PRODUCT MONOGRAPH

pms-LORAZEPAM
Lorazepam Tablets, USP
0.5 mg, 1 mg and 2 mg

Anxiolytic-Sedative

PHARMASCIENCE INC.
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H4P 2T4

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ACTION AND CLINICAL PHARMACOLOGY

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of pms-LORAZEPAM and opioids may result in profound sedation, respiratory depression, coma, and death (see WARNINGS-Risks from concomitant use of opioids and benzodiazepines).

- 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.

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.

Lorazepam has also been shown to possess anticonvulsant activity.

Lorazepam is rapidly absorbed after oral administration, with mean peak plasma concentrations of free lorazepam at 2 hours (range between 1-6 hours).

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.

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

Anterograde amnesia, a lack of recall of events during period of drug action, has been reported and appears to be dose-related.
A bioavailability study comparing two different formulations of lorazepam was performed. Pharmacokinetic and bioavailability data of pms-LORAZEPAM were measured from volunteers in the fasting state after a single 4 mg (2 x 2 mg tablets) dose of pms-LORAZEPAM was administered. The results can be summarized as follows:

Lorazepam (2 x 2 mg tablets) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test***	**Reference†**	**Ratio of Geometric Mean**	**Confidence Interval 90%**
AUC_T (ng.h/mL)	611.66 637.69 (31.1)	577.73 601.05 (29.9)	106	102-110
AUC_I (ng.h/mL)	657.18 686.43 (31.7)	620.08 645.16 (30.0)	106	102-110
C_{MAX} (ng.h/mL)	35.26 35.57 (13.3)	32.52 32.80 (13.7)	108	---
T_{MAX}§ (h)	1.80 (44.8)	2.40 (48.7)	---	---
$T_{1/2}$ (h)	14.84 (22.2)	14.09 (25.0)	---	---

* pms-LORAZEPAM 2 mg tablet (Pharmascience Inc.)
† ATIVAN® 2 mg tablets (Wyeth-Ayerst Canada Inc.), were purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only.
2 Expressed as the arithmetic mean (CV%) only.

INDICATIONS AND CLINICAL USE

pms-LORAZEPAM (lorazepam) is useful for the short-term relief of manifestations of excessive anxiety in patients with anxiety neurosis.

It is also useful as an adjunct for the relief of excessive anxiety that might be present prior to surgical interventions.

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

CONTRAINDICATIONS

pms-LORAZEPAM (lorazepam) is contraindicated in patients with myasthenia gravis or acute narrow angle glaucoma, and in those with known hypersensitivity to benzodiazepines.

WARNINGS

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.

pms-LORAZEPAM (lorazepam) is not recommended for the use in depressive neurosis or in psychotic reactions. Because of the lack of sufficient clinical experience, lorazepam is not recommended for use in patients less than 18 years of age (see PRECAUTIONS). Since lorazepam has a central nervous system depressant effect, patients should be advised against the simultaneous use of other CNS depressant drugs. Patients should also be cautioned not to take alcohol during the administration of lorazepam because of the potentiation of effects that may occur.

Excessive sedation has been observed with lorazepam at standard therapeutic doses. Therefore, patients on pms-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 with any premedicant, extreme care must be used in administering pms-LORAZEPAM to elderly or very ill patients and to those with limited pulmonary reserve, because of the possibility that apnea and/or cardiac arrest may occur.

There is no evidence to support the use of lorazepam in coma, shock or acute alcohol intoxication at this time. When pms-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.

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.

Risks from concomitant use of opioids and benzodiazepines:
Concomitant use of benzodiazepines, including lorazepam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patents 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 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 opioid analgesics.

If a decision is made to prescribe pms-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 pms-LORAZEPAM than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking 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 DRUG INTERACTIONS).

Advise both patients and caregivers about the risks of respiratory depression and sedation when pms-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.

Use in Pregnancy:

pms-LORAZEPAM (lorazepam) should not be used during pregnancy. Several studies have suggested an increased risk of congenital malformations associated with the use of the benzodiazepines chlordiazepoxide and diazepam, and meprobamate, during the first trimester of pregnancy.

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.

Use in Nursing Mothers:

Lorazepam has been detected in human breast milk; therefore it should not be administered to breast-feeding 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).

PRECAUTIONS

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

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

lorazepam. The use of benzodiazepines may unmask suicidal tendencies in depressed patients and should not be used without adequate antidepressant therapy.

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

Use in the Elderly:

Elderly 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.

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

Dependence Liability:

pms-LORAZEPAM (lorazepam) should not be administered to individuals prone to drug abuse. Lorazepam may have abuse potential, especially in patients with a history of drug and/or alcohol abuse.

Caution should be observed in patients who are considered to have potential for psychological dependence. It is suggested that the drug should be withdrawn gradually if it has been used in high dosage.

The use of benzodiazepines, including lorazepam, may lead to physical and psychological dependence. The risk of dependence increases with higher doses and longer term use and is further increased in patients with a history of alcoholism or drug abuse or in patients with significant personality disorders. The dependence potential is reduced when lorazepam is used at the appropriate dose for short-term treatment. In general, benzodiazepines should be prescribed for short periods only (e.g., 2 to 4 weeks). Continuous long-term use of lorazepam is not recommended.

Use in Mental and Emotional Disorders:

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

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 pms-LORAZEPAM be used in patients with mild to moderate hepatic or renal disease. In patients for whom prolonged therapy with pms-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.

DRUG INTERACTIONS

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 pms-LORAZEPAM (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.

Opioids:

Due to additive CNS depressant effect, the concomitant use of benzodiazepines, including pms-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 Serious Warning and Precautions box, and WARNINGS-Risks from concomitant use of opioids and benzodiazepines).

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.

pms-LORAZEPAM (lorazepam) produces depression of the CNS when administered with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants.

ADVERSE REACTIONS

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, 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;

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.

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 to 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 to 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 immediately.

DOSAGE AND ADMINISTRATION

Dosage:
The dosage and duration of therapy of pms-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 lowest effective dose of pms-LORAZEPAM should be prescribed for the shortest duration possible. The risk of withdrawal and rebound phenomena is greater after abrupt discontinuation; therefore the drug should be discontinued gradually. Withdrawal symptoms (e.g., rebound insomnia) can appear following cessation of recommended doses after as little as one week of therapy. Abrupt discontinuation of lorazepam should be avoided and a gradual, dose-tapering schedule followed after extended therapy.

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

Generalized Anxiety Disorder:
The recommended initial adult daily oral dosage is 2 mg in divided doses of 0.5 mg, 0.5 mg 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 elderly 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.

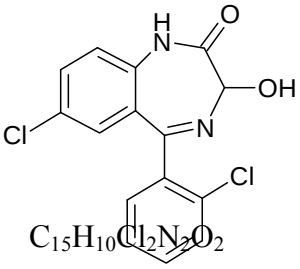
PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: Lorazepam

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

Structural Formula:



Molecular Formula: $C_{15}H_{10}Cl_2N_2O_2$

Molecular Weight: 321.16 g/mol

Description: Lorazepam is a white or practically white, practically odorless powder. It is insoluble in water; sparingly soluble in alcohol; slightly soluble in chloroform.

Melting point: 166-168°C

pK values: pK_1: 13 pK_2: 11.5

Composition:

pms-LORAZEPAM (Lorazepam tablets) contains the label amount of lorazepam as active ingredient and the following non-medicinal ingredients: Lactose, magnesium stearate, microcrystalline cellulose and polacrilin potassium.

Stability and Storage Recommendations:

pms-LORAZEPAM should be stored between 15°C and 30°C, protected from light.

DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Tablets

0.5 mg: Each white to off-white, flat-face, beveled edge, round tablet, engraved "P" logo on one side and "0.5" on the other side, contains 0.5 mg lorazepam. Supplied in bottles of 100, 500 and 1,000 tablets.

1 mg: Each white to off-white, capsule-shaped, flat-face, beveled edge tablet, engraved "P" logo scored "1" on one side and plain on the other side, contains 1 mg lorazepam. Supplied in bottles of 100, 500, 1,000 and 3,000 tablets.

2 mg: Each white to off-white, oval-shaped flat face beveled edge tablet, engraved "P" logo scored "2" on one side and plain on the other side, contains 2 mg lorazepam. Supplied in bottles of 100, 500 and 1,000 tablets.

DETAILED PHARMACOLOGY

Lorazepam is a benzodiazepine with CNS depressant properties. In laboratory animals, it produces disinhibitory, sedative, anti-convulsant, muscle relaxant, ataxic and hypnotic effects.

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 to 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 to 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 to 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 IV 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.

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 IV 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.

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.

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.

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

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.

TOXICOLOGY

Acute Toxicity:
LD_{50}s ranged from 1,850-5,010 mg/kg in mice to 5,000 mg/kg in rats and 2,000 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.

Long Term Toxicity:
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.

Reproductive Studies:
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 13^{th} 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.

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PART III: CONSUMER INFORMATION

pms-LORAZEPAM
Oral Tablets

This leaflet is part III of a three-part "Product Monograph" published for pms-LORAZEPAM and is designed specifically for Consumers.

Please read this information before you start to take your medicine. Keep this leaflet until you have finished all your tablets, as you may need to read it again. If you are helping someone else to take pms-LORAZEPAM, read this leaflet before you give the first tablet.

This leaflet is a summary and will not tell you everything about pms-LORAZEPAM. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
pms-LORAZEPAM is useful for the short-term relief of manifestations of severe anxiety in people with anxiety neurosis**.**

It is also useful for the relief of excessive anxiety that might be present prior to surgical interventions.

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

What it does:
pms-LORAZEPAM is a benzodiazepine with sedative properties which help in the treatment of anxiety.

When it should not be used:
- If you are allergic to the group of medicines known as benzodiazepines (examples: diazepam, clonazepam, chlordiazepoxide, bromazepam, or flurazepam)
- If you are allergic to any of the ingredients it contains (see "**What the nonmedicinal ingredients are**")
- If you have myasthenia gravis, a chronic disease characterized by weakness of the skeletal muscles.
- If you have acute narrow angle glaucoma (a disease of the eye which causes progressive vision loss).

What the medicinal ingredient is:
Lorazepam

What the nonmedicinal ingredients are:
Each 0.5 mg, 1 mg, 2 mg pms-LORAZEPAM oral tablet contains: Lactose, Magnesium Stearate, Microcrystalline Cellulose, Polacrilin Potassium.

What dosage forms it comes in:
0.5, 1 and 2 mg Oral Tablets.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Taking pms-LORAZEPAM with opioid medicines can cause severe drowsiness, breathing problems, coma, and death.

- **Severe anaphylactic/anaphylactoid allergic reactions have been reported with the use of benzodiazepines. Cases of angioedema (swelling inside the mouth and throat) 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 (difficult respiration), 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 re-start the drug.**
- pms-LORAZEPAM may affect your ability to be alert. Driving, operating machinery and other hazardous activities should therefore be avoided altogether or at least during the first few days of treatment. This effect of pms-LORAZEPAM may be made worse if you take alcoholic drinks. If your doctor has increased your dose or if you have changed the timings of when you take your medication this may also modify your reactions.
- You must not consume alcohol or other drugs that affect the central nervous system while taking pms-LORAZEPAM (see "**INTERACTIONS WITH THIS MEDICATION"** below).
- Benzodiazepines such as pms-LORAZEPAM have produced dependence (addiction) and withdrawal symptoms can occur when treatment is stopped suddenly. The risk of dependence

(addiction) increases with higher doses and longer duration of treatment.
- Always contact your doctor before stopping or reducing your dosage of pms-LORAZEPAM, as suddenly stopping treatment or a large decrease in dose can cause withdrawal symptoms (See Withdrawal-related side effects in the section "**SIDE EFFECTS AND WHAT TO DO ABOUT THEM"** below).
- An increased risk of falls and fractures has been reported in elderly people who take benzodiazepines such as pms-LORAZEPAM.
- Memory loss may occur when pms-LORAZEPAM is used at therapeutic doses.
- A variety of abnormal thinking and behaviour changes may occur when you use a benzodiazepine, including aggressiveness, extroversion, confusion, strange behaviour, restlessness, illusions, hallucinations, feeling like you are not yourself, worsening of insomnia or worsening of depression including suicidal thinking. It is rarely clear whether such symptoms are caused by the medication, by an illness that was present before the medication was used or are simply spontaneous happenings. If you develop any unusual or disturbing thoughts or behavior while using pms-LORAZEPAM, discuss the matter immediately with your doctor.
- pms-LORAZEPAM is not recommended for use in depressive neurosis or in psychotic reactions.
- Certain benzodiazepines have been linked to birth defects when taken during the early months of pregnancy. In addition, benzodiazepines taken during the last weeks of pregnancy have been known to sedate the baby and may also cause withdrawal symptoms after birth. Do not take this medicine if you are pregnant, or might become pregnant, unless advised by your doctor. Contact your doctor if you think you may be pregnant, or are intending to become pregnant.
- pms-LORAZEPAM passes into breast milk. Therefore, if you are breast feeding, this medicine should be avoided. Your doctor will discuss this with you.

BEFORE you use talk to your doctor or pharmacist if:
- You have lung disease or breathing problems (e.g., chronic obstructive pulmonary disease (COPD), sleep apnea syndrome)
- You have a history of depression, suicide attempts or psychosis
- You regularly drink alcohol or use recreational drugs or have a history of dependence /addiction to alcohol or drugs.
- You have liver disease
- You have kidney disease
- You are pregnant or plan on becoming pregnant
- You are breastfeeding.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor if you are taking any other medicines, including medicines you can buy without a prescription and herbal products.

Drugs that may interact with pms-LORAZAPAM include:
- barbiturates
- antipsychotics
- sedative/hypnotics (sleeping pills)
- anxiolytics
- antidepressants
- antipsychotics (including Haloperidol, Clozapine)
- narcotic analgesics (pain relievers) (opioids) (see **Serious Warning and Precautions box**)
- sedative antihistamines (allergy medications)
- anticonvulsants (including Valproate)
- anesthetics
- Probenecid (to reduce uric acid levels)
- Theophylline or aminophylline (respiratory treatments)
- alcohol

Do not take pms-LORAZEPAM if you drink alcohol.
Do not use pms-LORAZEPAM along with other medications without first discussing this with your doctor.

PROPER USE OF THIS MEDICATION

Always take the tablets exactly as your doctor tells you to. Your doctor will prescribe a suitable dose for you. The dose your doctor prescribes will depend on your illness and how you respond to the medicine. The table below shows the different doses that your doctor may prescribe according to your illness.

	Usual Daily Dose
Generalized anxiety disorders	0.5-2 mg, two to three times per day. Maximum 6 mg/day.

The total daily dose should be taken as advised by your doctor.

Do not change the prescribed dose yourself. If you think the effect of your medicine is too weak or too strong, talk to your doctor.

Do not take pms-LORAZEPAM if it is not prescribed for you.

Your doctor will advise you when to stop taking the medicine. Your doctor will slowly decrease the dosage as sudden discontinuation of treatment can cause the appearance of withdrawal symptoms.

Because elderly patients can be more sensitive to the effects of pms-LORAZEPAM, lower doses may be prescribed.

pms-LORAZEPAM is not for use in children under 18 years of age.

Overdose:

If you think you have taken too much pms-LORAZEPAM contact your doctor, nurse, pharmacist, hospital emergency department, or regional Poison Control Centre immediately, even if there are no symptoms.

Contact your doctor, regional Poison Control Centre or pharmacist immediately if you suspect you have taken an overdose or someone else accidentally takes your pms-LORAZEPAM. If you are unable to contact them, go to a hospital emergency department for medical help, even though you may not feel sick. Show the doctor your bottle of tablets.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The adverse reaction most frequently reported for lorazepam was drowsiness. Dizziness, weakness and unsteadiness were also common.

Release of hostility and other paradoxical effects such as irritability and excitability, are known to occur with the use of benzodiazepines. Please tell your doctor right away if you feel these effects when taking pms-LORAZEPAM. Paradoxical reactions may be more likely to occur in children or the elderly. In addition, hypotension (low blood pressure), mental confusion, slurred speech, over sedation and abnormal laboratory test results indicating changes in the liver, kidney and blood cells have been reported with these drugs.

If you develop symptoms of myasthenia gravis or the symptoms of your existing myasthenia gravis worsen, tell your doctor right away. These symptoms could include muscle weakness that gets worse with activity and gets better with rest, drooping eyelid, blurred or double vision, difficulty chewing and swallowing, or trouble breathing.

Withdrawal-related side effects:

- With sudden discontinuation of treatment with pms-LORAZEPAM symptoms of withdrawal may occur, including: headache, muscle pain, convulsions, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases of withdrawal, symptoms may include numbness and tingling of the extremities, hallucinations, increased sensitivity to light, noise and physical contact and seizures.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/ effect		Talk with your doctor or pharmacist right away		Stop taking drug and seek immediate emergency help
		Only if severe	In all cases	
Uncommon	Unusual 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		√	
	Anaphylactic /anaphylactoid reactions, severe allergic reactions (red			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/ effect		Talk with your doctor or pharmacist right away		Stop taking drug and seek immediate emergency help
		Only if severe	In all cases	
	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)			
Uncommon	Myasthenia gravis (muscle weakness, drooping eyelid, vision changes, difficulty chewing and swallowing, trouble breathing)			√
	Liver disorder (symptoms include abdominal pain, nausea, vomiting, yellowing of skin and eyes, dark urine)		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/ effect		Talk with your doctor or pharmacist right away		Stop taking drug and seek immediate emergency help
		Only if severe	In all cases	
Rare	Depression. Symptoms, may include: 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.		√	

This is not a complete list of side effects. For any unexpected effects while taking pms-LORAZEPAM, contact your doctor or pharmacist.

HOW TO STORE IT

Store pms-LORAZEPAM between 15°C and 30°C, protected from light.

Keep out of reach and sight of children.

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (http://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.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be obtained by contacting Pharmascience Inc. at 1-888-550-6060.

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