

PRODUCT MONOGRAPH

APO-LORATADINE

Loratadine Tablets USP

10 mg

Histamine H₁ Receptor Antagonist

**APOTEX INC.
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Toronto, Ontario
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APO-LORATADINE

loratadine Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	Tablet / 10 mg	colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

INDICATIONS AND CLINICAL USE

APO-LORATADINE (loratadine) Tablets are indicated for:

- the relief of symptoms associated with seasonal and perennial allergic rhinitis, such as sneezing, nasal discharge and itching, and ocular itching and burning.
- the relief of symptoms and signs of chronic urticaria and other allergic dermatologic disorders.

Clinical studies to date support treatment for up to six months, thus medical recommendation is advised for longer-term use. APO-LORATADINE is not recommended for pregnant or lactating women.

Geriatrics:

The pharmacokinetic parameters of loratadine and its major metabolite are comparable in healthy adult volunteers and healthy geriatric volunteers. (See DETAILED PHARMACOLOGY / Pharmacokinetics and Metabolism).

Pediatrics (2 to 12 years of age):

In children, it is intended for short-term use only unless taken under medical supervision.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug, or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Hepatic/Biliary/Pancreatic

Patients with severe liver impairment should be administered a lower initial dose because they may have reduced clearance of loratadine; an initial dose of 5 mg once daily or 10 mg every other day is recommended.

Special Populations

Pregnant Women: The safe use of loratadine during pregnancy has not been established and is therefore not recommended.

Nursing Women: The safe use of loratadine during lactation has not been established and is therefore not recommended. (See DETAILED PHARMACOLOGY / Human Pharmacology for information on secretion into breast milk).

Pediatrics (2 to 12 years of age): The safety and efficacy of loratadine in children younger than 2 years of age have not been established. Long-term safety and efficacy of loratadine in children between the ages of 2 and 12 has not been demonstrated. Therefore, it is desirable that loratadine not be administered to children between the ages of 2 and 12 for longer than 14 days, unless recommended by a physician.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse experiences reported with loratadine in adults during clinical trials were mild and consisted of fatigue, headache, dry mouth, sedation, gastrointestinal disorders such as nausea, gastritis, and also allergic symptoms like rash.

Nervousness and hyperkinesia were among the reported adverse experiences in pediatric patients. Gastrointestinal adverse reactions reported during pediatric trials may have been slightly more frequent in the younger patients (less than or equal to 30 kg).

During the marketing of loratadine, alopecia, anaphylaxis, abnormal hepatic function, dizziness, palpitations and tachycardia have been reported rarely.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information, from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1: Loratadine Tablets, 10 mg Once Daily vs. Placebo and Comparatives

Number (%) of Adult Patients Reporting Frequently Occurring (>2% of loratadine treated patients) Adverse Experiences in Adults Possibly or Probably Related to Treatment: Patients Treated with Loratadine, Placebo and Comparatives

	Loratadine 10mg QD	Placebo	Clemastine 1mg BID	Terfenadine 60mg BID	Astemizole 10mg OD
	n = 1241	n = 1652	n = 687	n = 506	n = 342
Adverse Experience					
Fatigue	54(4)	62(4)	62(9)	17(3)	22(6)
Headache	97(8)	104(6)	32(5)	40(8)	26(7)
Dry Mouth	49(4)	32(2)	22(3)	15(3)	2(1)
Dryness in Nose	9(<1)	-	6(<1)	3(<1)	-
Sedation*	99(8)	101(6)	151(22)	41(8)	50(15)

*Reported as somnolence, sleepiness, drowsiness, lethargy, slow or "drugged feeling"

Adverse experiences reported with loratadine conventional tablets in adults during the clinical trials were mild and consisted of fatigue, headache, dry mouth, sedation, gastrointestinal disorders such as nausea, gastritis, and also allergic symptoms like rash. The incidence of sedation was similar to that of the comparative agents terfenadine, astemizole and placebo, but statistically different ($p < 0.01$) from clemastine.

Less Common Clinical Trial Adverse Drug- Reactions (<1%)

In addition to those listed in Table 1, the following were reported less frequently (less than 1%): appetite increased, coughing, dizziness and palpitations.

Abnormal Hematologic and Clinical Chemistry Findings

Not applicable

Post-Market Adverse Drug Reactions

During the marketing of loratadine, in addition to the adverse events reported during clinical trials, alopecia, anaphylaxis (including angioedema), abnormal hepatic function, dizziness, palpitations and tachycardia have been reported rarely. Convulsions and seizures have been reported very rarely.

DRUG INTERACTIONS

Serious Drug Interactions

None to report

Overview

When administered concomitantly with alcohol, loratadine has no potentiating effects as measured by psychomotor performance studies (see DETAILED PHARMACOLOGY / Human Pharmacology).

Drug-Drug Interactions

Increases in plasma concentrations of loratadine have been reported after concomitant use with ketoconazole, erythromycin or cimetidine in controlled clinical trials, but without clinically significant changes (including electrocardiographic). Other drugs known to inhibit hepatic metabolism should be coadministered with caution until definitive interaction studies can be completed.

Drug-Food Interactions

See ACTION AND CLINICAL PHARMACOLOGY / Pharmacokinetics / Absorption.

Drug-Herb Interactions

Interactions with herbs have not been established.

Drug-Laboratory Interactions

Loratadine should be discontinued approximately 48 hours prior to skin testing procedures since antihistamines may prevent or diminish otherwise positive reactions to dermal reactivity indicators.

Drug-Lifestyle Interactions

Interactions with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

Dosing- Considerations

Patients with severe liver impairment: an initial dose of 5 mg once daily or 10 mg every other day is recommended.

Recommended Dose and Dosage Adjustment

APO-LORATADINE should not be administered to children between 2 and 12 years of age for longer than 14 days, unless recommended by a physician.

Adults and Children 12 years of age and over: One APO-LORATADINE tablet, 10 mg, once daily.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Somnolence, tachycardia and headache have been reported with overdoses of the conventional loratadine formulation. A single acute ingestion of 160 mg produced no adverse effects.

In the event of overdosage, treatment, which should be started immediately, is symptomatic and supportive.

Consider standard measures to remove any unabsorbed drug in the stomach, such as adsorption by activated charcoal administered as a slurry with water. The administration of gastric lavage should be considered. Physiologic saline solution is the lavage solution of choice, particularly in children. In adults, tap water can be used; however, as much as possible of the amount administered should be removed before the next instillation. Saline cathartics draw water into the bowel by osmosis, and therefore, may be valuable for their action in rapid dilution of bowel content.

Loratadine is not cleared by hemodialysis to any appreciable extent. It is not known if loratadine is removed by peritoneal dialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Loratadine is a long-acting tricyclic antihistamine with selective peripheral H₁ receptor antagonistic activity. It exhibits a dose-related inhibition of the histamine-induced skin wheal and flare response in humans which is rapid in onset, is apparent at two hours and persists throughout the 24 hour observation period. Single oral doses up to 160 mg and repeat daily doses of 40 mg for up to 13 weeks were well tolerated with the incidence of sedation and dry mouth being no different from placebo.

Loratadine is well absorbed by all species studied and is almost totally metabolized (See DETAILED PHARMACOLOGY / Pharmacokinetics and Metabolism).

Pharmacodynamics

Loratadine has a lower affinity for central receptors than for peripheral receptors, and it does not readily penetrate into the brain tissue. (See DETAILED PHARMACOLOGY / Animal Pharmacology).

Wheal and Flare: The antihistaminic activity and dose-response profile of loratadine were evaluated in three clinical pharmacologic studies using a histamine-induced skin wheal suppression model in healthy male volunteers. All doses were significantly more effective than placebo in suppressing the formation of histamine-induced skin wheals (See DETAILED PHARMACOLOGY / Human Pharmacology).

Alcohol: The ability of healthy male volunteers to concentrate was not impaired by loratadine in combination with alcohol. Loratadine did not potentiate the effects of alcohol on driving performance (See DETAILED PHARMACOLOGY / Human Pharmacology).

Pharmacokinetics

Absorption: ¹⁴C-loratadine is rapidly absorbed reaching C_{max} values (4.7, 10.8 and 26.1 ng/mL) at 1.5, 1.0 and 1.3 hours for the 10, 20 and 40 mg dose, respectively. The loratadine elimination half-life (T-1/2) ranged from 7.8 to 11.0 hours. Descarboethoxyloratadine, the major active metabolite, reached C_{max} values (4.0, 9.9 and 16.0 ng/mL) at 3.7, 1.5 and 2.0 hours after a dose of 10, 20 and 40 mg, respectively. Its T-1/2 ranged from 17 to 24 hours. The accumulation indices, calculated by C_{max} and the area under the curve (AUC) ratios did not change after the 5th day, indicating little or no accumulation of either loratadine or its

metabolite after a multiple once per day dosage regimen. The T-1/2 at steady state levels for loratadine and its metabolite were 14.4 and 18.7 hours, respectively, similar to that reported following a single oral dose.

Table 2: Mean (n=18) pharmacokinetic parameters for loratadine and descarboethoxyloratadine

Parameter	Mean (%CV)	
	Loratadine Tablets USP, 10 mg	
	Loratadine	DCL*
C _{max} (ng/ml)	2.11 (90)	3.66 (45)
T _{max} (hr)	1.00 (34)	1.97 (98)
AUC (l) (ng.hr/ml)	4.64 (106)	48.4 (44)

* DCL: Descarboethoxyloratadine

After administration of a single 10 mg, dose of loratadine as a conventional tablet, peak plasma concentrations of loratadine and its metabolite were achieved at approximately 1 and 2 hours, respectively; mean elimination half-life of the active metabolite ranged between 19 and 21 hours.

Since loratadine is extensively metabolized there was a high inter-subject variability in the plasma drug concentrations. Hence, the percent CV of the pharmacokinetic parameters was large.

Table 3: Loratadine, administered as 10 mg Tablet (Conventional Tablet) to healthy subjects (n=24) once daily for 10 days

Parameter	Mean (%CV)					
	Loratadine			DCL*		
	Day 5	Day 7	Day 10	Day 5	Day 7	Day 10
Loratadine Tablet USP, 10 mg (Conventional tablet)						
C _{max} (ng/ml)	3.12 (77)	3.43 (64)	3.81 (67)	4.56 (63)	5.12 (68)	4.60 (81)
AUC(r) ^a (ng.hr/ml)	10.6 (67)	11.6 (61)	11.3 (64)	75.4 (94)	85.0 (99)	73.5 (114)

* DCL: Descarboethoxyloratadine

a: Area under the plasma concentration-time curve from time 0 to 24 hr (for day 10, using concentration time points matching those on day 5 and 7)

Following administration of 10 mg of loratadine once daily for 10 days as a conventional tablet, plasma concentrations of loratadine and its active metabolite were at steady state by day 5. Mean peak plasma concentrations (T_{max}) of loratadine and its metabolite were attained at 1.3 hours; peak to trough fluctuations observed were similar with respect to loratadine and its metabolite. Mean elimination half-life of the active metabolite was 20 hours.

Excretion: Approximately 82% of the ¹⁴C-loratadine dose is excreted in the urine (40%) and faeces (42%) over a 10-day period. Approximately 27% of the dose, eliminated during the first 24 hours is present only in trace quantities in the urine. The active metabolite, descarboethoxyloratadine, represents only 0.4 to 0.6% of the administered loratadine dose.

Special Populations and Conditions

Geriatrics: The pharmacokinetic parameters of loratadine and its major metabolite are comparable in healthy adult volunteers and healthy geriatric volunteers. (See DETAILED PHARMACOLOGY / Pharmacokinetics and Metabolism)

STORAGE AND STABILITY

Temperature and Moisture

Store between 15°C and 30°C. Protect from exposure to excessive moisture.

Others

Keep in a safe place out of reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

none

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-LORATADINE Tablets 10 mg: Each white, oval, biconvex tablet, scored and engraved 'LO' over '10' on one side and 'APO' on the other, contains 10 mg loratadine (as base). Available in bottles of 100, unit dose blister packages of 2, 6, 10, 12, 18, 20, 24, 30, 36, 48, 50, 60, 72 and 100.

In addition to loratadine, each tablet contains the non-medicinal ingredients colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

PART II: SCIENTIFIC INFORMATION

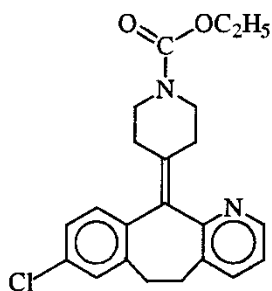
PHARMACEUTICAL INFORMATION

Drug Substance

Common name: loratadine (INN, USAN)

Chemical name: 1 -Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11 H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-ylidene)-,ethyl ester.

Structural formula:



Molecular formula: C₂₂H₂₃ClN₂O₂

Molecular weight: 382.89 g/mol

Description: Loratadine is a white to off-white powder which melts between 132.0°C and 137.0°C.

CLINICAL TRIALS

Comparative Bioavailability

A comparative bioavailability study was performed using 48 healthy human volunteers. The rate and extent of absorption of loratadine were measured and compared following administration of single 40 mg oral doses of Apo-Loratadine (four 10 mg tablets) or Claritin (four 10 mg tablets). Statistical analysis was conducted on data from the 46 volunteers who completed the study, and the results are summarized as follows:

Summary Table of the Comparative Bioavailability Data Loratadine (4 x 10 mg) From Measured Data/Fasting Conditions Geometric Mean ^{##} Arithmetic Mean (CV%)				
Parameter	Apo-Loratadine	Claritin® [†]	Ratio of Geometric Means (%) ^{##}	90% Confidence Interval (%) ^{##}
AUC _T (ng•h/mL)	29.4 44.4 (95)	27.6 39.9 (90)	106.6	96.4 – 117.8
AUC _I (ng•h/mL)	30.9 46.5 (94)	28.9 41.7 (90)	106.7	96.8 – 117.7
C _{max} (ng/mL)	10.0 15.3 (100)	9.38 13.9 (103)	106.5	92.9 – 122.2
T _{max} [#] (h)	1.19 (36)	1.33 (45)		
T _{1/2} [#] (h)	9.72 (72)	8.72 (74)		

[#] Arithmetic means (CV%) only.

^{##} Based on the least squares estimate.

[†] Claritin® is manufactured by Schering Canada Inc., and was purchased in Canada.

DETAILED PHARMACOLOGY

Animal Pharmacology:

Loratadine is an orally effective antihistamine in both mice and guinea pigs. The oral PD₅₀^{*} value for preventing histamine-induced lethality in guinea pigs is 0.19 mg/kg for loratadine compared to 0.009 mg/kg for azatadine (which of the marketed antihistamines is most closely related in structure to loratadine), and 0.15 mg/kg for chlorpheniramine. In terms of duration of antihistamine action, loratadine at twice its antihistamine PD₅₀ (0.5 mg/kg) is longer acting (duration: 18 to 24 hours) than an equi-effective dose of azatadine (duration 8 to 12 hours). For preventing histamine-induced paw edema in mice, loratadine has an oral PD₅₀ value of 1.3 mg/kg compared to 0.068 mg/kg for azatadine and 9.6 mg/kg for chlorpheniramine. On the

basis of these two tests of antihistamine activity, loratadine is at least equipotent to chlorpheniramine but less potent than azatadine. Loratadine also exhibited antihistamine activity when tested *in vitro* against histamine-induced contraction of the guinea pig ileum. In this test, loratadine (pA_2^\dagger : 7.3) was less potent than azatadine (pA_2 : 9.1) or chlorpheniramine (pA_2 : 9.6).

* Dose that provides protection in 50% of animals tested.

$^\dagger pA_2$ = the negative logarithm of the concentration of the antagonist

Because there is no single laboratory test which itself can be considered predictive of the sedating effects of antihistamines, a multidimensional approach was used to assess the CNS activity of loratadine with several standard antihistamines.

In contrast to the standards, loratadine had only weak or no CNS activity in mice, rats, dogs and monkeys after oral administration. These observations included: a lack of effect vs. acetic acid writhing and electroconvulsive shock (ECS) seizures in mice at doses up to 320 mg/kg, no overt behavioral, neurologic or autonomic effects in mice or rats after doses of 10 to 300 mg/kg, in dogs at doses of 15 to 30 mg/kg and in monkeys at doses of 30 to 60 mg/kg.

Ex vivo studies indicate that loratadine does not readily penetrate into the CNS. Loratadine exhibited a greater affinity for peripheral H_1 -receptors (K_i^\ddagger : 35 nM) than for central H_1 -receptors (K_i - 118 nM) as determined by 3H -mepyramine binding inhibition at membrane receptor sites from the cerebral cortex and lungs of guinea pigs. Loratadine also had no effect on brain 3H -mepyramine binding in mice following an oral dose of 2.6 mg/kg (twice its antihistamine ED₅₀ in this species). In studies determining the binding inhibition of 3H -WB4101, an α -1 receptor ligand, loratadine was the weakest inhibitor (IC_{50} value ranging from 13 to 64 μM) of the several standard antihistamines studied.

$^\ddagger K_i$ = the dissociation constant of an enzyme inhibitor

The compound has a lower affinity for central receptors than for peripheral receptors, and it does not readily penetrate into the brain tissue.

In terms of other pharmacologic actions studied, loratadine does not have significant H_2 -receptor activity *in vitro* at concentrations up to 5×10^{-6} mmol, and does not seem to inhibit norepinephrine uptake as evidenced by its lack of effect on tetrabenazine-induced ptosis in mice at oral doses of 160 or 320 mg/kg. Loratadine also did not exhibit *in vivo* anticholinergic activity as measured by the lack of mydriasis in mice or rats at oral doses up to 200 mg/kg, in dogs at oral doses up to 60 mg/kg and in monkeys at doses up to 90 mg/kg. Moreover, loratadine did not antagonize physostigmine-induced lethality, which is another measure of anticholinergic activity, at oral doses up to 320 mg/kg in mice.

Loratadine had no effect on blood pressure or electrocardiogram in conscious dogs after oral doses of 1, 2.5 or 10 mg/kg. At 10 mg/kg, loratadine significantly increased heart rate. Loratadine did not significantly increase heart rate in monkeys at 2.5 mg/kg, which is about 12 times the maximum projected daily human dose. Moreover, loratadine did not increase the rate of contraction of isolated guinea pig atria which suggests that it does not directly affect pacemaker activity.

Drug interaction studies in mice showed that at 80 mg/kg of loratadine (approximately 50 times its ED₅₀ for blocking histamine-induced paw edema), loratadine potentiated the anticonvulsant effects of diazepam.

At a high dose of 320 mg/kg, loratadine potentiated the ability of high doses of ethanol and hexobarbital to induce loss of righting reflexes. No interaction was seen with propranolol, alpha methyl dopa, cimetidine, pseudoephedrine or d-amphetamine. A nearly identical interaction profile was seen with terfenadine.

Pharmacokinetics and Metabolism: The absorption, tissue distribution, metabolism and excretion (ADME) of ³H- and/or ¹⁴C-loratadine were evaluated in rats, rabbits and cynomolgus monkeys after oral and intravenous administration. Biliary excretion, enterohepatic circulation and placental transfer were evaluated in rats and enzyme induction was determined in hepatic microsomes of rats. In man, the pharmacokinetic and metabolic disposition of ³H- and ¹⁴C-loratadine was investigated in healthy normal volunteers, following single and multiple oral doses.

Loratadine is well absorbed by all species studied and is almost totally metabolized. First pass metabolism is extensive. The time to maximum plasma concentration was shortest in rats (0.5 hours) and longest in monkeys (3.3 hours) while normal volunteers exhibited a T_{max} of 1.1 hours.

The plasma half-life of loratadine varies between species; the shortest half-life (14.0 hours) occurs in the rat and the longest in man. The half-life of the major metabolite, descarboethoxyloratadine, could not be determined in animal species. The pharmacokinetic parameters of loratadine and its major metabolite are comparable in healthy adult volunteers and healthy geriatric volunteers. Steady-state levels of loratadine are reached after the fifth 40 mg daily dose.

In rats, given ¹⁴C-loratadine, loratadine and its metabolites are widely distributed throughout the tissues examined. Concentrations of radioactivity are highest in lungs, liver, kidneys, adrenals, pituitary and spleen. Lowest concentrations occur in brain. Radioactivity in all tissues decreases with time and no drug accumulation occurs in tissues with multiple dosing.

In animals, loratadine and its metabolites are excreted in urine (largely during the first 24 hours) and feces, after drug administration. In animals, a larger portion of the loratadine dose is excreted into the feces than into urine. In man, approximately 40% of the dose is excreted in the urine and 42% in feces over a 10-day period. Approximately 27% of the dose is eliminated in the urine during the first 24 hours.

In rats, loratadine and its metabolites undergo enterohepatic circulation. The radioactivity is eliminated in the gastrointestinal tract via the biliary route (major) and direct passage through the gastrointestinal mucosa (minor).

In pregnant rats, ¹⁴C-loratadine crosses the placental barrier both at the end of embryonic formation (day 14 of pregnancy) and at near-term (day 20 of pregnancy). At 20 days, the tissue distribution pattern in fetuses is similar to that in dams; however, the concentrations of radioactivity in fetal tissues are considerably lower than the concentrations in corresponding maternal tissues. The radioactivity disappears with time from both fetuses and dams and does not accumulate in fetal tissues.

The metabolic profiles of loratadine in fetal and maternal plasma are similar.

Enzyme induction studies with high doses demonstrate that loratadine is only a weak inducer of hepatic drug metabolizing enzyme systems in rats. Results from plasma protein binding studies revealed that loratadine is highly bound (97% to 99% in man, 98% to 99% in rat and 96% to 99% in monkey) and its active metabolite moderately bound (73% to 76% in man, 70% to 71% in rat and monkey) to human and animal plasma proteins.

Human Pharmacology:

Suppression of Histamine-Induced Skin Wheals: The antihistaminic activity and dose-response profile of loratadine were evaluated in three clinical pharmacologic studies using a histamine-induced skin wheal suppression model in healthy male volunteers.

Two randomized, single-blind studies evaluated the wheal suppression effects of loratadine at single oral doses ranging from 10 to 160 mg. At these doses, loratadine demonstrated a rapid onset of action; wheal suppression was observed within two hours of treatment. All doses were significantly more effective than placebo in suppressing the formation of histamine-induced skin wheals ($p < 0.05$); the suppression of wheal formation by loratadine was dose related.

In a third randomized, double-blind study the suppressant effects of loratadine on histamine-induced wheal formation were measured at doses ranging from 10 to 40 mg administered orally twice daily (b.i.d.) for 28 days. Wheal suppression was observed at two hours after the first dose, and by four hours, each of the four active treatments (loratadine 10 mg, 20 mg, & 40 mg and chlorpheniramine 12 mg) caused a significantly greater suppression of the wheal formation than placebo ($p < 0.05$); this effect remained consistent over the entire 28 day study period.

Loratadine and Alcohol:

Special tests were designed to assess the effects of loratadine either alone or in combination with alcohol on driving and psychomotor performance. In a double-blind study, the ability of healthy male volunteers to concentrate, as measured by multiple choice reactions and visuomotor coordination tests was not impaired by either 40 mg loratadine alone or in combination with 0.75 g/kg of alcohol. In another double-blind study on driving performance, 10 or 20 mg loratadine and placebo were without effect while 10 mg triprolidine significantly impaired performance. Furthermore, after ingestion of alcohol in quantities of 1.07 g/kg of lean body weight, a second test demonstrated that loratadine did not potentiate the effects of alcohol on driving performance.

Loratadine and Nursing Mothers

Loratadine and its active metabolite are eliminated in the breast milk of lactating women with milk concentrations being similar to plasma concentrations. Through 48 hours after dosing, only 0.029% of the loratadine dose is eliminated in the milk as unchanged loratadine and its active metabolite, descarboethoxyloratadine (DCL).

MICROBIOLOGY

Not applicable

TOXICOLOGY

Acute Toxicity

The oral LD_{50s} were estimated to be greater than 5000 mg/kg in both species. In mice, intraperitoneal LD₅₀ values were calculated to be 1601 and 1458 mg/kg for males and females, respectively. In male and female rats, the intraperitoneal LD₅₀ values were determined to be 5134 and 2908 mg/kg respectively. Rising single doses up to 1280 mg/kg were relatively well tolerated in monkeys with emesis at this high dose precluding the determination of acute lethal levels.

Table 4: Acute Oral Toxicity of Loratadine in Young Animals

Species	Sex	LD ₅₀ Value* mg/kg	Maximum Asymptomatic mg/kg	Maximum Non Lethal mg/kg
Rat [7 day old]	M	125-200 ^a	<125	125
	F	191	<125	125 ^b
Rat [30 day old]	M	[138-242] 5734 [4020→10,000]	1580	2000
	F	5500	<1580	1580 ^c
Monkey [7-15 mos]	M&F	[4114→10,000] ---	100	>200

* 95% fiducial limits

a LD₅₀ value could not be calculated due to the distribution of the data.

b One of 10 pups died at this dose, but no signs of toxicity were observed, suggesting that the death may not have been compound-related.

c Although 1 of 10 rats died at this dose, no deaths occurred at 2000 mg/kg.

Results of studies of loratadine in adult animals suggest that there are no significant differences in acute toxicity between adults and juvenile rats or young monkeys. Repeated dose studies in young rats for one month and young monkeys for three months indicate that loratadine was well tolerated when given in a suspension up to 25 mg/kg for rats and up to 24 mg/kg for monkeys.

Plasma concentrations of loratadine from monkeys indicated that absorption of loratadine was dose-related with no trend toward accumulation during the three-month dosing period.

Intermediate-Term Studies

Table 5: Repeated Dose Studies

Species/Type/No. Used	Duration of Study	Dosage mg/kg (once daily)	Method and Vehicle
Rats, 10/sex/group	2 weeks	15, 60, 240	gavage, 0.25% aqueous methylcellulose
Rats, 15 or 20/group	3 months	8, 32, 128	gavage, 0.4% methylcellulose
Rats, 15/sex/group	6 months	4, 16, 72	In diet
Monkeys, 4 or 6/sex/group	3 months	8, 24, 72	gavage, 0.4% aqueous methylcellulose
Monkeys, 6/sex/group	3 months	0.4, 1.2, 2.4	gavage, 0.4% aqueous methylcellulose
Monkeys, 4/sex/group	6 months	4, 16, 72	gavage, 0.4% aqueous methylcellulose

Charles River CD Type rats or cynomolgus monkeys were used. All groups had similar controls and were given the vehicle or diet alone.

Rats were more sensitive than monkeys to the effects of loratadine; females more sensitive than males. Anticholinergic effects, evidence by reduced fecal excretion and/or mydriasis were observed in both species. In long-term studies, anticholinergic effects were apparent in rats at a dose of 128 mg/kg/day or greater; in monkeys such effects were observed at a dose of 16 mg/kg/day. Phospholipidosis was also observed; the incidence and severity were dose related and were more pronounced in the rat. Minimal signs of phospholipidosis were observed in rats at a dose of 8 mg/kg/day; in monkeys evidence was apparent at 4 mg/kg/day or more. The degree of phospholipidosis did not interfere with cellular function, appeared to lessen over time and appeared to be reversible. No evidence of phospholipidosis was observed in man following treatment with 40 mg/kg for three months. Other compounds currently in therapeutic use (e.g. imipramine and chlorphentermine) which are amphiphilic as is loratadine, have been reported to produce phospholipidosis in animals. Prolongation of QRS-interval was observed in monkeys at a dose 200 times the proposed clinical dose. The quinidine-like effect is commonly seen with antihistamines and is not associated with significant clinical effects.

Long-Term Toxicity Studies

During long-term toxicity studies conducted in mice, rats and monkeys, changes were observed in reproductive organs of male rats, consisting of weight reduction of the prostate gland and the testes; those changes were without consequence after a recovery period of 28 days. Similar changes in the male rat have been observed after administering drugs like antazoline, dexchlorpheniramine, meclizine, phenbenzamine and pyribenzamine.

Table 6: Long-term Toxicity Studies

<u>Species</u>	<u>Duration</u>	<u>Loratadine</u>			<u>Vehicle and Method Used</u>
		Dosage mg/kg/day			
Rat	12 mos	0.2	0.5	1.0	Diet oral

<u>Species</u>	<u>Duration</u>	<u>Loratadine</u>			<u>Vehicle and Method Used</u>
		Dosage mg/kg/day			
	12 mos	2	8	32	Diet oral
	24 mos	4	10	25	Diet oral
Mouse	18 mos	4	12	40	Diet oral
Monkey	17 mos	4	12	40	0.4% methylcellulose, esophageal intubation

Mutagenicity Studies

In five distinctly different genetic toxicity assays designed to detect the major types of genotoxicity i.e. Ames test, Mouse Lymphoma, Chinese Hamster Ovary, Human Lymphocyte and the Mouse Micronucleus Assays, the only activity elicited by loratadine was observed in the nonactivation phase of the mouse lymphoma assay. This activity was not dose-related.

Reproduction Studies

Loratadine was not teratogenic in rats or rabbits. In rats, decreased fertility was observed at the highest dose tested, approximately 320 times the proposed clinical dose. Subsequent matings within this segment of the reproduction studies demonstrated this effect to be readily reversible. Other pregnancy parameters (pregnancy rate, litter size, number of implantations, corpora lutea) were not affected at doses approximately 40 to 120 times the anticipated clinical dose. Effects on these parameters above these dose levels were generally related to the pharmacodynamic activity of loratadine, and have been reported to be associated with other antihistamines.