

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-793

APPROVED DRAFT LABELING

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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 lorazepam injection. 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 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 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 µg, 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 6 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

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Lorazepam injection is contraindicated in patients with 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 scopalamine 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 **DOSE 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 **DOSE 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.

An increased risk of congenital malformations 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.

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 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.

Endoscopic Procedures

There are insufficient data to support the use of lorazepam injection for outpatient endoscopic procedures. Inpatient en-

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Drug/Laboratory Test Interactions

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Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenic potential emerged in rats and

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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

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

Praeseesthetic

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

Praeseesthetic

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 **DOSE 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 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

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.

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 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. The 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

When given intramuscularly, lorazepam injection, undiluted, should be injected deep into 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. 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.

Lorazepam injection is compatible for dilution 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 vial: NDC 55370-205-01

2 mg per mL, in 10 mL vial: NDC 55370-205-10

4 mg per mL, in 1 mL vial: NDC 55370-204-01

4 mg per mL, in 10 mL vial: NDC 55370-204-10

Packaged in 20 units per box.

For IM or IV injection.

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

Protect from light.

Use cartons to protect contents from light.

Rx only.

Manufactured by:

MOVA PHARMACEUTICAL CORPORATION

Caguas, Puerto Rico 00725, USA

ITEM# 632402MV

Issued 01/98

MOVA

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Cardiovascular System

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

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Handwritten mark



Rx only

Manufactured by
Cephalon, Inc. (USA) Corporation
Cephalon, Pennsylvania 15712, USA
©2008 Cephalon, Inc. NDA 021-108



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Margo

NDC 55370-205-10

MOVA
10 mL MULTIPLE - DOSE VIAL

LORAZEPAM
Injection, USP

2 mg / mL

for IM injection
for IV route, see directions

For IV use, additional dilution is required; see accompanying information.
Each mL contains 2 mg lorazepam, 0.18 mL polyethylene glycol 400 in propylene glycol with 2% benzyl alcohol preservative. See package insert for Usual Dosage. See package insert for dosage information.
Protect from light. Do not use if solution is discolored or contains a precipitate.
Store in Refrigerator 2°-8°C (36°-46°F).
CAUTION: Federal law prohibits dispensing without prescription.
Manufactured by:
MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725, USA
Item #6228601M Rev 07/87
Lot #:
Exp. Date:

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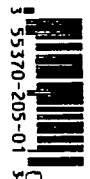
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1 mL
2 mg / mL
for IM injection
for IV route,
see directions

LORAZEPAM
Injection, USP

MOVA

NDC 55370-205-01

Protect from light
Use this carton
to protect
contents from light.
Store in Refrigerator
2°-8°C (36°-46°F)

LORAZEPAM
Injection, USP

2 mg / mL
1 mL

Item #6111202M
Rev 07/87

LORAZEPAM
Injection, USP

2 mg / mL
1 mL

Item #6111202M
Rev 07/87

Mango

NDC 55370-205-10
 MOVA
 10 mL MULTIPLE - DOSE VIAL
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 MOVA (HUMAN) INC. (US) 11111
 Manufactured by:
 MOVA (HUMAN) INC. (US) 11111
 Capriol, Puerto Rico 00725, USA
 Lot #: 4822801MV Rev 07/97
 Exp. Date:

NDC 55370-205-10
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 Exp. Date:

MVA

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REFRIGERATE
LORAZEPAM
 Injection, USP
 2 mg / mL
 1 mL

REFRIGERATE
LORAZEPAM
 Injection, USP
 2 mg / mL
 1 mL

Item #6111202MV
 Rev 07/97

Item #6111202MV
 Rev 07/97

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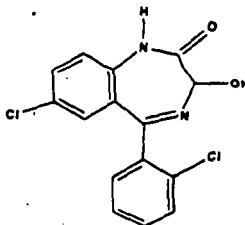
LORAZEPAM INJECTION, USP



632402MV

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(2-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one. The molecular weight is 321.16, and the C.A.S. No. is [846-49-1]. The structural formula is:



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 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 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 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, 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 meprobamate 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 mg to 10 mg of intravenous lorazepam 12 to 24 hours before the maximum recom-

2

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 mg to 10 mg of intravenous lorazepam (2 to 2.7 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 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 mg of lorazepam IM, the amount of lorazepam delivered to the circulation is proportional to the dose administered.

Distribution/Metabolism/Excretion

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=8) 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 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 22-59 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 pro-