norethindrone acetate, 1 mg, and ethinyl estradiol, 50 mg, 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 Injection in female patients who are concomitantly taking oral contraceptives (see also DOSAGE 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 Injection dosage needs to be reduced by 50% when coadministered with probenecid (see also DOSAGE 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 situation is not recommended.

NURSING MOTHERS

Injectable lorazepam should not be administered to nursing mothers, because, like other benzodiazepines, the possibility exists that lorazepam may be excreted in human milk and sedate the infant.

PEDIATRIC USE

Preanesthetic

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

ADVERSE REACTIONS

PREANESTHETIC

Central Nervous System

The most frequent adverse effects seen with injectable lorazepam are an extension of the central-nervous-system-depressant effects of the drug. The incidence varied from one study to another, depending on the dosage, route of administration, use of other central-nervous-system depressants and the investigator's opinion concerning the degree and duration of desired sedation. Excessive sleepiness and drowsiness were the main side effects. This interfered with patient cooperation in approximately 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years of age had a higher incidence of excessive sleepiness or drowsiness when compared with those under 50 (21/106 versus 24/245) when lorazepam was given intravenously (see DOSAGE AND ADMINISTRATION). On rare occasions (3/1580), the patient was unable to give personal identification in the operating room on arrival, and one patient fell when attempting premature ambulation in the postoperative period.

Symptoms such as restlessness, confusion, depression, crying, sobbing and delirium occurred in about 1.3% (20/1580). One patient injured himself by picking at his incision during the immediate postoperative period.

Hallucinations were present in about 1% (14/1580) of patients and were visual and self-limiting.

An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during the peak-effect period.

An occasional patient had a prolonged recovery room stay, either because of excessive sleepiness or because of some form of inappropriate behavior. The latter was seen most commonly when scopolamine was given concomitantly as a premedicant.

Limited information derived from patients who were discharged the day after receiving injectable lorazepam showed that one patient complained of some unsteadiness of gait and a reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages has been reported more than 24 hours after receiving injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects

Intramuscular injection of lorazepam has resulted in pain at the injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. The overall incidence of pain and burning in patients was about 17% (146/859) in the immediate postinjection period and about 1.4% (12/859) at the 24-hour observation time. Reactions at the injection site (redness) occurred in approximately 2% (17/859) in the immediate postinjection period and were present 24 hours later in about 0.8% (7/859).

Intravenous administration of lorazepam resulted in painful responses in 13/771 patients or approximately 1.6% in the immediate postinjection period, and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately following intravenous injection but was noted in 19/771 patients at the 24-hour observation period. This incidence is similar to that observed with an intravenous infusion before lorazepam is given.

Cardiovascular System

Hypertension (0.1%) and hypotension (0.1%) have occasionally been observed after patients have received injectable lorazepam.

Respiratory System

Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at the time of the procedure and resulted in temporary underventilation. Immediate attention to the airway, employing the usual countermeasures, will usually suffice to manage this condition (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences

Skin rash, nausea and vomiting have occasionally been noted in patients who have received injectable lorazepam combined with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE

As with other benzodiazepines, Lorazepam Injection has a low potential for abuse and may lead to limited dependence. Although there are no clinical data available for injectable lorazepam in this respect, physicians should be aware that repeated doses over a prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE

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.

Treatment of overdosage is mainly supportive until the drug is eliminated from the body. Vital signs and fluid balance should be carefully monitored. An adequate airway should be maintained and assisted respiration used as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines from the body. In addition, osmotic diuretics, such as mannitol, may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated.

The benzodiazepine antagonist flumazenil may be used in hospitalized patients as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS should be consulted prior to use.

DOSAGE AND ADMINISTRATION

PREANESTHETIC

Intramuscular Injection

For the designated indications as a premedicant, the usual recommended dose of lorazepam for intramuscular injection is 0.05 mg/kg up to a maximum of 4 mg. As with all premedicant drugs, the dose should be individualized (see also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS). Doses of other central-nervous-system-depressant drugs should be ordinarily reduced (see PRECAUTIONS). *For optimum effect, measured as lack of recall, intramuscular lorazepam should be administered at least 2 hours before the anticipated operative procedure.* Narcotic analgesics should be administered at their usual preoperative time. There are insufficient data to support efficacy to make dosage recommendations for intramuscular lorazepam in patients less than 18 years of age, therefore, such use is not recommended.

Intravenous Injection

For the primary purpose of sedation and relief of anxiety, the usual recommended initial dose of lorazepam for intravenous injection is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adult patients and should not ordinarily be exceeded in patients over 50 years of age. In those patients in whom a greater likelihood of lack of recall for perioperative events would be beneficial, larger doses as high as 0.05 mg/kg up to a total of 4 mg may be administered (see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS). Doses of other injectable central-nervous-system-depressant drugs should ordinarily be reduced (see PRECAUTIONS). *For optimum effect, measured as lack of recall, intravenous lorazepam should be administered 15 to 20 minutes before the anticipated operative procedure.*

EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO INTRAVENOUS ADMINISTRATION OF LORAZEPAM (see WARNINGS).

There are insufficient data to support efficacy or make dosage recommendations for intravenous lorazepam in patients less than 18 years of age; therefore, such use is not recommended.

ADMINISTRATION

Lorazepam Injection, USP 2 mg/mL and 4 mg/mL is available in the DOSETTE® Sterile Cartridge-Needle Unit.

The DOSETTE® Sterile Cartridge-Needle Unit is suitable for substances to be administered intravenously or intramuscularly.

When given intramuscularly, Lorazepam Injection, undiluted, should be injected deep in the muscle mass.

Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics and muscle relaxants.

Immediately prior to intravenous use, Lorazepam Injection must be diluted with an equal volume of compatible solution. When properly diluted, the drug may be injected directly into a vein or into the tubing of an existing intravenous infusion. The rate of injection should not exceed 2 mg per minute.

Lorazepam Injection is compatible for dilution purposes with the following solutions: Sterile Water for Injection, USP; Sodium Chloride Injection, USP; 5% Dextrose Injection, USP.

DIRECTIONS FOR DILUTION FOR IV USE

To dilute, adhere to the following procedure:

1. Extrude the entire amount of air in the half-filled cartridge.
2. Slowly aspirate the desired volume of diluent.
3. Pull back slightly on the plunger to provide additional mixing space.
4. Immediately mix contents thoroughly by gently inverting the cartridge repeatedly until a homogenous solution results. Do not shake vigorously as this will result in air entrapment.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

HOW SUPPLIED

Lorazepam Injection, USP — 2 mg/mL
1 mL fill (2 mg/mL) in 2.5 mL DOSETTE® Sterile Cartridge-Needle Unit (22 gauge, 1 1/4 inch needle) packaged in 10s (*NDC* 0641-3291-03)

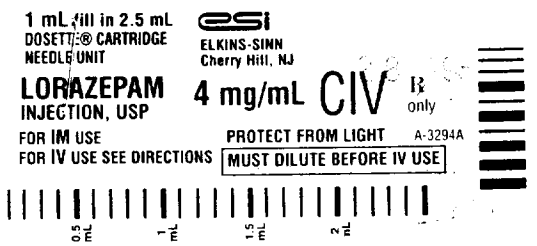
Lorazepam Injection, USP — 4 mg/mL
1 mL fill (4 mg/mL) in 2.5 mL DOSETTE® Sterile Cartridge-Needle Unit (22 gauge, 1 1/4 inch needle) packaged in 10s (*NDC* 0641-3294-03)

STORAGE

Store refrigerated at 2°-8°C (36°-46°F). **Protect from light**: Keep covered in carton until time of use.

Manufactured by ELKINS-SINN, Cherry Hill, NJ 08003-4099

J-3291B Revised February 1998


1 mL fill in 2.5 mL
DOSETTE® CARTRIDGE
NEEDLE UNIT
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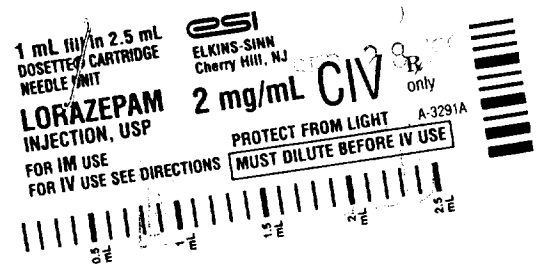
ELKINS-SINN
Cherry Hill, NJ
LORAZEPAM
INJECTION, USP
4 mg/mL
CIV
℞ only
FOR IM USE
FOR IV USE SEE DIRECTIONS
PROTECT FROM LIGHT
A-3294A
MUST DILUTE BEFORE IV USE
0.5 mL
1 mL
1.5 mL
2 mL


1 mL fill in 2.5 mL
DOSETTE® CARTRIDGE
NEEDLE UNIT
esi
ELKINS-SINN
Cherry Hill, NJ
LORAZEPAM
INJECTION, USP
2 mg/mL
CIV
℞ only
FOR IM USE
FOR IV USE SEE DIRECTIONS
PROTECT FROM LIGHT
A-3291A
MUST DILUTE BEFORE IV USE
0.5 mL
1 mL
1.5 mL
2 mL
2.5 mL

ESi LEDERLE

LORAZEPAM INJECTION, USP, 2 mg/mL and 4 mg/mL
DOSETTE® Sterile Cartridge - Needle Units
ANDA #74-496

FINAL PRINTED LABELING
4/20/98

4 mg/mL
INJECTION, USP
LORAZEPAM
CIV

SEP 28 1998

NDC 0641- 3294- 03
6505-01-156-2161

10 DOSETTE® CARTRIDGES
STERILE CARTRIDGE-NEEDLE UNITS

22 gauge
1¼ inch needle
1 mL fill in
2.5 mL cartridge

CIV

LORAZEPAM
INJECTION, USP
4 mg/mL

FOR IM USE
FOR IV USE SEE DIRECTIONS

Must Dilute Before IV Use

PROTECT FROM LIGHT
REFRIGERATE

Product Code: 3294-03
B-33294a

℞ only

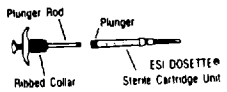
ESi ELKINS-SINN
Cherry Hill, NJ 08003
A division of A. H. Robins Co.

Each mL contains lorazepam 4 mg, polyethylene glycol 400 0.18 mL and benzyl alcohol 0.02 mL in propylene glycol.
USUAL DOSAGE: See package insert for complete prescribing information and dilution requirements for IV use.

Store refrigerated at 2°-8°C (36°-46°F).
PROTECT FROM LIGHT: Keep covered in carton until time of use.
Do not use if solution is discolored or contains a precipitate.
Each DOSETTE® Sterile Cartridge-Needle Unit contains excess space of approximately 1 mL to permit mixture with other compatible medicaments before injection.

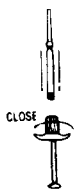
DIRECTIONS FOR USING THE DOSETTE® STERILE CARTRIDGE UNIT IN THE TUBEX® BRAND INJECTOR

The TUBEX® Injector is reusable and should not be discarded.



To load an ESI DOSETTE® Sterile Cartridge Unit into the TUBEX® Injector:

1. Turn the ribbed collar to the "OPEN" position until it stops.



2. Hold the injector with the open end up and fully insert the DOSETTE® Sterile Cartridge Unit.

Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.

3. Thread the plunger rod into the plunger of the DOSETTE® Sterile Cartridge Unit until slight resistance is felt.

4. Engage the needle-cap assembly by pulling the cap down over the silver cartridge hub. The needle is fully engaged when the silver hub is completely covered.

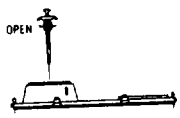
The injector is now ready for use in the usual manner.

TO ADMINISTER: Method of administration is the same as with conventional syringe. Remove needle cover by grasping it securely; twist and pull. Introduce needle into patient, aspirate by pulling back slightly on the plunger, and inject.

To remove the empty DOSETTE® Cartridge Unit and dispose into a vertical disposal container:

1. Do not recap. Disengage the plunger rod.

2. Hold the injector, point pointing down, over a vertical disposal container and loosen the ribbed collar. The DOSETTE® Cartridge Unit will drop into the container.



3. Discard the cover.

To remove the empty DOSETTE® Cartridge Unit and dispose into a horizontal (mailbox) disposal container:

1. Do not recap. Disengage the plunger rod.

2. Open the horizontal (mailbox) disposal container. Insert the DOSETTE® Cartridge Unit, point pointing down, halfway into the container. Close the container lid on the cartridge. Loosen the ribbed collar. The DOSETTE® Cartridge Unit will drop into the container.

3. Discard the cover.

The TUBEX® injector is reusable and should not be discarded.

Used DOSETTE® Cartridge Units should not be employed for successive injections or as multiple-dose containers. They are intended to be used only once and discarded. **NOTE:** Any graduated markings on DOSETTE® Sterile Cartridge Units are to be used only as a guide in mixing, withdrawing or administering measured doses.

Wyeth-Ayerst does not recommend and will not accept responsibility for the use of any cartridge unit or needleless system other than TUBEX® or ESI DOSETTE® Cartridge Units in the TUBEX® Injector. The ESI DOSETTE® cartridge holder has been discontinued. For instructions on its use, contact: Medical Affairs, Wyeth-Ayerst Laboratories, P. O. Box 8299, Phila., PA 19101.

ESi LEDERLE

LORAZEPAM INJECTION, USP, 2 mg/mL and 4 mg/mL
DOSETTE® Sterile Cartridge - Needle Units
ANDA #74-496

FINAL PRINTED LABELING
4/20/98

2 mg/mL
INJECTION, USP
LORAZEPAM
CIV

SEP 28 1998

NDC 0641- 3291- 03
6505-01-178-9760

10 DOSETTE® CARTRIDGES
STERILE CARTRIDGE-NEEDLE UNITS

22 gauge
1¼ inch needle
1 mL fill in
2.5 mL cartridge

CIV

LORAZEPAM
INJECTION, USP
2 mg/mL

FOR IM USE
FOR IV USE SEE DIRECTIONS

Must Dilute Before IV Use

PROTECT FROM LIGHT
REFRIGERATE

Product Code: 3291-03
B-33291a

℞ only

ELKINS-SINN
Cherry Hill, NJ 08003
A division of A. H. Robins Co

Each mL contains lorazepam 2 mg, polyethylene glycol 400 0.18 mL and benzyl alcohol 0.02 mL in propylene glycol.
USUAL DOSAGE: See package insert for complete prescribing information and dilution requirements for IV use.