PRODUCT MONOGRAPH

CLARITIN*

(loratadine)

10 mg Tablets
10 mg Rapid Dissolve Tongue Tablets
1 mg/mL Syrup

Histamine H_1 receptor antagonist

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PRODUCT MONOGRAPH

NAME OF DRUG

CLARITIN*

(loratadine)

Tablets - 10 mg
Rapid Dissolve Tongue Tablets - 10 mg
Syrup - 1 mg/mL

THERAPEUTIC CLASSIFICATION

Histamine H_1 receptor antagonist

ACTIONS AND CLINICAL PHARMACOLOGY

Loratadine is a long-acting tricyclic antihistamine with selective peripheral H_1 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.

^{14}C-loratadine is rapidly absorbed reaching Cmax 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 7.8-11.0 hours. Descarboethoxyloratadine, the major active metabolite, reached Cmax 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 Cmax 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.

The confidence intervals for Cmax and AUC(I) are within the 80-125% range indicating that the CLARITIN* Rapid Dissolve Tongue Tablets were bioequivalent with respect to the active metabolite Descarboethoxyloratadine

After administration of a single 10 mg dose of loratadine as either the Rapid Dissolve Tongue Tablet, a conventional tablet, or the syrup formulation (1mg/mL), 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.

Table 1

Mean (n=18) pharmacokinetic parameters for loratadine and Descarboethoxyloratadine (CLARITIN* Rapid Dissolve Tongue 10 mg Tablet vs. CLARITIN* 10 mg Tablet (Conventional))

Parameter	Mean (%CV)			
	CLARITIN* Rapid Dissolve Tongue 10 mg Tablet		CLARITIN* 10 mg Tablet (Conventional)	
	Loratadine	DCL*	Loratadine	DCL*
Cmax (ng/ml) Tmax (hr) AUC (I) (ng.hr/ml)	2.56 (83) 1.14 (72) 6.14 (100)	3.72 (53) 1.97 (129) 49.1 (50)	2.11 (90) 1.00 (34) 4.64 (106)	3.66 (45) 1.97 (98) 48.4 (44)

* DCL: Descarboethoxyloratadine

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 2

Mean (n=18) pharmacokinetic parameters for loratadine and Descarboethoxyloratadine (CLARITIN* Rapid Dissolve Tongue 10 mg Tablet vs. Loratadine Syrup 1mg/ml)

Parameter	Mean (%CV)			
	CLARITIN* Rapid Dissolve Tongue 10 mg Tablet		Loratadine Syrup (1mg/ ml)	
	Loratadine	DCL*	Loratadine	DCL*
Cmax (ng/ml) Tmax (hr) AUC (I) (ng.hr/ml)	2.65 (193) 1.00 (30) 6.33 (201)	3.46 (44) 1.42 (39) 40.8 (29)	3.62 (150) 0.86 (44) 10.1 (147)	3.65 (35) 0.94 (17) 38.8 (27)

* DCL: Descarboethoxyloratadine

Following administration of 10 mg of loratadine once daily for 10 days as either a Rapid Dissolve Tongue or a conventional tablet, plasma concentrations of loratadine and its active metabolite were at steady state by day 5 with both formulations. Mean peak plasma concentrations (Tmax) of loratadine and its metabolite in both formulations were attained at 1.3 hours; peak to trough fluctuations observed for the Rapid Dissolve Tongue Tablet and the conventional Tablet were similar with respect to loratadine and its metabolite. Mean elimination half-life of the active metabolite was 20 hours for both formulations.

Table 3

Loratadine, administered as either CLARITIN* Rapid Dissolve Tongue 10 mg Tablet or CLARITIN* 10 mg Tablet (Conventional Tablet) to healthy subjects once daily for 10 days

Parameter	Mean (%CV)					
	Loratadine			DCL*		
	Day 5	Day 7	Day 10	Day 5	Day 7	Day 10
CLARITIN* Rapid Dissolve Tongue 10 mg Tablet						
Cmax (ng/ml)	3.79 (83)	3.35 (73)	4.04 (80)	4.65 (58)	4.69 (68)	4.69 (73)
AUC(r)[a] (ng.hr/ml)	12.0 (76)	11.2 (75)	12.2 (71)	71.9 (88)	82.1 (93)	72.9 (103)
CLARITIN* 10 mg Tablet (Conventional tablet)						
Cmax (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)

In a single-dose, two-way cross-over study with CLARITIN* Rapid Dissolve Tongue Tablets, food increased the AUC of loratadine and descarboethoxyloratadine by 90% and 6% respectively. Food decreased the mean Cmax of loratadine and descarboethoxyloratadine by 9% and 15% respectively. The time to peak plasma concentration (Tmax) of loratadine and descarboethoxyloratadine were delayed by approximately 2.4 and 3.7 hours, respectively, when food was consumed prior to administration of CLARITIN* Rapid Dissolve Tongue Tablets.

In a single-dose, randomized, two-way cross-over study with 10 mg CLARITIN* Rapid Dissolve Tongue Tablets in twenty-four subjects, under fasting condition, the mean AUC(tf) and Cmax values were increased by 84% and 30%, respectively, when administered without water compared to administration with water, demonstrating that bioavailability was not attenuated when CLARITIN* Rapid Dissolve Tongue Tablet was dissolved on the tongue and subsequently swallowed without concomitant consumption of a liquid. The bioavailability of descarboethoxyloratadine was not different when administered without water.

Approximately 82% of the ^{14}C-loratadine dose is excreted in the urine (40%) and feces (42%) over a 10-day period. Approximately 27% of the dose is eliminated in the urine during the first 24 hours largely in the conjugated form. Unchanged drug is present only in trace quantities in the urine and the active metabolite descarboethoxyloratadine represents only 0.4 to 0.6% of the administered loratadine dose.

Two randomized, multicenter, double-blind, placebo-controlled, parallel groups studies performed in patients with seasonal allergic rhinitis, the safety and efficacy of CLARITIN* Rapid Dissolve Tongue Tablets and the conventional CLARITIN* tablets vs. placebo were evaluated. CLARITIN* Rapid Dissolve Tongue Tablets administered as 10 mg once daily for 15 days, was significantly more effective than placebo in reducing physician-evaluated and patient daily-assessed total combined, total nasal, and total nonnasal symptoms in patients with seasonal allergic rhinitis. CLARITIN* Rapid Dissolve Tongue Tablet had a clinical effect comparable to or greater than conventional CLARITIN* tablet. Both of the drugs were safe and well tolerated in this patient population. From clinical studies conducted on healthy individuals with allergic rhinitis, no clinical consequences are anticipated in this population, whether or not CLARITIN* Rapid Dissolve Tongue Tablets are administered with or without food.

INDICATIONS AND CLINICAL USE

CLARITIN* (loratadine) Tablets and CLARITIN* (loratadine) Rapid Dissolve Tongue 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, and for 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. CLARITIN* Rapid Dissolve Tongue Tablets should be taken on an empty stomach.

CLARITIN* (loratadine) Syrup is indicated for the relief of symptoms associated with seasonal allergic rhinitis, such as sneezing, nasal discharge and itching, and ocular itching and burning, and for the relief of symptoms and signs of chronic urticaria and other allergic dermatologic disorders. In children, it is intended for short-term use only unless taken under medical supervision.

CONTRAINDICATIONS

Contraindicated in patients who have shown hypersensitivity or idiosyncrasy to the drug or its components.

PRECAUTIONS

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.

Use in Pregnancy and in Nursing Mothers:

The safe use of loratadine during pregnancy or lactation has not been established and is therefore not recommended for use in pregnant or nursing mothers. (See PHARMACOLOGY for information on secretion into breast milk).

Use in Children:

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.

Drug Interactions:

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

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/Laboratory Test 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.

ADVERSE REACTIONS

Clinical Study Reports

Adverse experiences reported with CLARITIN* conventional (loratadine) 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 (see Table 4). In addition to those listed in the table, the following were reported less frequently (less than 1%): appetite increased, coughing, dizziness and palpitations.

Table 4

CLARITIN* (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 CLARITIN* (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”

CLARITIN* Rapid Dissolve Tongue Tablets were well tolerated and did not cause local irritation or taste abnormalities. The most frequently reported adverse experience was headache. Overall, the incidence of adverse reactions was comparable to that of CLARITIN* conventional (loratadine) tablets and to that of placebo (see Table 5).

Table 5

CLARITIN* Rapid Dissolve Tongue (loratadine) Tablets, vs
CLARITIN* (loratadine) Conventional Tablets vs Placebo

Number (%) of Patients Reporting Frequently Occurring (≥2% of loratadine Rapid Dissolve Tongue Tablet-treated patients) Adverse Experiences Possibly or Probably Related to Treatment in Seasonal Allergic Rhinitis Studies.

	Number (%) of Patients		
Adverse Experience	Loratadine 10mg Rapid Dissolve Tongue Tablet (n=495)	Loratadine 10mg Tablet (n=328)	Placebo (n=497)
Dry Mouth	8(2)	8(2)	5(1)
Fatigue	13(3)	12(4)	16(3)
Headache	40(8)	23(7)	55(11)
Somnolence	22(4)	13(4)	3(3)

Adverse experiences reported in pediatric patients are shown in Table 6. Nervousness and hyperkinesia were among the reported adverse experiences. One case of hyperkinesia was graded as severe and was judged by the physician to be possibly related to loratadine treatment. Gastrointestinal adverse reactions reported during pediatric trials may have been slightly more frequent in the younger patients (less than or equal to 30 kg), but in older children (greater than 30 kg) are similar to placebo (Table 7).

Table 6

CLARITIN* (loratadine) Syrup, 1 mg/mL, 5-10 mg Once Daily
Number (%) of Patients Reporting Frequently Occurring (≥2% of loratadine-treated patients) Treatment-Related Adverse Experiences: Placebo-Controlled Clinical Trials in Pediatric Studies in Seasonal Allergic Rhinitis and Allergic Skin Disorders Studies

	Loratadine		Chlorpheniramine		Placebo
	5mg	10mg	2mg	4mg	
	N=46	N=119	N=48	N=122	N=168
Adverse Experiences					
Nervousness	2(4)	5(4)	1(2)	2(2)	2(1)
Hyperkinesia	0(0)	4(3)	0(0)	1(1)	1(0.6)
Sedation	2(4)	6(5)	4(8)	13(11)	9(5)
Headache	3(6)	4(3)	4(8)	5(4)	13(8)

Table 7

Number of Patients Reporting GI Adverse Experiences
in Placebo-Controlled Clinical Trials Possibly or Probably Related to Study Medication,
Grouped According to Treatment, Dose, Weight, in Pediatric Studies

	5mg Dose Wt ≤ 30kg (N=46)	10mg Dose Wt>30kg (N=119)	Placebo Wt>30kg (N=168)
Adverse Event			
Diarrhea	1	0	0
Nausea	2	2	5
Dyspepsia	2	3	3
Vomiting	2	0	0
Abdominal Pain	0	2	0
Total	7(15%)	7(5.9%)	8(4.8%)

Post-Marketing Reports

During the marketing of loratadine, in addition to the adverse events reported during clinical trials, alopecia, anaphylaxis, abnormal hepatic function, palpitations and tachycardia have been reported rarely.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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.

Treatment:

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.

DOSAGE AND ADMINISTRATION

Tablets

Adults and Children 12 years of age and over:

One CLARITIN* (loratadine) tablet, 10 mg, once daily.

One CLARITIN* (loratadine) Rapid Dissolve Tongue Tablet, 10 mg, placed in the mouth once daily. The tablet disperses instantly and water or other liquid is not needed.

Syrup

Adults, children over 10 years of age [body weight greater than 30 kg]:

10 mL (two teaspoonsful) of CLARITIN* (loratadine) Syrup once daily.

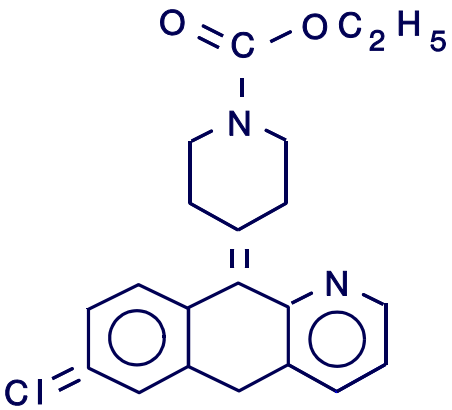
Children 2 through 9 years of age [body weight less than or equal to 30 kg]: 5 mL (one teaspoonful) of CLARITIN* (loratadine) Syrup once daily.

PHARMACEUTICAL INFORMATION

Proper name: loratadine (INN, USAN)

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

Structural formula:



Molecular formula $C_{22}H_{23}ClN_20_2$

Molecular weight: 382.89

Appearance: white to off-white powder which melts between 132° and 137°C.

Composition

Each CLARITIN* Conventional tablet contains 10 mg loratadine (as base). Non-medicinal ingredients: corn starch, lactose, and magnesium stearate.

Each CLARITIN* Rapid Dissolve Tongue Tablet contains 10 mg micronized loratadine (as base). Non-medicinal ingredients: gelatin, mannitol, citric acid, and mint flavour.

Each mL of CLARITIN* syrup contains 1 mg loratadine (as base). Non-medicinal ingredients: propylene glycol, glycerin, citric acid monohydrate, sodium benzoate, sucrose, artificial peach flavour, and purified water.

Stability and Storage conditions:

CLARITIN* tablets and Syrup: Between 15° and 30°C.

CLARITIN* Rapid Dissolve Tongue Tablets: Between 15° and 30°C.

Use within 6 months of opening sachet, immediately upon opening tablet blister.

Protect tablets from exposure to excessive moisture.

DOSAGE FORM

CLARITIN* Tablets: 10 mg loratadine (as base) tablets for oral use. Description: white, oval, shallow tablet with deep score. The flask and dish logo are above the score, and the number 10 below the score.

Packaging: blister packaged in 6's, 12', 18's, 24's and in bottles of 100's.

CLARITIN* Rapid Dissolve Tongue Tablets***:*** 10 mg loratadine (as base) tablets for oral use. Description: White round tablet-shaped units. Packaging: blister packaged in 4's, 8's and 12's.

CLARITIN* Syrup: 1 mg/mL loratadine (as base) for oral use. Description: clear, colourless to light yellow syrup with peach flavouring. Packaging: 100 mL and 240 mL amber glass or amber plastic bottle.

PHARMACOLOGY

Animal Pharmacology:

Loratadine is an orally effective antihistamine in both mice and guinea pigs. The oral PD^*_{50} value for preventing histamine-induced lethality in guinea pigs is 0.19 mg/kg for loratadine compared to 0.009 mg/kg for azatadine, the most closely related structure of the marketed antihistamines, and 0.15 mg/kg for chlorpheniramine. In terms of duration of antihistamine action, loratadine at twice its antihistamine PD_{50} (0.5 mg/kg) is longer acting (duration: 18-24 hours) than an equi-effective dose of azatadine (duration 8-12 hours). For preventing histamine-induced paw edema in mice, loratadine has an oral PD_{50} value of l.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: 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.

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 10-300 mg/kg, in dogs at doses of 15-30 mg/kg and in monkeys at doses of 30-60 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 (Ki: 35 nM) than for central H_1-receptors (Ki - 118 nM) as determined by ^{3}H-mepyramine binding inhibition at membrane receptor sites from the cerebral cortex and lungs of guinea pigs. Loratadine also had no effect on brain ^{3}H-mepyramine binding in mice following an oral dose of 2.6 mg/kg (twice its antihistamine ED_{50} in this species). In studies determining the binding inhibition of ^{3}H-WB4101, an alpha-1 receptor ligand, loratadine was the weakest inhibitor (IC_{50} value ranging from 13 to 64 uM) of the several standard antihistamines studied.

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 $5x10^{-6}$ 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 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 ED_{50} 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 methyldopa, 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 ^{3}H- and/or ^{14}C-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 ^{3}H- and ^{14}C-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 Tmax 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 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, 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, ^{14}C-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

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.

In a comparative study of loratadine syrup, terfenadine suspension and placebo in reducing histamine-induced wheals and flares, single doses of 10 mg loratadine syrup and 60 mg terfenadine suspension were comparable in reducing histamine-induced wheals and flares and both were significantly more effective than placebo.

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).

TOXICOLOGY

Acute Toxicity in Mice/Rats

The oral LD_{50s} were estimated to be greater than 5000 mg/kg in both species. In mice, intraperitoneal LD_{50} values were calculated to be 1601 and 1458 mg/kg for males and females, respectively. In male and female rats, the intraperitoneal LD_{50} 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.

Intermediate-Term Studies

Table 8

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 9

Long term Toxicity Studies

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

Pediatric Studies

Table 10

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	M	125-200[a]	<125	125
[7 day old]	F	191	<125	125[b]
		[138-242]		
Rat	M	5734	1580	2000
[30 day old]		[4020→ 10, 000]		
	F	5500	<1580	1580[c]
		[4114→ 10,000]		
Monkey	M&F	---	100	>200
[7-15 mos]				

* 95% fiducial limits

a LD_{50} 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. Although 1 of 10 rats died at this

c 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.

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 40-120 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.

Mucous membrane irritation study

No evidence of mucous membrane irritation was observed after daily administration of up to 12 tablets (120mg) of loratadine Rapid Dissolve Tongue Tablets into the hamster cheek pouch for five days.

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