CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-641/SE5-007

Final Printed Labeling

CLARITIN®

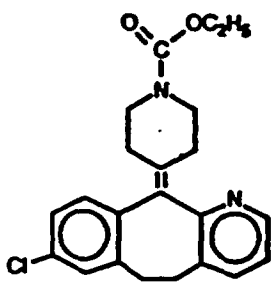
brand of loratadine

TABLETS, SYRUP, and

RAPIDLY-DISINTEGRATING TABLETS

PRODUCT INFORMATION

DESCRIPTION: Loratadine is a white to off-white powder not soluble in water, but very soluble in acetone, alcohol, and chloroform. It has a molecular weight of 382.89, and empirical formula of $C_{22}H_{23}ClN_2O_2$; its chemical name is ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidine-carboxylate and has the following structural formula:



CLARITIN Tablets contain 10 mg micronized loratadine, an antihistamine, to be administered orally. It also contains the following inactive ingredients: corn starch, lactose and magnesium stearate.

CLARITIN Syrup contains 1 mg/mL micronized loratadine, an antihistamine, to be administered orally. It also contains the following inactive ingredients: citric acid, edetate disodium, artificial flavor, glycerin, propylene glycol, sodium benzoate, sugar, and water. The pH is between 2.5 and 3.1.

CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) contain 10 mg micronized loratadine, an antihistamine, to be administered orally. It disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be

subsequently swallowed with or without water. CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) also contain the following inactive ingredients: citric acid, gelatin, mannitol, and mint flavor.

CLINICAL PHARMACOLOGY: Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic activity.

Human histamine skin wheal studies following single and repeated 10 mg oral doses of CLARITIN have shown that the drug exhibits an antihistaminic effect beginning within 1 to 3 hours, reaching a maximum at 8 to 12 hours and lasting in excess of 24 hours. There was no evidence of tolerance to this effect after 28 days of dosing with CLARITIN.

Whole body autoradiographic studies in rats and monkeys, radiolabeled tissue distribution studies in mice and rats, and *in vivo* radioligand studies in mice have shown that neither loratadine nor its metabolites readily cross the blood-brain barrier. Radioligand binding studies with guinea pig pulmonary and brain H_1-receptors indicate that there was preferential binding to peripheral versus central nervous system H_1- receptors.

Repeated application of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) to the hamster cheek pouch did not cause local irritation.

Pharmacokinetics: Loratadine was rapidly absorbed following oral administration of 10 mg tablets, once daily for 10 days to healthy adult volunteers with times to maximum concentration (T_{max}) of 1.3 hours for loratadine and 2.5 hours for its major active metabolite, descarboethoxyloratadine. Based on a cross-study comparison of single doses of loratadine syrup and tablets given to healthy adult volunteers, the plasma concentration profile of descarboethoxyloratadine for the two formulations is comparable. The pharmacokinetics of loratadine and descarboethoxyloratadine are independent of dose over the dose range of 10 to 40 mg and are not altered by the duration of treatment. In a single-dose study, food increased the systemic bioavailability (AUC) of loratadine and descarboethoxyloratadine by approximately 40% and 15%, respectively. The time to peak plasma concentration

(T_{max}) of loratadine and descarboethoxyloratadine was delayed by 1 hour. Peak plasma concentrations (C_{max}) were not affected by food.

Pharmacokinetic studies showed that CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) provide plasma concentrations of loratadine and descarboethoxyloratadine similar to those achieved with CLARITIN Tablets. Following administration of 10 mg loratadine once daily for 10 days with each dosage form in a randomized crossover comparison in 24 normal adult subjects, similar mean exposures (AUC) and peak plasma concentrations (C_{max}) of loratadine were observed. CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) mean AUC and C_{max} were 11% and 6% greater than that of the CLARITIN Tablet values, respectively. Descarboethoxyloratadine bioequivalence was demonstrated between the two formulations. After 10 days of dosing, mean peak plasma concentrations were attained at 1.3 hours and 2.3 hours (T_{max}) for parent and metabolite, respectively.

In a single-dose study with CLARITIN REDITABS (loratadine rapidly-disintegrating tablets), food increased the AUC of loratadine by approximately 48% and did not appreciably affect the AUC of descarboethoxyloratadine. The times to peak plasma concentration (T_{max}) of loratadine and descarboethoxyloratadine were delayed by approximately 2.4 and 3.7 hours, respectively, when food was consumed prior to CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) administration. Parent and metabolite peak concentrations (C_{max}) were not affected by food.

In a single-dose study with CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in 24 subjects, the AUC of loratadine was increased by 26% when administered without water compared to administration with water, while C_{max} was not substantially affected. The bioavailability of descarboethoxyloratadine was not different when administered without water.

Approximately 80% of the total loratadine dose administered can be found equally distributed between urine and feces in the form of metabolic products within 10 days. In nearly all patients, exposure (AUC) to the metabolite is greater than to

the parent loratadine. The mean elimination half-lives in normal adult subjects (n = 54) were 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for descarboethoxyloratadine. Loratadine and descarboethoxyloratadine reached steady-state in most patients by approximately the fifth dosing day. There was considerable variability in the pharmacokinetic data in all studies of CLARITIN Tablets and Syrup, probably due to the extensive first pass metabolism.

In vitro studies with human liver microsomes indicate that loratadine is metabolized to descarboethoxyloratadine predominantly by cytochrome P450 3A4 (CYP3A4) and, to a lesser extent, by cytochrome P450 2D6 (CYP2D6). In the presence of a CYP3A4 inhibitor ketoconazole, loratadine is metabolized to descarboethoxyloratadine predominantly by CYP2D6. Concurrent administration of loratadine with either ketoconazole, erythromycin (both CYP3A4 inhibitors), or cimetidine (CYP2D6 and CYP3A4 inhibitor) to healthy volunteers was associated with substantially increased plasma concentrations of loratadine (See **Drug Interactions** section).

The pharmacokinetic profile of loratadine in children in the 6- to 12-year age group is similar to that of adults. In a single-dose pharmacokinetic study of 13 pediatric volunteers (aged 8-12 years) given 10 mL of CLARITIN Syrup containing 10 mg loratadine, the ranges of individual subject values of pharmacokinetic parameters (AUC and C_{max}) were comparable to those following administration of a 10 mg tablet or syrup to adult volunteers.

In 2- to 5-year old subjects (n=18), a single dose of 5 ml of CLARITIN syrup containing 5 mg of loratadine, resulted in pharmacokinetic profiles for loratadine and descarboethoxyloratadine, similar to those achieved following 10 mg of loratadine administered to adults and children eight years of age and older. Maximal concentrations (C_{max}) for loratadine and descarboethoxyloratadine were 7.8 ng/ml and 5.1 ng/ml, respectively; and were attained (T_{max}) by 1.2 hours and 2.3 hours, respectively.

Special Populations: In a study involving twelve healthy geriatric subjects (66 to 78 years old), the AUC and peak plasma levels (C_{max}) of both loratadine and descarboethoxyloratadine were approximately 50% greater than those observed in studies of younger subjects. The mean elimination half-lives for the geriatric subjects were 18.2 hours (range = 6.7 to 37 hours) for loratadine and 17.5 hours (range = 11 to 38 hours) for descarboethoxyloratadine.

In a study involving 12 subjects with chronic renal impairment (creatinine clearance ≤ 30 mL/min) both AUC and C_{max} increased by approximately 73% for loratadine and by 120% for descarboethoxyloratadine, as compared to 6 subjects with normal renal function (creatinine clearance ≥ 80 mL/min). The mean elimination half-lives of loratadine (7.6 hours) and descarboethoxyloratadine (23.9 hours) were not substantially different from that observed in normal subjects. Hemodialysis does not have an effect on the pharmacokinetics of loratadine or descarboethoxyloratadine in subjects with chronic renal impairment.

In seven patients with chronic alcoholic liver disease, the AUC and C_{max} of loratadine were double while the pharmacokinetic profile of descarboethoxyloratadine was not substantially different from that observed in other trials enrolling normal subjects. The elimination half-lives for loratadine and descarboethoxyloratadine were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

Clinical Trials: Clinical trials of CLARITIN Tablets involved over 10,700 patients, 12 years of age and older, who received either CLARITIN Tablets or another antihistamine and/or placebo in double-blind randomized controlled studies. In placebo-controlled trials, 10 mg once daily of CLARITIN Tablets was superior to placebo and similar to clemastine (1 mg BID) or terfenadine (60 mg BID) in effects on nasal and non-nasal symptoms of allergic rhinitis. In these studies somnolence occurred less frequently with CLARITIN Tablets than with clemastine and at about the same frequency as terfenadine or placebo. In studies with CLARITIN Tablets at doses 2 to 4 times higher than the recommended dose of 10 mg, a dose related increase in the incidence of somnolence was observed. Therefore, some patients,

particularly those with hepatic or renal impairment and the elderly, or those on medications that Impair clearance of loratadine and its metabolites may experience somnolence. In addition, three placebo-controlled, double-blind, 2-week trials in 188 pediatric patients with seasonal allergic rhinitis aged 6 to 12 years, were conducted at doses of CLARITIN Syrup up to 10 mg once daily. In a double-blind, placebo-controlled study, the safety of 5 mg loratadine, administered in 5 ml of CLARITIN Syrup, was evaluated in 60 pediatric patients between 2 and 5 years of age. No unexpected adverse events were observed.

Clinical trials of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) involved over 1300 patients who received either CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) CLARITIN Tablets, or placebo. In placebo controlled trials, one CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) once daily was superior to placebo and similar to CLARITIN Tablets in effects on nasal and non-nasal symptoms of seasonal allergic rhinitis.

Among those patients involved in double-blind, randomized, controlled studies of CLARITIN Tablets, approximately 1000 patients (age 12 and older), were enrolled in studies of chronic idiopathic urticaria. In placebo-controlled clinical trials, CLARITIN Tablets 10 mg once daily were superior to placebo in the management of chronic idiopathic urticaria, as demonstrated by reduction of associated itching, erythema, and hives. In these studies, the incidence of somnolence seen with CLARITIN Tablets was similar to that seen with placebo.

In a study in which CLARITIN Tablets were administered to adults at 4 times the clinical dose for 90 days, no clinically significant increase in the QT_c was seen on ECGs.

In a single-rising dose study in which doses up to 160 mg (16 times the clinical dose) were studied, loratadine did not cause any clinically significant changes on the Qt_c interval in the ECGs.

INDICATIONS AND USAGE: CLARITIN is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria in patients ~~6~~2 years of age or older.

CONTRAINDICATIONS: CLARITIN is contraindicated in patients who are hypersensitive to this medication or to any of its ingredients.

PRECAUTIONS: General: Patients with liver impairment or renal insufficiency (GFR < 30 mL/min) should be given a lower initial dose (10 mg every other day). (See **CLINICAL PHARMACOLOGY: Special Populations.**)

Drug Interactions: Loratadine (10 mg once daily) has been coadministered with therapeutic doses of erythromycin, cimetidine, and ketoconazole in controlled clinical pharmacology studies in adult volunteers. Although increased plasma concentrations (AUC 0-24 hrs) of loratadine and/or descarboethoxyloratadine were observed following coadministration of loratadine with each of these drugs in normal volunteers (n = 24 in each study), there were no clinically relevant changes in the safety profile of loratadine, as assessed by electrocardiographic parameters, clinical laboratory tests, vital signs, and adverse events. There were no significant effects on QT_c intervals, and no reports of sedation or syncope. No effects on plasma concentrations of cimetidine or ketoconazole were observed. Plasma concentrations (AUC 0-24 hrs) of erythromycin decreased 15% with coadministration of loratadine relative to that observed with erythromycin alone. The clinical relevance of this difference is unknown. These above findings are summarized in the following table:

Effects on Plasma Concentrations (AUC 0-24 hrs) of Loratadine and Descarboethoxyloratadine After 10 Days of Coadministration (Loratadine 10 mg) in Normal Volunteers

	Loratadine	Descarboethoxyloratadine
Erythromycin (500 mg Q8h)	+ 40%	+ 46%
Cimetidine (300 mg QID)	+ 103%	+ 6%
Ketaconazole (200 mg Q12h)	+ 307%	+ 73%

There does not appear to be an increase in adverse events in subjects who received oral contraceptives and loratadine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: In an 18-month carcinogenicity study in mice and a 2-year study in rats, loratadine was

administered in the diet at doses up to 40 mg/kg (mice) and 25 mg/kg (rats). In the carcinogenicity studies, pharmacokinetic assessments were carried out to determine animal exposure to the drug. AUC data demonstrated that the exposure of mice given 40 mg/kg of loratadine was 3.6 (loratadine) and 18 (descarboethoxyloratadine) times higher than in humans given the maximum recommended daily oral dose. Exposure of rats given 25 mg/kg of loratadine was 28 (loratadine) and 67 (descarboethoxyloratadine) times higher than in humans given the maximum recommended daily oral dose. Male mice given 40 mg/kg had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg and males and females given 25 mg/kg. The clinical significance of these findings during long-term use of CLARITIN is not known.

In mutagenicity studies, there was no evidence of mutagenic potential in reverse (Ames) or forward point mutation (CHO-HGPRT) assays, or in the assay for DNA damage (rat primary hepatocyte unscheduled DNA assay) or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenesis assay and the mouse bone marrow erythrocyte micronucleus assay). In the mouse lymphoma assay, a positive finding occurred in the nonactivated but not the activated phase of the study.

Decreased fertility in male rats, shown by lower female conception rates, occurred at an oral dose of 64 mg/kg (approximately 50 times the maximum recommended human daily oral dose on a mg/m^2 basis) and was reversible with cessation of dosing. Loratadine had no effect on male or female fertility or reproduction in the rat at an oral dose of approximately 24 mg/kg (approximately 20 times the maximum recommended human daily oral dose on a mg/m^2 basis).

Pregnancy Category B: There was no evidence of animal teratogenicity in studies performed in rats and rabbits at oral doses up to 96 mg/kg (approximately 75 times and 150 times, respectively, the maximum recommended human daily oral dose on a mg/m^2 basis). There are, however, no adequate and well-controlled

studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CLARITIN should be used during pregnancy only if clearly needed.

Nursing Mothers: Loratadine and its metabolite, descarboethoxyloratadine, pass easily into breast milk and achieve concentrations that are equivalent to plasma levels with an AUC_{milk}/AUC_{plasma} ratio of 1.17 and 0.85 for loratadine and descarboethoxyloratadine, respectively. Following a single oral dose of 40 mg, a small amount of loratadine and descarboethoxyloratadine was excreted into the breast milk (approximately 0.03% of 40 mg over 48 hours). A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when CLARITIN is administered to a nursing woman.

Pediatric Use: The safety of CLARITIN Syrup at a daily dose of 10 mg has been demonstrated in 188 pediatric patients 6-12 years of age in placebo-controlled 2-week trials. The safety and tolerance of CLARITIN syrup at a daily dose of 5 mg has been demonstrated in 60 pediatric patients 2 to 5 years of age in a double-blind, placebo-controlled, 2-week study. The effectiveness of CLARITIN for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in ~~this pediatric age group~~children aged 2 to 12 years is based on an extrapolation of the demonstrated efficacy of CLARITIN in adults in these conditions and the likelihood that the disease course, pathophysiology, and the drug's effect are substantially similar to that of the adults. The recommended dose for the pediatric population is based on cross-study comparison of the pharmacokinetics of CLARITIN in adults and pediatric subjects and on the safety profile of loratadine in both adults and pediatric patients at doses equal to or higher than the recommended doses. The safety and effectiveness of CLARITIN ~~in pediatric patients~~children under ~~6~~2 years of age have not been established.

ADVERSE REACTIONS: CLARITIN Tablets: Approximately 90,000 patients, aged 12 and older, received CLARITIN Tablets 10 mg once daily in controlled and uncontrolled studies. Placebo-controlled clinical trials at the recommended dose of

10 mg once-a-day varied from 2 weeks' to 6 months' duration. The rate of premature withdrawal from these trials was approximately 2% in both the treated and placebo groups.

REPORTED ADVERSE EVENTS WITH AN INCIDENCE OF MORE THAN 2% IN PLACEBO-CONTROLLED ALLERGIC RHINITIS CLINICAL TRIALS IN PATIENTS 12 YEARS OF AGE AND OLDER

PERCENT OF PATIENTS REPORTING

	LORATADINE 10 mg QD N = 1926	PLACEBO N = 2545	CLEMASTINE 1 mg BID N = 536	TERFENADINE 60 mg BID N = 684
Headache	12	11	8	8
Somnolence	8	6	22	9
Fatigue	4	3	10	2
Dry Mouth	3	2	4	3

Adverse events reported in placebo-controlled chronic idiopathic urticaria trials were similar to those reported in allergic rhinitis studies.

Adverse event rates did not appear to differ significantly based on age, sex, or race, although the number of non-white subjects was relatively small.

CLARITIN REDITABS (loratadine rapidly-disintegrating tablets): Approximately 500 patients received CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in controlled clinical trials of 2 weeks' duration. In these studies, adverse events were similar in type and frequency to those seen with CLARITIN Tablets and placebo.

Administration of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) did not result in an increased reporting frequency of mouth or tongue irritation.

CLARITIN Syrup: Approximately 300 pediatric patients 6 to 12 years of age received 10 mg loratadine once daily in controlled clinical trials for a period of 8-15 days. Among these, 188 children were treated with 10 mg loratadine syrup once daily in placebo-controlled trials. Adverse events in these pediatric patients were observed to occur with type and frequency similar to those seen in the adult population. The rate of premature discontinuance due to adverse events among pediatric patients receiving loratadine 10 mg daily was less than 1%.

ADVERSE EVENTS OCCURRING WITH A FREQUENCY OF ≥ 2% IN LORATADINE SYRUP-TREATED PATIENTS (6-12 YEARS OLD) IN PLACEBO-CONTROLLED TRIALS, AND MORE FREQUENTLY THAN IN THE PLACEBO GROUP

	PERCENT OF PATIENTS REPORTING		
	Loratadine 10 mg QD (n = 188)	**Placebo** (n = 262)	**Chlorpheniramine** 2-4 mg BID/TID (n = 170)
Nervousness	4%	2%	2%
Wheezing	4%	2%	5%
Fatigue	3%	2%	5%
Hyperkinesia	3%	1%	1%
Abdominal Pain	2%	0%	0%
Conjunctivitis	2%	<1%	1%
Dysphonia	2%	<1%	0%
Malaise	2%	0%	1%
Upper Respiratory Tract Infection	2%	<1%	0%

Sixty pediatric patients 2 to 5 years of age received 5 mg loratadine once daily in a double-blind, placebo-controlled clinical trial for a period of 14 days. Adverse events in these pediatric patients occurred in both type and frequency similar to those seen in patients 6 to 12 years of age. No serious adverse events were reported and no patients discontinued treatment because of adverse events. There were no reports of hyperkinesia in the loratadine group.

ADVERSE EVENTS OCCURRING WITH A FREQUENCY OF ≥ 2% IN LORATADINE SYRUP-TREATED PATIENTS (2-5 YEARS OLD) IN PLACEBO-CONTROLLED TRIALS, AND MORE FREQUENTLY THAN IN THE PLACEBO GROUP

PERCENT OF PATIENTS REPORTING

	Loratadine 5 mg QD (n = 60)	**Placebo** (n = 61)
Diarrhea	3%	0%
Epistaxis	3%	0%
Pharyngitis	3%	2%
Influenza-like symptoms	2%	0%
Fatigue	2%	0%
Stomatitis	2%	0%
Tooth disorder	2%	0%
Earache	2%	0%
Viral infection	2%	0%
Rash	2%	0%

In addition to those adverse events reported above (≥2%), the following adverse events have been reported in at least one patient in CLARITIN clinical trials in adult and pediatric patients:

Autonomic Nervous System: Altered lacrimation, altered salivation, flushing, hypoesthesia, impotence, increased sweating, thirst.

Body As A Whole: Angioneurotic edema, asthenia, back pain, blurred vision, chest pain, earache, eye pain, fever, leg cramps, malaise, rigors, tinnitus, ~~viral infection~~, weight gain.

Cardiovascular System: Hypertension, hypotension, palpitations, supraventricular tachyarrhythmias, synocope, tachycardia.

Central and Peripheral Nervous System: Blepharospasm, dizziness, dysphonia, hypertonia, migraine, paresthesia, tremor, vertigo.

Gastrointestinal System: Altered taste, anorexia, constipation, diarrhea, dyspepsia, flatulence, gastritis, hiccup, increased appetite, ~~nausea, stomatitis, toothache~~ loose stools, nausea, , vomiting.

Musculoskeletal System: Arthralgia, myalgia.

Psychiatric: Agitation, amnesia, anxiety, confusion, decreased libido, depression, impaired concentration, insomnia, irritability, paroniria.

Reproductive System: Breast pain, dysmenorrhea, menorrhagia, vaginitis.

Respiratory System: Bronchitis, bronchospasm, coughing, dyspnea, ~~epistaxis~~, hemoptysis, laryngitis, nasal dryness, ~~pharyngitis~~, sinusitis, sneezing.

Skin and Appendages: Dermatitis, dry hair, dry skin, photosensitivity reaction, pruritus, purpura, ~~rash~~, urticaria.

Urinary System: Altered micturition, urinary discoloration, urinary incontinence, urinary retention.

In addition, the following spontaneous adverse events have been reported rarely during the marketing of loratadine: abnormal hepatic function, including jaundice, hepatitis, and hepatic necrosis; alopecia; anaphylaxis; breast enlargement; erythema multiforme; peripheral edema; and seizures.

DRUG ABUSE AND DEPENDENCE: There is no information to indicate that abuse or dependency occurs with CLARITIN.

OVERDOSAGE: In adults, somnolence, tachycardia, and headache have been reported with overdoses greater than 10 mg with the Tablet formulation (40 to 180 mg). Extrapyramidal signs and palpitations have been reported in children with

overdoses of greater than 10 mg of CLARITIN Syrup. In the event of overdosage, general symptomatic and supportive measures should be instituted promptly and maintained for as long as necessary.

Treatment of overdosage would reasonably consist of emesis (ipecac syrup), except in patients with impaired consciousness, followed by the administration of activated charcoal to absorb any remaining drug. If vomiting is unsuccessful, or contraindicated, gastric lavage should be performed with normal saline. Saline cathartics may also be of value for rapid dilution of bowel contents. Loratadine is not eliminated by hemodialysis. It is not known if loratadine is eliminated by peritoneal dialysis.

No deaths occurred at oral doses up to 5000 mg/kg in rats and mice (greater than 2400 and 1200 times, respectively, the maximum recommended human daily oral dose on a mg/m^2 basis). Single oral doses of loratadine showed no effects in rats, mice, and monkeys at doses as high as 10 times the maximum recommended human daily oral dose on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION: Adults and children ~~12~~6 years of age and over: The recommended dose of CLARITIN is one 10 mg tablet or reditab, or 2 teaspoonfuls (10 mg) of syrup once daily.

~~Children 6-11~~Children 2-5 years of age: The recommended dose of CLARITIN ~~is 10 mg (2 teaspoonsful)~~Syrup is 5 mg (1 teaspoonful) once daily.

In patients with liver failure or renal insufficiency (GFR < 30 mL/min), one tablet or two teaspoonfuls every other day should be the starting dose.

Administration of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets): Place CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) on the tongue. Tablet disintegration occurs rapidly. Administer ~~with~~ or without water.

HOW SUPPLIED: CLARITIN Tablets: 10 mg, white to off-white compressed tablets; impressed with the product identification number "458" on one side and "CLARITIN 10" on the other; high-density polyethylene plastic bottles of 100 (NDC

0085-0458-03) and 500 (NDC 0085-0458-06). Also available, CLARITIN Unit-of-Use packages of 14 tablets (7 tablets per blister card) (NDC 0085-0458-01) and 30 tablets (10 tablets per blister card) (NDC 0085-0458-05); and 10 x 10 tablet Unit Dose-Hospital Pack (NDC 0085-0458-04).

Protect Unit-of-Use packaging and Unit Dose-Hospital Pack from excessive moisture.

Store between 2° and 30°C (36° and 86°F).

CLARITIN Syrup: Clear, colorless to light-yellow liquid, containing 1 mg loratadine per mL; amber glass bottles of 16 fluid ounces (NDC 0085-1223-01).

Store between 2° and 25°C (36° and 77°F).

CLARITIN REDITABS (loratadine rapidly-disintegrating tablets): CLARITIN REDITABS (loratadine rapidly-disintegrating tablets), 10 mg, white to off-white blister-formed tablet; Unit-of-Use polyvinyl chloride blister packages of 30 tablets (3 laminated foil pouches, each containing one blister card of 10 tablets) supplied with Patient's Instructions for Use (NDC 0085-1128-02);

Keep CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in a dry place.

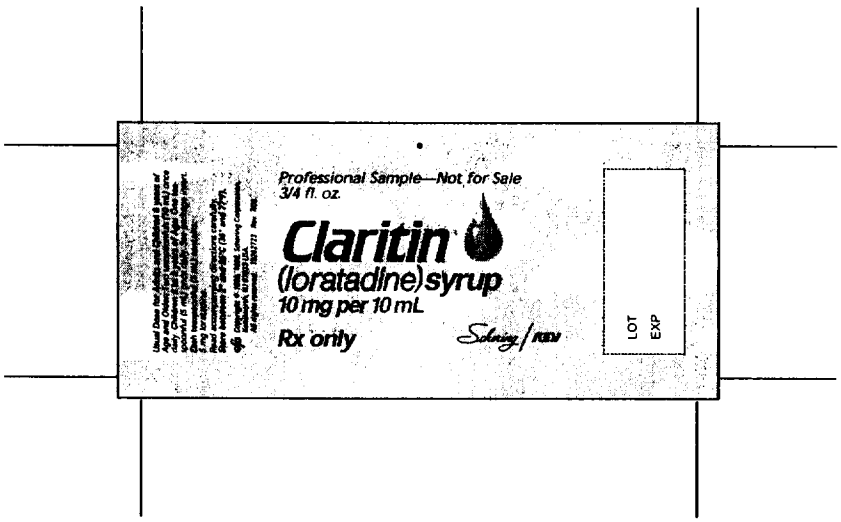
Store between 2° and 25°C (36° and 77°F). Use within 6 months of opening laminated foil pouch, and immediately upon opening individual tablet blister.

Schering Corporation
Kenilworth, New Jersey 07033 USA

X/XX XXXXXXXX

CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) are manufactured for Schering Corporation by Scherer DDS, England.

U.S. Patent Nos. 4,282,233, and 4,371,516

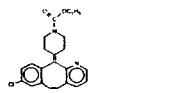

Professional Sample—Not for Sale
3/4 fl. oz.
Claritin
(loratadine) syrup
10 mg per 10 mL
Rx only
Schering / REV
LOT
EXP

F 1964987 3 1711

PRODUCT INFORMATION

CLARITIN®
brand of loratadine
TABLETS, SYRUP, and RAPIDLY-DISINTEGRATING TABLETS

DESCRIPTION Loratadine is a white to off white powder not soluble in water, but very soluble in acetone, alcohol, and chloroform. It has a molecular weight of 382.89, and empirical formula of $C_{22}H_{23}ClN_2O_2$. Its chemical name is ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate and has the following structural formula:



CLARITIN Tablets contain 10 mg micronized loratadine, an antihistamine, to be administered orally. It also contains the following inactive ingredients: corn starch, lactose, and magnesium stearate.

CLARITIN Syrup contains 1 mg/mL micronized loratadine, an antihistamine, to be administered orally. It also contains the following inactive ingredients: citric acid, edetate disodium, artificial flavor, glycerin, propylene glycol, sodium benzoate, sorbitol, and water. The pH is between 2.5 and 3.1.

CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) contain 10 mg micronized loratadine, an antihistamine, to be administered orally. It disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be subsequently swallowed with or without water. CLARITIN REDITABS (loratadine rapidly disintegrating tablets) also contain the following inactive ingredients: citric acid, gelatin, mannitol, and mint flavor.

CLINICAL PHARMACOLOGY Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic activity.

Human histamine skin wheal studies following single and repeated 10 mg oral doses of CLARITIN have shown that the drug exhibits an antihistaminic effect beginning within 1 to 3 hours, reaching a maximum at 8 to 12 hours, and lasting in excess of 24 hours. There was no evidence of tolerance to this effect after 28 days of dosing with CLARITIN.

Whole body autoradiographic studies in rats and monkeys, radiolabelled tissue distribution studies in mice and rats, and *in vivo* radioligand studies in mice have shown that neither loratadine nor its metabolites readily cross the blood-brain barrier. Radioligand binding studies with guinea pig pulmonary and brain H_1-receptors indicate that there was preferential binding to peripheral versus central nervous system H_1-receptors.

Repeated application of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) to the hamster cheek pouch did not cause local irritation.

Pharmacokinetics: Absorption: Loratadine was rapidly absorbed following oral administration of 10 mg tablets, once daily for 10 days to healthy adult volunteers with times to maximum concentration (T_{max}) of 1.3 hours for loratadine and 2.5 hours for its major active metabolite, descarboethoxyloratadine. Based on a cross-study comparison of single doses of loratadine syrup and tablets given to healthy adult volunteers, the plasma concentration profile of descarboethoxyloratadine for the two formulations is comparable. The pharmacokinetics of loratadine and descarboethoxyloratadine are independent of dose over the dose range of 10 mg to 40 mg and are not altered by the duration of treatment. In a single dose study, food increased the systemic bioavailability (AUC) of loratadine and descarboethoxyloratadine by approximately 40% and 15%, respectively. The time to peak plasma concentration (T_{max}) of loratadine and descarboethoxyloratadine was delayed by 1 hour. Peak plasma concentrations (C_{max}) were not affected by food.

Pharmacokinetic studies showed that CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) provide plasma concentrations of loratadine and descarboethoxyloratadine similar to those achieved with CLARITIN Tablets. Following administration of 10 mg loratadine once daily for 10 days with each dosage form in a randomized crossover comparison in 24 normal adult subjects, similar mean steady-state areas under the plasma concentration-time curves (AUC) and peak plasma concentrations (C_{max}) of loratadine were observed. CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) mean AUC and C_{max} were 11% and 6% greater than that of the CLARITIN Tablet values, respectively. Descarboethoxyloratadine bioequivalence was demonstrated between the two formulations. After 10 days of dosing, mean peak plasma concentrations were attained at 1.3 hours and 2.3 hours (T_{max}) for parent and metabolite, respectively.

In a single-dose study with CLARITIN REDITABS (loratadine rapidly-disintegrating tablets), food increased the AUC of loratadine by approximately 48% and did not appreciably affect the AUC of descarboethoxyloratadine. The times to peak plasma concentration (T_{max}) of loratadine and descarboethoxyloratadine were delayed by approximately 2.4 and 3.7 hours, respectively, when food was consumed prior to CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) administration. Parent and metabolite peak concentrations (C_{max}) were not affected by food.

In a single-dose study with CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in 24 subjects, the AUC of loratadine was increased by 26% when administered without water compared to administration with water, while C_{max} was not substantially affected. The bioavailability of descarboethoxyloratadine was not different when administered without water.

Metabolism: In vitro studies with human liver microsomes indicate that loratadine is metabolized to descarboethoxyloratadine predominantly by cytochrome P450 3A4 (CYP3A4) and, to a lesser extent, by cytochrome P450 2D6 (CYP2D6). In the presence of a CYP3A4 inhibitor (ketoconazole), loratadine is metabolized to descarboethoxyloratadine predominantly by CYP2D6. Concurrent administration of loratadine with either ketoconazole, erythromycin (both CYP3A4 inhibitors), or cimetidine (CYP2D6 and CYP3A4 inhibitor) to healthy volunteers was associated with substantially increased plasma concentrations of loratadine (see Drug Interactions section).

Elimination: Approximately 80% of the total loratadine dose administered can be found equally distributed between urine and feces in the form of metabolic products within 10 days. In nearly all patients, exposure (AUC) to the metabolite is greater than to the parent loratadine. The mean elimination half-lives in normal adult subjects ($n = 54$) were 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for descarboethoxyloratadine. Loratadine and descarboethoxyloratadine reached steady-state in most patients by approximately the fifth dosing day. There was considerable variability in the pharmacokinetic data in all studies of CLARITIN Tablets and Syrup, probably due to the extensive first-pass metabolism.

Special Populations: Pediatric: The pharmacokinetic profile of loratadine in children in the 6- to 12-year age group is similar to that of adults. In a single-dose pharmacokinetic study of 13 pediatric volunteers (aged 8 to 12 years) given 10 mL of CLARITIN Syrup containing 10 mg loratadine, the ranges of individual subject values of pharmacokinetic parameters (AUC and C_{max}) were comparable to those following administration of a 10 mg tablet or syrup to adult volunteers.

The pharmacokinetic profile of loratadine in children in the 2 to 5 year age group ($n = 18$) is similar to that of adults. In a single dose pharmacokinetic study of pediatric subjects (age 2 to 5 years) given 5 mL of CLARITIN Syrup containing 5 mg loratadine, the range of individual subject values of pharmacokinetic parameters (AUC and C_{max}) were comparable to those following administration of a 10 mg tablet or syrup to adult volunteers or children eight years of age and older.

Geriatric: In a study involving 12 healthy geriatric subjects (66 to 78 years old), the AUC and peak plasma levels (C_{max}) of both loratadine and descarboethoxyloratadine were approximately 50% greater than those observed in studies of younger subjects. The mean elimination half-lives for the geriatric subjects were 18.2 hours (range = 6.7 to 37 hours) for loratadine and 17.5 hours (range = 11 to 38 hours) for descarboethoxyloratadine.

Renal Impairment: In a study involving 12 subjects with chronic renal impairment (creatinine clearance ≤ 30 mL/min), both AUC and C_{max} increased by approximately 73% for loratadine and by 120% for descarboethoxyloratadine, as compared to six subjects with normal renal function (creatinine clearance ≥ 80 mL/min). The mean elimination half-lives of loratadine (76 hours) and descarboethoxyloratadine (23.9 hours) were not substantially different from that observed in normal subjects. Hemodialysis does not have an effect on the pharmacokinetics of loratadine or descarboethoxyloratadine in subjects with chronic renal impairment.

Hepatic Impairment: In seven patients with chronic alcoholic liver disease, the AUC and C_{max} of loratadine were double while the pharmacokinetic profile of descarboethoxyloratadine was not substantially different from that observed in other trials involving normal subjects. The elimination half-lives for loratadine and descarboethoxyloratadine were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

Clinical Trials: Clinical trials of CLARITIN Tablets involved over 10,700 patients, 12 years of age and older, who received either CLARITIN Tablets or another antihistamine and/or placebo in double-blind randomized controlled studies. In placebo-controlled trials, 10 mg once daily of CLARITIN Tablets was superior to placebo and similar to clemastine (1 mg BID) or terfenadine (60 mg BID) in effects on nasal and non-nasal symptoms of allergic rhinitis. In these studies, somnolence occurred less frequently with CLARITIN Tablets than with clemastine and at about the same frequency as terfenadine or placebo. In studies with CLARITIN Tablets at doses two to four times higher than the recommended dose of 10 mg, a dose-related increase in the incidence of somnolence was observed. Therefore, some patients, particularly those with hepatic or renal impairment and the elderly, or those on medications that impair clearance of loratadine and its metabolites, may experience somnolence. In addition, three placebo-controlled, double-blind, 2-week trials in 188 pediatric patients with seasonal allergic rhinitis aged 6 to 12 years, were conducted at doses of CLARITIN Syrup up to 10 mg once daily. In a double-blind, placebo-controlled study, the safety of 5 mg loratadine, administered in 5 mL of CLARITIN Syrup, was evaluated in 80 pediatric patients between 2 and 5 years of age. No unexpected adverse events were observed.

Clinical trials of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) involved over 1300 patients who received either CLARITIN REDITABS (loratadine rapidly-disintegrating tablets), CLARITIN Tablets, or placebo in placebo-controlled trials. One CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) once daily was superior to placebo and similar to CLARITIN Tablets in effects on nasal and non-nasal symptoms of seasonal allergic rhinitis.

Among those patients involved in double-blind, randomized, controlled studies of CLARITIN Tablets, approximately 1000 patients (age 12 and older) were enrolled in studies of chronic idiopathic urticaria. In placebo-controlled clinical trials, CLARITIN Tablets 10 mg once daily were superior to placebo in the management of chronic idiopathic urticaria, as demonstrated by reduction of associated itching, erythema, and hives. In these studies, the incidence of somnolence seen with CLARITIN Tablets was similar to that seen with placebo.

In a study in which CLARITIN Tablets were administered to adults at four times the clinical dose for 90 days, no clinically significant increase in the QT, was seen on ECGs.

In a single-rising dose study in which doses up to 180 mg (18 times the clinical dose) were studied, loratadine did not cause any clinically significant changes on the QT, interval in the ECGs.

INDICATIONS AND USAGE CLARITIN is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria in patients 2 years of age or older.

CONTRAINDICATIONS CLARITIN is contraindicated in patients who are hypersensitive to this medication or to any of its ingredients.

PRECAUTIONS *General:* Patients with liver impairment or renal insufficiency (GFR < 30 mL/min) should be given a lower initial dose (10 mg every other day). (See CLINICAL PHARMACOLOGY: Special Populations.)

Drug Interactions: Loratadine (10 mg once daily) has been coadministered with therapeutic doses of erythromycin, cimetidine, and ketoconazole in controlled clinical pharmacology studies in adult volunteers. Although increased plasma concentrations (AUC 0-24 hrs) of loratadine and/or descarboethoxyloratadine were observed following coadministration of loratadine with each of these drugs in normal volunteers ($n = 24$ in each study), there were no clinically relevant changes in the safety profile of loratadine, as assessed by electrocardiographic parameters, clinical laboratory tests, vital signs, and adverse events. There were no significant effects on QT, intervals, and no reports of sedation or syncope. No effects on plasma concentrations of cimetidine or ketoconazole were observed. Plasma concentrations (AUC 0-24 hrs) of erythromycin decreased 15% with coadministration of loratadine relative to that observed with erythromycin alone. The clinical relevance of this difference is unknown. These above findings are summarized in the following table:

Effects on Plasma Concentrations (AUC 0-24 hrs) of Loratadine and Descarboethoxyloratadine After 10 Days of Coadministration (Loratadine 10 mg) in Normal Volunteers

	Loratadine	Descarboethoxyloratadine
Erythromycin (500 mg Q8h)	+ 40%	+46%
Cimetidine (300 mg Q8h)	+103%	+ 6%
Ketoconazole (200 mg Q12h)	+307%	+73%

There does not appear to be an increase in adverse events in subjects who received oral contraceptives and loratadine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: In an 18-month carcinogenicity study in mice and a 2-year study in rats, loratadine was administered in the diet at doses up to 40 mg/kg (mice) and 25 mg/kg (rats). In the carcinogenicity studies, pharmacokinetic assessments were carried out to determine animal exposure to the drug. AUC data demonstrated that the exposure of mice given 40 mg/kg of loratadine was 3.6 (loratadine) and 18 (descarboethoxyloratadine) times the exposure in adults and 5 (loratadine) and 20 (descarboethoxyloratadine) times the exposure in children given the maximum recommended daily oral dose. Exposure of rats given 25 mg/kg of loratadine was 28 (loratadine) and 67 (descarboethoxyloratadine) times the exposure in adults and 40 (loratadine) and 80 (descarboethoxyloratadine) times the exposure in children given the maximum recommended daily oral dose. Male mice given 40 mg/kg had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg and males and females given 25 mg/kg. Exposure of rats given 10 mg/kg of loratadine was 10 (loratadine) and 15 (descarboethoxyloratadine) times the exposure in adults and 15 (loratadine) and 20 (descarboethoxyloratadine) times the exposure in children given the maximum recommended daily oral dose. The clinical significance of these findings during long-term use of CLARITIN is not known.

In mutagenicity studies, there was no evidence of mutagenic potential in reverse (Ames) or forward point mutation (CHO-HGPRT) assays, or in the assay for DNA damage (rat primary hepatocyte unscheduled DNA assay) or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenesis assay and the mouse bone marrow erythrocyte micronucleus assay). In the mouse lymphoma assay, a positive finding occurred in the noninactivated but not the activated phase of the study.

Decreased fertility in male rats, shown by lower female conception rates, occurred at an oral dose of 64 mg/kg (approximately 50 times the maximum recommended human daily oral dose on a mg/m² basis) and was reversible with cessation of dosing. Loratadine had no effect on male or female fertility or reproduction in the rat at an oral dose of approximately 24 mg/kg (approximately 20 times the maximum recommended human daily oral dose on a mg/m² basis).

Pregnancy Category B: There was no evidence of animal teratogenicity in studies performed in rats and rabbits at oral doses up to 96 mg/kg (approximately 75 times and 150 times, respectively, the maximum recommended human daily oral dose on a mg/m² basis). There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CLARITIN should be used during pregnancy only if clearly needed.

Nursing Mothers: Loratadine and its metabolite, descarboethoxyloratadine, pass easily into breast milk and achieve concentrations that are equivalent to plasma levels with an AUC_{milk}/AUC_{plasma} ratio of 1.17 and 0.85 for loratadine and descarboethoxyloratadine, respectively. Following a single oral dose of 40 mg, a small amount of loratadine and descarboethoxyloratadine was excreted into the breast milk (approximately 0.07% of 40 mg over 48 hours). A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when CLARITIN is administered to a nursing woman.

Pediatric Use: The safety of CLARITIN Syrup at a daily dose of 10 mg has been demonstrated in 188 pediatric patients 6 to 12 years of age in placebo-controlled 2 week trials. The safety and tolerability of CLARITIN Syrup at a daily dose of 5 mg has been demonstrated in 60 pediatric patients 2 to 5 years of age in a double-blind, placebo-controlled, 2 week study. The effectiveness of CLARITIN for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in children aged 2 to 12 years is based on an extrapolation of the demonstrated efficacy of CLARITIN in adults in these conditions and the likelihood that the disease course, pathophysiology, and the drug's effect are substantially similar to that of the adults. The recommended dose for the pediatric population is based on cross-study comparison of the pharmacokinetics of CLARITIN in adults and pediatric subjects and on the safety profile of loratadine in both adults and pediatric patients at doses equal to or higher than the recommended doses. The safety and effectiveness of CLARITIN in children under 2 years of age have not been established.

ADVERSE REACTIONS **CLARITIN Tablets:** Approximately 80,000 patients, aged 12 and older, received CLARITIN Tablets 10 mg once daily in controlled and uncontrolled studies. Placebo-controlled clinical trials at the recommended dose of 10 mg once a day varied from 2 weeks to 6 months' duration. The rate of premature withdrawal from these trials was approximately 2%, in both the treated and placebo groups.

REPORTED ADVERSE EVENTS WITH AN INCIDENCE OF MORE THAN 2% IN PLACEBO CONTROLLED ALLERGIC RHINITIS CLINICAL TRIALS IN PATIENTS 12 YEARS OF AGE AND OLDER

	PERCENT OF PATIENTS REPORTING			
	LORATADINE 10 mg QD n = 1926	PLACEBO n = 2545	CLEMASTINE 1 mg BID n = 536	TERFENADINE 60 mg BID n = 684
Headache	12	11	8	8
Somnolence	8	6	22	9
Fatigue	4	3	10	2
Dry Mouth	3	2	4	3

Adverse events reported in placebo-controlled chronic idiopathic urticaria trials were similar to those reported in allergic rhinitis studies.

Adverse event rates did not appear to differ significantly based on age, sex, or race, although the number of nonwhite subjects was relatively small.

CLARITIN REDITABS (loratadine rapidly-disintegrating tablets): Approximately 500 patients received CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in controlled clinical trials of 2 weeks' duration. In these studies, adverse events were similar in type and frequency to those seen with CLARITIN Tablets and placebo.

Administration of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) did not result in an increased reporting frequency of mouth or tongue irritation.

CLARITIN Syrup: Approximately 300 pediatric patients 6 to 12 years of age received 10 mg loratadine once daily in controlled clinical trials for a period of 8 to 15 days. Among these, 188 children were treated with 10 mg loratadine syrup once daily in placebo-controlled trials. Adverse events in these pediatric patients were observed to occur with type and frequency similar to those seen in the adult population. The rate of premature discontinuance due to adverse events among pediatric patients receiving loratadine 10 mg daily was less than 1%.

ADVERSE EVENTS OCCURRING WITH A FREQUENCY OF ≥ 2% IN LORATADINE SYRUP-TREATED PATIENTS (6 TO 12 YEARS OLD) IN PLACEBO-CONTROLLED TRIALS, AND MORE FREQUENTLY THAN IN THE PLACEBO GROUP

	PERCENT OF PATIENTS REPORTING		
	LORATADINE 10 mg QD n = 188	PLACEBO n = 262	CHLORPHENIRAMINE 2.4 mg BID/TID n = 170
Nervousness	4	2	2
Wheezing	4	2	5
Fatigue	3	2	5
Hyperkinesia	3	1	1
Abdominal Pain	2	0	0
Conjunctivitis	2	<1	1
Dysphonia	2	<1	0
Malaise	2	0	1
Upper Respiratory Tract Infection	2	<1	0

Sixty pediatric patients, 2 to 5 years of age received 5 mg loratadine once daily in a double-blind, placebo-controlled clinical trial for a period of 14 days. No unexpected adverse events were seen given the known safety profile of loratadine and likely adverse reactions for this patient population. The following adverse events occurred with a frequency of 2 to 3 percent in the loratadine syrup-treated patients (2 to 5 years old) during the placebo-controlled trial, and more frequently than in the placebo group: diarrhea, epistaxis, pharyngitis, influenza-like symptoms, fatigue, stomatitis, tooth disorder, earache, viral infection, and rash.

In addition to those adverse events reported above (≥ 2%), the following adverse events have been reported in at least one patient on CLARITIN clinical trials in adult and pediatric patients:

Autonomic Nervous System: altered lacrimation, altered salivation, flushing, hypoesthesia, impotence, increased sweating, thirst.

Body as a Whole: angioneurotic edema, asthenia, back pain, blurred vision, chest pain, earache, eye pain, fever, leg cramps, malaise, rigors, tinnitus, weight gain.

Cardiovascular System: hypertension, hypotension, palpitations, supraventricular tachyarrhythmias, syncope, tachycardia.

Central and Peripheral Nervous System: blepharospasm, dizziness, dysphonia, hypertonia, migraine, paresthesia, tremor, vertigo.

Gastrointestinal System: altered taste, anorexia, constipation, diarrhea, dyspepsia, flatulence, gastritis, hiccup, increased appetite, loose stools, nausea, vomiting.

Musculoskeletal System: arthralgia, myalgia.

Psychiatric: agitation, amnesia, anxiety, confusion, decreased libido, depression, impaired concentration, insomnia, irritability, paronoria.

Reproductive System: breast pain, dysmenorrhea, menorrhagia, vaginitis.

Respiratory System: bronchitis, bronchospasm, coughing, dyspnea, hemoptysis, laryngitis, nasal dryness, sinusitis, sneezing.

Skin and Appendages: dermatitis, dry hair, dry skin, photosensitivity reaction, pruritus, purpura, urticaria.

Urinary System: altered micturition, urinary discoloration, urinary incontinence, urinary retention.

In addition, the following spontaneous adverse events have been reported rarely during the marketing of loratadine: abnormal hepatic function, including jaundice, hepatitis, and hepatic necrosis; alopecia; anaphylaxis; breast enlargement; erythema multiforme; peripheral edema; thrombocytopenia; and seizures.

DRUG ABUSE AND DEPENDENCE There is no information to indicate that abuse or dependency occurs with CLARITIN.

OVERDOSAGE In adults, somnolence, tachycardia, and headache have been reported with overdoses greater than 10 mg with the Tablet formulation (40 mg-180 mg). Extrapyramidal signs and palpitations have been reported in children with overdoses of greater than 10 mg of CLARITIN Syrup. In the event of overdosage, general symptomatic and supportive measures should be instituted promptly and maintained for as long as necessary.

Treatment of overdosage would reasonably consist of emesis (ipecac syrup), except in patients with impaired consciousness, followed by the administration of activated charcoal to absorb any remaining drug. If vomiting is unsuccessful or contraindicated, gastric lavage should be performed with normal saline. Saline cathartics may also be of value for rapid dilution of bowel contents. Loratadine is not eliminated by hemodialysis. It is not known if loratadine is eliminated by peritoneal dialysis.

No deaths occurred at oral doses up to 5000 mg/kg in mice (approximately 1200 and 1400 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m² basis). No deaths occurred at oral doses up to 5000 mg/kg in matured rats (approximately 2400 and 2900 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m² basis). However, lethality occurred in juvenile rats at an oral dose of 125 mg/kg (approximately 100 and 70 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m² basis). No deaths occurred at oral doses up to 1280 mg/kg in monkeys (approximately 2100 and 1500 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m² basis).

DOSAGE AND ADMINISTRATION Adults and children 6 years of age and over: The recommended dose of CLARITIN is one 10 mg tablet or reditab, or 2 teaspoonfuls (10 mg) of syrup once daily.

Children 2 to 5 years of age: The recommended dose of CLARITIN Syrup is 5 mg (1 teaspoonful) once daily.

In adults and children 6 years of age and over with liver failure or renal insufficiency (GFR < 30 mL/min): the starting dose should be 10 mg (one tablet or two teaspoonfuls) every other day. In children 2 to 5 years of age with liver failure or renal insufficiency, the starting dose should be 5 mg (one teaspoonful) every other day.

Administration of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets): Place CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) on the tongue. Tablet disintegration occurs rapidly. Administer with or without water.

HOW SUPPLIED **CLARITIN Tablets:** 10 mg, white to off-white compressed tablets, impressed with the product identification number "458" on one side and "CLARITIN 10" on the other; high-density polyethylene plastic bottles of 100 (NDC 0085-0458-03) and 500 (NDC 0085-0458-06). Also available, CLARITIN Unit-of-Use packages of 30 tablets (10 tablets per blister card) (NDC 0085-0458-05) and 10 x 10 tablet Unit Dose Hospital Pack (NDC 0085-0458-04).

Protect Unit-of-Use packaging and Unit Dose Hospital Pack from excessive moisture.

Store between 2° and 30°C (36° and 86°F).

CLARITIN Syrup: Clear, colorless to light-yellow liquid, containing 1 mg loratadine per mL; amber glass bottles of 16 fluid ounces (NDC 0085-1227-01).

Store between 2° and 25°C (36° and 77°F).

CLARITIN REDITABS (loratadine rapidly-disintegrating tablets): CLARITIN REDITABS (loratadine rapidly-disintegrating tablets), 10 mg, white to off-white blister-formed tablet, impressed with the letter "C" on one side. Unit-of-Use polyvinyl chloride blister packages of 30 tablets (three laminated foil pouches, each containing one blister card of 10 tablets) supplied with Patient's Instructions for Use (NDC 0085-1178-02).

Keep CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in a dry place.

Store between 2° and 25°C (36° and 77°F). Use within 6 months of opening laminated foil pouch, and immediately upon opening individual tablet blister.

Schering Corporation
Kenilworth, NJ 07033 USA

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CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) are manufactured for Schering Corporation by Scherer DDS, England.

U.S. Patent Nos. 4,282,233 and 4,371,516

CLARITIN®
brand of loratadine
TABLETS, SYRUP, and RAPIDLY-DISINTEGRATING TABLETS