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enomas 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 a 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 effectiveness of CLARITIN for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in this pediatric age group 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 under 6 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.

[See first table at top of previous page]

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 8–15 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%.

[See second table on previous page]

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, fever, malaise, rigors.

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, nausea, stomatitis, toothache, vomiting.

Musculoskeletal System: Arthralgia, myalgia.

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

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 years of age and over: The recommended dose of CLARITIN is 10 mg once daily.

Children 6–11 years of age: The recommended dose of CLARITIN is 10 mg (2 teaspoonfuls) 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

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.

Shown in Product Identification Guide, pages 335 and 336

CLARITIN-D® 12 HOUR

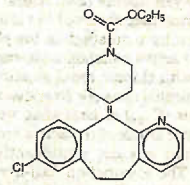
brand of loratadine and pseudoephedrine sulfate, USP Extended Release Tablets

CAUTION: Federal Law Prohibits Dispensing Without Prescription

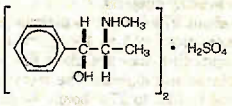
DESCRIPTION

CLARITIN-D 12 HOUR Extended Release Tablets contain 5 mg loratadine in the tablet coating for immediate release and 120 mg pseudoephedrine sulfate, USP equally distributed between the tablet coating for immediate release and the barrier-coated extended release core.

Loratadine is a white to off-white powder, not soluble in water, but very soluble in acetone, alcohol, and chloroform. Loratadine has a molecular weight of 382.89 and empirical formula of $C_{22}H_{23}ClN_2O_2$; the chemical name, 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 chemical structure:



Pseudoephedrine sulfate is the synthetic salt of one of the naturally occurring dextrorotatory diastereomers of ephedrine and is classified as an indirect sympathomimetic amine. The empirical formula for pseudoephedrine sulfate is $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$; the chemical name is [S-(R*,R*)]-α-[1(methylamino)ethyl] benzenemethanol sulfate (2:1) (salt), and the following chemical structure:



The molecular weight of pseudoephedrine sulfate is 428.54. It is a white powder, freely soluble in water and methanol and sparingly soluble in chloroform.

The inactive ingredients for CLARITIN-D 12 HOUR Extended Release Tablets are acacia, butylparaben, calcium sulfate, carnauba wax, corn starch, lactose, magnesium stearate, microcrystalline cellulose, neutral soap, oleic acid, povidone, rosin, sugar, talc, titanium dioxide, white wax, and zein.

CLINICAL PHARMACOLOGY

The following information is based upon studies of loratadine alone or psudoephedrine alone, except as indicated.

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 oral doses of loratadine 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 developing after 28 days of dosing with loratadine.

Pharmacokinetic studies following single and multiple oral doses of loratadine in 115 volunteers showed that loratadine is rapidly absorbed and extensively metabolized to an active metabolite (descarboethoxyloratadine). Approximately 80% of the total dose administered can be found equally distributed between urine and feces in the form of metabolic products after 10 days. The mean elimination half-lives found in studies 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 the major active metabolite (descarboethoxyloratadine). In nearly all patients, exposure (AUC) to the metabolite is greater than exposure to parent loratadine. Loratadine and descarboethoxyloratadine reached steady-state in most patients by approximately the fifth dosing day. The pharmacokinetics of loratadine and descarboethoxyloratadine are dose independent over the dose range of 10 to 40 mg and are not significantly altered by the duration of treatment.

In vitro studies with human liver microsomes indicate that loratadine is metabolized to descarboethoxyloratadine predominantly by P450 CYP3A4 and, to a lesser extent, by

Continued on next page

P450 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 significantly increased plasma concentrations of loratadine (see **Drug Interactions** section).

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 significantly higher (approximately 50% increased) than in studies of younger subjects. The mean elimination half-lives for the elderly subjects were 18.2 hours (range = 6.7 to 37 hours) for loratadine and 17.5 hours (range = 11 to 38 hours) for the active metabolite.

In the clinical efficacy studies, loratarine was administered before meals. In a single-dose study, food increased the AUC of loratadine by approximately 40% and of descarboethoxyloratadine by approximately 15%. The time of peak plasma concentration (T_{max}) of loratadine and descarboethoxyloratadine was delayed by 1 hour with a meal.

In patients with chronic renal impairment (creatinine clearance ≤ 30 mL/min) both the AUC and peak plasma levels (C_{max}) increased on average by approximately 73% for loratadine; and approximately by 120% for descarboethoxyloratadine, compared to individuals with normal renal function. The mean elimination half-lives of loratadine (7.6 hours) and descarboethoxyloratadine (23.9 hours) were not significantly different from that observed in normal subjects. Hemodialysis does not have an effect on the pharmacokinetics of loratadine or its active metabolite (descarboethoxyloratadine) in subjects with chronic renal impairment.

In patients with chronic alcoholic liver disease the AUC and peak plasma levels (C_{max}) of loratadine were double while the pharmacokinetic profile of the active metabolite (descarboethoxyloratadine) was not significantly changed from that in normals. The elimination half-lives for loratadine and descarboethoxyloratadine were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

There was considerable variability in the pharmacokinetic data in all studies of loratadine, probably due to the extensive first-pass metabolism. Individual histograms of area under the curve, clearance, and volume of distribution showed a log normal distribution with a 25-fold range in distribution in healthy subjects.

Loratadine is about 97% bound to plasma proteins at the expected concentrations (2.5 to 100 ng/mL) after a therapeutic dose. Loratadine does not affect the plasma protein binding of warfarin and digoxin. The metabolite descarboethoxyloratadine is 73% to 77% bound to plasma proteins (at 0.5 to 100 ng/mL).

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.

In a study in which loratadine was administered at four 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 of loratadine alone in which doses up to 160 mg (16 times the clinical dose) were administered, no clinically significant changes on the QT_c interval in the ECGs were observed.

Pseudoephedrine sulfate (d-isoephedrine sulfate) is an orally active sympathomimetic amine which exerts a decongestant action on the nasal mucosa. It is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects.

The pseudoephedrine component of CLARITIN-D 12 HOUR Extended Release Tablets were absorbed at a similar rate and was equally available from the combination tablet as from a pseudoephedrine sulfate repetabs 120 mg tablet. Mean (%CV) steady-state peak plasma concentration of 464 ng/mL (22) was attained at 3.9 hours (50). The terminal half-life of pseudoephedrine from the combination tablet administered twice daily was 6.3 hours (23). The ingestion of food was found not to affect the absorption of pseudoephedrine from CLARITIN-D 12 HOUR Extended Release Tablets. Loratadine and pseudoephedrine sulfate do not influence the pharmacokinetics of each other when administered concomitantly.

Clinical Studies: Clinical trials of CLARITIN-D 12 HOUR Extended Release Tablets in seasonal allergic rhinitis involved approximately 3700 patients who received either the combination product, a comparative treatment, or placebo, in double-blind, randomized controlled studies. Four of the largest studies involved approximately 1600 patients in comparisons of the combination product, loratadine (5 mg bid), pseudoephedrine sulfate (120 mg bid), and placebo. Improvement in symptoms of seasonal allergic rhinitis for patients receiving CLARITIN-D 12 HOUR Extended Release Tablets was significantly greater than placebo for sneezing, rhinorrhea, nasal pruritus, and eye tearing more than pseudoephedrine and reduced the intensity of nasal congestion more than loratadine, demonstrating a contribution of each of the components. The onset of antihistamine and nasal decongestant actions occurred after the first dose of CLARITIN-D 12 HOUR Extended Release Tablets. CLARITIN-D 12 HOUR Extended Release Tablets were well tolerated, with a frequency of sedation similar to that seen with placebo, and an adverse event profile clinically similar to that of pseudoephedrine.

In a 6-week, placebo-controlled study of 193 patients with seasonal allergic rhinitis and concomitant mild to moderate asthma, CLARITIN-D 12 HOUR Extended Release Tablets twice daily improved seasonal allergic rhinitis signs and symptoms with no decrease in pulmonary function or adverse effects of asthma symptoms. This supports the safety of administering CLARITIN-D 12 HOUR Extended Release Tablets to seasonal allergic rhinitis patients with asthma.

INDICATIONS AND USAGE

CLARITIN-D 12 HOUR Extended Release Tablets are indicated for the relief of symptoms of seasonal allergic rhinitis. CLARITIN-D 12 HOUR Extended Release Tablets should be administered when both the antihistaminic properties of CLARITIN (loratadine) and the nasal decongestant activity of pseudoephedrine are designed (see **CLINICAL PHARMACOLOGY**).

CONTRAINDICATIONS

CLARITIN-D 12 HOUR Extended Release Tablets are contraindicated in patients who are hypersensitive to this medication or to any of its ingredients.

This product, due to its pseudoephedrine component, is contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen (14) days of stopping such treatment (see **Drug Interactions** section).

It is also contraindicated in patients with severe hypertension, severe coronary artery disease, and in those who have shown hypersensitivity or idiosyncrasy to its components, to adrenergic agents, or to other drugs of similar chemical structures. Manifestations of patient idiosyncrasy to adrenergic agents include: insomnia, dizziness, weakness, tremor, or arrhythmias.

WARNINGS

CLARITIN-D 12 HOUR Extended Release Tablets should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy. Central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension may be produced by sympathomimetic amines.

Use in Patients Approximately 60 Years and Older: The safety and efficacy of CLARITIN-D 12 HOUR Extended Release Tablets in patients greater than 60 years old have not been investigated in placebo-controlled clinical trials. The elderly are more likely to have adverse reactions to sympathomimetic amines.

PRECAUTIONS

General: Because the doses of this fixed combination product cannot be individually titrated and hepatic insufficiency results in a reduced clearance of loratadine to a much greater extent than pseudoephedrine, CLARITIN-D 12 HOUR Extended Release Tablets should generally be avoided in patients with hepatic insufficiency. Patients with renal insufficiency (GFR < 30 mL/min) should be given a lower initial dose (one tablet per day) because they have reduced clearance of loratadine and pseudoephedrine.

Information for Patients: Patients taking CLARITIN-D 12 HOUR Extended Release Tablets should receive the following information: CLARITIN-D 12 HOUR Extended Release Tablets are prescribed for the relief of symptoms of seasonal allergic rhinitis. Patients should be instructed to take CLARITIN-D 12 HOUR Extended Release Tablets only as prescribed and not to exceed the prescribed dose. Patients should also be advised against the concurrent use of CLARITIN-D 12 HOUR Extended Release Tablets with over-the-counter antihistamines and decongestants.

This product should not be used by patients who are hypersensitive to it or to any of its ingredients. Due to its pseudoephedrine component, this product should not be used by patients with narrow-angle glaucoma, urinary retention, or by patients receiving a monoamine oxidase (MAO) inhibitor or within 14 days of stopping use of an MAO inhibitor. It also should not be used by patients with severe hypertension or severe coronary artery disease.

Patients who are or may become pregnant should be told that this product should be used in pregnancy or during lactation only if the potential benefit justifies the potential risk to the fetus or nursing infant.

Patients should be instructed not to break or chew the tablet.

Drug Interactions: No specific interaction studies have been conducted with CLARITIN-D 12 HOUR Extended Release Tablets. However, loratadine (10 mg once daily) has been safely coadministered with therapeutic doses of erythromycin, cimetidine, and ketoconazole in controlled clinical pharmacology studies. Although increased plasma concentrations (AUC 0-24 hrs) or 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 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%
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.

CLARITIN-D 12 HOUR Extended Release Tablets (pseudoephedrine component) are contraindicated in patients taking monoamine oxidase inhibitors and for 2 weeks after stopping use of an MAO inhibitor. The antihypertensive effects of beta-adrenergic blocking agents, methyldopa, mecamylamine, reserpine, and veratrum alkaloids may be reduced by sympathomimetics. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis.

Drug/Laboratory Test Interactions: The *in vitro* addition of pseudoephedrine to sera containing the cardiac isoenzyme MB of serum creatinine phosphokinase progressively inhibits the activity of the enzyme. The inhibition becomes complete over 6 hours.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There are no animal laboratory studies on the combination product loratadine and pseudoephedrine sulfate to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

In an 18-month oncogenicity 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 (active metabolite) times higher than a human given 10 mg/day. Exposure of rats given 25 mg/kg of loratadine was 28 (loratadine) and 67 (active metabolite) times higher than a human given 10 mg/day. 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 loratadine is not known.

In mutagenicity studies with loratadine alone, 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.

Loratadine administration produced hepatic microsomal enzyme induction in the mouse at 40 mg/kg and rat at 25 mg/kg, but not at lower doses.

Decreased fertility in male rats, shown by lower female conception rates, occurred at approximately 64 mg/kg of loratadine and was reversible with cessation of dosing. Loratadine had no effect on male or female fertility or reproduction in the rat at doses approximately 24 mg/kg.

Pregnancy Category B: There was no evidence of animal teratogenicity in reproduction studies performed on rats and rabbits with this combination at oral doses up to 150 mg/kg (885 mg/m^2 or 5 times the recommended daily human dosage of 250 mg or 185 mg/m^2), and 120 mg/kg (1416 mg/m^2 or 8 times the recommended daily human dosage), respectively. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CLARITIN-D 12 HOUR Extended Release Tablets should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known if this combination product is excreted in human milk. However, loratadine when administered alone 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 the parent and active metabolite, respectively. Following a single oral dose of 40 mg, a small amount of loratadine and metabolite was excreted into the breast milk (approximately 0.03% of 40 mg after 48 hours). Pseudoephedrine administered alone also distributes into breast milk of the lactating human female. Pseudoephedrine concentrations in milk are consistently higher than those in plasma. The total amount of drug in milk as judged by the area under the curve (AUC) is 2 to 3 times greater than in plasma. The fraction of a pseudoephedrine dose excreted in milk is estimated to be 0.4% to

REPORTED ADVERSE EVENTS WITH AN INCIDENCE OF ≥2% ON CLARITIN-D 12 HOUR EXTENDED RELEASE TABLETS IN PLACEBO-CONTROLLED CLINICAL TRIALS PERCENT OF PATIENTS REPORTING

	CLARITIN-D® 12 HOUR n=1023	Loratadine n=543	Pseudo-ephedrine n=548	Placebo n=922
Headache	19	18	17	19
Insomnia	16	4	19	3
Dry Mouth	14	4	9	3
Somnolence	7	8	5	4
Nervousness	5	3	7	2
Dizziness	4	1	5	2
Fatigue	4	6	3	3
Dyspepsia	3	2	3	1
Nausea	3	2	3	2
Pharyngitis	3	3	2	3
Anorexia	2	1	2	1
Thirst	2	1	2	1

ercised when CLARITIN-D 12 HOUR Extended Release Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 years have not been established.

ADVERSE REACTIONS

Experience from controlled and uncontrolled clinical studies involving approximately 10,000 patients who received the combination of loratadine and pseudoephedrine sulfate for a period of up to 1 month provides information on adverse reactions. The usual dose was one tablet every 12 hours for up to 28 days.

In controlled clinical trials using the recommended dose of one tablet every 12 hours, the incidence of reported adverse events was similar to those reported with placebo, with the exception of insomnia (16%) and dry mouth (14%).

[See table above]

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.

In addition to those adverse events reported above (≥2%), the following less frequent adverse events have been reported in at least one patient treated with CLARITIN-D 12 HOUR Extended Release Tablets:

Autonomic Nervous System: Abnormal lacrimation, dehydration, flushing, hypoesthesia, increased sweating, mydriasis.

Body As A Whole: Asthenia, back pain, blurred vision, chest pain, conjunctivitis, earache, ear infection, eye pain, fever, flu-like symptoms, leg cramps, lymphadenopathy, malaise, photophobia, rigors, tinnitus, viral infection, weight gain.

Cardiovascular System: Hypertension, hypotension, palpitations, peripheral edema, syncope, tachycardia, ventricular extrasystoles.

Central and Peripheral Nervous System: Dysphonia, hyperkinesia, hypertonia, migraine, paresthesia, tremors, vertigo.

Gastrointestinal System: Abdominal distension, abdominal distress, abdominal pain, altered taste, constipation, diarrhea, eructation, flatulence, gastritis, gingival bleeding, hemorrhoids, increased appetite, stomatitis, taste loss, tongue discoloration, toothache, vomiting.

Liver and Biliary System: Hepatic function abnormal.

Musculoskeletal System: Arthralgia, myalgia, torticollis.

Psychiatric: Aggressive reaction, agitation, anxiety, apathy, confusion, decreased libido, depression, emotional lability, euphoria, impaired concentration, irritability, paroniria.

Reproductive System: Dysmenorrhea, impotence, intermenstrual bleeding, vaginitis.

Respiratory System: Bronchitis, bronchospasm, chest congestion, coughing, dry throat, dyspnea, epistaxis, halitosis, nasal congestion, nasal irritation, sinusitis, sneezing, sputum increased, upper respiratory infection, wheezing.

Skin and Appendages: Acne, bacterial skin infection, dry skin, eczema, edema, epidermal necrolysis, erythema, hematoma, pruritus, rash, urticaria.

Urinary System: Dysuria, micturition frequency, nocturia, polyuria, urinary retention.

The following additional adverse events have been reported with the use of CLARITIN Tablets: alopecia, altered salivation, amnesia, anaphylaxis, angioneurotic edema, blepharospasm, breast enlargement, breast pain, dermatitis, dry hair, erythema multiforme, hemoptysis, hepatic necrosis, hepatitis, jaundice, laryngitis, menorrhagia, nasal dryness, photosensitivity reaction, purpura, seizures, supraventricular tachyarrhythmias, and urinary discoloration.

Pseudoephedrine may cause mild CNS stimulation in hypersensitive patients. Nervousness, excitability, restlessness, dizziness, weakness, or insomnia may occur. Headache, drowsiness, tachycardia, palpitation, pressor activity, and cardiac arrhythmias have been reported. Sympathomimetic drugs have also been associated with other untoward effects, such as fear, anxiety, tenseness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse.

DRUG ABUSE AND DEPENDENCE

There is no information to indicate that abuse or dependency occurs with loratadine or the combination of loratadine and pseudoephedrine. Pseudoephedrine, like other central nervous system stimulants, has been abused. At high doses, sympathomimetics may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscular weakness and tenseness, anxiety, restlessness, and insomnia. Many patients can present a toxic psychosis with delusions and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsions, coma, and respiratory failure.

The oral LD_{50} values for the mixture of the two drugs were greater than 525 and 1839 mg/kg in mice and rats, respectively. Oral LD_{50} values for loratadine were greater than 5000 mg/kg in rats and mice. Doses of loratadine as high as 10 times the recommended daily clinical dose showed no effect in rats, mice, and monkeys.

DOSAGE AND ADMINISTRATION

Adults and children 12 years of age and over: one tablet twice a day (every 12 hours). Because the doses of this fixed combination product cannot be individually titrated and hepatic insufficiency results in a reduced clearance of loratadine to a much greater extent than pseudoephedrine, CLARITIN-D 12 HOUR Extended Release Tablets should generally be avoided in patients with hepatic insufficiency. Patients with renal insufficiency (GFR < 30 mL/min) should be given a lower initial dose (one tablet per day) because they have reduced clearance of loratadine and pseudoepherine.

HOW SUPPLIED

CLARITIN-D 12 HOUR Extended Release Tablets contain 5 mg loratadine and 120 mg pseudoephedrine sulfate. CLARITIN-D 12 HOUR Extended Release Tablets are white tablets branded in green with "CLARITIN-D", which are supplied in high-density polyethylene bottles of 100 (NDC 0085-0635-01). Also available are CLARITIN-D 12 HOUR Extended Release Tablets Unit-of-Use packages of 30 tablets (3 packs of 10 tablets each) (NDC 0085-0635-05); and 10 × 10 tablets Unit Dose-Hospital Pack (NDC 0085-0635-04).

Keep Unit-of-Use packaging and Unit Dose-Hospital Pack in a dry place.

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

Schering Corporation
Kenilworth, NJ 07033 USA

Rev. 5/98

17762664T

Shown in Product Identification Guide, page 336

CLARITIN-D® 24 HOUR

brand of loratadine and pseudoephedrine sulfate, USP Extended Release Tablets

℞

DESCRIPTION

CLARITIN-D® 24 HOUR (loratadine and pseudoephedrine sulfate, USP) Extended Release Tablets contain 10 mg loratadine in the tablet coating for immediate release and 240 mg pseudoephedrine sulfate, USP in the tablet core which is quacious. In addition to the marked euphoria, the user experiences a sense of markedly enhanced physical strength and mental capacity. With continued use, tolerance develops, the user increases the dose, and toxic signs and symptoms appear. Depression may follow rapid withdrawal.

OVERDOSAGE

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. Somnolence, tachycardia, and headache have been reported with doses of 40 to 180 mg of CLARITIN Tablets. In large doses, sympathomimetics may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscular weakness and tenseness, anxiety, restlessness, and insomnia. Many patients can present a toxic psychosis with delusions and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsions, coma, and respiratory failure.

The oral LD_{50} values for the mixture of the two drugs were greater than 525 and 1839 mg/kg in mice and rats, respectively. Oral LD_{50} values for loratadine were greater than 5000 mg/kg in rats and mice. Doses of loratadine as high as 10 times the recommended daily clinical dose showed no effect in rats, mice, and monkeys.

DOSAGE AND ADMINISTRATION

Adults and children 12 years of age and over: one tablet twice a day (every 12 hours). Because the doses of this fixed combination product cannot be individually titrated and hepatic insufficiency results in a reduced clearance of loratadine to a much greater extent than pseudoephedrine, CLARITIN-D 12 HOUR Extended Release Tablets should generally be avoided in patients with hepatic insufficiency. Patients with renal insufficiency (GFR < 30 mL/min) should be given a lower initial dose (one tablet per day) because they have reduced clearance of loratadine and pseudoepherine.

HOW SUPPLIED

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Keep Unit-of-Use packaging and Unit Dose-Hospital Pack in a dry place.

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

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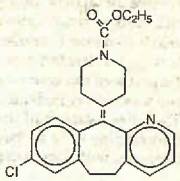
CLARITIN-D® 24 HOUR

brand of loratadine and pseudoephedrine sulfate, USP Extended Release Tablets

℞

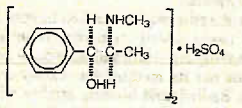
DESCRIPTION

CLARITIN-D® 24 HOUR (loratadine and pseudoephedrine sulfate, USP) Extended Release Tablets contain 10 mg loratadine in the tablet coating for immediate release and 240 mg pseudoephedrine sulfate, USP in the tablet core which is chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate; and the following chemical structure:



The molecular weight of loratadine is 382.89. It is a white to off-white powder, not soluble in water, but very soluble in acetone, alcohol, and chloroform.

Pseudoephedrine sulfate is the synthetic salt of one of the naturally occurring dextrorotatory diastereomers of ephedrine and is classified as an indirect sympathomimetic amine. The empirical formula for pseudoephedrine sulfate is $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$; the chemical name is α-[1-(methylamino) ethyl]-[*S*-(*R**, *R**)]-benzenemethanol sulfate (2:1)(salt); and the chemical structure is:



The molecular weight of pseudoephedrine sulfate is 428.54. It is a white powder, freely soluble in water and methanol and sparingly soluble in chloroform.

The inactive ingredients for oval, biconvex CLARITIN-D 24 HOUR Extended Release Tablets are calcium phosphate, carnauba wax, ethylcellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, povidone, silicon dioxide, sugar, titanium dioxide, and white wax.

CLINICAL PHARMACOLOGY

The following information is based upon studies of loratadine alone or pseudoephedrine alone, except as indicated.

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 oral doses of loratadine 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 developing after 28 days of dosing with loratadine.

Pharmacokinetic studies following single and multiple oral doses of loratadine in 115 volunteers showed that loratadine is rapidly absorbed and extensively metabolized to an active metabolite (descarboethoxyloratadine). Approximately 80% of the total dose administered can be found equally distributed between urine and feces in the form of metabolic products after 10 days. The mean elimination half-lives found in studies 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 the major active metabolite (descarboethoxyloratadine). In nearly all patients, exposure (AUC) to the metabolite is greater than exposure to parent loratadine. Loratadine and descarboethoxyloratadine reached steady state in most patients by approximately the fifth dosing day. The pharmacokinetics of loratadine and descarboethoxyloratadine are dose independent over the dose range of 10 to 40 mg and are not significantly altered by the duration of treatment.

In vitro studies with human liver microsomes indicate that loratadine is metabolized to descarboethoxyloratadine predominantly by P450 CYP3A4 and, to a lesser extent, by P450 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 significantly increased plasma concentrations of loratadine (see **Drug Interactions** section).

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 significantly higher (approximately 50% increased) than in studies of younger subjects. The mean elimination half-lives for the elderly subjects were 18.2 hours (range = 6.7 to 37 hours) for loratadine and 17.5 hours (range = 11 to 38 hours) for the active metabolite.

In patients with chronic renal impairment (creatinine clearance ≤30 mL/min) both the AUC and peak plasma levels (C_{max}) increased on average by approximately 73% for loratadine; and approximately by 120% for descarboethoxyloratadine, compared to individuals with normal renal function. The mean elimination half-lives of loratadine (7.6 hours) and descarboethoxyloratadine (23.9 hours) were not significantly different from that observed in normal subjects. He-

Continued on next page

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