

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LOREEV XR safely and effectively. See full prescribing information for LOREEV XR.

LOREEV XR (lorazepam) extended-release capsules, for oral use, CIV
Initial U.S. Approval: 1977

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

See full prescribing information for complete boxed warning.

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for use in 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 (5.1, 7)
- The use of benzodiazepines, including LOREEV XR, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing LOREEV XR and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (5.2)
- Abrupt discontinuation or rapid dosage reduction of LOREEV XR 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 LOREEV XR or reduce the dosage (2.4, 5.3)

INDICATIONS AND USAGE

LOREEV XR is a benzodiazepine indicated for the treatment of anxiety disorders in adults who are receiving stable, evenly divided, three times daily dosing with lorazepam tablets (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage of LOREEV XR is equal to the total daily dose of lorazepam tablets (at the previous three times daily dosage) (2.1)
- Administer LOREEV XR orally once daily in the morning (2.2)
- Capsules may be swallowed whole or opened and the entire contents sprinkled onto applesauce. Do not crush or chew (2.2)
- For dosage adjustments, discontinue LOREEV XR and switch to lorazepam tablets to adjust dosage (2.3)

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DOSAGE FORMS AND STRENGTHS

Extended-release capsules: 1 mg, 1.5 mg, 2 mg, and 3 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to benzodiazepines or any ingredients in LOREEV XR (4)
- Acute narrow-angle glaucoma (4)

WARNINGS AND PRECAUTIONS

- CNS Depression: May cause CNS depression. Caution patients receiving LOREEV XR against operating machinery or driving a motor vehicle as well to avoid the concomitant use of alcohol and other CNS depressant drugs during treatment (5.4, 7)
- Patients with Depression or Psychosis: Use with caution in patients with signs or symptoms of depression. Prescribe the least number of capsules feasible to avoid intentional overdose (5.5)
- Allergic Reactions to FD&C Yellow No. 5 (Tartrazine): Contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons (5.7)
- Neonatal Sedation and Withdrawal Syndrome: Use of LOREEV XR during pregnancy can result in neonatal sedation and/or withdrawal (5.8, 8.1)

ADVERSE REACTIONS

Most frequent adverse reactions: sedation, dizziness, weakness, unsteadiness (6)

To report SUSPECTED ADVERSE REACTIONS, contact Almatica Pharma LLC at 1-877-447-7979 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Use with Opioids: Increase the risk of respiratory depression (7)
- CNS depressants: Additive CNS depressant effects (7)
- Alcohol: Avoid use. Increases the release rate of LOREEV XR (7)
- UGT Inhibitors: Avoid initiation of UGT inhibitors. Dose reduction requires switching to lorazepam tablets for dose adjustment (7)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding not recommended (8.2)

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FULL PRESCRIBING INFORMATION

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 (5.1), Drug Interactions (7)].**
- **The use of benzodiazepines, including LOREEV XR, 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 LOREEV XR and throughout treatment, assess each patient's risk for abuse, misuse, and addiction [see Warnings and Precautions (5.2)].**
- **The continued use of benzodiazepines, including LOREEV XR, 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 LOREEV XR 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 LOREEV XR or reduce the dosage [see Dosage and Administration (2.4), Warnings and Precautions (5.3)].**

1 INDICATIONS AND USAGE

LOREEV XR is indicated for the treatment of anxiety disorders in adults who are receiving stable, evenly divided, three times daily dosing with lorazepam tablets.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Initiate LOREEV XR in patients who are being treated with lorazepam tablets, administered three times daily in evenly divided doses (refer to the Prescribing Information of lorazepam tablets for the recommended dosage of lorazepam tablets).

Discontinue lorazepam tablets and administer the first dose of LOREEV XR in the morning the day after the final dose of lorazepam tablets.

The recommended once daily dosage of LOREEV XR is equal to the total daily dose of lorazepam tablets. For example, the recommended dosage for patients who have been receiving lorazepam tablets at a dosage of 1 mg three times daily is LOREEV XR 3 mg once daily in the morning.

The effectiveness of LOREEV XR use for more than 4 months has not been assessed in clinical studies. Healthcare providers should periodically re-evaluate longer term use of LOREEV XR.

2.2 Administration Information

Administer LOREEV XR orally once daily, in the morning, with or without food. Do not crush or chew LOREEV XR.

Swallow LOREEV XR capsules whole or open the capsule and sprinkle the entire contents over a tablespoon of applesauce, followed by drinking water. Consume all the sprinkled LOREEV XR in its entirety, (without chewing) within 2 hours; do not store for future use.

2.3 Dosage Increase for Inadequate Clinical Response

If the clinical response to LOREEV XR is inadequate and a dosage increase is needed, discontinue LOREEV XR and switch to lorazepam tablets to increase the dosage. If an adequate clinical response is achieved with a stable, evenly divided three times daily dosage of lorazepam tablets, resume LOREEV XR once daily dosing with the total daily dose of lorazepam tablets [see *Dosage and Administration (2.1)*].

2.4 Discontinuation or Dosage Reduction of LOREEV XR

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue LOREEV XR 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 and Precautions (5.3), Drug Abuse and Dependence (9.3)*].

2.5 Concomitant Use with UDP-glucuronosyltransferase (UGT) Inhibitors

If an UGT inhibitor is initiated during treatment with LOREEV XR, discontinue LOREEV XR and switch to lorazepam tablets to reduce the dosage [see *Dosage and Administration (2.4), Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

LOREEV XR (lorazepam) extended-release capsules are available as:

1 mg: Hard gelatin capsules with an opaque white body, yellow cap and grey printing ink; "ALM" is printed axially on the yellow cap and "658" is printed axially on the opaque white body

1.5 mg: Hard gelatin capsules with an opaque white body, purple cap and black printing ink; "ALM" is printed axially on the purple cap and "661" is printed axially on the opaque white body

2 mg: Hard gelatin capsules with an opaque white body, orange cap and grey printing ink; "ALM" is printed axially on the orange cap and "663" is printed axially on the opaque white body

3 mg: Hard gelatin capsules with an opaque white body, yellowish-green cap and grey printing ink; "ALM" is printed axially on the yellowish-green cap and "667" is printed axially on the opaque white body

4 CONTRAINDICATIONS

LOREEV XR is contraindicated in patients with:

- hypersensitivity to benzodiazepines or to any of the ingredients in LOREEV XR [see *Warnings and Precautions (5.7)*].
- acute narrow-angle glaucoma

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including LOREEV XR, 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 LOREEV XR 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 LOREEV XR than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking LOREEV XR, 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 LOREEV XR 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 Drug Interactions (7)*].

5.2 Abuse, Misuse, and Addiction

The use of benzodiazepines, including LOREEV XR, 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 (9.2)*].

Before prescribing LOREEV XR and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (e.g., using a standardized screening tool). Use of LOREEV XR, particularly in patients at elevated risk, necessitates counseling about the risks and proper use of LOREEV XR 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.

5.3 Dependence and Withdrawal Reactions

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue LOREEV XR or reduce the dosage (a patient-specific plan should be used to taper the dose) [*see Dosage and Administration (2.4)*].

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 LOREEV XR, may lead to clinically significant physical dependence. Abrupt discontinuation or rapid dosage reduction of LOREEV XR 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 (9.3)*].

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 (9.3)*].

5.4 Central Nervous System (CNS) Depression

Benzodiazepines, including LOREEV XR, may produce CNS depression. Caution patients receiving LOREEV XR against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle.

Use of benzodiazepines, including LOREEV XR, both used alone and in combination with other CNS depressants, may lead to potentially fatal respiratory depression. Alcohol should be avoided and other CNS depressant drugs used with caution during treatment with LOREEV XR [*see Drug Interactions (7)*].

5.5 Patients with Depression or Psychosis

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

In patients with depression, a possibility for suicide should be borne in mind. Consequently, appropriate precautions (e.g., limiting the total prescription size and increased monitoring for suicidal ideation) should be considered in patients with depression. LOREEV XR should not be used in such patients without adequate antidepressant therapy.

5.6 Risk of Paradoxical Reactions

Paradoxical reactions (agitation, irritability, impulsivity, violent behavior, confusion, restlessness, excitement, and

talkativeness) have been reported during benzodiazepine use [see *Adverse Reactions (6)*]. Such reactions may be more likely to occur in the elderly [see *Adverse Reactions (8.5)*]. Discontinue LOREEV XR if the patient experiences these reactions.

5.7 Allergic Reactions to FD&C Yellow No. 5 (Tartrazine)

LOREEV XR 1 mg capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity [see *Contraindications (4)*].

5.8 Neonatal Sedation and Withdrawal Syndrome

Use of LOREEV XR during the later stages of 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 *Use in Specific Populations (8.1)*]. Monitor neonates exposed to benzodiazepines during pregnancy and labor for signs of sedation and neonates exposed to LOREEV XR during pregnancy for signs of withdrawal; manage these infants accordingly.

5.9 Risk in Patients with Impaired Respiratory Function

In patients with impaired respiratory function, respiratory depression and apnea have been reported with benzodiazepines. Closely monitor patients with impaired respiratory function. If signs and symptoms of respiratory depression or apnea occur, consider discontinuing LOREEV XR.

5.10 Laboratory Tests

Leukopenia and elevations of LDH have developed in patients receiving lorazepam tablets [see *Adverse Reactions (6)*]. Periodic blood counts and liver function tests are recommended for patients on long-term therapy.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Risks from Concomitant Use with Opioids [see *Warnings and Precautions (5.1)*]
- Abuse, Misuse, and Addiction [see *Warnings and Precautions (5.2)*]
- Dependence and Withdrawal Reactions [see *Warnings and Precautions (5.3)*]
- Central Nervous System (CNS) Depression [see *Warnings and Precautions (5.4)*]
- Patients with Depression or Psychosis [see *Warnings and Precautions (5.5)*]
- Allergic Reactions to FD&C Yellow No. 5 (Tartrazine) [see *Warnings and Precautions (5.7)*]
- Risk in Patients with Impaired Respiratory Function [see *Warnings and Precautions (5.9)*]

The safety of LOREEV XR in adults is based on studies with lorazepam tablets. The following adverse reactions associated with the use of lorazepam tablets were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In a sample of approximately 3,500 patients treated for anxiety, the most frequent adverse reactions to lorazepam tablets were sedation (15.9%), dizziness (6.9%), weakness (4.2%), and unsteadiness (3.4%). The incidence of sedation and unsteadiness increased with age.

The following reported adverse reactions are categorized by System Organ Class (SOC):

Blood and Lymphatic System Disorders: agranulocytosis, leukopenia, pancytopenia, thrombocytopenia

Endocrine Disorders: syndrome of inappropriate antidiuretic hormone (SIADH)

Eye Disorder: eye function/visual disturbance (including diplopia and blurred vision)

Gastrointestinal Disorder: constipation, gastrointestinal symptoms including nausea

General Disorders and Administration Site Conditions: asthenia, fatigue, hypothermia

Hepatobiliary Disorders: jaundice

Immune System Disorders: anaphylactoid reactions, hypersensitivity reactions

Investigations: increase in bilirubin, increase in liver transaminases (including elevated LDH), increase in alkaline phosphatase

Metabolism and Nutrition Disorders: change in appetite, hyponatremia

Nervous System Disorders: ataxia, autonomic manifestations, coma, convulsions/seizures, drowsiness, dysarthria/slurred speech, extrapyramidal symptoms, headache, tremor, vertigo, memory impairment

Psychiatric Disorders: amnesia, change in libido, confusion, decreased orgasm, depression, disinhibition, disorientation, euphoria, suicidal ideation/attempt, unmasking of depression

Reproductive System and Breast Disorders: impotence

Respiratory Thoracic and Mediastinal Disorders: apnea, respiratory depression, worsening of obstructive pulmonary disease, worsening of sleep apnea

Skin and Subcutaneous Tissue Disorder: allergic skin reactions, alopecia, dermatological symptoms

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 have been reported with immediate-release lorazepam.

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

7 DRUG INTERACTIONS

Table 1 presents clinically significant interactions with LOREEV XR.

Table 1: Clinically Significant Drug Interactions with LOREEV XR.

Opioids	
<i>Clinical Impact</i>	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 gamma-aminobutyric acid (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 [see <i>Warnings and Precautions (5.1)</i>].
<i>Intervention</i>	Limit dosage and duration of concomitant use of LOREEV XR and opioids, and monitor patients closely for respiratory depression and sedation.
Alcohol	
<i>Clinical Impact</i>	Based on an <i>in vitro</i> study, alcohol increases the release rate of LOREEV XR [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention</i>	Avoid concomitant use of alcohol during treatment with LOREEV XR [see <i>Warnings and Precautions (5.4)</i>].
CNS-Depressants	
<i>Clinical Impact</i>	Benzodiazepines, including LOREEV XR, increase CNS-depressant effects when administered with other CNS depressants. Concomitant use of clozapine and LOREEV XR may produce marked sedation, excessive salivation, hypotension, ataxia, delirium, and respiratory arrest.
<i>Intervention</i>	Avoid co-administration of alcohol with LOREEV XR. Use caution if LOREEV XR is co-administered with other CNS-depressants [see <i>Warnings and Precautions (5.4)</i>].

Inhibitors of UGT	
<i>Clinical Impact</i>	Concomitant use of LOREEV XR with UGT inhibitors may increase lorazepam exposure [see <i>Clinical Pharmacology (12.3)</i>], which may increase the risk of adverse reactions.
<i>Intervention</i>	Avoid initiating an UGT inhibitor during treatment with LOREEV XR. If an UGT inhibitor is initiated, discontinue LOREEV XR and switch to lorazepam tablets [see <i>Dosage and Administration (2.5)</i>].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LOREEV XR during pregnancy. Health care providers are encouraged to register patients by calling the National Pregnancy Registry for Psychiatric Medications at 1-866-961-2388 or by visiting online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/othermedications>.

Risk Summary

Infants born to mothers using benzodiazepines during the later stages of pregnancy have been reported to experience symptoms of sedation and/or neonatal withdrawal [see *Warnings and Precautions (5.8)*, *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*). Available data from observational studies have identified a small increased relative risk with benzodiazepine use in early pregnancy and miscarriage, and a small increase in relative risk with benzodiazepine use later in pregnancy and preterm birth (see *Data*).

In animal studies, administration of lorazepam during the organogenesis period of pregnancy resulted in increased incidences of fetal malformations at doses greater than those used clinically. Data for benzodiazepines suggest the possibility of increased neuronal cell death and long-term effects on neurobehavioral function based on findings in animals following prenatal or early postnatal exposure at clinically relevant doses (see *Data*).

The estimated 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 background risk of major birth defects and 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 benzodiazepines during pregnancy and labor for signs of sedation, respiratory depression, hypotonia, and feeding problems. Monitor neonates exposed to benzodiazepines during pregnancy for signs of withdrawal. Manage these neonates accordingly [see *Warnings and Precautions (5.8)*].

Data

Human Data

Available data from observational studies suggest a possible association between benzodiazepine use in early pregnancy and risk of miscarriage. Data from observational studies also suggest a small increased relative risk with benzodiazepine use later in pregnancy and preterm birth. Important methodological limitations with these studies include the uncertainty of whether women who filled a prescription actually took the medication and inability to control for severity of underlying disease. 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. A low incidence of malformations (reduction of tarsals, tibia, metatarsals, mal-rotated 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.

In published animal studies, administration of benzodiazepines or other drugs that enhance GABAergic inhibition to neonatal rats has been reported to result in widespread apoptotic neurodegeneration in the developing brain. The window of vulnerability to these changes in rats (postnatal days 0-14) includes a period of brain development that takes place during the third trimester of pregnancy in humans.

8.2 Lactation

Risk Summary

Lorazepam is present in breastmilk.

There are reports of sedation, poor feeding and poor weight gain in infants exposed to benzodiazepines through breast milk (*see Clinical Considerations*). The effects of lorazepam on milk production are unknown. Because of the potential for serious adverse reactions, including sedation and withdrawal, advise patients that breastfeeding is not recommended during treatment with LOREEV XR.

Clinical Considerations

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

8.4 Pediatric Use

The safety and effectiveness of LOREEV XR has not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of lorazepam tablets were not adequate to determine whether patients age 65 years and older responded differently than younger patients; however, the incidence of sedation and unsteadiness was observed to increase with age [*see Adverse Reactions (6)*].

Age does not appear to have a significant effect on lorazepam pharmacokinetics [*see Clinical Pharmacology (12.3)*].

In general, dose selection for an elderly patient should start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Greater sensitivity (e.g., sedation) of some older individuals cannot be ruled out [*see Warnings and Precautions (5.6)*].

8.6 Hepatic Impairment

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

LOREEV XR contains lorazepam, a Schedule IV controlled substance.

9.2 Abuse

LOREEV XR 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 and Precautions (5.2)*].

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).

9.3 Dependence

Physical Dependence

LOREEV XR 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 and Precautions (5.3)*].

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue LOREEV XR or reduce the dosage [see *Dosage and Administration (2.4)*, *Warnings and Precautions (5.3)*].

Acute Withdrawal Signs and Symptoms

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 LOREEV XR 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 LOREEV XR may develop; however, little tolerance develops to the amnesic reactions and other cognitive impairments caused by benzodiazepines.

10 OVERDOSAGE

Clinical Experience

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

Manifestations of benzodiazepine overdose include varying degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, paradoxical reactions, dysarthria and lethargy. In more serious cases, and especially when other drugs or alcohol were ingested, symptoms may include ataxia, hypotonia, hypotension, cardiovascular depression, respiratory depression, hypnotic state, coma, and death.

Management of Overdose

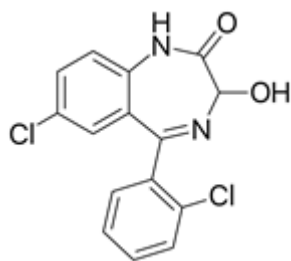
General supportive measures should be employed, with consideration that multiple agents may have been taken in combination with lorazepam. Vital signs must be monitored and the patient closely observed. When there is a risk of aspiration, induction of emesis is not recommended. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Administration of activated charcoal may also limit drug absorption. Hypotension, though unlikely, may be controlled with norepinephrine bitartrate injection. Lorazepam is poorly dialyzable. Lorazepam glucuronide, the inactive metabolite, may be highly dialyzable.

Flumazenil, a benzodiazepine antagonist, 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.

In case of an overdosage, consult a Certified Poison Control Center at 1-800-222-1222 for latest recommendations.

11 DESCRIPTION

LOREEV XR contains lorazepam, a benzodiazepine. Lorazepam is a nearly white crystalline powder and is practically insoluble in water and slightly soluble in alcohol. It is a 1:1 mixture of (R) and (S) isomers. The chemical name is \pm -7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one and its structural formula is:



Molecular formula: C₁₅H₁₀Cl₂N₂O₂; Molecular weight: 321.16

LOREEV XR is intended for oral administration. Each capsule contains 1 mg, 1.5 mg, 2 mg, or 3 mg of lorazepam. The inactive ingredients are colloidal silicon dioxide, corn starch, gelatin, glyceryl monostearate, hypromellose, lactose monohydrate, methyl acrylate methyl methacrylate and methacrylic acid (7:3:1) copolymer 280000 dispersion,

microcrystalline cellulose, polysorbate 80, talc, titanium dioxide, and triethyl citrate. Additionally, the capsule shells contain the following colorants:

1 mg capsules: FD&C Yellow No. 5

1.5 mg capsules: FD&C Blue No. 1 and FD&C Red No. 3

2 mg capsules: D&C Yellow No. 10 and FD&C Red No. 3

3 mg capsules: D&C Yellow No. 10, FD&C Blue No. 1, FD&C Yellow No. 6

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lorazepam exerts its effect for the treatment of anxiety disorders through binding to the benzodiazepine site of the gamma-aminobutyric acid-A (GABA_A) receptors in the brain and enhances GABA-mediated synaptic inhibition.

12.3 Pharmacokinetics

LOREEV XR pharmacokinetics are dose proportional over the dose range of 1 mg to 3 mg. Steady-state plasma concentrations are typically achieved after 5 days of once-daily administration.

At steady-state, the mean area under concentration curve ($AUC_{T_{au}}$), the mean peak plasma concentration (C_{max}), and the mean minimum plasma concentration (C_{min}) of lorazepam following LOREEV XR 3 mg once-daily administration was 694 ng*h/mL, 35 ng/mL and 25 ng/mL, respectively. $AUC_{T_{au}}$, C_{max} , and C_{min} of lorazepam from lorazepam tablets following 1 mg, three-times daily administration were 765 ng*h/mL, 41 ng/mL and 29 ng/mL, respectively.

Absorption

Following a single 3 mg dose of LOREEV XR under fasted conditions, the median time to attain C_{max} (T_{max}) is 14 hours, with a range of 7 to 24 hours.

Effect of Food

Administration of LOREEV XR with a high-fat and high calorie meal did not have a significant effect on exposure of LOREEV XR. However, median T_{max} of lorazepam delayed by approximately 2 hours.

LOREEV XR administered under fasted conditions after sprinkling the entire contents onto one-tablespoon (15 mL) of applesauce did not significantly affect exposure and T_{max} of lorazepam.

Distribution

Following a single 3 mg dose of LOREEV XR under fasted conditions, the mean apparent volume of distribution is approximately 117 L. At clinically relevant concentrations, lorazepam is approximately 85% bound to plasma proteins.

Elimination

Oral mean plasma clearance (CL/F) is about 72 mL/min in adults following a single 3 mg dose of LOREEV XR and the mean elimination half-life of lorazepam is approximately 20.2 ± 7.2 hours.

Metabolism

Lorazepam is conjugated at its 3-hydroxy group in the liver into lorazepam glucuronide, which has no demonstratable CNS activity in animals.

Excretion

Lorazepam glucuronide is excreted in the urine.

Specific Populations

Geriatric Patients

Studies comparing young and elderly subjects have shown that advancing age does not have a significant effect on the pharmacokinetics of lorazepam tablets. However, a 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 of 19 to 38 years of age. The clinical significance of the decrease in mean total body clearance of lorazepam injection in geriatric patients is unknown.

Patients with Hepatic Impairment

No pharmacokinetic studies were conducted with LOREEV XR in patients with hepatic impairment.

Patients with Renal Impairment

No pharmacokinetic studies were conducted with LOREEV XR in patients with renal impairment. Lorazepam is poorly dialyzable. Lorazepam glucuronide, the inactive metabolite, may be highly dialyzable.

Drug Interaction Studies

Concurrent administration of lorazepam with valproate, an inhibitor of UGT, results in increased plasma concentrations and reduced clearance of lorazepam [see *Dosage and Administration (2.5)*, *Drug Interactions (7)*].

Concurrent administration of lorazepam with probenecid, an inhibitor of UGT, may result in a more rapid onset or prolonged effect of lorazepam due to increased half-life and decreased total clearance [see *Dosage and Administration (2.5)*, *Drug Interactions (7)*].

Alcohol: An in vitro study showed significant increases of lorazepam release from LOREEV XR capsules at 2 hours with approximately 91-95% and 37-42% of the drug release in the presence of 40% and 20% alcohol, respectively [see *Drug Interactions (7)*]. Effects of 5% and 10% alcohol on drug release were not significant at 2 hours. There is no in vivo study conducted for the effect of alcohol on drug exposure.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenic potential emerged in rats during an 18-month study with lorazepam.

Mutagenesis

No studies regarding mutagenesis have been performed.

Impairment of Fertility

Animal fertility studies have not been conducted with LOREEV XR.

13.2 Animal Toxicology and/or Pharmacology

Esophageal dilation occurred in rats treated with lorazepam for more than one year at 6 mg/kg/day. The no-effect dose was 1.25 mg/kg/day (approximately 1.2 times the maximum recommended human dose of 10 mg/day based on mg/m² body surface area). The effect was reversible only when the treatment was withdrawn within two months of first observation of the phenomenon. The clinical significance of this is unknown.

16 HOW SUPPLIED/STORAGE AND HANDLING

LOREEV XR (lorazepam) extended-release capsules are available as:

1 mg: Hard gelatin capsules with an opaque white body, yellow cap and grey printing ink; "ALM" is printed axially on the yellow cap and "658" is printed axially on the opaque white body.

NDC 52427-658-30, bottle of 30 capsules with child-resistant closure

NDC 52427-658-01, bottle of 100 capsules with child-resistant closure

1.5 mg: Hard gelatin capsules with an opaque white body, purple cap and black printing ink; "ALM" is printed axially on the purple cap and "661" is printed axially on the opaque white body.

NDC 52427-661-30, bottle of 30 capsules with child-resistant closure

NDC 52427-661-01, bottle of 100 capsules with child-resistant closure

2 mg: Hard gelatin capsules with an opaque white body, orange cap and grey printing ink; "ALM" is printed axially on the orange cap and "663" is printed axially on the opaque white body.

NDC 52427-663-30, bottle of 30 capsules with child-resistant closure

NDC 52427-663-01, bottle of 100 capsules with child-resistant closure

3 mg: Hard gelatin capsules with an opaque white body, yellowish-green cap and grey printing ink; "ALM" is printed axially on the yellowish-green cap and "667" is printed axially on the opaque white body.

NDC 52427-667-30, bottle of 30 capsules with child-resistant closure

NDC 52427-667-01, bottle of 100 capsules with child-resistant closure

Storage

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

Keep bottles tightly closed. Dispense in a tight container.

17 PATIENT COUNSELING INFORMATION

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

Risks from Concomitant Use with Opioids

Advise patients and caregivers about the risks of potentially fatal respiratory depression and sedation when LOREEV XR 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 and Precautions (5.1)*, *Drug Interactions (7)*].

Abuse, Misuse, and Addiction

Inform patients that the use of LOREEV XR, even at recommended dosages, 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 and Precautions (5.2)*, *Drug Abuse and Dependence (9.2)*].

Withdrawal Reactions

Inform patients that the continued use of LOREEV XR may lead to clinically significant physical dependence and that abrupt discontinuation or rapid dosage reduction of LOREEV XR 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 LOREEV XR may require a slow taper [see *Warnings and Precautions (5.3)*, *Drug Abuse and Dependence (9.3)*].

CNS Depression

Advise patients about the risks of CNS depression. Instruct patients to avoid the consumption of alcohol during treatment with LOREEV XR. Advise patients to not drive a car or operate heavy machinery until they know how LOREEV XR affects them [see *Warnings and Precautions (5.4)*, *Drug Interactions (7)*].

Patients with Depression or Psychosis

Advise patients, their families, and caregivers to look for signs of suicidal ideation or worsening depression, and to inform the patient's healthcare provider immediately [see *Warnings and Precautions (5.5)*].

Concomitant Medications

Advise patients to inform their healthcare provider of all medicines they take, including prescription and nonprescription medicines, vitamins and herbal supplements [see *Drug Interactions (7)*].

Administration Information

Advise patients to take LOREEV XR capsules whole or open the capsule and sprinkle the entire contents over a tablespoon of applesauce, followed by drinking water. Advise patients to consume the mixture immediately, without chewing, within 2 hours; do not store for future use [*see Dosage and Administration (2.2)*].

Pregnancy Registry

Advise pregnant women that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to LOREEV XR [*see Use in Specific Populations (8.1)*].

Lactation

Advise women not to breastfeed during treatment with LOREEV XR [*see Use in Specific Populations (8.2)*].

Distributed by:

Almatica Pharma LLC
Morristown, NJ 07960 USA

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