PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

TEVA-LORAZEPAM

Lorazepam Tablets

Tablets, 0.5 mg, 1 mg, 2 mg, Oral

Teva Standard

Anxiolytic-Sedative

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RECENT MAJOR LABEL CHANGES

1 Indications	03/2023
1 Indications, 1.2 Geriatrics	12/2021
3 Serious Warnings and Precautions Box	12/2021
4 Dosage and Administration, 4.1 Dosing Considerations	12/2021
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	03/2023
7 Warnings and Precautions	03/2023
7 Warnings and Precautions, 7.1.4 Geriatrics	12/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TEVA-LORAZEPAM (lorazepam) is indicated for:

- the short-term relief of manifestations of excessive anxiety in patients with anxiety neurosis.

Anxiety and tension associated with the stresses of everyday life usually do not require treatment with anxiolytic drugs.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

Long-term use of TEVA-LORAZEPAM should be avoided in geriatric patients. Enhanced monitoring is recommended (see **7 WARNINGS AND PRECAUTIONS, Falls and fractures**; **4 DOSAGE AND ADMINISTRATION, 4.1 Dosing considerations**).

2 CONTRAINDICATIONS

- Lorazepam is contraindicated in patients with myasthenia gravis or acute narrow angle glaucoma, and in those with known hypersensitivity to benzodiazepines.
- Lorazepam is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Addiction, Abuse and Misuse

The use of benzodiazepines, including TEVA-LORAZEPAM can lead to abuse, misuse, addiction, physical dependence and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol or illicit drugs.

- Assess each patient's risk prior to prescribing TEVA-LORAZEPAM

- Monitor all patients regularly for the development of these behaviours or conditions
- TEVA-LORAZEPAM should be stored securely to avoid theft or misuse

Withdrawal
Benzodiazepines, like TEVA-LORAZEPAM can produce severe or life-threatening withdrawal symptoms
- Avoid abrupt discontinuation or rapid dose reduction of TEVA-LORAZEPAM
- Terminate treatment with TEVA-LORAZEPAM by gradually tapering the dosage schedule under close monitoring

(**see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance**)

Risks from Concomitant use with Opioids
Concomitant use of TEVA-LORAZEPAM and opioids may result in profound sedation, respiratory depression, coma and death (see **7 WARNINGS AND PRECAUTIONS – Risks from concomitant use of opioids and benzodiazapines**).
- 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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- TEVA-LORAZEPAM should always be prescribed at the lowest effective dose for the shortest duration possible.
- TEVA-LORAZEPAM can produce withdrawal signs and symptoms or rebound phenomena following abrupt discontinuation or rapid dose reduction (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal**; **7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance**). Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring. Withdrawal symptoms (e.g., rebound insomnia) can appear following cessation of recommended doses after as little as one week of therapy.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal signs and symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.

Symptoms reported following discontinuation of benzodiazepines include: headache, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, rebound phenomena, dysphoria, dizziness, derealization, depersonalization, hyperacusis, numbness/tingling of extremities, hypersensitivity to light, noise and physical contact/perceptual changes, involuntary movements, nausea, vomiting, diarrhea, loss of

appetite, hallucinations,/delirium, convulsions/seizures, tremor, abdominal and muscle cramps, myalgia, agitation, palpitations, tachycardia, panic attacks, vertigo, hyperreflexia, short-term memory loss, and hyperthermia. Convulsions/seizures may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold, such as antidepressants.

Renal or hepatic disease

The dose should be titrated should TEVA-LORAZEPAM be used in patients with mild to moderate hepatic or renal disease. In patients for whom prolonged therapy with TEVA-LORAZEPAM is indicated, periodic blood counts and liver function tests should be carried out.

When lorazepam is used in patients with mild to moderate hepatic or renal disease, the lowest effective dose should be considered since drug effect may be prolonged (see **7 WARNINGS AND PRECAUTIONS, Renal**)

Geriatrics

For geriatric patients and debilitated patients reduce the initial dose by approximately 50% and adjust the dosage as needed and tolerated. Geriatric patients in particular may be more sensitive to benzodiazepines (see **7 WARNINGS AND PRECAUTIONS, Falls and Fractures**). Long-term use of TEVA-LORAZEPAM should be avoided in geriatric patients. Enhanced monitoring is recommended.

(See **7.1.4 Geriatrics**)

4.2 Recommended Dose and Dosage Adjustment

The dosage and duration of therapy of TEVA-LORAZEPAM (lorazepam) must be individualized and carefully titrated in order to avoid excessive sedation or mental and motor impairment.

As with other anxiolytic sedatives, short courses of treatment should usually be the rule for the symptomatic relief of disabling anxiety in psychoneurotic patients and the initial course of treatment should not last longer than one week without reassessment of the need for a limited extension. Initially, not more than one week's supply of the drug should be provided, and automatic prescription renewals should not be allowed. Subsequent prescriptions, when required, should be limited to short courses of therapy.

The risk of dependence may increase with dose and duration of treatment; therefore, the lowest effective dose should be prescribed for the shortest duration and the need for continued treatment reassessed frequently.

Abrupt discontinuation or rapid dosage reduction of lorazepam after continued use may precipitate withdrawal reactions which can be life threatening, and/or rebound phenomena;

therefore, the drug should be discontinued gradually or reduce the dosage (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal**; **7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance**).

Generalized Anxiety Disorder: The recommended initial adult daily oral dosage is 2 mg in divided doses of 0.5, 0.5 and 1 mg, or of 1 mg and 1 mg. The daily dosage should be carefully increased or decreased by 0.5 mg depending upon tolerance and response. The usual daily dosage is 2 to 3 mg. However, the optimal dosage may range from 1 to 4 mg daily in individual patients. Usually, a daily dosage of 6 mg should not be exceeded.

In geriatric patients and debilitated patients, the initial daily dose should not exceed 0.5 mg and should be very carefully and gradually adjusted, depending upon tolerance and response.

Health Canada has not authorized an indication for pediatric use.

4.5 Missed Dose

Patients who miss taking a dose should contact their healthcare provider for instructions.

5 OVERDOSAGE

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

Symptoms: With benzodiazepines, including lorazepam, symptoms of mild overdosage include drowsiness, mental confusion and lethargy. In more serious overdoses, symptoms may include ataxia, hypotonia, hypotension, hypnosis, Stages I to III coma, and, very rarely, death. Symptoms can range in severity and include, in addition to the above, dysarthria, paradoxical reactions, CNS depression, respiratory depression, and cardiovascular depression.

Treatment: In the case of an oral overdose, if vomiting has not occurred spontaneously and the patient is fully awake, emesis may be induced with syrup of ipecac 20-30 mL (where there is risk of aspiration, induction of emesis is not recommended). Gastric lavage should be instituted as soon as possible and 50-100 g of activated charcoal should be introduced to and left in the stomach.

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

General supportive therapy should be instituted as indicated. Vital signs and fluid balance should be carefully monitored. An adequate airway should be maintained and assisted respiration used as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines from the body. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more

critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that intravenous infusion of 0.5 to 4 mg of physostigmine at the rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with the use of physostigmine (i.e., induction of seizures) should be weighed against its possible clinical benefit.

The benzodiazepine antagonist flumazenil may be used in hospitalized patients as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. The physician should be aware of the risk of a seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet, 0.5 mg, 1 mg, 2 mg	Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose, Sodium Lauryl Sulfate and Starch.

Small, round, white, flat with bevelled-edge, compressed tablets. Engraved N on one side, 0.5 on the reverse. Each TEVA-LORAZEPAM tablet contains lorazepam 0.5 mg. Available in bottles of 100 and 1000.

Small, white, capsule shaped, flat with beveled-edge, compressed tablets. Engraved N, vertical scoreline and 1 on one side, plain on the reverse. Each TEVA-LORAZEPAM tablet contains lorazepam 1 mg. Available in bottles of 100, 1000 and 3000.

White, oval-shaped, flat with beveled-edge, compressed tablets. Engraved N, vertical scoreline and 2 on one side, plain on the reverse. Each TEVA-LORAZEPAM tablet contains lorazepam 2 mg. Available in bottles of 100 and 1000.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**

Concomitant Use with Opioids

Concomitant use of benzodiazepines, including TEVA-LORAZEPAM, and opioids may result in

profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risks from Concomitant use with Opioids; 9 DRUG INTERACTIONS, Serious Drug Interactions**).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with benzodiazepines.

If a decision is made to prescribe TEVA-LORAZEPAM concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of TEVA-LORAZEPAM than indicated, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking TEVA-LORAZEPAM, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation (see **5 OVERDOSAGE**).

Advise both patients and caregivers about the risks of respiratory depression and sedation when TEVA-LORAZEPAM is used with opioids.

Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined.

Dependence/Tolerance

Use of benzodiazepines such as TEVA-LORAZEPAM can lead to abuse, misuse, addiction, physical dependence (including tolerance) and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol or illicit drugs. Benzodiazepines may be subject to diversion.

The risk of dependence increases with higher doses and longer term use but can occur with short-term use at recommended therapeutic doses. The risk of dependence is greater in patients with a history of psychiatric disorders and/or substance (including alcohol) use disorder. Interdose daytime anxiety and rebound anxiety may increase the risk of dependency in TEVA-LORAZEPAM treated patients.

- Discuss the risks of treatment with TEVA-LORAZEPAM with the patient, considering alternative (including non-drug) treatment options.
- Carefully evaluate each patient's risk of abuse, misuse and addiction, considering their medical condition and concomitant drug use, prior to prescribing TEVA-LORAZEPAM. In individuals prone to substance use disorder, TEVA-LORAZEPAM should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- TEVA-LORAZEPAM should always be prescribed at the lowest effective dose for the shortest

duration possible.

- All patients receiving benzodiazepines should be monitored for signs of misuse and abuse. If a substance use disorder is suspected, evaluate the patient and refer them for substance abuse treatment, as appropriate.

Withdrawal: Benzodiazepines, such as TEVA-LORAZEPAM, can produce withdrawal signs and symptoms, ranging from mild to severe and even life threatening, following abrupt discontinuation or rapid dose reduction. Other factors that may precipitate withdrawal are switching from a long-acting to a short-acting benzodiazepine, decreasing blood levels of the drug or administration of an antagonist. The risk of withdrawal is higher with higher dosages and/or prolonged use but can occur with short-term use (days to weeks) at recommended therapeutic doses.

The onset of withdrawal signs and symptoms can range from hours to weeks following drug cessation and occur even with tapered dosage. Some symptoms can persist for months. Since symptoms are often similar to those for which the patient is being treated, it may difficult to distinguish from a relapse of the patient's condition.

Severe or life-threatening signs and symptoms of withdrawal include catatonia, delirium tremens, depression, dissociative effects (e.g. hallucinations), mania, psychosis, seizures (including status epilepticus) and suicidal ideation and behavior have been observed.

Other withdrawal signs and symptoms include abdominal and muscle cramps, cognitive impairment, diarrhea, dysphoria, extreme anxiety or panic attacks, headache, hypersensitivity to light, noise and physical contact, insomnia, irritability, muscle pain or stiffness, paresthesia, restlessness, sweating, tension, tremors and vomiting. There is also a possibility of rebound anxiety or rebound insomnia.

- Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal signs and symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Inform patients of risk of discontinuing abruptly, reducing dosage rapidly or switching medications.
- Stress the importance of consulting with their health care professional in order to discontinue safely.
- Patients experiencing withdrawal signs and symptoms should seek immediate medical attention. (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse, Withdrawal**; **4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations**)

Driving and Operating Machinery

Excessive sedation has been observed with lorazepam at standard therapeutic doses. Therefore, patients on TEVA-LORAZEPAM should be warned against engaging in hazardous activities requiring mental alertness and motor coordination, such as operating dangerous machinery or driving motor vehicles.

As is true of other similar CNS-acting drugs, patients receiving lorazepam should not operate machinery or engage in hazardous occupations or drive a motor vehicle for a period of 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, concomitant use of other drugs, stress of surgery or the general condition of the patient.

Falls and Fractures

There have been reports of falls and fractures among benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), geriatric or debilitated patients.

Immune

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

Neurologic

Since TEVA-LORAZEPAM has a central nervous system depressant effect, patients should be advised against the simultaneous use of other CNS depressant drugs.

Psychiatric

TEVA-LORAZEPAM (lorazepam) is not recommended for use in depressive neurosis or in psychotic reactions.

Use in Mental and Emotional Disorders: TEVA-LORAZEPAM (lorazepam) is not recommended for the treatment of psychotic or depressed patients. Since excitement and other paradoxical reactions can result from the use of these drugs in psychotic patients, they should not be used in ambulatory patients suspected of having psychotic tendencies.

As with other anxiolytic-sedative drugs, lorazepam should not be used in patients with non-pathological anxiety. These drugs are also not effective in patients with characterological

and personality disorders or those with obsessive-compulsive neurosis.

When using TEVA-LORAZEPAM, it should be recognized that suicidal tendencies may be present and that protective measures may be required.

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

Renal

Use in Patients with Impaired Renal or Hepatic Function: Since the liver is the most likely site of conjugation of lorazepam and since excretion of conjugated lorazepam (glucuronide) is a renal function, the usual precaution of carefully titrating the dose should be taken, should TEVA-LORAZEPAM be used in patients with mild to moderate hepatic or renal disease. In patients for whom prolonged therapy with TEVA-LORAZEPAM is indicated, periodic blood counts and liver function tests should be carried out.

When lorazepam is used in patients with mild to moderate hepatic or renal disease, the lowest effective dose should be considered since drug effect may be prolonged.

Dosage for patients with severe hepatic insufficiency should be adjusted carefully according to patient response. Lower doses may be sufficient in such patients.

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.

Reproductive Health: Female and Male Potential

- **Teratogenic Risk**

Use in Pregnancy: TEVA-LORAZEPAM should not be used during pregnancy. Several studies have suggested an increased risk of congenital malformations associated with the use of the benzodiazepines during pregnancy (see **16 NON-CLINICAL TOXICOLOGY**).

Infants of mothers who ingested benzodiazepines for several weeks or more preceding delivery have been reported to have withdrawal symptoms during the postnatal period. Symptoms such as hypoactivity, hypotonia, hypothermia, respiratory depression, apnea, feeding problems, and impaired metabolic response to cold stress have been reported in neonates born of mothers who have received benzodiazepines during the late phase of pregnancy or at delivery.

Since lorazepam is also a benzodiazepine derivative, its administration is rarely justified in

women of child-bearing potential. If the drug is prescribed to a woman of child-bearing potential, she should be warned to contact her physician regarding discontinuation of the drug if she intends to become or suspects that she is pregnant.

In women, blood levels obtained from umbilical cord blood indicate placental transfer of lorazepam and lorazepam glucuronide. TEVA-LORAZEPAM should not be used during pregnancy. There are insufficient data regarding obstetrical safety of parenteral lorazepam, including use in caesarean section. Such use, therefore, is not recommended.

Respiratory

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

7.1 Special Populations

7.1.1 Pregnant Women

Lorazepam should not be used during pregnancy.

7.1.2 Breastfeeding

Use in Nursing Mothers: TEVA-LORAZEPAM has been detected in human breast milk; therefore it should not be administered to breastfeeding women, unless the expected benefit to the mother outweighs the potential risk to the infant.

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

7.1.3 Pediatrics

Use in Children: TEVA-LORAZEPAM is not intended for use in children under 18 years of age. The safety and effectiveness of lorazepam in children less than 18 years of age has not been established (see **16 NONCLINICAL TOXICOLOGY**). Because of the lack of sufficient clinical experience, TEVA-LORAZEPAM is not recommended for use in patients less than 18 years of age (see **7 WARNINGS AND PRECAUTIONS**).

Paradoxical reactions have been occasionally reported during benzodiazepine use (see **8 ADVERSE REACTIONS**). Such reactions may be more likely to occur in children and the elderly. Should these occur, use of the drug should be discontinued.

7.1.4 Geriatrics

Geriatric patients and debilitated patients, or those with organic brain syndrome, have been found to be prone to CNS depression after even low doses of benzodiazepines. Therefore, medication should be initiated with very low initial doses in these patients, depending on the response of the patient, in order to avoid over sedation or neurological impairment.

As with any premedicant, extreme care must be used in administering TEVA-LORAZEPAM to geriatric patients or very ill patients and to those with limited pulmonary reserve, because of the possibility that apnea and/or cardiac arrest may occur.

Clinical trials have shown that patients over the age of 50 years may have a more profound and prolonged sedation with intravenous lorazepam.

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

Long-term use of TEVA-LORAZEPAM should be avoided in geriatric patients or debilitated patients who may be more sensitive to benzodiazepines. There is an increased risk of cognitive impairment, delirium, falls, fractures, hospitalizations and motor vehicle accidents in these users. Enhanced monitoring is recommended in this population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The adverse reaction most frequently reported was drowsiness.

Reported adverse reactions (by system) are:

Body as a Whole
Angioedema, asthenia, muscle weakness, anaphylactic reactions, change in weight, drug withdrawal syndrome, hypersensitivity reactions, hyponatremia, hypothermia, SIADH;

Cardiovascular

Hypotension, lowering in blood pressure;

Digestive

Nausea, constipation, change in appetite, increase in bilirubin, jaundice, increase in liver transaminases, increase in alkaline phosphatase;

Hematological/Lymphatic

Agranulocytosis, pancytopenia, thrombocytopenia;

Nervous System and Special Senses (benzodiazepine effects on the CNS are dose dependent,

with more severe CNS depression with higher doses)
Anterograde amnesia, drowsiness, fatigue, sedation, ataxia, confusion, depression, unmasking of depression, dizziness, change in libido, impotence, decreased orgasm, extrapyramidal symptoms, tremor, vertigo, visual disturbances (including diplopia, and blurred vision), dysarthria/slurred speech, headache, convulsions/seizures, amnesia, disinhibition, euphoria, coma, suicidal ideation/attempt, impaired attention/concentration, balance disorder, paradoxical reactions (including anxiety, agitation, excitation, hostility, aggression, rage, sleep disturbances/insomnia, sexual arousal, hallucinations), psychomotor agitation, drug abuse, drug dependence;

Respiratory

Respiratory depression, apnea, worsening of sleep apnea (the extent of respiratory depression with benzodiazepines is dose dependent - more severe depression at higher doses), worsening of obstructive pulmonary disease, and ear, nose and throat disturbances;

Skin
Allergic skin reactions, alopecia.

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

Release of hostility and other paradoxical effects such as irritability and excitability, are known to occur with the use of benzodiazepines. Paradoxical reactions may be more likely to occur in children or the elderly. Should paradoxical reactions occur, use of the drug should be discontinued. In addition, hypotension, mental confusion, slurred speech, over sedation and abnormal liver and kidney function tests and hematocrit values have been reported with these drugs.

8.5 Post-Market Adverse Reactions

Injury, Poisoning and Procedural Complications
There have been reports of falls and fractures in benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), geriatric and debilitated patients.

Dependence/Withdrawal
Development of physical dependence and withdrawal following discontinuation of therapy has been observed with benzodiazepines such as TEVA-LORAZEPAM. Severe and life-threatening symptoms have been reported. (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse**; **7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance**).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

Concomitant use of TEVA-LORAZEPAM 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 not possible
- Limit dosage and durations to the minimum required
- Follow patients for signs and symptoms of respiratory depression and sedation

(see **3 WARNINGS AND PRECAUTIONS BOX, Risks from Concomitant use with Opioids**)

9.2 Drug Interactions Overview

If lorazepam is to be used together with other drugs acting on the CNS, careful consideration should be given to the pharmacology of the agents to be employed because of the possible potentiation of drug effects. The benzodiazepines, including lorazepam produce additive CNS depressant effects when administered with other CNS depressants such as barbiturates, antipsychotics, sedative/hypnotics, anxiolytics, antidepressants, narcotic analgesics, sedative antihistamines, anticonvulsants, anesthetics and alcohol.

9.3 Drug-Behavioural Interactions

Patients should be cautioned not to take alcohol during the administration of lorazepam because of the potentiation of effects that may occur.

Lorazepam produces depression of the CNS when administered with ethyl alcohol, phenothiazines, barbiturates, monoamine oxidase (MAO) inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam, an increased incidence of sedation, hallucinations and irrational behaviour has been observed.

9.4 Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (ie. those identified as contraindicated).

Opioids: Due to additive CNS depressant effect, the concomitant use of benzodiazepines, including TEVA-LORAZEPAM, and opioids increases the risk of 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 of concomitant use of benzodiazepines and opioids to the minimum required. Follow patients closely for respiratory depression and sedation (see **3 SERIOUS WARNINGS AND PRECAUTIONS**

BOX; **7 WARNINGS AND PRECAUTIONS - Risks from Concomitant Use of Opioids and benzodiazepines**).

Other drugs: There have been reports of apnea, coma, bradycardia, heart arrest, and death with the concomitant use of lorazepam injection and haloperidol.

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

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

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Lorazepam is an active benzodiazepine with a depressant action on the central nervous system. It has anxiolytic and sedative properties which are of value in the symptomatic relief of pathologic anxiety in patients with anxiety disorders giving rise to significant functional disability but is not considered indicated in the management of trait anxiety.

In laboratory animals, lorazepam produces disinhibitory, sedative, anti-convulsant, muscle relaxant, ataxic and hypnotic effects.

Lorazepam has also been shown to possess anticonvulsant activity.

Anterograde amnesia, a lack of recall of events during period of drug action, has been reported and appears to be dose-related.

10.2 Pharmacodynamics

Studies with lorazepam in rats demonstrated a decrease in treadmill avoidance without modifying the escape response, an increase in responding during the shock schedule in the conflict test, an increase in incorrect responses in a discrimination test, and a reduction of conditioned suppression if lorazepam was given prior to the fear conditioning trial, while increasing conditioned suppression, if given prior to re-testing. These effects were observed at doses from 0.05 to 20 mg/kg i.p. In some of the tests, diazepam was also used with similar results obtained at approximately 2-5 times the lorazepam dose.

Lorazepam was the most potent of several benzodiazepines tested in affecting state-dependent learning in trained, hungry rats rewarded with sweetened milk and conditioned to simple fear responses by mild electric shock. While 70-75% inhibition of conditioned fear was achieved with intraperitoneal doses of 0.9 mg/kg of lorazepam on the training day, 2.7 mg/kg of diazepam and 5 mg/kg of either chlordiazepoxide or oxazepam were required to obtain similar results. Consistent with state-dependent learning interpretations, a second injection of lorazepam administered to rats just prior to being tested for fear retention fully reinstated the conditioned suppression response.

Daily intraperitoneal injections of lorazepam, diazepam, oxazepam, chlordiazepoxide, scopolamine, or amobarbital, after initially interfering with feeding behaviour, later facilitated it. Following fear conditioning of the animals, all of the drugs, with the exception of scopolamine, increased conditioned suppression in the retention test. These repeated dose experiments, which permit tolerance of depressant side effects to develop, make it unlikely that benzodiazepines or amobarbital increase conditioned suppression retention through some depressant side effect.

In rats, fear-conditioned by electric shocks of different intensities, lorazepam increased retention-test drinking latencies of strongly shocked rats more than it did those of rats given shocks of intermediate or weak intensities.

In mice, lorazepam prevented pentylenetetrazol-induced convulsions at low doses (ED_{50}-0.07 mg/kg p.o.), while much higher doses (0.5-5.0 mg/kg p.o.) were required to raise the threshold to electroshock-induced convulsions. It was demonstrated that lorazepam was more potent than diazepam in antagonizing pentylenetetrazol-induced convulsions by all three routes tested: oral, intraperitoneal, and intravenous. Lorazepam also inhibited the stimulation caused by morphine. Both lorazepam and clonazepam had ED_{50}s for the antagonism of convulsions of less than 1

mg/kg when they were given intravenously or orally only 1 minute before the pentylenetetrazol challenge.

Observations of monkeys provided strong evidence of the sedative action of lorazepam. Here, relatively high doses of lorazepam caused brief initial depression followed by long periods of obvious sedation. The behaviour of cats and mice, after receiving lorazepam supported these findings. In mice, it was shown that lorazepam is a more potent sedative than diazepam or flurazepam.

Its ability to inhibit foot shock induced fighting between mice, together with reactions of rats and squirrel monkeys in a series of conflict tests considered specific predictors of anti-anxiety activity, confirmed the anxiolytic potential of lorazepam.

The general depressant effects of repeated dosings of lorazepam in rats diminished rapidly while its anticonflict action remained, findings suggesting that while the anti-anxiety effects of lorazepam endure, any behaviour disruption is transitory.

Doses of 5 to 50 mg/kg I.V. caused ataxia and obvious CNS depression in rhesus monkeys, lasting for over 5 hours at the highest dose. Suppression of the linguomandibular reflex was demonstrated in anaesthetized cats suggesting a central muscle-relaxant effect of lorazepam in this species. Higher doses, however, were required than with diazepam to produce significant reflex inhibition.

Using suppression of linguomandibular reflexes in cats as a measure of centrally mediated muscle relaxation, it was demonstrated that intravenous doses of 0.25 to 2 mg/kg of lorazepam were active in a dose-related manner, that the patellar reflex was not suppressed indicated a preferential effect on polysynaptic pathways.

Studies on the cardiovascular system in anaesthetized animals demonstrated that lorazepam, at a dose of 0.1 mg/kg, given by intraperitoneal injection had little effect on either blood pressure or heart rate. Second injections of 0.9 mg/kg one hour later caused some depression of cardiovascular parameters of anaesthetized cats and dogs. Doses greater than 0.9 mg/kg resulted in an average decrease of approximately 40% in both blood pressure and heart rate. Electrocardiograms taken near the conclusion of a 33-34 day study in which beagle dogs received daily intramuscular injections of lorazepam showed only slight increases in the heart rates of both vehicle control and drug-treated animals.

10.3 Pharmacokinetics

The serum half-life of lorazepam ranges between 12 to 15 hours, while that of the conjugate varied between 16 to 20 hours.

Absorption

Lorazepam is rapidly absorbed after oral administration, with mean peak plasma concentrations of free lorazepam at 2 hours (range between 1-6 hours). Following intravenous administration, peak plasma levels are reached within minutes, whereas following administration by the intramuscular route, peak plasma levels occur between 60 to 90 minutes. After sublingual administration, peak plasma levels occur at 60 minutes. By the intramuscular route, the absorption half-life values of lorazepam average 12 and 19 minutes, whereas by the oral route, there is an additional lag period averaging 15 and 17 minutes. Bioavailability was shown to be identical by all routes of administration.
Lorazepam is rapidly conjugated to a glucuronide which has no demonstrable psychopharmacological activity and is excreted mainly in the urine. Very small amounts of other metabolites and their conjugates have been isolated from urine and plasma.

Distribution

Except for the organs of absorption and excretion, tissue distribution of ^{14}C-lorazepam in rats was nearly uniform.

Metabolism

Metabolic studies in mice, rats, cats, dogs and miniature swine were conducted on the absorption, excretion, tissue distribution and biotransformation of lorazepam. Both ^{14}C-labelled and unlabelled drug was used. The most important finding was the conjugation of lorazepam with glucuronic acid in all investigated species. Lorazepam glucuronide, essentially inactive as an anti-anxiety agent, accounted for most of the drug-related urinary excretion products in all species except the rat in which, in addition to glucuronide formation, more extensive biotransformation took place.

Elimination

Most of the drug (88%) is excreted in the urine, with 75% excreted as the glucuronide. At the clinically relevant concentrations, approximately 85% of lorazepam is bound to plasma proteins.

Maximum concentrations of unchanged lorazepam in whole blood and plasma of rats occurred one-half to one hour after oral drug administration, and these concentrations declined to low levels within 24 hours. In dogs and miniature swine, concentrations of orally administered lorazepam peaked and declined rapidly, but they consisted principally of lorazepam glucuronide. These findings correlated with the rapid elimination observed in dogs administered lorazepam intravenously when no free drug was detected in plasma six hours later, and the half-life was estimated to be 1.6 hours. The major route of lorazepam excretion for the dog and the miniature swine is by the kidneys. Biliary excretion has been demonstrated in the rat.

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Species differences in urinary excretion patterns were investigated qualitatively in the mouse, rat, cat, dog, and miniature swine. The major urinary excretion product was the glucuronide conjugate of lorazepam. In dogs, the pattern of biotransformation of lorazepam seemed independent of dose; in rats, it appeared dose-dependent and produced significant amounts of several metabolites rather than the predominance of glucuronide found in other species, including the human. No sex differences were noted in the urinary excretion patterns of the several species tested. Peak urinary excretion was noted at 2-6 hours and total recovery in urine and feces over 48 hours was as high as 100% in some species.

Special Populations and Conditions

The special populations and conditions pharmacokinetics data on which the original indication was authorized is not available.

11 STORAGE, STABILITY AND DISPOSAL

Bottles: Store at controlled room temperature (15°C - 30 °C).
Unite Dose (blister): Store between 15°C - 25°C

12 SPECIAL HANDLING INSTRUCTIONS

None

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

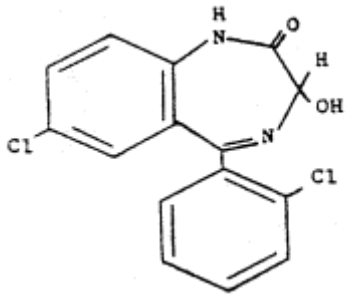
Drug Substance

Proper name: Lorazepam

Chemical name: 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1, 4- benzodiazepin-2-one

Molecular formula and molecular mass: $C_{15}H_{10}C_{l2}N_2O_2$, 321.16

Structural formula:



Physicochemical properties: White or practically white, practically odourless, crystalline powder.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity: Oral. LD_{50}s ranged from 1850-5010 mg/kg in mice to 5000 mg/kg in rats and 2000 mg/kg in dogs. The intraperitoneal LD_{50}s were 700 mg/kg in rats and mice. In newborn rats

and mice, intragastric LD_{50} values were 200 and 250 mg/kg respectively.

Signs exhibited during acute toxicity testing included moderate to marked sedation, shortness of breath, paralysis of hind legs, loss of righting reflex and convulsions. Acute respiratory depression was noted as the mode of death.

Injectable. The acute toxicity of lorazepam in adult mice and rats were determined to be:

SPECIES	ROUTE	LD_{50} mg/kg
Mouse	i.m.	70
	i.p.	46
	i.v.	24
Rat	i.m.	59
	i.p.	48

In beagle dogs, the approximate LD_{50} for intravenous lorazepam was 50 mg/kg (equivalent to 10 mL/kg). The highest intramuscular dose of lorazepam that, because of its volume, could be given to dogs was 25 mg/kg (equivalent to 5 mL/kg). The toxicity of injectable lorazepam in all three species seemed due almost entirely to the vehicle employed.

Long-Term Toxicity: Oral. Lorazepam was administered in the diet to rats in a number of studies extending for periods of 4 to 82 weeks at doses ranging from 14.5 to 400 mg/kg/day. In the long-term studies, decreased food consumption and body weight gain were observed at the higher dose levels, while at lower dose levels weight gain tended to be increased relative to controls. Transient, dose-related sedation and ataxia also occurred, and convulsions were noted, particularly following drug withdrawal. The only gross pathological finding was esophageal dilatation, which was observed in a number of animals at different dose levels. This condition also occurred with diazepam, and the significance of this finding is at present unknown.

Increased liver, kidney, thyroid, adrenal and testicular weights, as well as centrilobular hypertrophy of the liver, cloudy swelling and loss of glycogen were observed in drug-treated animals. At the highest dose levels, changes in the nuclei of the hypertrophied liver cells also occurred. In one study, the colloid follicles of the thyroid were lined with tall cells and were reported to be increased in a dose-related manner. Effects on blood chemistry included increases in serum protein and cholesterase levels and a decrease in serum alkaline phosphatase. These changes were observed mostly at the higher dose levels and were more marked in females. Three oral studies were conducted in dogs, ranging from 6 to 52 weeks in duration at doses of up to 480 mg/kg/day. A high incidence of emesis occurred in the early stages of the studies. Most drug treated dogs exhibited the following signs: sedation, ataxia, tremors, restlessness, excitement, apprehension, salivation, panting, vocalization, muscle weakness and depression; of these only sedation persisted. Polydipsia was also observed.

There were some increases in spleen, liver and testicular weight, and, at the highest dose, serum alkaline phosphatase and hematocrit values were elevated. Increased platelet and cholesterol values were also noted in the long-term study.

Injectable. In two studies in adult rats, lorazepam was administered either intravenously for ten days or intramuscularly for 33 to 37 days. Food consumption and body weight gain were little affected.

Most animals were sedated to some extent, and even ataxic at the high doses. Statistically significant differences to hematologic values between treated and control animals of both studies were within normal limits. With the possible exception of decreases in serum glucose in the second study, allserum chemical differences were small and considered biologically unimportant. Ophthalmoscope examinations made in both studies revealed no ocular abnormalities.

Some organ weights of lorazepam-treated animals differed significantly from those of control animals, but there was no consistent pattern to the variations.

Histopathologic examinations at the end of both studies revealed marked tissue reactions at the injection sites of rats treated with either lorazepam or vehicle alone. The only other pathological change thought to be related to treatment was an unusual degree of extramedullary splenic hematopoiesis, a condition confined chiefly to high-dose animals of Study 2. There were no accompanying changes in bone marrow or lymphoid tissues.

Purebred beagle dogs received daily intramuscular injections of 2.5, 5.0 or 10.0 mg/kg of lorazepam for 33-34 days. Their behaviour was only mildly and occasionally affected; appetite and mean body weight changes were similar in treated and untreated dogs. The drug-treated animals drank more water. There were episodes of emesis, and occasionally some stools were loose. Injection site sores developed on drug-treated and vehicle control dogs. Electrocardiograms taken near the study's conclusion showed slight increases in heart rate of vehicle control and lorazepam-treated animals. Alterations in several hematologic parameters in lorazepam-treated and vehicle control dogs were attributed to loss of blood and inflammatory reactions at injection sites. Statistical analysis of group mean blood chemical values showed several significant differences in mid and high-dose lorazepam dogs and those given the vehicle only. With the possible exception of elevated cholesterol, SGPT, and SGOT values, these differences were small and believed to be of no biological importance. The elevated SGOT levels were attributed to injection site inflammation. While some changes were suggestive of liver involvement, no histological alterations to that organ were discovered. Marked inflammatory injection site reactions were found on all dogs treated with lorazepam or its vehicle. Splenic hematopoiesis occurred in varying degrees among drug-treated and vehicle control animals. Hypercellularity of the bone marrow was discovered in four lorazepam-treated dogs and two vehicle control animals. It is likely this resulted from injection site stress and blood loss.

In anticipation of lorazepam being used concomitantly with other therapeutic agents in a variety

of clinical situations, drug interaction studies were undertaken. Lorazepam was without effect on the LD_{50} of morphine in rats. Although the oral LD_{50} of lorazepam in mice was not modified by phenelzine, the depressor effect of intravenous lorazepam or diazepam in the presence of phenelzine, was increased in rats. In common with other anxiolytic-sedatives, oral lorazepam in mice reduced the amount of I.V. thiopental required for hypnosis and respiratory arrest.

Oral doses of lorazepam administered daily for 59 days to beagle dogs did not alter the anticoagulant activity of bishydroxycoumarin. In decerebrate cats, the intensity and duration of the skeletal neuromuscular blocking action of gallamine and suxamethonium were unaffected by intravenous doses of either diazepam or lorazepam.

The drug dependency potential of lorazepam (10 mg/kg), diazepam (5 mg/kg) and chlordiazepoxide (20 mg/kg) by several routes of administration was evaluated in normal, barbital-dependent and withdrawn rhesus monkeys. Like chlordiazepoxide and diazepam, lorazepam suppressed signs of barbital withdrawal. In long-term toxicity studies, convulsions were noted, at the high-dose levels, particularly following withdrawal of lorazepam.

The irritant potential of injectable lorazepam was compared with that of diazepam in mice and rabbits. While the degrees of irritation produced by either compound varied with the routes of administration, it appeared that the experimental vehicles were the principle cause of irritation. The degree of hemolytic potential of lorazepam in an experimental vehicle varied from mild to moderate in rabbit blood, and slight to mild in human or dog blood.

Reproductive and Developmental Toxicology:

Oral. A number of reproductive studies, covering various stages of the reproductive cycle, were carried out in rats, rabbits and mice. Lorazepam was administered orally in doses of up to 50 mg/kg/day. The observed effects in drug-treated groups of all three species included decreased maternal weight gain, increased resorptions, increased incidence of complete litter loss, decreased litter size, increased number of stillborn, increased neonatal mortality and decreased fetal body weight. Major and minor malformations, including cleft palate, hindlimb malrotation, extra 13th ribs, gastroschisis and major skull deficiency, were noted in rabbit and mouse experiments; some of these were qualitatively similar and/or dose related, and possibly drug induced.

Developmental Neurotoxicity: Nonclinical research has shown that administration of anesthetic and sedation drugs that block N-methyl-D-aspartate (NDMA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity can increase neuronal cell death in the brain and result in long term deficits in cognition and behavior of juvenile animals when administered during the period of peak brain development. Based on comparisons across nonclinical species, the window of vulnerability of the brain to these effects is believed to correlate with human exposures in the third trimester of pregnancy through the first year of life, but may extend to approximately 3 years of age. While there is limited information of this effect with lorazepam, since the mechanism of action includes potentiation of GABA activity, a

similar effect may occur. The relevance of these nonclinical findings to human use is unknown.

Injectable. Lorazepam, intravenously administered, was studied in rats and rabbits for its possible impact on reproduction and fetal development. Injectable lorazepam was associated to some extent with the number of resorptions, litter sizes and weights in both species, but these effects were neither consistent nor dose related.

In rats and rabbits, injectable lorazepam was not teratogenic.

17 SUPPORTING PRODUCT MONOGRAPHS

ATIVAN® (Tablets, 0.5 mg, 1 mg and 2 mg), submission control #267182, Product Monograph, Pfizer Canada ULC. (DEC 28, 2022)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

TEVA-LORAZEPAM

lorazepam oral tablets

Read this carefully before you start taking **TEVA-LORAZEPAM** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TEVA-LORAZEPAM**.

Serious Warnings and Precautions

Addiction, Abuse and Misuse:
Even if you take TEVA-LORAZEPAM exactly as you are told, you are at risk for abuse, misuse and addiction, physical dependence and withdrawal. Abuse and misuse can result in overdose or death, especially if you take TEVA-LORAZEPAM with:

- opioids
- alcohol or
- illicit drugs

Your healthcare professional should:

- talk to you about the risks of treatment with TEVA-LORAZEPAM as well as other treatment (including non-drug) options
- assess your risk for these behaviours before prescribing TEVA-LORAZEPAM
- monitor you while you are taking TEVA-LORAZEPAM for the signs and symptoms of misuse and abuse. IF you feel like you are craving TEVA-LORAZEPAM, or not using it as directed, talk to your healthcare professional right away.

Store TEVA-LORAZEPAM in a secure place to avoid theft or misuse.

Withdrawal:
If you suddenly stop taking TEVA-LORAZEPAM, lower your dose too fast, or switch to another medication, you can experience severe or life-threatening withdrawal symptoms (see Other warnings you should know about).

- Always contact your healthcare professional before stopping or lowering your dose of TEVA-LORAZEPAM or changing your medicine

TEVA-LORAZEPAM with Opioids:
Taking TEVA-LORAZEPAM with opioid medicines can cause:

- severe drowsiness
- decreased awareness
- breathing problems
- coma
- death

What is TEVA-LORAZEPAM used for?

TEVA-LORAZEPAM is used in adults for:

- the short-term relief of severe anxiety symptoms in people with anxiety

TEVA-LORAZEPAM is not recommended for mild to moderate anxiety and tension associated with the stresses of everyday life.

If you are 65 years or older, talk to your healthcare professional before starting TEVA-LORAZEPAM. TEVA-LORAZEPAM may not be an effective treatment for you and you may be more sensitive to experiencing side effects.

How does TEVA-LORAZEPAM work?

TEVA-LORAZEPAM is a benzodiazepine with sedative (calming) properties which help in the treatment of anxiety.

Wh**at are the ingredients in TEVA-LORAZEPAM?**

Medicinal ingredients: Lorazepam.

Non-medicinal ingredients:

TEVA-LORAZEPAM oral tablets: Each 0.5 mg, 1 mg, 2 mg TEVA-LORAZEPAM oral tablet contains: Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose, Sodium Lauryl Sulfate and Starch.

TEVA-LORAZEPAM comes in the following dosage forms:

0.5 mg, 1 mg and 2mg Oral Tablets.

Do not use TEVA-LORAZEPAM if you:

- are allergic to the group of medicines known as benzodiazepines (such as diazepam, clonazepam, chlordiazepoxide, bromazepam or flurazepam)
- are allergic to lorazepam or any of the other ingredients in TEVA-LORAZEPAM (see What are the ingredients in TEVA-LORAZEPAM)
- have myasthenia gravis (a chronic disease with muscle weakness)
- have acute narrow angle glaucoma (a disease of the eye which causes progressive vision loss)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-LORAZEPAM. Talk about any health conditions or problems you may have, including if you:

- have ever had a problem with:
  - substance use, including prescribed or illegal drugs, or
  - alcohol
- have ever had seizures or convulsions (violent uncontrollable shaking of the body with or without loss of consciousness)
- have a lung disease or breathing problems (such as chronic obstructive pulmonary disease (COPD), sleep apnea syndrome)
- have a history of depression, suicide attempts or a mental health problem called psychosis
- have liver problems
- have kidney problems

Other warnings you should know about:

Severe Allergic Reactions: Taking TEVA-LORAZEPAM can cause severe allergic reactions that can lead to death. For symptoms of severe allergic reactions, see the **Serious side effects and what to do about them** table (below).

Driving and Using Machines: TEVA-LORAZEPAM may affect your ability to be alert. Do NOT drive or operate machinery while you are taking TEVA-LORAZEPAM:

- until you know how ATIVAN affects you
- for the first few days after you start or change dose
- If you are taking an opioid or drink alcohol

Addiction, Abuse and Misuse: Taking TEVA-LORAZEPAM can lead to physical dependence, abuse and misuse, even if you take it as directed. See the **Serious Warnings and Precautions** box (above).

Behavioural Problems: Changes in thinking and behaviour may happen when you take TEVA-LORAZEPAM. This can include aggressiveness, extroversion, confusion, strange behaviour, restlessness, illusions, hallucinations, feeling like you are not yourself, worsening of insomnia or worsening of depression including suicidal thinking. If you develop any unusual or disturbing thoughts or behavior while taking TEVA-LORAZEPAM, talk to your healthcare professional immediately.

Pregnancy: Do not take TEVA-LORAZEPAM if you are pregnant. TEVA-LORAZEPAM may harm your unborn baby. It may also cause side effects and withdrawal symptoms in your baby after birth. Talk to your healthcare professional if you think you are pregnant or become pregnant while taking TEVA-LORAZEPAM.

Breastfeeding: TEVA-LORAZEPAM passes into breast milk. You should not breastfeed while taking TEVA-LORAZEPAM. Talk to your healthcare professional about the best way to feed your baby while you are taking TEVA-LORAZEPAM.

Withdrawal: If you suddenly stop your treatment, lower your dose too fast, or switch to another medication, you can experience withdrawal symptoms that can range from mild symptoms to severe or life threatening. Some of your withdrawal symptoms can last for months after you stop TEVA-LORAZEPAM.
Your risk of going through withdrawal is higher if you are taking TEVA-LORAZEPAM for a long time or at high doses. However, symptoms can still occur if you are taking TEVA-LORAZEPAM as directed for a short period of time or slowly reducing the dose.
The symptoms of withdrawal often resemble the condition that you are being treated for. After stopping your treatment, it may be hard to tell if you are experiencing withdrawal or a return of your condition (relapse).
Tell your healthcare professional **right away** if you experience any symptoms of withdrawal after changing or stopping your treatment.

Severe symptoms of withdrawal include:

- feeling like you cannot move or respond (catatonia)
- severe confusion, shivering, irregular heart rate and excessive sweating (delirium tremens)
- feeling depressed
- feeling disconnected from reality (dissociation)
- seeing or hearing things that are not there (hallucinations)
- overactive behavior and thoughts (mania)
- believing in things that are not true (psychosis)
- convulsions (seizures), including some that do not stop
- thoughts or actions of suicide

For other symptoms of withdrawal, see the **Serious side effects and what to do about them** table (below).
To reduce your chances of going through withdrawal:

- always contact your healthcare professional before stopping or reducing your dose of TEVA-LORAZEPAM or changing medications
- always follow your healthcare professional's instructions on how to reduce your dose carefully and safely
- tell your healthcare professional **right away** if you experience any unusual symptoms after changing or stopping your treatment

TEVA-LORAZEPAM with Opioids: Taking TEVA-LORAZEPAM with opioid medicines can cause severe drowsiness and breathing problems.

Tell your healthcare professional if you:

- are taking opioid medicines
- are prescribed an opioid medicine after you start taking TEVA-LORAZEPAM

Falls and Fractures: Benzodiazepines like TEVA-LORAZEPAM can cause you to feel sleepy, dizzy and affect your balance. This increases your risks of falling, which can cause fractures or other fall related-injuries, especially if you:

- take other sedatives
- drink alcohol
- are elderly or
- have a condition that causes weakness or frailty

Blood Tests: TEVA-LORAZEPAM can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Taking TEVA-LORAZEPAM and opioids may cause:

- severe drowsiness
- trouble breathing
- coma
- death

The following may interact with TEVA-LORAZEPAM:

- medicines used to treat anxiety and insomnia
- sedative/hypnotics (sleeping pills)
- monoamine oxidase inhibitors (MAOIs) and other antidepressants
- medicines used to treat mental health problems such as haloperidol, clozapine
- narcotic analgesics (pain relievers, opioids), see **Serious Warnings and Precautions** box (above)
- allergy medication
- medicines used to prevent seizures such as valproate
- anesthetics, used during surgery
- probenecid, used to treat gout
- medicines used to treat breathing problems such as theophylline, aminophylline

Do not take TEVA-LORAZEPAM if you drink alcohol.

How to take TEVA-LORAZEPAM:

- Always take TEVA-LORAZEPAM exactly as your healthcare professional tells you to. Your healthcare professional will prescribe the dose that is right for you depending on your medical condition and how you respond to TEVA-LORAZEPAM.
- Do not change your dose without taking to your healthcare professional.
- Your healthcare professional will tell you when to stop taking TEVA-LORAZEPAM. Always follow your healthcare professional's instructions on how to lower your dose carefully and safely to avoid experiencing withdrawal symptoms.

Usual adult dose:

Anxiety problems: 2 - 3 mg per day, in divided doses. Maximum: 6 mg per day.

Before surgery: Your healthcare professional will decide on the dose that is best for you based on your weight.

If you are 65 years of age or older you may be more sensitive to the effects of TEVA-LORAZEPAM. Your healthcare professional might prescribe you a lower dose.

Overdose:

If you think you, or a person you are caring for, have taken too much TEVA-LORAZEPAM, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of TEVA-LORAZEPAM, contact your healthcare professional for instructions.

What are possible side effects from using TEVA-LORAZEPAM?

These are not all the possible side effects you may have when taking TEVA-LORAZEPAM. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- drowsiness
- dizziness
- confusion
- weakness and unsteadiness
- falls and fractures
- memory loss

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Behavioural Problems: aggression, rage, sudden anxiety or excitation; restlessness, agitation, irritability; hallucinations (see or hear things that are not there) or delusions; severe sleep disturbances, nightmares, inappropriate behavior		**√**	
Severe Allergic Reactions: red skin, hives, itching, swelling of the lips, face, tongue, throat, trouble breathing, wheezing, shortness of breath, skin rashes, blisters of the skin, sores or pain in the mouth or eyes, nausea, vomiting			**√**
Myasthenia Gravis: muscle weakness, drooping eyelid, vision changes, difficulty chewing and swallowing, trouble breathing			√
Liver Problems: abdominal pain, nausea, vomiting, yellowing of skin and eyes, dark urine		√	
RARE			
Depression: difficulty sleeping, changes in weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family gatherings and activities with friends, reduced libido (sex drive), and thoughts of death or suicide		√	
UNKNOWN			
Overdose: extreme sleepiness, confusion, slurred speech, slow reflexes, slow shallow breathing, coma, loss of balance and coordination, uncontrolled rolling of the eyes, low blood pressure			√
Respiratory Depression: slow, shallow or weak breathing			√
Withdrawal: Severe symptoms include: **Catatonia**: feeling like you cannot move or respond **Delirium Tremens**: severe confusion, shivering, irregular heart rate and excessive sweating **Feeling depressed** **Dissociation**: feeling disconnected from reality **Hallucinations**: seeing or hearing things that are not there **Mania**: overactive behaviour and thoughts **Psychosis**: Believing in things that are not true **Convulsions**: (seizures – including some that do		√	

not stop): loss of consciousness with uncontrollable shaking **Thoughts or actions of suicide** **Other symptoms includ**e: Stomach and muscle cramps; trouble remembering or concentrating; diarrhea; feeling uneasy or restless; severe anxiety or panic-attacks; headache; sensitivity to light, noise or physical contact; shaking; vomiting; trouble sleeping; feeling irritable; muscle pain or stiffness; a burning or prickling feeling in the hands, arms, legs or feet; sweating			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Bottles: Store at controlled room temperature (15°C - 30 °C).
Unite Dose (blister): Store between 15°C - 25°C.
Keep out of reach and sight of children.

If you want more information about TEVA-LORAZEPAM:

- Talk to your healthcare professional
  - Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario, M1B 2K9

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