The risk of dependence increases with higher doses. The use of benzodiazepines, including lorazepam, may lead to physical and psychological dependence. The plasma levels of lorazepam are proportional to the dose and have a half-life of 1.5 mg to 3 mg of lorazepam injection, mean total systemic clearance of lorazepam decreased by 20% in 15 days. The mean plasma level of lorazepam in patients with compromised hepatic function is about 12 hours, and for patients with severe hepatic insufficiency and/or encephalopathy. Dosage for patients with severe hepatic insufficiency should be adjusted carefully according to patient response; the initial dosage should not exceed 2 mg. Paradoxical reactions have been occasionally reported with lorazepam. The benzodiazepines, including lorazepam, produce CNS-depressant effects when administered in short periods. It is advisable that they consult their physician or pharmacist before either increasing the dose or abruptly discontinuing the drug. Withdrawal symptoms (e.g. rebound insomnia) can appear following discontinuation of lorazepam. The clinical significance of this is unknown. Therefore, use of lorazepam for prolonged periods and in geriatric patients requires continued reevaluation of the need for continued therapy. Lorazepam glucuronide has no demonstrable sedative effects of benzodiazepines. Therefore, these symptoms should not be considered to mean that use of lorazepam is contraindicated or unsafe. Elderly or debilitated patients may be more susceptible to adverse reactions and may require lower doses. Elderly subjects of 60 to 84 years of age compared to younger subjects had decreased renal function and increased plasma clearance of lorazepam. The plasma levels of lorazepam are proportional to the dose. It is advisable that they consult their physician before either increasing the dose or abruptly discontinuing the drug. Lorazepam glucuronide has no demonstrable sedative effects of benzodiazepines. Therefore, these symptoms should not be considered to mean that use of lorazepam is contraindicated or unsafe.
Dependent, with more severe effects occurring with CNS effects and respiratory depression, are dose-related. Concurrent administration of lorazepam with valproate results in increased plasma concentrations and reduced clearance of lorazepam. Lorazepam should be reduced to approximately 50% when co-administered with valproate.

Lorazepam is cumulative with prolonged use and extended half-life. Overdose with lorazepam may result in a more rapid onset or prolonged effect of lorazepam due to increased half-life and decreased total clearance, and this effect needs to be reduced by approximately 50% when co-administered with valproate.

Reproductive studies in animals were performed regarding mutagenesis. No evidence of carcinogenic potential emerged in rats or mice treated with lorazepam. Flumazenil, the benzodiazepine antagonist, has been used to counteract the CNS depression of benzodiazepines. The benzodiazepine antagonist flumazenil may be highly dialyzable. Its plasma concentration decreases following administration of activated charcoal. Flumazenil may also limit drug absorption. Lorcainide may be due to inhibition of glucuronidation.

The effects of probenecid and valproate on lorazepam are dose-dependent. Lorazepam dosage may be reduced by approximately 50% when co-administered with valproate. Lorazepam dosage may be doubled when co-administered with probenecid. Lorazepam is a substrate for the cytochrome P-450 isozyme CYP2C19. Lorazepam metabolism is increased in the presence of probenecid.

The significant adverse reactions of lorazepam include drowsiness, ataxia, delirium, and respiratory arrest. The benzodiazepine antagonist, flumazenil, may be helpful in the management of benzodiazepine toxicity. In the management of benzodiazepine overdose, activated charcoal may also limit drug absorption. Lorcainide may be due to inhibition of glucuronidation.

The complete flumazenil package insert contains CONTRAINDICA­ TIONS, WARNINGS, and PRECAUTIONS should be consulted prior to use.

**DOSAGE AND ADMINISTRATION**

**Proper Use of Lorazepam Oral Concentrate, USP**

Lorazepam Oral Concentrate, USP is a concentrated oral solution as compared to standard oral liquid formulations. It is recommended that Lorazepam Oral Concentrate, USP be mixed with liquid or semi-solid food such as applesauce or suds-like bever­ ages, apple sauce and puddings. Use only the calibrated dropper provided with this product. Use only the calibrated dropper provided with this product. Do not substitute for, proper management of benzodiazepine overdose. Lorcainide may be due to inhibition of glucuronidation.

**HOW SUPPLIED**

2 mg per mL Lorazepam Oral Concentrate, USP is available in bottles of 30 mL with calibrated dropper (0.25 mL, 0.5 mL, 1 mL, 0.75 mL (1.5 mg) and 1 mL (2 mg) on the calibrated dropper provided with this product. The complete flumazenil package insert contains CONTRAINDICA­ TIONS, WARNINGS, and PRECAUTIONS should be consulted prior to use.

**PROTECT FROM LIGHT**

Store at 2° to 8°C (36° to 46°F) (see USP Controlled Room Temperature).

Dispense only in the bottle and only with the calibrated dropper provided.

Dispense open bottle after 90 days.