Ativan®
(lorazepam)

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Tablets

Description

Lorazepam is a white or almost white, almost odorless crystalline powder.

Active ingredients

Lorazepam (INN)

Pharmacological class, therapeutic class

Benzodiazepine
Anxiolytic

Dosage forms and intended routes of administration

Oral tablets

Indications

- *Short-term management of anxiety disorders, including the following:*
  - *Short-term relief of symptoms of anxiety*
  - *Generalized anxiety disorders*
  - *Anxiety in psychotic states*
  - *Anxiety associated with somatic symptoms*
  - *Anxiety associated with depression or depressive symptoms*
  - *Reactive anxiety*
- *Insomnia associated with anxiety*
- *Alcohol withdrawal*
- *Prevention of delirium tremens*
- *Surgical premedication*
- *Adjunctive therapy to standard antiemetic drugs forthe prophylactic and symptomatic treatment of nausea and vomiting associated with cancer chemotherapy*

Dosage and Administration

Dosage and duration of therapy should be individualized. The lowest effective dose should be prescribed for the shortest duration possible. The risk of withdrawal and rebound phenomena is greater after abrupt discontinuation; therefore, the drug should be discontinued gradually (see section *SPECIAL WARNINGS*).

Extension of the treatment period should not take place without re-evaluation of the need for continued therapy.

The recommended dosage range is 2 to 6 mg/day, but the daily dosage may vary from 1 to 10 mg/day.

Increases in the dosage of lorazepam should be made gradually to help avoid adverse effects. The evening dose should be increased before the daytime doses.

Short-term management of anxiety disorders

The initial recommended dose is 2 to 3 mg/day, in divided doses 2 or 3 times daily.

Insomnia associated with anxiety

The recommended dose is 0.5 mg to 4 mg/day, at bedtime.

Alcohol withdrawal

The initial recommended dose is 2 to 3 mg/day, in divided doses 2 or 3 times daily.

Prevention of delirium tremens

The initial recommended dose is 2 to 3 mg/day, in divided doses 2 or 3 times daily.

Surgical premedication

The recommended dosage is 2 to 4 mg the night before a procedure and/or 1-2 hours pre-procedure.

Adjunctive therapy to standard antiemetic drugs for the prophylactic and symptomatic treatment of nausea and vomiting associated with cancer chemotherapy

The recommended dosage is 1 mg at bedtime the night before chemotherapy and/or 1mg given 60 minutes prior to chemotherapy, and repeated 6 hours and 12 hours after chemotherapy, if needed.

Elderly and debilitated patients

For elderly and debilitated patients reduce the initial dose by approximately 50% and adjust the dosage as needed and tolerated.

Use in patients with hepatic impairment

Dosage for patients with severe hepatic insufficiency should be adjusted carefully according to patient's response. Lower doses may be sufficient in such patients. See also section *PRECAUTIONS*.

Use in patients with renal impairment

No specific dosage recommendations. See also section *PHARMACOKINETICS*.

Contraindications

Hypersensitivity to benzodiazepines or to any components of the formulation.

Special Warnings

Use of benzodiazepines, including lorazepam, may lead to potentially fatal respiratory depression.

The use of benzodiazepines, including lorazepam, may

lead to physical and psychological dependence (see section *ABUSE AND DEPENDENCE*).

Severe anaphylactic/anaphylactoid reactions have been reported with the use of benzodiazepines. Cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of benzodiazepines. Some patients taking benzodiazepines have had additional symptoms such as dyspnea, throat closing, or nausea and vomiting. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with a benzodiazepine should not be rechallenged with the drug.

Precautions

Ativan® (lorazepam) should be used with caution in patients with compromised respiratory function (eg, COPD, sleep apnea syndrome).

Pre-existing depression may emerge or worsen during use of benzodiazepines, including lorazepam. The use of benzodiazepines may unmask suicidal tendencies in depressed patients and should not be used without adequate antidepressant therapy.

Elderly or debilitated patients may be more susceptible to the effects of lorazepam; therefore, these patients should be monitored frequently and have their dosage adjusted carefully according to patient response (see section *DOSAGE AND ADMINISTRATION*).

Paradoxical reactions have been occasionally reported during benzodiazepine use (see section *ADVERSE REACTIONS*).

Such reactions may be more likely to occur in children and the elderly. Should these occur, use of the drug should be discontinued.

Use in patients with hepatic impairment

As with all benzodiazepines, the use of lorazepam may worsen hepatic encephalopathy; therefore, lorazepam should be used with caution in patients with severe hepatic insufficiency and/or encephalopathy.

Pregnancy

Ativan® (lorazepam) should not be used during pregnancy.

An increased risk of congenital malformations associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested in several studies. In humans, umbilical cord blood samples indicate placental transfer of benzodiazepines and their glucuronide metabolites. Infants of mothers who ingested benzodiazepines for several weeks or more preceding delivery have been reported to have withdrawal symptoms during the postnatal period. Symptoms such as hypoactivity, hypotonia, hypothermia, respiratory depression, apnea, feeding problems, and impaired metabolic response to cold stress have been reported in neonates born of mothers who have received benzodiazepines during the late phase of pregnancy or at delivery.

Lactation

Lorazepam has been detected in human breast milk; therefore, it should not be administered to breast-feeding women, unless the expected benefit to the woman outweighs the potential risk to the infant.

Sedation and inability to suckle have occurred in neonates of lactating mothers taking benzodiazepines. Infants of lactating mothers should be observed for pharmacological effects (including sedation and irritability).

Geriatric Use

See sections *DOSAGE AND ADMINISTRATION* and *PRECAUTIONS*.

Interactions

The benzodiazepines, including lorazepam, produce additive CNS depressant effects when co-administered with other CNS depressants such as alcohol, barbiturates, antipsychotics, sedative/hypnotics, anxiolytics, antidepressants, narcotic analgesics, sedative antihistamines, anticonvulsants, and anesthetics.

Concomitant use of clozapine and lorazepam may produce marked sedation, excessive salivation, and ataxia.

Concurrent administration of lorazepam with valproate may result in increased plasma concentrations and reduced clearance of lorazepam. Lorazepam dosage should be reduced to approximately 50% when coadministered with valproate.

Concurrent administration of lorazepam with probenecid may result in a more rapid onset or prolonged effect of lorazepam due to increased half-life and decreased total clearance. Lorazepam dosage needs to be reduced by approximately 50% when coadministered with probenecid.

Administration of theophylline or aminophylline may reduce the sedative effects of benzodiazepines, including lorazepam.

Effects on Activities Requiring Concentration and Performance

As with all patients on CNS-acting drugs, patients should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from lorazepam

Abuse and Dependence

The use of benzodiazepines may lead to physical and psychological dependence. The risk of dependence increases with higher doses and longer term use and is further increased in patients with a history of alcoholism or drug abuse or in patients with significant personality disorders. The dependence potential is reduced when

lorazepam is used at the appropriate dose for short-term treatment.

In general, benzodiazepines should be prescribed for short periods only (eg, 2-4 weeks). Continuous long-term use of lorazepam is not recommended.

Withdrawal symptoms (eg, rebound insomnia) can appear following cessation of recommended doses after as little as one week of therapy. Abrupt discontinuation of lorazepam should be avoided and a gradual dosage-tapering schedule followed after extended therapy.

Abrupt termination of treatment may be accompanied by withdrawal symptoms. Symptoms reported following discontinuation of benzodiazepines include headache, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, rebound phenomena, dysphoria, dizziness, derealization, depersonalization, hyperacusis, numbness/tingling of extremities, hypersensitivity to light, noise, and physical contact/perceptual changes, involuntary movements, nausea, vomiting, diarrhea, loss of appetite, hallucinations/delirium, convulsions/seizures, tremor, abdominal cramps, myalgia, agitation, palpitations, tachycardia, panic attacks, vertigo, hyperreflexia, short-term memory loss, and hyperthermia.
Convulsions/seizures may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold, such as antidepressants.

There is evidence that tolerance develops to the sedative effects of benzodiazepines.

Ativan® (lorazepam) may have abuse potential, especially in patients with a history of drug and/or alcohol abuse.

Adverse Reactions

Adverse reactions are listed in the Table in CIOMS frequency categories:

Very Common	≥ 10%
Common:	≥ 1%
Uncommon:	≥ 0.1% and < 1%
Rare:	≥ 0.01%and < 0.1%
Very rare:	< 0.01%

Body As A Whole	
Frequency undetermined:	Hypersensitivity reactions, anaphylactic/oid reactions, angioedema Hypothermia SIADH, hyponatremia
Common:	Muscle weakness, asthenia
Cardiovascular	
Frequency undetermined:	Hypotension, lowering in blood pressure
Digestive	
Uncommon:	Nausea
Frequency undetermined:	Constipation, increase in bilirubin, jaundice, increase in liver transaminases, increase in alkaline phosphatase
Hematological/Lymphatic	
Frequency undetermined:	Thrombocytopenia, agranulocytosis, pancytopenia
Nervous system and special senses	
Frequency undetermined:	Benzodiazepine effects on the CNS are dose-dependent, with more severe CNS depression occurring with high doses. Extrapyramidal symptoms, tremor, vertigo, visual disturbances (including diplopia and blurred vision), dysarthria/slurred speech, headache, convulsions/seizures, amnesia, disinhibition, euphoria, coma, suicidal ideation/attempt, impaired attention/concentration, balance disorder. Paradoxical reactions, including anxiety, agitation, excitation, hostility, aggression, rage, sleep disturbances/insomnia, sexual arousal, hallucinations.
Very common:	Sedation, fatigue, drowsiness
Common:	Ataxia, confusion, depression, unmasking of depression, dizziness
Uncommon:	Change in libido, impotence, decreased orgasm
Respiratory	
Frequency undetermined:	Respiratory depression, apnea, worsening of sleep apnea (the extent of respiratory depression with benzodiazepines is dose-dependent, with more severe depression occurring with high doses) Worsening of obstructive pulmonary disease
Skin	
Frequency undetermined:	Allergic skin reactions, alopecia

Overdosage

In postmarketing experience, overdose with lorazepam has occurred predominantly in combination with alcohol and/or other drugs.

Symptoms

Symptoms can range in severity and include drowsiness, mental confusion, lethargy, dysarthria, ataxia, paradoxical reactions, CNS depression, hypotonia, hypotension, respiratory depression, cardiovascular depression, coma, and death.

Treatment

General supportive and symptomatic measures are recommended; vital signs must be monitored.

When there is a risk of aspiration, induction of emesis is not recommended.
Gastric lavage may be indicated if performed soon after

ingestion or in symptomatic patients. Administration of activated charcoal may also limit drug absorption.

Lorazepam is poorly dialyzable. Lorazepam glucuronide, the inactive metabolite, may be highly dialyzable.

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 physician should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.

Mode of Action

Ativan® (lorazepam) is a benzodiazepine that interacts with the γ-aminobutyric acid (GABA)-benzodiazepine receptor complex and enhances the affinity of GABA.

Pharmacodynamics, Clinical Efficacy

The pharmacodynamic consequences of benzodiazepine agonist actions include antianxiety effects, sedation, and reduction of seizure activity.

The intensity of action is directly related to the degree of benzodiazepine receptor occupancy.

Pharmacokinetics

Absorption

Absolute bioavailability is greater than 90% following oral and sublingual administration to healthy subjects.

Peak plasma concentration occurs in approximately 2 hours following oral administration to healthy subjects.

Distribution

The volume of distribution is approximately 1.3 L/kg. Unbound lorazepam penetrates the blood/brain barrier freely by passive diffusion. Lorazepam is approximately 92% bound to human plasma proteins at lorazepam concentration of 160 mg/mL.

Metabolism

Lorazepam is rapidly conjugated at its 3-hydroxy group into lorazepam glucuronide, an inactive metabolite.

Elimination

The elimination half-life of unconjugated lorazepam in human plasma is approximately 12-16 hours.

Following a single 2 mg oral dose of ^{14}C-lorazepam to 8 healthy subjects, approximately 88% of the administered dose was recovered in urine and 7% was recovered in feces. Approximately 74% of lorazepam glucuronide was recovered in the urine.

Elderly

Elderly patients typically respond to lower benzodiazepine doses than younger patients.

Renal insufficiency

Single-dose pharmacokinetic studies in patients with degrees of renal insufficiency ranging from mild impairment to renal failure have reported no significant changes in absorption, clearance, or excretion of lorazepam. Hemodialysis did not have any significant effect on the pharmacokinetics of intact lorazepam, but substantially removed the inactive glucuronide from the plasma.

Hepatic insufficiency

No change in the clearance of lorazepam was reported in patients with mild to moderate hepatic impairment (ie, hepatitis, alcoholic cirrhosis).

Concentration-effect relationship

The plasma levels of lorazepam are proportional to the dose given.

There is no evidence of accumulation of lorazepam after oral administration for up to six months.

STORAGE

Protect from heat, light and moisture.

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Manufactured by:
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