dialysis, hemodialysis, or hemoperfusion should be considered (see CLINICAL PHARMACOLOGY: WARNINGS).

Concomitant administration of lorazepam (2 mg intravenously) with verapamil (250 mg twice daily orally for 3 days) to 6 healthy male subjects resulted in decreased total clearance of lorazepam by 49% and increased terminal half-life 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 postdose administration during verapamil treatment. Lorazepam dosage should be reduced to 50% of the normal adult dose when the drug combination is prescribed in patients (see also DOSAGE AND ADMINISTRATION).

Lorazepam Oral Contraceptive Studies Interaction
Concomitant administration of lorazepam (2 mg intravenously) with oral contraceptive steroids (norethisterone acetate, 1 mg, and ethyl estradiol, 50 mg, for at least 8 months) to healthy females (n = 7) was associated with a 35% decrease in hirsutism, a 20% increase in the volume of distribution, thereby resulting in an almost 3-fold increase in total clearance of lorazepam compared with control healthy females (n = 8). It may be necessary to increase the dose of lorazepam in female patients who are concurrently taking oral contraceptives (see also DOSAGE AND ADMINISTRATION).

Lorazepam Pregnancy Interaction
Concurrent administration of lorazepam (2 mg intravenously) with probenecid (500 mg orally every 6 hours) to 8 healthy volunteers resulted in a prolongation of lorazepam half-life by 13% and a decrease in its total clearance by 49%. No change in volume of distribution was noted during probenecid co-treatment. Lorazepam reaction dosage needs to be reduced by 50% when concomitantly 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 norethisterone acetate, nafprinol, amoxicillin, amoxycillin, and a variety of tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of carcinogenic potential emerged in rats and in mice during prolonged exposure to lorazepam at doses that produced plasma concentrations in the higher therapeutic range. Lorazepam may cause fetal harm when administered to pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Lorazepam injection is contraindicated in patients known to be hypersensitive to benzodiazepines or its vehicle (propylene 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 interference, resulting in gangrene which may require amputation (see WARNINGS).

WARNINGS

Pneumothorax

Pneumothorax 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 with all 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. Immediate postoperative 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.

Dosage in Older Patients

Dosage in geriatric 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 sedation is desired.

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

There is no added beneficial effect from the addition of acepromazine to injectable lorazepam, and their combined effects 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 intravascular, and that 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 exclude use of the drug in patients with mild-to-moderate hepatic or renal disease (see DOSAGE 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 situations where other drugs cannot be used or are ineffective.

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

There are insufficient data regarding the teratogenic safety of lorazepam injection, including use in oral/oral injection. Such use, therefore, is not recommended.

Reproductive studies in animals were performed in mice, rats, and two strains of rabbits. Occasional limb and/or bone deformities, or other skeletons, and hepatomegaly, or other skeletal abnormalities 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 0.5 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 en-
Endoscopic procedures require adequate recovery room observations.
Pharyngeal reflexes are not impaired when lorazepam injection is used for oral endoscopic procedures; therefore, adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS

General
The sedative central-nervous-system effects of other drugs, such as phenothiazines, narcotic antagonists, barbiturates, antidepressants, anticonvulsants, and monoamine oxidase inhibitors, should be borne in mind when these drugs are used concomitantly with or during the period of recovery from lorazepam injection (see CLINICAL PHARMACOLOGY).

Lorazepam 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 overdosage and/or hypoventilation and/or hypoxia cardiac arrest may occur. Resuscitative equipment for ventilatory support should be readily available (see WARNINGS and DOSAGE AND ADMINISTRATION).

When lorazepam injection is used as the premeditant 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 anaesthetics are used concomitantly with the recommended dose (see ADVERSE REACTIONS).

Interactions for Patients
As appropriate, the patient should be informed of the pharmacological effects of the drug, such as sedation, reflex of anxiety, and loss of memory, 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 hazardous activities, should be delayed for 24 to 48 hours following the injection. Sedatives, tranquilizers, and narcotic anaesthetics may produce a more prolonged and profound effect when administered along with lorazepam injection. This effect may take the form of excessive sleepiness or drowsiness and, on rare occasions, interferes with recall and recognition of events of the day of surgery and the day after.
Feeling out of touch unsteadiness may result in falling and injury if undertaken within 6 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 depressant seen with benzodiazepines in general. Elderly patients should be told that lorazepam injection may make them very sleepy for a period longer than six (6) to eight (8) hours following surgery.

Lorazepam:
Lorazepam injection, like other injectable benzodiazepines, produces depression of the central nervous system when administered with other sedative hypnotics, tranquilizers, barbiturates, MAO inhibitors, and other antidepressants. When sedatives are used concomitantly with injectable lorazepam, an increased incidence of sedation, hallucinations, and emotional behavior has been observed.

Concurrent administration of any of the following drugs with lorazepam had no effect on the pharmacokinetics of lorazepam, lorazepam metabolite, temazepam, nitrazepam, promethazine, metoclopramide, and pyridoxine. No change in lorazepam injection dosage is necessary when concomitantly given with any of these drugs.

Lorazepam-Vincristine Interaction
Concurrent administration of lorazepam (2 mg intravenously) with vincristine (50 mg twice daily for 3 days to 6 healthy male subjects resulted in decreased total clearance of lorazepam by 20% and decreased formation rate of lorazepam-glucuronide by 50%, as compared with lorazepam administered alone. Accordingly, lorazepam plasma concentrations were about two-fold higher for at least 12 hours post-dose administration during vincristine treatment. Lorazepam dosage should be reduced to 50% of the normal adult dose when the drug combination is prescribed in patients (see also DOSAGE AND ADMINISTRATION).

Lorazepam-Oral Contraceptive Steroids Interaction
Concomitant administration 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 male volunteers resulted in a 58% decrease in total clearance of lorazepam as compared with control healthy males (n=7). 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 8 healthy volunteers resulted in a prolongation of lorazepam half-life by 130% and a decrease in 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, immobilization anesthesia, sedatives, anesthetics, and a variety of tranquilizing agents.
Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of carcinogenic potential emerged in rats and
healthy rats subjects resulted in decreased plasma 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 concurrent 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).

**Lorazepam-Oral Contraceptive Steroid Interaction**

Co-administration of lorazepam (2 mg intravenously) with oral contraceptive steroids (ethinyl estradiol acetate, 1 mg, and ethinyl estradiol, 50 mg, for at least 5 months) to healthy female volunteers was associated with a 55% decrease in half-life, a 50% increase in the volume of distribution, thereby resulting in an almost 3-fold increase in total clearance of lorazepam as compared with control healthy females (n=6). It may be necessary to increase the dose of lorazepam in female patients who are concurrently taking oral contraceptives (see also DOSEAGE AND ADMINISTRATION).

**Lorazepam-Pyridocine Interaction**

Concurrent administration of lorazepam (2 mg intravenously) with pyridoxine (1500 mg orally every 6 hours for 9 to 10 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 pyridoxine co-treatment. Lorazepam injection dosage needs to be reduced by 50% when coadministered with pyridoxine (see also DOSAGE AND ADMINISTRATION).

**Intramuscular Test Interpretation**

No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, such as aminoglycosides, thiazide diuretics, phenytoin, chlordiazepoxide, 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 postmarketing study in rats, in which the oral lorazepam dose was 20 mg/kg, showed no impairment of fertility.

**Pregnancy**

**Pregnancy Category D:** See WARNINGS.

**Labor and Delivery**

There is 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**

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

**ADVERSE REACTIONS**

Preanesthetics

**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 5% (25446) of patients undergoing regional anesthesia in that they were unable to absorb levels of anesthetic in regional blocks or with caudal epidural anesthesia. Patients over 50 years of age had a higher incidence of excessive sleepiness or drowsiness when compared with those under 50 (21106 versus 24245) when lorazepam was given intravenously (see DOSAGE AND ADMINISTRATION). On rare occasions (31540), the patient was unable to give personal identification in the operating room or 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% (201586). One patient injured himself by jumping at the incision during the immediate postoperative period.

Nausea and vomiting were present in about 1% (141580) of patients and were usually self-limiting.

An occasional patient complained of dizziness, drowsiness, and/or blurred vision. Decreased hearing was infrequently reported during the pre-anesthetic 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 1 day after receiving injectable lorazepam showed that one patient complained of some somnolence of dailies and a reduced ability to perform complex mental maneuvers. 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, and 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% (116539) in the immediate postinjection period and about 1% (132855) at the 24-hour observation time. Reactions at the injection site (redness) occurred in approximately 7% (112852) in the immediate postinjection period and were present 24 hours later in about 0.8% (17859).

Intravenous administration of lorazepam resulted in painful responses in 13771 patients or approximately 1.6% in the immediate postinjection period, and 24 hours later, 4771 patients or about 0.5% still complained of pain. Redness did not occur immediately following intravenous injection but was noted in 19771 patients at 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 occasion-}

ally been observed after patients received injectable lorazepam.

**Respiratory System**

There is 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.
clinical situations, renal or hepatic failure, or exchange blood transfusions may be indicated.

The benzodiazepine antagonists flumazenil may be used in non-anesthetic patients as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Pain

The patient should be aware of the risk of tolerance to medications with flumazenil treatment. Particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. The combination flumazenil packaging inserts including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS should be consulted prior to use.

DOSEAGE AND ADMINISTRATION

Precautions

CONTRAINDICATIONS

For the desensitization indications as a premedication, the usual recommended dose of lorazepam for intramuscular injection is 0.05 mg/kg up to a maximum of 4 mg. As with all premedication 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. Nonsedative anticonvulsant drugs should be administered in their usual preoperative time. There is insufficient data to support efficacy of an oral dosage form of lorazepam in patients less than 15 years of age; therefore, use of the oral route is not recommended.

ADVERSE REACTIONS

Seizures

and BENZODIAZEPINES.

INTRAOPERATIVE ADMINISTRATION (see WARNINGS). There is insufficient data to support efficacy of oral dosage forms of lorazepam in patients less than 15 years of age; therefore, such use is not recommended.

ADDITIONAL ADMINISTRATION

When given intramuscularly, lorazepam injection, undiluted, should be injected deep into the muscle mass. Injectable lorazepam can be used with atropine suilvea, narcotic analgesics, other intravenously used analgesics, commonly used anesthetics, and other IV drugs receivably prior to intravenous use. Intravenous injection must be given 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. Parenteral drug products should be inspected visually for particular matters and discoloration prior to administration. In case of a solution or container change, the drug may be administered if the nature or contains a precipitate. Lorazepam injection is compatible for division purposes with the following solutions: Sterile Water for Injection, USP; Sodium Chloride Injection, USP; 5% Dextrose Injection, USP.

HOW SUPPLIED

Lorazepam Injection, USP is available in the following dosage strengths in single-dose and multiple-dose vials:

2 mg per ml in 1-ml vials: NDC 55370-205-01
2 mg per ml in 10-ml vials: NDC 55370-209-10
4 mg per ml in 1-ml vials: NDC 55370-204-01
4 mg per ml in 10-ml vials: NDC 55370-204-10

Package of 10 units per box.

For 10 ml in 1-ml vials.

Store at Refrigerator 2° - 8°C (36°-46°F)

Protect from light.

Use vials to protect contents from light.

For only.

Manufactured by:

MOVA PHARMACEUTICAL CORPORATION

Caguas, Puerto Rico 00725, USA

ITEM 6324204

Issued 01/98

MOVA
intramuscular injection of lorazepam has resulted in pain at the injection site, a sensation of burning, or observed redness at the same area in a very variable incidence from one study to another. The overall incidence of pain and burning at injection sites was about 17% (144/858) in the immediate postinjection period and about 1.4% (12/858) at the 24-hour observation time. Reactions at the injection site (redness) occurred in approximately 2% (17/830) in the intravenous postinjection period and were present 24 hours later in about 0.8% (7/855).

Intravenous administration of lorazepam resulted in painful responses in 37/771 patients (1.8%) in the intravenous postinjection period, and 4 hours later. 47/771 patients of 0.5% still complained of pain. Redness did not occur immediately following intravenous injection but was noted in 19/771 patients at 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 received injectable lorazepam.

Respiratory System
Five patients (5/444) who underwent regional anesthesia were observed to have slight airway obstruction. This was believed to be due to excessive alveolar pressure and was possibly due to the relaxation of the muscles of the respiratory system. A minority of the cases will usually resolve at the termination of the injection. Appropriate attention to the airway, employing the usual countermeasures, will usually resolve the condition (see also CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

Other Adverse Reactions
Skin rash, pruritus, and urticaria 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 new potential for abuse and may lead to limited dependence. Although there are no clinical data available for injectable lorazepam in man, prior experience with other benzodiazepines suggests that physical and psychological dependence may occur because of prolonged use of the drug. The primary withdrawal symptoms with serious benzodiazepines include anxiety, tension, somnolence, muscle cramps, and seizures. These withdrawal states may be treated with benzodiazepines or other appropriate treatments.

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, hyporeflexia, stupor one to three (3) coma, and, very rarely, death.

Treatment of overdose 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, toxic doses of benzodiazepines may necessitate elimination of benzodiazepines from the body. In addition, osmotic diuretics (e.g., mannitol, furosamide) may be effective in reducing extracellular fluid and the pressure on the central nervous system. The complete triazolam package insert containing CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS should be consulted prior to use.

DOSEAGE AND ADMINISTRATION
Preanesthetic

Intramuscular Injection
For the designated indications as a premedicant, the usual recommended dose of lorazepam for intramuscular injection is 0.05 to 0.1 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 centrally-acting depressant drugs should be correspondingly 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 presurgical time. There are insufficient data to support efficacy for maintenance administration of lorazepam in patients less than 1 year 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/kg (0.044 mg/lb), whichever is smaller. The dose will vary for sedating older patients and should not ordinarily be exceeded in patients over 50 years of age. In these patients, in whom a greater likelihood of lack of recall for cooperative 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 centrally-acting depressant drugs should be correspondingly 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 PATIENT 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 1 year of age; therefore, such use is not recommended.

ADMINISTRATION
When given intramuscularly, lorazepam injection, undiluted, should be injected deeply into the muscle mass. Intramuscular lorazepam can be used with droperidol, butyrophenones, narcotic analgesics, other parenteral used anesthetics, 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. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use a solution is discolored or contains a precipitate.

Lorazepam injection is compatible for admixture prepara-
For IV use, administer directly in a peripheral or central vein. Do not dilute. Each ml contains 2 mg LORAZEPAM in 0.9% sodium chloride injection as the base. Do not use for subcutaneous or intramuscular administration. Store in Refrigerator 2°-8°C (36°-46°F). CAUTION: Federal law prohibits dispensing without prescription. Manufactured by: Alza Corporation, Redwood City, CA 94063. USA MA: 001-001048-40-01 Lot L 000. Expiration Date: __/__/__

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DESCRIPTION
Lorazepam injection, USP, a benzodiazepine with amnestic and sedative effects, is intended for the intramuscular or intravenous route of administration. It has the chemical formula 7-chloro-5-phenyl-1,3-benzodiazepine-2,4-dione. The molecular weight is 321.5, and the CAS No. is [946-40-9]. The structural formula is:

![Structural formula of lorazepam](attachment:image)

Lorazepam is a nearly white powder almost insoluble in water. Each mL of sterile injection contains either 2 or 4 mg of lorazepam, 0.18 mL polyethylene glycol 400 in propylene glycol with 2% benzyl alcohol as preservative.

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 receptor site but does not displace GABA. Attaching to the specific binding site enhances the affinity of GABA for its receptor site on the same receptor complex. The pharmacological consequences of benzodiazepine agonists include amnestic effects and sedation. The intensity of action is directly related to the degree of benzodiazepine receptor occupancy.

Effects in Pre-Operative Patients
Intolerance or intramuscular administration of the recommended dose of 2 mg or 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) noted as 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 by careful patient questioning and testing, using props designed to enhance recall. The majority of patients under these recommended conditions had difficulty recalling periparative events or recognizing props from before surgery. The lack of recall and recognition determined under conditions of careful patient questioning and testing, using props designed to enhance recall. The majority of patients under these recommended conditions had difficulty recalling periparative 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, intravenous, enhanced sensitivity to CNS-depressant effects of alcohol and other drugs were noted in older adults and rare cases for greater than 24 hours.

Physiologic Effects in Healthy Adults
Studies in healthy adult volunteers reveal that intravenous lorazepam at doses up to 3.5 mg/70 kg does not alter sensitivity to the respiratory stimulatory 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 remained unresponsive for greater than the recommended dose and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically meaningful doses of lorazepam injection do not greatly affect the cardiovascular system in the supine position or employing a 70-degree tilt test. Doses of 8 mg to 10 mg of intravenous lorazepam injection (1.0 to 1.5 times the anesthetic dose)
Studies in healthy adult volunteers revealed 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 given in the order of carbon dioxide challenge. This is, as long as patients remain sufficiently awake to understand the instructions, upper airway obstruction has been observed in rare instances where the patient required greater than the recommended dose and was acutely sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Concurrent use of lorazepam and morphine does not greatly affect the circulatory system in the supine position or in the sitting position following administration of 30 mg/kg of intravenous morphine. Doses of 10 mg/kg of intravenous lorazepam (2 to 2.1/2 times the maximum recommended dose) will produce less than 10% increase in left ventricular outflow tract area within 15 minutes.

Studies in six healthy young adults who received lorazepam injection and other drugs revealed that visual tracking and the ability to keep a moving line of the target was impaired for 1 to 2 hours following administration of 1 mg/kg of intravenous lorazepam and 4 hours following administration of 2 mg/kg intramuscularly with concomitant paraldehyde subcutaneously. Similar impairments were noted with pentobarbital: 150 mg/kg orally in 1 hour and 75 mg/kg by intravenous injection in 1 hour. Impairment of this type and postural and oculomotor abnormalities with eye-hand coordination of the drug are insufficient to predict whether the drug might alter normal driving or ability to operate a motor vehicle or engage in hazardous activities. Unlike oxazepam, however, lorazepam is not known to be highly metabolized by the liver and is excreted almost entirely in the urine.

Pharmacokinetics and Metabolism

Absorption

Intravenous

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

Intramuscular

Following intramuscular administration, lorazepam is completely and rapidly absorbed reaching peak concentrations within 0.5 hours. A 4-mg dose provides 14% of the dose absorbed in 0.5 hours, 35% in 0.5 hours, and 70% in 0.5 hours. Following administration of 30 mg/kg of intravenous lorazepam, the amount of lorazepam recovered in the circulation is proportional to the dose administered.

Distribution and Elimination

A lipophilic, water-soluble lorazepam is 91.2% bound to plasma proteins; its volume of distribution is approximately 1.5 L/kg. Unbound lorazepam penetrates the blood-brain barrier freely by passive diffusion, a fact confirmed by CCF sampling. Following intravenous administration, the terminal half-life and total clearance averaged 18.5 hours and 1.2 L/hour, respectively. Lorazepam is extensively conjugated to the 3-0-phenolic glucuronide in the liver and excreted into the small intestine for reabsorption. Lorazepam-glucuronide is an inactive metabolite and is eliminated mainly by the kidneys. Following a single 3-mg oral dose of lorazepam to 6 healthy subjects, 86% of the administered dose was recovered in urine and 7% was retained in the feces. The percent of administered dose recovered in urine as lorazepam-glucuronide was 14%. Only 0.3% of the dose was recovered as unchanged lorazepam, and the remainder of the radiolabeled lorazepam represented minor metabolites.

Special Populations

Effect of Age

Pediatrics

Recovery (birth to 1 month)

Following a single 0.25 mg/kg (n=6) or 0.5 mg/kg (n=4) intravenous dose of lorazepam, mean total clearance normalized to body weight was reduced by 86% compared to normal adults. The total clearance for lorazepam was approximately 83% compared to normal adults. All medications were of 1:37 weeks of postnatal age.

Infants (1 month to 2 years)

There is no information on the pharmacokinetics 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 10% longer mean half-life in children with acute lymphocytic leukemia in complete remission (12-19 years, n=13) 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 to three days longer in patients with acute lymphocytic leukemia in complete remission (12-19 years, n=13) compared to non-malignant adults (n=10). Unbound lorazepam clearance normalized to body weight was comparable in adult males, non-surgical adults.

Elderly

Following single intravenous doses of 1.5-3 mg of lorazepam, 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 19-26 years of age. Consequently, no dosage adjustment is needed in elderly subjects based solely on their age.

Effect of Gender

Gender has no effect on the pharmacokinetics of lorazepam.

Effect of Race

Young American (n=15) and Japanese subjects (n=17) had very comparable mean total clearance value of 1 mL/min/kg, however, young Japanese subjects had a 20% lower mean total clearance than young Americans, 0.59 mL/min/kg vs. 0.77 mL/min/kg, respectively.

Patients with Renal Impairment

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 glucuronide (and inactive) fraction of lorazepam. There is a possibility that the diaphragmatic circulation of lorazepam-glucuronide leads to a reduced efficiency of the net clearance of lorazepam in this population. Six normal subjects, six patients with mild renal impairment (CI of 22.2 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 patients with impaired renal function than in normal subjects. Both parameters were 75% higher in patients undergoing hemodialysis than in normal subjects. Overall, though, the group of subjects the mean total clearance of lorazepam did not change. About 5% 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 function. The mean renal clearance was approximately.