PRESCRIBING INFORMATION

NTP-LORAZEPAM
(Lorazepam)

Oral Tablets

Anxiolytic - Sedative

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ACTION

NTP-LORAZEPAM (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). 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.

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.

INDICATIONS AND CLINICAL USE

NTP-LORAZEPAM (lorazepam) is useful 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.

CONTRAINDICATIONS

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

WARNINGS

NTP-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 NTP-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 NTP-LORAZEPAM should be warned against engaging in hazardous activities requiring mental alertness and motor coordination, such as operating dangerous machinery or driving motor vehicles.

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

Use in Pregnancy: The safety of the use of lorazepam in pregnancy has not been established. NTP-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. 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: NTP-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., 2-4 weeks). Continuous long-term use of lorazepam is not recommended.

Use in Mental and Emotional Disorders: NTP-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 NTP-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 NTP-LORAZEPAM be used in patients with mild to moderate hepatic or renal disease. In patients for

whom prolonged therapy with NTP-LORAZEPAM is indicated, periodic blood counts and liver function tests should be carried out.

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 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.

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.

ADVERSE REACTIONS

The adverse reaction most frequently reported was drowsiness.

Reported adverse reactions (by system) are:

Body as a Whole
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, 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.

SYMPTOMS AND TREATMENT OF 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.

DOSAGE AND ADMINISTRATION

DOSAGE: The dosage and duration of therapy of NTP-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 NTP-LORAZEPAM (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, 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 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.

AVAILABILITY OF DOSAGE FORMS

Small, round, white, flat with bevelled-edge, compressed tablets. Engraved N on one side, 0.5 on the reverse. Each NTP-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 NTP-LORAZEPAM tablet contains lorazepam 1.0 mg. Available in bottles of 100 and 1000.

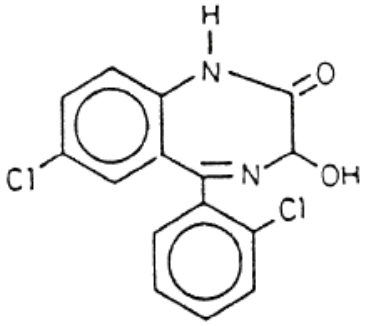
White, oval-shaped, flat with beveled-edge, compressed tablets. Engraved N, vertical scoreline and 2 on one side, plain on the reverse. Each NTP-LORAZEPAM tablet contains lorazepam 2.0 mg. Available in bottles of 100 and 1000.

Store at controlled room temperature (15-30^{o}C).

Non-Medicinal Ingredients:
Each 0.5 mg, 1 mg, 2 mg NTP-LORAZEPAM tablet contains:
Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose,
Sodium Lauryl Sulfate and Starch.

PHARMACOLOGY

NTP-LORAZEPAM (lorazepam) is chemically 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one has the following structural formula:



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 2-5 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 behavior 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 behavior 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.

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.

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 labeled 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: 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, all serum 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 behavior 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 emnesis, 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.

Reproductive Studies: 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 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, hind limb 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.

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.

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