LORAZEPAM- lorazepam tablet
Leading Pharma, LLC

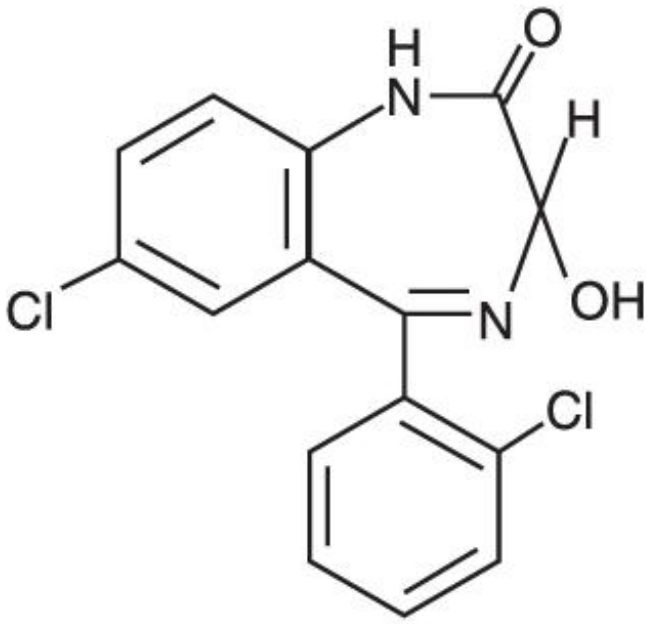
Lorazepam Tablets, USP CIV
Rx only

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

- **Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation (see WARNINGS and PRECAUTIONS).**
- **The use of benzodiazepines, including lorazepam, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing lorazepam and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (see WARNINGS).**
- **The continued use of benzodiazepines, including lorazepam may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of lorazepam after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue lorazepam or reduce the dosage (DOSAGE AND ADMINISTRATION and WARNINGS).**

DESCRIPTION

Lorazepam, an antianxiety agent, has the chemical formula, 7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one:



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

It is a nearly white powder almost insoluble in water. Each Lorazepam tablet, to be taken orally, contains 0.5 mg, 1 mg, or 2 mg of lorazepam. The inactive ingredients present are lactose anhydrous, magnesium stearate, microcrystalline cellulose, and polacrilin potassium.

CLINICAL PHARMACOLOGY

Studies in healthy volunteers show that in single high doses lorazepam has a tranquilizing action on the central nervous system with no appreciable effect on the respiratory or cardiovascular systems.

Lorazepam is readily absorbed with an absolute bioavailability of 90%. Peak concentrations in plasma occur approximately 2 hours following administration. The peak plasma level of lorazepam from a 2 mg dose is approximately 20 ng/mL.

The mean half-life of unconjugated lorazepam in human plasma is about 12 hours and for its major metabolite, lorazepam glucuronide, about 18 hours. At clinically relevant concentrations, lorazepam is approximately 85% bound to plasma proteins. Lorazepam is rapidly conjugated at its 3-hydroxy group into lorazepam glucuronide which is then excreted in the urine. Lorazepam glucuronide has no demonstrable central nervous system (CNS) activity in animals.

The plasma levels of lorazepam are proportional to the dose given. There is no evidence of accumulation of lorazepam on administration up to 6 months.

Studies comparing young and elderly subjects have shown that advancing age does not have a significant effect on the pharmacokinetics of lorazepam. However, in one study involving single intravenous doses of 1.5 to 3 mg of lorazepam injection, mean total body clearance of lorazepam decreased by 20% in 15 elderly subjects of 60 to 84 years of age compared to that in 15 younger subjects 19 to 38 years of age.

INDICATIONS AND USAGE

Lorazepam is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The effectiveness of lorazepam in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Lorazepam is contraindicated in patients with:

- hypersensitivity to benzodiazepines or to any components of the formulation
- acute narrow-angle glaucoma.

WARNINGS

Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including Lorazepam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe Lorazepam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of Lorazepam than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking Lorazepam, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Lorazepam is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined (see PRECAUTIONS: Drug Interactions).

Abuse, Misuse, and Addiction

The use of benzodiazepines, including Lorazepam, exposes users to the risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death (see **DRUG ABUSE AND DEPENDENCE: Abuse**).

Before prescribing Lorazepam and throughout treatment, assess each patient’s risk for abuse, misuse, and addiction (e.g., using a standardized screening tool). Use of

Lorazepam, particularly in patients at elevated risk, necessitates counseling about the risks and proper use of Lorazepam along with monitoring for signs and symptoms of abuse, misuse, and addiction. Prescribe the lowest effective dosage; avoid or minimize concomitant use of CNS depressants and other substances associated with abuse, misuse, and addiction (e.g., opioid analgesics, stimulants); and advise patients on the proper disposal of unused drug. If a substance use disorder is suspected, evaluate the patient and institute (or refer them for) early treatment, as appropriate.

Dependence and Withdrawal Reactions

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue Lorazepam or reduce the dosage (a patient-specific plan should be used to taper the dose) (see **DOSAGE AND ADMINSTRATION: Discontinuation or Dosage Reduction of Lorazepam**).

Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages, and those who have had longer durations of use.

Acute Withdrawal Reactions

The continued use of benzodiazepines, including Lorazepam, may lead to clinically significant physical dependence. Abrupt discontinuation or rapid dosage reduction of Lorazepam after continued use, or administration of flumazenil (a benzodiazepine antagonist) may precipitate acute withdrawal reactions, which can be life-threatening (e.g., seizures) (see **DRUG ABUSE AND DEPENDENCE: Dependence**).

Protracted Withdrawal Syndrome

In some cases, benzodiazepine users have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months (see **DRUG ABUSE AND DEPENDENCE: Dependence**).

Pre-existing depression may emerge or worsen during use of benzodiazepines including lorazepam. Lorazepam is not recommended for use in patients with a primary depressive disorder or psychosis.

Use of benzodiazepines, including lorazepam, both used alone and in combination with other CNS depressants, may lead to potentially fatal respiratory depression (see **PRECAUTIONS: Drug Interactions**).

As with all patients on CNS-depressant drugs, patients receiving lorazepam should be warned not to operate dangerous machinery or motor vehicles and that their tolerance for alcohol and other CNS depressants will be diminished.

Neonatal Sedation and Withdrawal Syndrome

Use of lorazepam late in pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in the neonate (see **PRECAUTIONS: Pregnancy**). Monitor neonates exposed to lorazepam during pregnancy or labor for signs of sedation and monitor neonates exposed to lorazepam during pregnancy for signs of withdrawal; manage these neonates accordingly.

PRECAUTIONS

In patients with depression, a possibility for suicide should be borne in mind; benzodiazepines should not be used in such patients without adequate antidepressant therapy.

Lorazepam should be used with caution in patients with compromised respiratory function (e.g. COPD, sleep apnea syndrome).

Elderly or debilitated patients may be more susceptible to the sedative effects of lorazepam. Therefore, these patients should be monitored frequently and have their dosage adjusted carefully according to patient response; the initial dosage should not exceed 2 mg.

Paradoxical reactions have been occasionally reported during benzodiazepine use. Such reactions may be more likely to occur in children and the elderly. Should these occur, use of the drug should be discontinued.

The usual precautions for treating patients with impaired renal or hepatic function should be observed. 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. Dosage for patients with severe hepatic insufficiency should be adjusted carefully according to patient response; lower doses may be sufficient in such patients.

In patients where gastrointestinal or cardiovascular disorders coexist with anxiety, it should be noted that lorazepam has not been shown to be of significant benefit in treating the gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6 mg/kg/day. The no-effect dose was 1.25 mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10 mg/day). The effect was reversible only when the treatment was withdrawn within 2 months of first observation of the phenomenon. The clinical significance of this is unknown. However, use of lorazepam for prolonged periods and in geriatric patients requires caution, and there should be frequent monitoring for symptoms of upper GI disease.

Safety and effectiveness of lorazepam in children of less than 12 years have not been established.

Information for Patients

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Risks from Concomitant Use with Opioids

Advise both patients and caregivers about the risks of potentially fatal respiratory depression and sedation when lorazepam is used with opioids and not to use such drugs concomitantly unless supervised by a health care provider. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined (see **WARNINGS: Risks from Concomitant Use of Opioids** and **PRECAUTIONS: Drug Interactions**).

Abuse, Misuse, and Addiction

Inform patients that the use of lorazepam even at recommended doses, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose and death,

especially when used in combination with other medications (e.g., opioid analgesics), alcohol, and/or illicit substances. Inform patients about the signs and symptoms of benzodiazepine abuse, misuse, and addiction; to seek medical help if they develop these signs and/or symptoms; and on the proper disposal of unused drug (see **WARNINGS: Abuse Misuse, and Addiction** and **DRUG ABUSE AND DEPENDENCE**).

Withdrawal Reactions

Inform patients that the continued use of lorazepam may lead to clinically significant physical dependence and that abrupt discontinuation or rapid dosage reduction of lorazepam may precipitate acute withdrawal reactions, which can be life-threatening. Inform patients that in some cases, patients taking benzodiazepines have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months. Instruct patients that discontinuation or dosage reduction of lorazepam may require a slow taper (see **WARNINGS: Dependence and Withdrawal Reactions** and**DRUG ABUSE AND DEPENDENCE**).

Pregnancy

Advise pregnant females that use of lorazepam late in pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in newborns (see **WARNINGS: Neonatal Sedation and Withdrawal Syndrome** and **PRECAUTIONS: Pregnancy**). Instruct patients to inform their healthcare provider if they are pregnant.

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to lorazepam during pregnancy (see **PRECAUTIONS: Pregnancy**).

Nursing

Instruct patients to notify their healthcare provider if they are breastfeeding or intend to breastfeed. Instruct breastfeeding patients using lorazepam to monitor infants for excessive sedation, poor feeding and poor weight gain, and to seek medical attention if they notice these signs (see **PRECAUTIONS: Nursing Mothers**).

Essential Laboratory Tests

Some patients on lorazepam have developed leukopenia, and some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended for patients on long-term therapy.

Drug Interactions

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and monitor patients closely for respiratory depression and sedation.

The benzodiazepines, including lorazepam, produce increased CNS-depressant effects when 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, hypotension, ataxia, delirium and respiratory arrest.

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.

The effects of probenecid and valproate on lorazepam may be due to inhibition of glucuronidation.

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

Carcinogenesis and Mutagenesis

No evidence of carcinogenic potential emerged in rats during an 18-month study with lorazepam. No studies regarding mutagenesis have been performed.

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to psychiatric medications, including lorazepam, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychiatric Medications at 1-866-961-2388 or visiting online at https://womensmentalhealth.org/pregnancyregistry/.

Risk Summary

Neonates born to mothers using benzodiazepines late in pregnancy have been reported to experience symptoms of sedation and/or neonatal withdrawal (see **WARNINGS: Neonatal Sedation and Withdrawal Syndrome** and *Clinical Considerations*). Available data from published observational studies of pregnant women exposed to benzodiazepines do not report a clear association with benzodiazepines and major birth defects *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Benzodiazepines cross the placenta and may produce respiratory depression, hypotonia and sedation in neonates. Monitor neonates exposed to lorazepam during pregnancy or

labor for signs of sedation, respiratory depression, hypotonia, and feeding problems. Monitor neonates exposed to lorazepam during pregnancy for signs of withdrawal. Manage these neonates accordingly (see **WARNINGS: Neonatal Sedation and Withdrawal Syndrome**).

Data

Human Data

Published data from observational studies on the use of benzodiazepines during pregnancy do not report a clear association with benzodiazepines and major birth defects. Although early studies reported an increased risk of congenital malformations with diazepam and chlordiazepoxide, there was no consistent pattern noted. In addition, the majority of more recent case-control and cohort studies of benzodiazepine use during pregnancy, which were adjusted for confounding exposures to alcohol, tobacco and other medications, have not confirmed these findings.

Animal Data

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 and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Nursing Mothers

Risk Summary

Lorazepam is present in breast milk. There are reports of sedation, poor feeding and poor weight gain in infants exposed to benzodiazepines through breast milk. The effects of lorazepam on milk production are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for lorazepam and any potential adverse effects on the breastfed infant from lorazepam or from the underlying maternal condition.

Clinical Considerations

Infants exposed to lorazepam **through breast milk should be monitored for sedation, poor feeding and poor weight gain.**

Geriatric Use

Clinical studies of lorazepam generally were not adequate to determine whether subjects aged 65 and over respond differently than younger subjects; however, the incidence of sedation and unsteadiness was observed to increase with age (see **ADVERSE REACTIONS**).

Age does not appear to have a significant effect on lorazepam kinetics (see **CLINICAL PHARMACOLOGY**).

Clinical circumstances, some of which may be more common in the elderly, such as hepatic or renal impairment, should be considered. Greater sensitivity (e.g. sedation) of some older individuals cannot be ruled out. In general, dose selection for an elderly

patient should be cautious, and lower doses may be sufficient in these patients (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Most adverse reactions to benzodiazepines, including CNS effects and respiratory depression, are dose dependent, with more severe effects occurring with high doses.

In a sample of about 3500 patients treated for anxiety, the most frequent adverse reaction to lorazepam was sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%), and unsteadiness (3.4%). The incidence of sedation and unsteadiness increased with age.

Other adverse reactions to benzodiazepines, including lorazepam are fatigue, drowsiness, amnesia, memory impairment, confusion, disorientation, depression, unmasking of depression, disinhibition, euphoria, suicidal ideation/attempt, ataxia, asthenia, extrapyramidal symptoms, convulsions/seizures, tremor, vertigo, eye-function/visual disturbance (including diplopia and blurred vision), dysarthria, slurred speech, change in libido, impotence, decreased orgasm; headache, coma; respiratory depression, apnea, worsening of sleep apnea, worsening of obstructive pulmonary disease; gastrointestinal symptoms including nausea, change in appetite, constipation, jaundice, increase in bilirubin, increase in liver transaminases, increase in alkaline phosphatase; hypersensitivity reactions, anaphylacticoid reactions; dermatological symptoms, allergic skin reactions, alopecia; syndrome of inappropriate antidiuretic hormone (SIADH), hyponatremia, thrombocytopenia, agranulocytosis, pancytopenia; hypothermia; and autonomic manifestations.

Paradoxical reactions, including anxiety, excitation, agitation, hostility, aggression, rage, sleep disturbances/insomnia, sexual arousal, and hallucinations may occur. Small decreases in blood pressure and hypotension may occur but are usually not clinically significant, probably being related to the relief of anxiety produced by lorazepam.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO THE FDA at 1-800-FDA-1088 or www.fda.gov/medwatch OR LEADING PHARMA, LLC AT 1-844-740-7500.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Lorazepam contains lorazepam, a Schedule IV controlled substance.

Abuse

Lorazepam is a benzodiazepine and a CNS depressant with a potential for abuse and addiction. Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and

obligations), and possible tolerance or physical dependence. Even taking benzodiazepines as prescribed may put patients at risk for abuse and misuse of their medication. Abuse and misuse of benzodiazepines may lead to addiction.

Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death. Benzodiazepines are often sought by individuals who abuse drugs and other substances, and by individuals with addictive disorders (see**WARNINGS: Abuse, Misuse, and Addiction**)

The following adverse reactions have occurred with benzodiazepine abuse and/or misuse: abdominal pain, amnesia, anorexia, anxiety, aggression, ataxia, blurred vision, confusion, depression, disinhibition, disorientation, dizziness, euphoria, impaired concentration and memory, indigestion, irritability, muscle pain, slurred speech, tremors, and vertigo.

The following severe adverse reactions have occurred with benzodiazepine abuse and/or misuse: delirium, paranoia, suicidal ideation and behavior, seizures, coma, breathing difficulty, and death. Death is more often associated with polysubstance use (especially benzodiazepines with other CNS depressants such as opioids and alcohol).

Dependence

Physical Dependence

Lorazepam may produce physical dependence from continued therapy. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Abrupt discontinuation or rapid dosage reduction of benzodiazepines or administration of flumazenil, a benzodiazepine antagonist, may precipitate acute withdrawal reactions, including seizures, which can be life-threatening. Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages (i.e., higher and/or more frequent doses) and those who have had longer durations of use (see **WARNINGS: Dependence and Withdrawal Reactions**).

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue lorazepam or reduce the dosage (see **DOSAGE and ADMINISTRATION: Discontinuation or Dosage Reduction of Lorazepam and WARNINGS**).

Acute Withdrawal Signs and Symptom

Acute withdrawal signs and symptoms associated with benzodiazepines have included abnormal involuntary movements, anxiety, blurred vision, depersonalization, depression, derealization, dizziness, fatigue, gastrointestinal adverse reactions (e.g., nausea, vomiting, diarrhea, weight loss, decreased appetite), headache, hyperacusis, hypertension, irritability, insomnia, memory impairment, muscle pain and stiffness, panic attacks, photophobia, restlessness, tachycardia, and tremor. More severe acute withdrawal signs and symptoms, including life-threatening reactions, have included catatonia, convulsions, delirium tremens, depression, hallucinations, mania, psychosis, seizures and suicidality.

Protracted Withdrawal Syndrome

Protracted withdrawal syndrome associated with benzodiazepines is characterized by anxiety, cognitive impairment, depression, insomnia, formication, motor symptoms (e.g., weakness, tremor, muscle twitches), paresthesia, and tinnitus that persists beyond 4 to 6 weeks after initial benzodiazepine withdrawal. Protracted withdrawal symptoms may last weeks to more than 12 months. As a result, there may be difficulty in differentiating withdrawal symptoms from potential reemergence or continuation of symptoms for which the benzodiazepine was being used.

Tolerance

Tolerance to lorazepam may develop from continued therapy. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance to the therapeutic effect of lorazepam may develop; however, little tolerance develops to the amnestic reactions and other cognitive impairments caused by benzodiazepines.

OVERDOSAGE

Overdosage of benzodiazepines is characterized by central nervous system depression ranging from drowsiness to coma. In mild to moderate cases, symptoms can include drowsiness, confusion, dysarthria, lethargy, hypnotic state, diminished reflexes, ataxia, and hypotonia. Rarely, paradoxical or disinhibitory reactions (including agitation, irritability, impulsivity, violent behavior, confusion, restlessness, excitement, and talkativeness) may occur. In severe overdosage cases, patients may develop respiratory depression and coma. Overdosage of benzodiazepines in combination with other CNS depressants (including alcohol and opioids) may be fatal (see **WARNINGS: Abuse, Misuse, and Addiction**). Markedly abnormal (lowered or elevated) blood pressure, heart rate, or respiratory rate raise the concern that additional drugs and/or alcohol are involved in the overdosage.

In managing benzodiazepine overdosage, employ general supportive measures, including intravenous fluids and airway management. Flumazenil, a specific benzodiazepine receptor antagonist indicated for the complete or partial reversal of the sedative effects of benzodiazepines in the management of benzodiazepine overdosage, can lead to withdrawal and adverse reactions, including seizures, particularly in the context of mixed overdosage with drugs that increase seizure risk (e.g., tricyclic and tetracyclic antidepressants) and in patients with long-term benzodiazepine use and physical dependency. The risk of withdrawal seizures with flumazenil use may be increased in patients with epilepsy. Flumazenil is contraindicated in patients who have received a benzodiazepine for control of a potentially life-threatening condition (e.g., status epilepticus). If the decision is made to use flumazenil, it should be used as an adjunct to, not as a substitute for, supportive management of benzodiazepine overdosage. See the flumazenil injection Prescribing Information.

Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

DOSAGE AND ADMINISTRATION

Lorazepam is administered orally. For optimal results, dose, frequency of administration, and duration of therapy should be individualized according to patient response. To facilitate this, 0.5 mg, 1 mg, and 2 mg tablets are available.

The usual range is 2 to 6 mg/day given in divided doses, the largest dose being taken before bedtime, but the daily dosage may vary from 1 to 10 mg/day.

For anxiety, most patients require an initial dose of 2 to 3 mg/day given two times a day or three times a day.

For insomnia due to anxiety or transient situational stress, a single daily dose of 2 to 4 mg may be given, usually at bedtime.

For elderly or debilitated patients, an initial dosage of 1 to 2 mg/day in divided doses is recommended, to be adjusted as needed and tolerated.

The dosage of lorazepam should be increased gradually when needed to help avoid adverse effects. When higher dosage is indicated, the evening dose should be increased before the daytime doses.

Discontinuation or Dosage Reduction of Lorazepam

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue lorazepam or reduce the dosage. If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level. Subsequently decrease the dosage more slowly (see **WARNINGS: Dependence and Withdrawal Reactions**and **DRUG ABUSE AND DEPENDENCE: Dependence**).

HOW SUPPLIED

Lorazepam® (lorazepam) Tablets are available in the following dosage strengths:

0.5 mg White color, round, flat face beveled edge compressed tablets, debossed "EP" and "904" on one side, and plain on the other side.

NDC# 69315-904-01 Bottles of 100 Tablets.
NDC# 69315-904-05 Bottles of 500 Tablets.
NDC# 69315-904-10 Bottles of 1000 Tablets.

1 mg White color, round, bisected flat face beveled edge compressed tablets, debossed "EP" above bisect and "905" below bisect on one side, and "1" on the other side.

NDC# 69315-905-01 Bottles of 100 Tablets.
NDC# 69315-905-05 Bottles of 500 Tablets.
NDC# 69315-905-10 Bottles of 1000 Tablets.

2 mg White color, round, bisected flat face beveled edge compressed tablets, debossed "EP" above bisect and "906" below bisect on one side, and "2" on the other side.

NDC# 69315-906-01 Bottles of 100 Tablets.
NDC# 69315-906-05 Bottles of 500 Tablets.
NDC# 69315-906-10 Bottles of 1000 Tablets.

Dispense in a tight container. light-resistant container as defined in the USP, using a child-resistant closure.

Keep this and all Medications out of the reach of children.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Excursions permitted to 59° to 86°F (15° to 30°C).

Manufactured and Distributed by
Leading Pharma, LLC
Fairfield, NJ 07004 USA

Rev. 08 03/23

MEDICATION GUIDE

Lorazepam Tablets, CIV

(lor az' e pam)

What is the most important information I should know about lorazepam tablets?

- **Lorazepam tablets are a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma and death.** Get emergency help right away if any of the following happens:
  - shallow or slowed breathing
  - breathing stops (which may lead to the heart stopping)
  - excessive sleepiness (sedation)

Do not drive or operate heavy machinery until you know how taking lorazepam tablets with opioids affects you.

- **Risk of abuse, misuse, and addiction.** There is a risk of abuse, misuse, and addiction with benzodiazepines including lorazepam tablets which can lead to overdose and serious side effects including coma and death.
  - **Serious side effects including coma and death have happened in people who have abused or misused benzodiazepines, including lorazepam tablets.** These serious side effects may also include delirium, paranoia, suicidal thoughts or actions, seizures, and difficulty breathing. **Call your healthcare provider or go to the nearest hospital emergency room right away if you get any of these serious side effects.**
  - **You can develop an addiction even if you take lorazepam tablets exactly as prescribed by your healthcare provider.**
  - **Take lorazepam tablets exactly as your healthcare provider prescribed.**
  - Do not share your lorazepam tablets with other people.
  - Keep lorazepam tabletsin a safe place and away from children.

- **Physical dependence and withdrawal reactions.** Lorazepam tablets can cause physical dependence and withdrawal reactions.
  - Do not suddenly stop taking lorazepam tablets. Stopping Lorazepam suddenly can cause serious and life-threatening side effects, including, unusual movements, responses or expressions, seizures, sudden and severe mental or nervous system changes, depression, seeing or hearing things that others do not see or hear, an extreme increase in activity or talking, losing touch with reality, and

suicidal thoughts or actions. **Call your healthcare provider or go to the nearest hospital emergency room right away if you get any of these symptoms.**
    - **Some people who suddenly stop benzodiazepines have symptoms that can last for several weeks to more than 12 months,** including anxiety, trouble remembering, learning, or concentrating, depression, problems sleeping, feeling like insects are crawling under your skin, weakness, shaking, muscle twitching, burning or prickling feeling in your hands, arms, legs or feet, and ringing in your ears.
    - Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.

- Do not take more lorazepam tablets than prescribed or take lorazepam tablets for longer than prescribed.

What is lorazepam tablets?

- Lorazepam tablets are a prescription medicine used:
    - to treat anxiety disorders
    - for the short-term relief of the symptoms of anxiety or anxiety that can happen with symptoms of depression
- **Lorazepam tablets is a federal controlled substance (CIV) because it contains lorazepam that can be abused or lead to dependence.** Keep lorazepam tablets in a safe place to prevent misuse and abuse. Selling or giving away lorazepam tablets may harm others and is against the law. Tell your healthcare provider if you have abused or been dependent on alcohol, prescription medicines or street drugs.
- It is not known if lorazepam tablets are safe and effective for use in children less than 12 years of age.
- It is not known if lorazepam tablets are safe and effective for use for longer than 4 months.

Do not take lorazepam if you:

- are allergic to lorazepam, other benzodiazepines, or any of the ingredients in lorazepam tablets. See the end of this Medication Guide for a complete list of ingredients inlorazepam tablets.

Before you take lorazepam , tell your healthcare provider about all of your medical conditions, including if you:

- have or have had depression, mood problems, or suicidal thoughts or behavior
- have a history of drug or alcohol abuse or addiction
- have lung disease or breathing problems (such as COPD, sleep apnea syndrome)
- have liver or kidney problems
- have or have had seizures
- are pregnant or plan to become pregnant.
- ◦ Taking lorazepam tablets late in pregnancy may cause your baby to have symptoms of sedation (breathing problems, sluggishness, low muscle tone), and/or withdrawal symptoms (jitteriness, irritability, restlessness, shaking, excessive crying, feeding problems).
    - Tell your healthcare provider right away if you become pregnant or think you are

pregnant during treatment with lorazepam tablets.
    - There is a pregnancy registry for women who take lorazepam tablets during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. If you become pregnant during treatment with lorazepam tablets, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychiatric Medications. You can register by calling 1-866-961-2388 or visiting https://womensmentalhealth.org/pregnancyregistry/.
    - are breastfeeding or plan to breastfeed. Lorazepam passes into your breast milk.
    - Breastfeeding during treatment with Lorazepam may cause your baby to have sleepiness, feeding problems, and decreased weight gain.
    - Talk to your healthcare provider about the best way to feed your baby if you take lorazepam tablets.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking lorazepam tablets with certain other medicines can cause side effects or affect how well lorazepam tablets or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

How should I take lorazepam tablets?

- Take lorazepam tablets exactly as your healthcare provider tells you to take it. Your healthcare provider will tell you how much lorazepam tablets to take and when to take it.
- If you take too much lorazepam tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of lorazepam tablets?

Lorazepam tablets may cause serious side effects, including:

- **See “What is the most important information I should know about lorazepam tablets?”**
- **Lorazepam tablets can make you sleepy or dizzy and can slow your thinking and motor skills.**
    - Do not drive, operate heavy machinery, or do other dangerous activities until you know how lorazepam tablets affects you.
    - **Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking lorazepam tablets without first talking to your healthcare provider.** When taken with alcohol or drugs that cause sleepiness or dizziness, lorazepam tablets may make your sleepiness or dizziness much worse.

- Depression. Pre-existing depression may emerge or worsen during use of benzodiazepines including lorazepam.

The most common side effects of lorazepam include:

- sedation
- dizziness
- weakness
- unsteadiness

These are not all the possible side effects of lorazepam tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-

1088 or LEADING PHARMA, LLC AT 1-844-740-7500.

How should I store lorazepam tablets?

- Store lorazepam tablets in a tightly closed container at 77°F (25°C); excursions permitted to 59° to 86°F (15° to 30°C).
- **Keep lorazepam tablets and all medicines out of the reach of children.**

General information about the safe and effective use of lorazepam tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use lorazepam tablets for a condition for which it was not prescribed. Do not give lorazepam tablets to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about lorazepam tablets that is written for health professionals

What are the ingredients in lorazepam tablets?

Active ingredient: lorazepam

Inactive ingredients: lactose anhydrous, magnesium stearate, microcrystalline cellulose, and polacrilin potassium.

Manufactured and Distributed by
Leading Pharma, LLC
Fairfield, NJ 07004 USA

Rev. 05 03/23



NDC 69315-905-01

Lorazepam Tablets, USP

1 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only

LEADING PHARMA

100 Tablets

Each Tablet Contains:

Lorazepam USP ..... 1 mg

Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

Usual Dosage: See Dosage and Administration section of the Prescribing Information.

Dispense in a tight, light-resistant container as defined in the USP, using a child-resistant closure.

Keep this and all Medications out of the reach of children.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Excursions permitted to 59° to 86°F (15° to 30°C).

Manufactured and Distributed by:
Leading Pharma, LLC
Fairfield, NJ 07004 USA

Tablet Imprinted: EP 905/1 Rev. 04

N 3 69315-905-01 2

.6" Unvarnished Area

NDC 69315-904-10

Lorazepam Tablets, USP

0.5 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only

LEADING PHARMA

1000 Tablets

Each Tablet Contains:

Lorazepam USP .....0.5 mg

Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

Usual Dosage: See Dosage and Administration section of the Prescribing Information.

Dispense in a tight, light-resistant container as defined in the USP, using a child-resistant closure.

Keep this and all Medications out of the reach of children.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Excursions permitted to 59° to 86°F (15° to 30°C).

Manufactured and Distributed by:
Leading Pharma, LLC
Fairfield, NJ 07004 USA

Tablet Imprinted: EP 904 Rev. 04

N 3 69315-904-10 7

.6" Unvarnished Area

NDC 69315-904-05

Lorazepam Tablets, USP

0.5 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only

LEADING PHARMA

500 Tablets

Each Tablet Contains:

Lorazepam USP .....0.5 mg

Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

Usual Dosage: See Dosage and Administration section of the Prescribing Information.

Dispense in a tight, light-resistant container as defined in the USP, using a child-resistant closure.

Keep this and all Medications out of the reach of children.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Excursions permitted to 59° to 86°F (15° to 30°C).

Manufactured and Distributed by:
Leading Pharma, LLC
Fairfield, NJ 07004 USA

Tablet Imprinted: EP 904 Rev. 04

N 3 69315-904-05 3

.6" Unvarnished Area

NDC 69315-906-01

Lorazepam Tablets, USP

2 mg

Rx only

LEADING PHARMA

100 Tablets

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Each Tablet Contains:
Lorazepam USP . . . . . 2 mg
Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

Usual Dosage: See Dosage and Administration section of the Prescribing Information.

Dispense in a tight, light-resistant container as defined in the USP, using a child-resistant closure.

Keep this and all Medications out of the reach of children.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Excursions permitted to 59° to 86°F (15° to 30°C).

Manufactured and Distributed by:
Leading Pharma, LLC
Fairfield, NJ 07004 USA

Tablet Imprinted: EP 906/2 Rev. 04

N 3 69315-906-01 9

.6" Unvarnished Area

NDC 69315-905-10

Lorazepam Tablets, USP

1 mg

Rx only

LEADING PHARMA

1000 Tablets

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Each Tablet Contains:
Lorazepam USP . . . . . 1 mg

Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

Usual Dosage: See Dosage and Administration section of the Prescribing Information.

Dispense in a tight, light-resistant container as defined in the USP, using a child-resistant closure.

Keep this and all Medications out of the reach of children.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Excursions permitted to 59° to 86°F (15° to 30°C).

Manufactured and Distributed by:
Leading Pharma, LLC
Fairfield, NJ 07004 USA

Tablet Imprinted: EP 905/1 Rev. 04

N 3 69315-905-10 4

.6" Unvarnished Area

NDC 69315-905-05

Lorazepam Tablets, USP

1 mg

Rx only

LEADING PHARMA

500 Tablets

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Each Tablet Contains:
Lorazepam USP . . . . . 1 mg

Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

Usual Dosage: See Dosage and Administration section of the Prescribing Information.

Dispense in a tight, light-resistant container as defined in the USP, using a child-resistant closure.

Keep this and all Medications out of the reach of children.

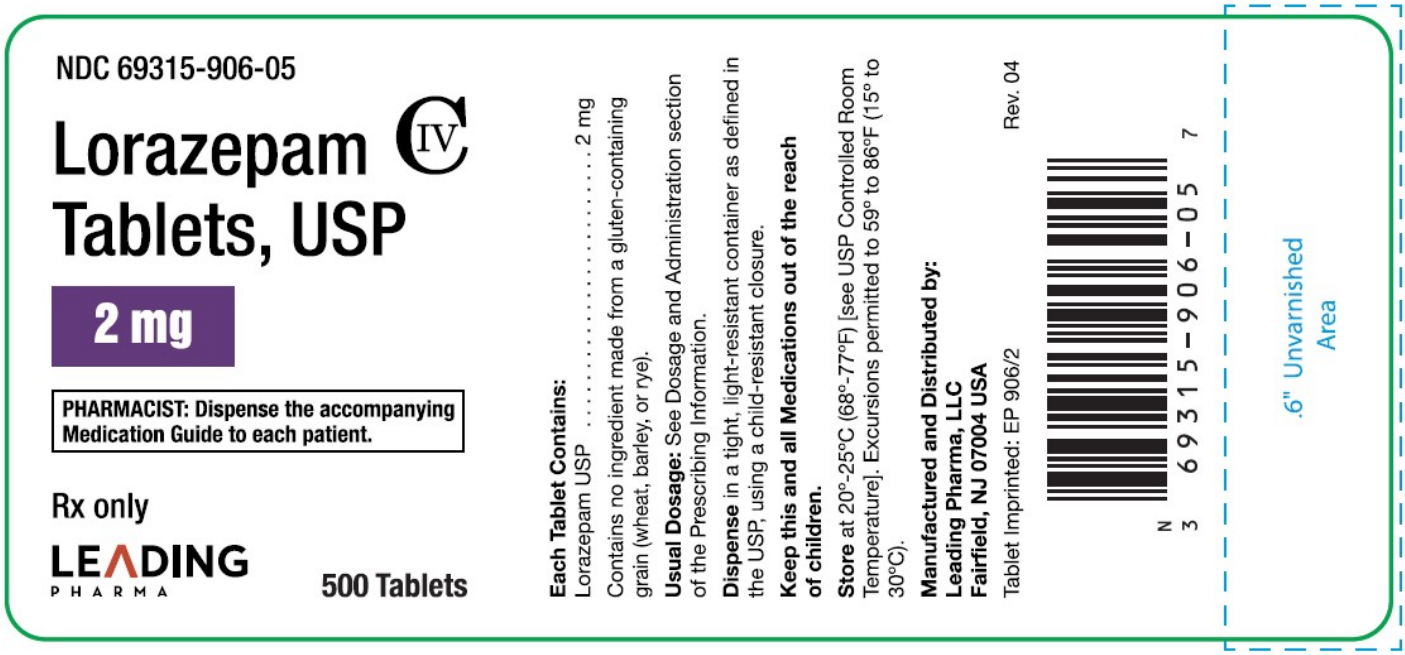
Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Excursions permitted to 59° to 86°F (15° to 30°C).

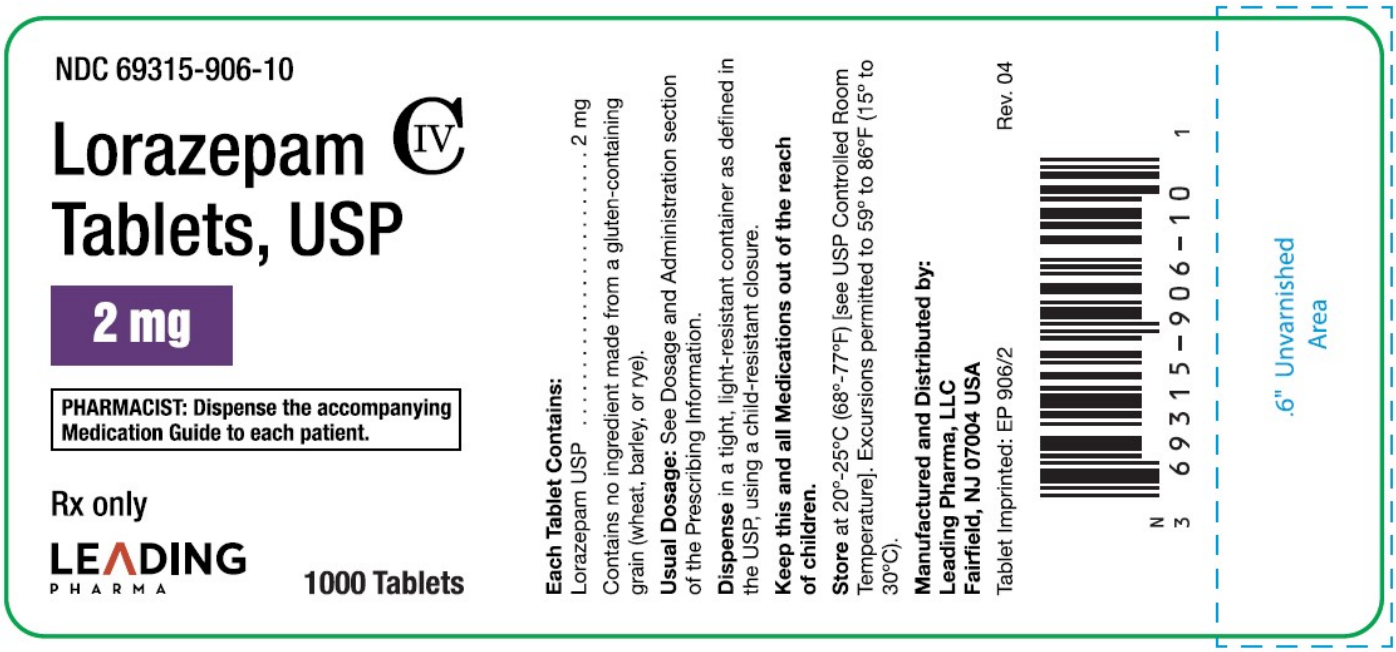
Manufactured and Distributed by:
Leading Pharma, LLC
Fairfield, NJ 07004 USA

Tablet Imprinted: EP 905/1 Rev. 04

N 3 69315-905-05 0

.6" Unvarnished Area





LORAZEPAM

lorazepam tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69315-904
Route of Administration	ORAL	**DEA Schedule**	CIV

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LORAZEPAM (UNII: O26FZP769L) (LORAZEPAM - UNII:O26FZP769L)	LORAZEPAM	0.5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLACRILIN POTASSIUM (UNII: 0BZ5A00FQU)	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	5mm
Flavor		**Imprint Code**	EP;904
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:69315-904-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/16/2023	
2	NDC:69315-904-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	05/16/2023	
3	NDC:69315-904-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	05/16/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078203	05/16/2023	

LORAZEPAM

lorazepam tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69315-905
Route of Administration	ORAL	**DEA Schedule**	CIV

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LORAZEPAM (UNII: O26FZP769L) (LORAZEPAM - UNII:O26FZP769L)	LORAZEPAM	1 mg

Inactive Ingredients	
Ingredient Name	**Strength**

ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLACRILIN POTASSIUM (UNII: 0BZ5A00FQU)	

Product Characteristics			
Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	EP;905;1
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69315-905-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/16/2023	
2	NDC:69315-905-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	05/16/2023	
3	NDC:69315-905-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	05/16/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078203	05/16/2023	

LORAZEPAM

lorazepam tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69315-906
Route of Administration	ORAL	**DEA Schedule**	CIV

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LORAZEPAM (UNII: O26FZP769L) (LORAZEPAM - UNII:O26FZP769L)	LORAZEPAM	2 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	

POLACRILIN POTASSIUM (UNII: 0BZ5A00FQU)	

Product Characteristics			
Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	EP;906;2
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69315-906-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/16/2023	
2	NDC:69315-906-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	05/16/2023	
3	NDC:69315-906-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	05/16/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078203	05/16/2023	

Labeler - Leading Pharma, LLC (079575060)

Registrant - Leading Pharma, LLC (079575060)

Establishment

Name	Address	ID/FEI	Business Operations
Leading Pharma, LLC		079575060	MANUFACTURE(69315-904, 69315-905, 69315-906)

Revised: 12/2023 Leading Pharma, LLC