

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CLARINEX-D 12 HOUR Extended Release Tablets safely and effectively. See full prescribing information for CLARINEX-D 12 HOUR Extended Release Tablets.

CLARINEX-D® 12 HOUR Extended Release Tablets
(desloratadine/pseudoephedrine sulfate) for oral use
Initial U.S. Approval: 2005

INDICATIONS AND USAGE

CLARINEX-D 12 HOUR is a combination product containing an H₁-receptor antagonist and a sympathomimetic amine indicated for:

- Relief of nasal and non-nasal symptoms of seasonal allergic rhinitis, including nasal congestion, in adults and adolescents 12 years of age and older. (1.1)

DOSAGE AND ADMINISTRATION

For oral use only (2)

Adults and adolescents 12 years of age and over: The recommended dose of CLARINEX-D 12 HOUR Extended Release Tablets is one tablet twice a day. (2.1)

DOSAGE FORMS AND STRENGTHS

Desloratadine 2.5 mg/Pseudoephedrine sulfate 120 mg tablets. (3)

CONTRAINDICATIONS

- Hypersensitivity (4)
- Narrow-Angle Glaucoma (4)
- Urinary Retention (4)
- Patients Receiving MAO Inhibitors or within 14 days of stopping such treatment (4)

- Severe hypertension or severe coronary artery disease. (4)

WARNINGS AND PRECAUTIONS

- Cardiovascular and central nervous system effects: Use with caution in patients with cardiovascular disorders. (5.1)
- Coexisting conditions: Use with caution in patients with increased intraocular pressure, prostatic hypertrophy, diabetes mellitus, or hyperthyroidism. (5.2)

ADVERSE REACTIONS

- The most common adverse reactions (reported in ≥2% of patients) were insomnia, headache, mouth dry, fatigue, somnolence, pharyngitis, dizziness, nausea, and anorexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Monoamine Oxidase (MAO) Inhibitors: Do not use. May potentiate the effect of pseudoephedrine on vascular system. (7.1)

USE IN SPECIFIC POPULATIONS

- Renal impairment: Avoid in patients with renal impairment. (8.6)
- Hepatic impairment: Avoid in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Seasonal Allergic Rhinitis

CLARINEX-D[®] 12 HOUR Extended Release Tablets is indicated for the relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis, including nasal congestion, in adults and adolescents 12 years of age and older. CLARINEX-D 12 HOUR Extended Release Tablets should be administered when the antihistaminic properties of desloratadine and the nasal decongestant properties of pseudoephedrine are desired [see *Clinical Pharmacology* (12)].

2 DOSAGE AND ADMINISTRATION

Administer CLARINEX-D 12 HOUR Extended Release Tablet by the oral route only. Do not break, chew, or crush the tablet. Swallow the tablet whole.

2.1 Adults and Adolescents 12 years of Age and Over

The recommended dose of CLARINEX-D 12 HOUR Extended Release Tablets is 1 tablet twice a day, administered approximately 12 hours apart and with or without a meal. Higher doses or increased dosing frequency of CLARINEX-D 12 HOUR Extended Release Tablets have not demonstrated increased effectiveness. Do not exceed the recommended dose as desloratadine and pseudoephedrine, the active components of CLARINEX-D 12 HOUR Extended Release Tablets have been associated with adverse effects at higher doses [see *Overdosage* (10.1) and (10.2)].

3 DOSAGE FORMS AND STRENGTHS

CLARINEX-D 12 HOUR Extended Release Tablets are oval shaped, blue and white bilayer tablets with "D12" embossed in the blue layer. Each tablet contains 2.5 mg desloratadine in the blue immediate-release layer and 120 mg of pseudoephedrine sulfate USP in the white extended-release layer.

4 CONTRAINDICATIONS

CLARINEX-D 12 HOUR Extended Release Tablets are contraindicated in:

- Patients with hypersensitivity to any of its ingredients, or to loratadine [see *Warnings and Precautions* (5.4) and *Adverse Reactions* (6.2)]
- Patients with narrow-angle glaucoma
- Patients with urinary retention
- Patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen (14) days of stopping such treatment [see *Drug Interactions* (7.1)]
- Patients with severe hypertension or severe coronary artery disease

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular and Central Nervous System Effects

The pseudoephedrine sulfate contained in CLARINEX-D 12 HOUR Extended Release Tablets, like other sympathomimetic amines, can produce cardiovascular and central nervous system (CNS) effects in some patients such as insomnia, dizziness, weakness, tremor, or arrhythmias. In addition, central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension has been reported. Therefore, CLARINEX-D 12 HOUR Extended Release Tablets should be used with caution in patients with cardiovascular disorders, and should not be used in patients with severe hypertension or severe coronary artery disease.

5.2 Coexisting Conditions

CLARINEX-D 12 HOUR Extended Release Tablets contain pseudoephedrine sulfate, a sympathomimetic amine, and therefore should be used with caution in patients with diabetes and hyperthyroidism. Also use with caution in patients with prostatic hypertrophy or increased intraocular pressure, as urinary retention and narrow-angle glaucoma may occur [see *Contraindications* (4)].

5.3 Co-Administration with Monoamine Oxidase (MAO) Inhibitors

CLARINEX-D 12 HOUR Extended Release Tablets should not be used in patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen (14) days of stopping such treatment as an increase in blood pressure or hypertensive crisis, may occur [see *Contraindications* (4) and *Drug Interactions* (7.1)].

5.4 Hypersensitivity Reactions

Hypersensitivity reactions including rash, pruritus, urticaria, edema, dyspnea, and anaphylaxis have been reported after administration of desloratadine a component of CLARINEX-D 12 HOUR Extended Release Tablets. If such a reaction occurs, therapy with CLARINEX-D 12 HOUR Extended Release Tablets should be stopped and alternative treatment should be considered [see *Adverse Reactions* (6.2)].

5.5 Renal Impairment

CLARINEX-D 12 HOUR Extended Release Tablets should generally be avoided in patients with renal impairment [see *Clinical Pharmacology* (12)].

5.6 Hepatic Impairment

CLARINEX-D 12 HOUR Extended Release Tablets should generally be avoided in patients with hepatic impairment [see *Clinical Pharmacology* (12)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Cardiovascular and Central Nervous System effects [see *Warnings and Precautions* (5.1)]
- Increased intraocular pressure [see *Warnings and Precautions* (5.2)]
- Urinary retention in patients with prostatic hypertrophy [see *Warnings and Precautions* (5.2)]
- Hypersensitivity reactions [see *Warnings and Precautions* (5.4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety data described below are from 2 clinical trials with CLARINEX-D 12 HOUR Extended Release Tablets that included 1248 patients with seasonal allergic rhinitis, of which 414 patients received CLARINEX-D 12 HOUR Extended Release Tablets twice daily for up to 2 weeks. The majority

of patients were between 18 and <65 years of age with a mean age of 35.8 years and were predominantly women (64%). Patient ethnicity was 82% Caucasian, 9% Black, 6% Hispanic and 3% Asian/other ethnicity. The percentage of subjects receiving CLARINEX-D 12 HOUR Extended Release Tablets and who discontinued from the clinical trials because of an adverse event was 3.6%. Adverse reactions that were reported by ≥2% of subjects receiving CLARINEX-D 12 HOUR Extended Release Tablets are shown in **Table 1**.

Table 1: Incidence of Adverse Reactions Reported by ≥2% of Subjects Receiving CLARINEX-D 12 HOUR Extended Release Tablets

Adverse Reaction	CLARINEX-D 12 HOUR BID (N=414)	Desloratadine 5 mg QD (N=412)	Pseudoephedrine 120 mg BID (N=422)
Gastrointestinal Disorders			
Mouth Dry	8%	2%	8%
Nausea	2%	1%	3%
General Disorders and Administration Site Conditions			
Fatigue	4%	2%	2%
Metabolism and Nutrition Disorders			
Anorexia	2%	0%	2%
Nervous System Disorders			
Headache	8%	8%	9%
Somnolence	3%	4%	2%
Dizziness	3%	2%	2%
Psychiatric Disorders			
Insomnia	10%	3%	13%
Respiratory, Thoracic, and Mediastinal Disorders			
Pharyngitis	3%	3%	3%

There were no relevant differences in adverse reactions for subgroups of patients as defined by gender, age, or race.

6.2 Post-Marketing Experience

In addition to the adverse reactions reported during clinical trials and listed above, adverse events have been identified during post approval use of CLARINEX-D 12 HOUR Extended Release Tablets. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Adverse events identified from post-marketing surveillance on the use of CLARINEX-D 12 HOUR Extended Release Tablets include tachycardia, palpitations, dyspnea, rash and pruritus.

In addition to these events, the following spontaneous adverse events have been reported during the marketing of desloratadine as a single ingredient product: headache, somnolence, dizziness and rarely hypersensitivity reactions (such as urticaria, edema and anaphylaxis), psychomotor hyperactivity, movement disorders (including dystonia, tics, and extrapyramidal symptoms), seizures, and elevated liver enzymes including bilirubin and, very rarely, hepatitis.

7 DRUG INTERACTIONS

No specific interaction studies have been conducted with CLARINEX-D 12 HOUR Extended Release Tablets.

7.1 Monoamine Oxidase Inhibitors

CLARINEX-D 12 HOUR Extended Release Tablets should not be used in patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen (14) days of stopping such treatment because the action of pseudoephedrine a component of CLARINEX-D 12 HOUR Extended Release tablets on the vascular system may be potentiated by these agents [see *Contraindications (4) and Warnings and Precautions (5.3)*].

7.2 Beta-Adrenergic Blocking Agents

The antihypertensive effects of beta-adrenergic blocking agents, methyldopa, and reserpine, may be reduced by sympathomimetics such as pseudoephedrine. Exercise caution when using CLARINEX-D 12 HOUR Extended Release Tablets with these agents.

7.3 Digitalis

Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis. Exercise caution when using CLARINEX-D 12 HOUR Extended Release Tablets with these agents.

7.4 Inhibitors of Cytochrome P450 3A4

In controlled clinical studies co-administration of desloratadine with ketoconazole, erythromycin, or azithromycin resulted in increased plasma concentrations of desloratadine and 3-hydroxydesloratadine but there were no clinically relevant changes in the safety profile of desloratadine [see *Clinical Pharmacology (12.3)*].

7.5 Fluoxetine

In controlled clinical studies co-administration of desloratadine with fluoxetine, a selective serotonin reuptake inhibitor (SSRI), resulted in increased plasma concentrations of desloratadine and 3-hydroxydesloratadine but there were no clinically relevant changes in the safety profile of desloratadine [see *Clinical Pharmacology (12.3)*].

7.6 Cimetidine

In controlled clinical studies co-administration of desloratadine with cimetidine a histamine H₂-receptor antagonist resulted in increased plasma concentrations of desloratadine and 3-hydroxydesloratadine but there were no clinically relevant changes in the safety profile of desloratadine [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies of desloratadine and pseudoephedrine in combination in pregnant women. Neither are there animal reproduction studies conducted with the combination of desloratadine and pseudoephedrine. Desloratadine was not teratogenic in rats or rabbits but affected implantation in rats. Because animal reproduction studies are not always predictive of human response, CLARINEX-D 12 HOUR Extended Release Tablets should be used during pregnancy only if clearly needed.

Desloratadine was not teratogenic in rats or rabbits at approximately 210 and 230 times, respectively, the AUC in humans at the recommended daily oral dose. An increase in pre-implantation loss and a decreased number of implantations and fetuses were noted, however, in a separate study in female rats at approximately 120 times the AUC in humans at the recommended daily oral dose. Reduced body weight and slow righting reflex were reported in pups at approximately 50 times or greater than the AUC in humans at the recommended daily oral dose. Desloratadine had no effect on pup development at approximately 7 times the AUC in humans at the recommended daily oral dose. The AUCs in comparison referred to the desloratadine exposure in rabbits and the sum of desloratadine and its metabolites exposures in rats, respectively [see *Nonclinical Toxicology* (13.2)].

8.3 Nursing Mothers

Desloratadine and pseudoephedrine both pass into breast milk; therefore, a decision should be made whether to discontinue nursing or to discontinue CLARINEX-D 12 HOUR Extended Release Tablets, taking into account the benefit of the drug to the nursing mother and the possible risk to the child.

8.4 Pediatric Use

CLARINEX-D 12 HOUR Extended Release Tablets are not indicated for use in pediatric patients under 12 years of age.

8.5 Geriatric Use

The number of subjects (n=10) ≥65 years old treated with CLARINEX-D 12 HOUR Extended Release Tablets was too limited to make any formal statistical comparison regarding the efficacy or safety of this drug product in this age group, or to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences between the elderly and younger patients, although the elderly are more likely to have adverse reactions to sympathomimetic amines. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see *Clinical Pharmacology* (12.3)].

Pseudoephedrine, desloratadine, and their metabolites are known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with renal impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor the patient for adverse events [see *Clinical Pharmacology* (12.3)].

8.6 Renal Impairment

No studies with CLARINEX-D 12 HOUR Extended Release Tablets were conducted in subjects with renal impairment.

CLARINEX-D 12 HOUR Extended Release Tablets should generally be avoided in patients with renal impairment [see *Warnings and Precautions* (5.5) and *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

No studies with CLARINEX-D 12 HOUR Extended Release Tablets or pseudoephedrine were conducted in subjects with hepatic impairment.

CLARINEX-D 12 HOUR Extended Release Tablets should generally be avoided in patients with hepatic impairment [see *Warnings and Precautions* (5.6) and *Clinical Pharmacology* (12.3)].

8.8 Gender

No clinically significant gender-related differences were observed in the pharmacokinetic parameters of desloratadine, 3-hydroxydesloratadine or pseudoephedrine following administration of CLARINEX-D 12 HOUR Extended Release Tablets.

8.9 Race

No studies have been conducted to evaluate the effect of race on the pharmacokinetics of CLARINEX-D 12 HOUR Extended Release Tablets.

9 DRUG ABUSE AND DEPENDENCE

There is no information to indicate that abuse or dependency occurs with CLARINEX or CLARINEX-D 12 HOUR Extended Release Tablets.

10 OVERDOSAGE

In the event of overdose, consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended. Desloratadine and 3-hydroxydesloratadine are not eliminated by hemodialysis.

10.1 Desloratadine

Information regarding acute overdosage with desloratadine is limited to experience from post-marketing adverse event reports and from clinical trials conducted during the development of the CLARINEX product. In the reported cases of overdose, there were no significant adverse events that were attributed to desloratadine. In a dose-ranging trial, at doses of 10 mg and 20 mg/day, somnolence was reported.

In another study, no clinically relevant adverse events were reported in normal male and female volunteers who were given single daily doses of CLARINEX 45 mg for 10 days [see *Clinical Pharmacology* (12.2)].

Lethality occurred in rats at oral doses of 250 mg/kg or greater (estimated desloratadine and desloratadine metabolite exposures were approximately 120 times the AUC in humans at the recommended daily oral dose). The oral median lethal dose in mice was 353 mg/kg (estimated desloratadine exposure was approximately 290 times the human daily oral dose on an mg/m² basis). No deaths occurred at oral doses up to 250 mg/kg in monkeys (estimated desloratadine exposure was approximately 810 times the human daily oral dose on an mg/m² basis).

10.2 Sympathomimetics

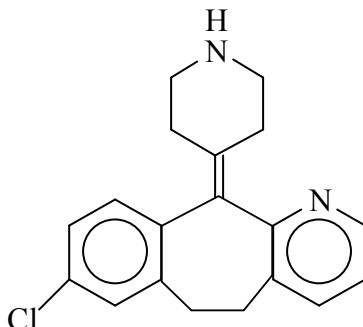
In large doses, sympathomimetics such as pseudoephedrine may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscle weakness and tenseness, anxiety, restlessness, and insomnia. Many patients can present a toxic psychosis with delusions and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsions, coma, and respiratory failure.

11 DESCRIPTION

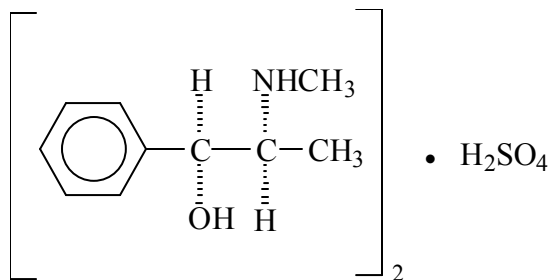
CLARINEX-D 12 HOUR Extended Release Tablets are oval-shaped blue and white bilayer tablets containing 2.5 mg desloratadine in the blue immediate-release layer and 120 mg of pseudoephedrine sulfate USP in the white extended-release layer which is released slowly, allowing for twice-daily administration.

The inactive ingredients contained in CLARINEX-D 12 HOUR Extended Release Tablets are hypromellose USP, microcrystalline cellulose NF, povidone USP, silicon dioxide NF, magnesium stearate NF, corn starch NF, edetate disodium USP, citric acid anhydrous USP, stearic acid NF, and FD&C Blue No. 2 aluminum lake dye.

Desloratadine, 1 of the 2 active ingredients of CLARINEX-D 12 HOUR Extended Release Tablets, is a white to off-white powder that is slightly soluble in water, but very soluble in ethanol and propylene glycol. It has an empirical formula: $C_{19}H_{19}ClN_2$ and a molecular weight of 310.8. The chemical name is 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine and has the following structure:



Pseudoephedrine sulfate, the other active ingredient of CLARINEX-D 12 HOUR Extended Release Tablets, is the synthetic salt of one of the naturally occurring dextrorotatory diastereomers of ephedrine and is classified as an indirect sympathomimetic amine. Pseudoephedrine sulfate is a colorless hygroscopic crystal or white, hygroscopic crystalline powder, practically odorless, with a bitter taste. It is very soluble in water, freely soluble in alcohol, and sparingly soluble in ether. The empirical formula for pseudoephedrine sulfate is $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$; the chemical name is benzenemethanol, α -[1-(methylamino)ethyl]-, [S-(R*,R*)]-, sulfate (2:1)(salt); and the chemical structure is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Desloratadine is a long acting tricyclic histamine antagonist with selective H_1 -receptor histamine antagonist activity. Receptor binding data indicate that at a concentration of 2 to 3 ng/mL (7 nanomolar), desloratadine shows significant interaction with the human histamine H_1 receptor. Desloratadine inhibited histamine release from human mast cells *in vitro*. Results of a radiolabeled tissue distribution study in rats and a radioligand H_1 -receptor-binding study in guinea pigs showed that desloratadine does not readily cross the blood brain barrier. The clinical significance of this finding is unknown.

Pseudoephedrine sulfate is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine sulfate 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.

12.2 Pharmacodynamics

Wheal and Flare: Human histamine skin wheal studies following single and repeated 5 mg doses of desloratadine have shown that the drug exhibits an antihistaminic effect by 1 hour; this activity may persist for as long as 24 hours. There was no evidence of histamine-induced skin wheal tachyphylaxis within the desloratadine 5 mg group over the 28-day treatment period. The clinical relevance of histamine wheal skin testing is unknown.

Effects on QT_c : In clinical trials for CLARINEX-D 12 HOUR Extended Release Tablets, ECGs were recorded at baseline and endpoint within 1 to 3 hours after the last dose. The majority of ECGs were normal at both baseline and endpoint. No clinically meaningful changes were observed following treatment with CLARINEX-D 12 HOUR Extended Release Tablets for any ECG parameter, including the QT_c interval. An increase in the ventricular rate of 7.1 and 6.4 bpm was observed in the CLARINEX-D 12 HOUR Extended Release Tablets and pseudoephedrine groups, respectively, compared to an increase of 3.2 bpm in subjects receiving desloratadine alone. Single daily doses of CLARINEX 45 mg were given to normal male and female volunteers for 10 days.

All ECGs obtained in this study were manually read in a blinded fashion by a cardiologist. In the CLARINEX-treated subjects, there was a mean increase in the maximum heart rate of 9.2 bpm relative to placebo. The QT interval was corrected for heart rate (QT_c) by both Bazett's and Fridericia methods. Using the QT_c (Bazett), there was a mean increase of 8.1 msec in the CLARINEX-treated subjects relative to placebo. Using QT_c (Fridericia) there was a mean increase of 0.4 msec in CLARINEX-treated subjects relative to placebo. No clinically relevant adverse events were reported.

12.3 Pharmacokinetics

Absorption: In a single dose pharmacokinetic study, the mean time to maximum plasma concentrations (T_{max}) for desloratadine occurred at approximately 4 to 5 hours post dose and mean peak plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) of approximately

1.09 ng/mL and 31.6 ng•hr/mL, respectively, were observed. In another pharmacokinetic study, food and grapefruit juice had no effect on the bioavailability (C_{max} and AUC) of desloratadine.

For pseudoephedrine, the mean T_{max} occurred at 6 to 7 hours post dose and mean peak plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) of approximately 263 ng/mL and 4588 ng•hr/mL, respectively, were observed. Food had no effect on the bioavailability (C_{max} and AUC) of pseudoephedrine.

Following oral administration of CLARINEX-D 12 HOUR Extended Release Tablets twice daily for 14 days in healthy volunteers, steady-state conditions were reached on Day 10 for desloratadine, 3-hydroxydesloratadine and pseudoephedrine. For desloratadine, mean steady-state peak plasma concentrations (C_{max}) and area under the concentration-time curve AUC_{0-12 hrs} of approximately 1.7 ng/mL and 16 ng•hr/mL were observed, respectively. For pseudoephedrine, mean steady-state peak plasma concentrations (C_{max}) and AUC_{0-12 hrs} of 459 ng/mL and 4658 ng•hr/mL were observed.

Distribution: Desloratadine and 3-hydroxydesloratadine are approximately 82% to 87% and 85% to 89%, bound to plasma proteins, respectively. Protein binding of desloratadine and 3-hydroxydesloratadine was unaltered in subjects with impaired renal function.

Metabolism: Desloratadine (a major metabolite of loratadine) is extensively metabolized to 3-hydroxydesloratadine, an active metabolite, which is subsequently glucuronidated. The enzyme(s) responsible for the formation of 3-hydroxydesloratadine have not been identified. Data from clinical trials with desloratadine indicate that a subset of the general population has a decreased ability to form 3-hydroxydesloratadine, and are poor metabolizers of desloratadine. In pharmacokinetic studies (n=3748), approximately 6% of subjects were poor metabolizers of desloratadine (defined as a subject with an AUC ratio of 3-hydroxydesloratadine to desloratadine less than 0.1, or a subject with a desloratadine half-life exceeding 50 hours). These pharmacokinetic studies included subjects between the ages of 2 and 70 years, including 977 subjects aged 2 to 5 years, 1575 subjects aged 6 to 11 years, and 1196 subjects aged 12 to 70 years. There was no difference in the prevalence of poor metabolizers across age groups. The frequency of poor metabolizers was higher in Blacks (17%, n=988) as compared to Caucasians (2%, n=1462) and Hispanics (2%, n=1063). The median exposure (AUC) to desloratadine in the poor metabolizers was approximately 6-fold greater than in the subjects who are not poor metabolizers. Subjects who are poor metabolizers of desloratadine cannot be prospectively identified and will be exposed to higher levels of desloratadine following dosing with the recommended dose of desloratadine. In multidose clinical safety studies, where metabolizer status was prospectively identified, a total of 94 poor metabolizers and 123 normal metabolizers were enrolled and treated with CLARINEX Syrup for 15 to 35 days. In these studies, no overall differences in safety were observed between poor metabolizers and normal metabolizers. Although not seen in these studies, an increased risk of exposure-related adverse events in patients who are poor metabolizers cannot be ruled out.

Pseudoephedrine alone is incompletely metabolized (less than 1%) in the liver by N-demethylation to an inactive metabolite. The drug and its metabolite are excreted in the urine. About 55% to 96% of an administered dose of pseudoephedrine hydrochloride is excreted unchanged in the urine.

Elimination: Following single dose administration of CLARINEX-D 12 HOUR Extended Release Tablets, the mean plasma elimination half-life of desloratadine was approximately 27 hours. In another study, following administration of single oral doses of desloratadine 5 mg, C_{max} and AUC values increased in a dose proportional manner following single oral doses between 5 and 20 mg. The degree of accumulation after 14 days of dosing was consistent with the half-life and dosing frequency. A human mass balance study documented a recovery of approximately 87% of the ¹⁴C-desloratadine dose, which was equally distributed in urine and feces as metabolic products. Analysis of plasma 3-hydroxydesloratadine showed similar T_{max} and half-life values compared to desloratadine.

The mean elimination half-life of pseudoephedrine is dependent on urinary pH. The elimination half-life is approximately 3 to 6 or 9 to 16 hours when the urinary pH is 5 or 8, respectively.

Geriatric Subjects: Following multiple-dose administration of CLARINEX Tablets, the mean C_{max} and AUC values for desloratadine were 20% greater than in younger subjects (< 65 years old). The oral total body clearance (CL/F) when normalized for body weight was similar between the 2 age groups. The mean plasma elimination half-life of desloratadine was 33.7 hr in subjects ≥65 years old. The pharmacokinetics for 3-hydroxydesloratadine appeared unchanged in older vs. younger subjects. These age-related differences are unlikely to be clinically relevant and no dosage adjustment is recommended in elderly patients.

Pediatric Subjects: CLARINEX-D 12 HOUR Extended Release Tablets are not an appropriate dosage form for use in pediatric patients below 12 years of age.

Renally Impaired: Following a single dose of desloratadine 7.5 mg, pharmacokinetics were characterized in subjects with mild (n=7; creatinine clearance 51-69 mL/min/1.73 m²), moderate (n=6; creatinine clearance 34-43 mL/min/1.73 m²) and severe (n=6; creatinine clearance 5-29 mL/min/1.73 m²) renal impairment or hemodialysis dependent (n=6) subjects. In subjects with mild and moderate renal impairment, median C_{max} and AUC values increased by approximately 1.2- and 1.9-fold, respectively, relative to subjects with normal renal function. In subjects with severe renal impairment or who were hemodialysis dependent, C_{max} and AUC values increased by approximately 1.7- and 2.5-fold, respectively. Minimal changes in 3-hydroxydesloratadine concentrations were observed. Desloratadine and 3-hydroxydesloratadine were poorly removed by hemodialysis. Plasma protein binding of desloratadine and 3-hydroxydesloratadine was unaltered by renal impairment.

Pseudoephedrine is primarily excreted unchanged in the urine as unchanged drug with the remainder apparently being metabolized in the liver. Therefore, pseudoephedrine may accumulate in patients with renal impairment.

Hepatically Impaired: Following a single oral dose of desloratadine, pharmacokinetics were characterized in subjects with mild (n=4), moderate (n=4) and severe (n=4) hepatic impairment as defined by the Child-Pugh classification of hepatic impairment and 8 subjects with normal hepatic function. Subjects with hepatic impairment, regardless of severity, had approximately a 2.4-fold increase in AUC as compared with normal subjects. The apparent oral clearance of desloratadine in subjects with mild, moderate, and severe hepatic impairment was 37%, 36%, and 28% of that in normal subjects, respectively. An increase in the mean elimination half-life of desloratadine in subjects with hepatic impairment was observed. For 3-hydroxydesloratadine, the mean C_{max} and AUC values for subjects with hepatic impairment combined were not statistically significantly different from subjects with normal hepatic function.

Gender: Female subjects treated for 14 days with CLARINEX Tablets had 10% and 3% higher desloratadine C_{max} and AUC values, respectively, compared with male subjects. The 3-hydroxydesloratadine C_{max} and AUC values were also increased by 45% and 48%, respectively, in females compared with males. However, these apparent differences are not considered to be clinically relevant.

Race: Following 14 days of treatment with CLARINEX Tablets, the C_{max} and AUC values for desloratadine were 18% and 32% higher, respectively in Blacks compared with Caucasians. For 3-hydroxydesloratadine there was a corresponding 10% reduction in C_{max} and AUC values in Blacks compared to Caucasians. These differences are not considered to be clinically relevant.

Drug Interaction: In 2 controlled crossover clinical pharmacology studies in healthy male (n=12 in each study) and female (n=12 in each study) subjects, desloratadine 7.5 mg (1.5 times the daily dose) once daily was co-administered with erythromycin 500 mg every 8 hours or ketoconazole 200 mg every 12 hours for 10 days. In 3 separate controlled, parallel group clinical pharmacology studies, desloratadine at the clinical dose of 5 mg has been co-administered with azithromycin 500 mg followed by 250 mg once daily for 4 days (n=18) or with fluoxetine 20 mg once daily for 7 days after a 23-day

pretreatment period with fluoxetine (n=18) or with cimetidine 600 mg every 12 hours for 14 days (n=18) under steady state conditions to healthy male and female subjects. Although increased plasma concentrations (C_{max} and $AUC_{0-24\text{ hrs}}$) of desloratadine and 3-hydroxydesloratadine were observed (see **Table 2**), there were no clinically relevant changes in the safety profile of desloratadine, as assessed by electrocardiographic parameters (including the corrected QT interval), clinical laboratory tests, vital signs and adverse events.

Table 2: Changes in Desloratadine and 3-hydroxydesloratadine Pharmacokinetics in Healthy Male and Female Subjects

	<u>Desloratadine</u>		<u>3-hydroxydesloratadine</u>	
	C_{max}	$AUC_{0-24\text{hrs}}$	C_{max}	$AUC_{0-24\text{hrs}}$
Erythromycin (500 mg Q8h)	+24%	+14%	+43%	+40%
Ketoconazole (200 mg Q12h)	+45%	+39%	+43%	+72%
Azithromycin (500 mg Day 1, 250 mg QD x 4 days)	+15%	+5%	+15%	+4%
Fluoxetine (20 mg QD)	+15%	+0%	+17%	+13%
Cimetidine (600 mg Q12h)	+12%	+19%	-11%	-3%

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or laboratory studies on the combination product of desloratadine and pseudoephedrine sulfate to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

Carcinogenicity Studies: The carcinogenic potential of desloratadine was assessed using a loratadine study in rats and a desloratadine study in mice. In a 2-year study in rats, loratadine was administered in the diet at doses up to 25 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 30 times the AUC in humans at the recommended daily oral dose). A significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg/day of loratadine and in males and females given 25 mg/kg/day of loratadine. The estimated desloratadine and desloratadine metabolite exposures in rats given 10 mg/kg of loratadine were approximately 7 times the AUC in humans at the recommended daily oral dose. The clinical significance of these findings during long-term use of desloratadine is not known.

In a 2-year dietary study in mice, males and females given up to 16 mg/kg/day and 32 mg/kg/day desloratadine, respectively, did not show significant increases in the incidence of any tumors. The estimated desloratadine and desloratadine metabolite exposures in mice at these doses were 12 and 27 times, respectively, the AUC in humans at the recommended daily oral dose.

Genotoxicity Studies: In genotoxicity studies with desloratadine, there was no evidence of genotoxic potential in a reverse mutation assay (*Salmonella/E. coli* mammalian microsome bacterial mutagenicity assay) or in 2 assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenicity assay and mouse bone marrow micronucleus assay).

Impairment of Fertility: There was no effect on female fertility in rats at desloratadine doses up to 24 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 130 times the AUC in humans at the recommended daily oral dose). A male-specific decrease in fertility, demonstrated by reduced female conception rates, decreased sperm numbers and motility, and histopathologic testicular changes, occurred at an oral desloratadine dose of 12 mg/kg (estimated desloratadine and desloratadine metabolite exposures were approximately 45 times the AUC in humans at the recommended daily oral dose). Desloratadine had no effect on fertility in rats at an oral dose of 3 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 8 times the AUC in humans at the recommended daily oral dose).

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies: Desloratadine was not teratogenic in rats at doses up to 48 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 210 times the AUC in humans at the recommended daily oral dose) or in rabbits at doses up to 60 mg/kg/day (estimated desloratadine exposures were approximately 230 times the AUC in humans at the recommended daily oral dose). In a separate study, an increase in pre-implantation loss and a decreased number of implantations and fetuses were noted in female rats at 24 mg/kg (estimated desloratadine and desloratadine metabolite exposures were approximately 120 times the AUC in humans at the recommended daily oral dose). Reduced body weight and slow righting reflex were reported in pups at doses of 9 mg/kg/day or greater (estimated desloratadine and desloratadine metabolite exposures were approximately 50 times or greater than the AUC in humans at the recommended daily oral dose). Desloratadine had no effect on pup development at an oral dose of 3 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 7 times the AUC in humans at the recommended daily oral dose).

14 CLINICAL STUDIES

14.1 Seasonal Allergic Rhinitis

The clinical efficacy and safety of CLARINEX-D 12 HOUR Extended Release Tablets was evaluated in two 2-week multicenter, randomized parallel group clinical trials involving 1248 subjects 12 to 78 years of age with seasonal allergic rhinitis, 414 of whom received CLARINEX-D 12 HOUR Extended Release Tablets. In the 2 trials, subjects were randomized to receive CLARINEX-D 12 HOUR Extended Release Tablets twice daily, CLARINEX Tablets 5 mg once daily, or sustained-release pseudoephedrine tablet 120 mg twice daily for 2 weeks. The majority of patients were between 18 and <65 years of age with a mean age of 35.8 years and were predominantly women (64%). Patient ethnicity was 82% Caucasian, 9% Black, 6% Hispanic and 3% Asian/other ethnicity. Primary efficacy variable was twice-daily reflective patient scoring of 4 nasal symptoms (rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing) and four non-nasal symptoms (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears/palate) on a 4 point scale (0=none, 1=mild, 2=moderate, and 3=severe). In both trials, the antihistaminic efficacy of CLARINEX-D 12 HOUR Extended Release Tablets, as measured by total symptom score excluding nasal congestion, was significantly greater than pseudoephedrine alone over the 2-week treatment period; and the decongestant efficacy of CLARINEX-D 12 HOUR Extended Release Tablets, as measured by nasal stuffiness/congestion, was

significantly greater than CLARINEX (desloratadine alone) over the 2-week treatment period. Primary efficacy variable results from 1 of 2 trials are shown in Table 3.

Table 3: Changes in Symptoms in a 2-Week Clinical Trial in Subjects With Seasonal Allergic Rhinitis

Treatment Group (n)	Mean Baseline* (SEM)	Change (% Change) from Baseline† (SEM)	CLARINEX-D 12 HOUR Comparison to Components‡ (P-value)
Total Symptom Score (Excluding Nasal Congestion)			
CLARINEX-D 12 HOUR Extended Release Tablets BID (199)	14.18 (0.21)	-6.54 (-46.0) (0.30)	-
Pseudoephedrine tablet 120 mg BID (197)	14.06 (0.21)	-5.07 (-35.9) (0.30)	P<0.001
CLARINEX 5 mg Tablets QD (197)	14.82 (0.21)	-5.09 (-33.5) (0.30)	P<0.001
Nasal Stuffiness/Congestion			
CLARINEX-D 12 HOUR Extended Release Tablets BID (199)	2.47 (0.027)	-0.93 (-37.4) (0.046)	-
Pseudoephedrine tablet 120 mg BID (197)	2.46 (0.027)	-0.75 (-31.2) (0.046)	P=0.006
CLARINEX 5 mg Tablets QD (197)	2.50 (0.027)	-0.66 (-26.7) (0.046)	P<0.001

SEM=Standard Error of the Mean

* To qualify at Baseline, the sum of the twice-daily diary reflective scores for the 3 days prior to Baseline and the morning of the Baseline visit were to total ≥ 42 for total nasal symptom score (sum of 4 nasal symptoms of rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing) and a total of ≥ 35 for total non-nasal symptoms score (sum of 4 non-nasal symptoms of itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears/palate), and a score of ≥ 14 for each of the individual symptoms of nasal stuffiness/congestion and rhinorrhea. Each symptom was scored on a 4-point severity scale (0=none, 1=mild, 2=moderate, 3=severe).

† Mean reduction in score averaged over the 2-week treatment period.

‡ The comparison of interest is shown bolded.

There were no significant differences in the efficacy of CLARINEX-D 12 HOUR Extended Release Tablets across subgroups of subjects defined by gender, age, or race.

16 HOW SUPPLIED/STORAGE AND HANDLING

CLARINEX-D 12 HOUR Extended Release Tablets are oval-shaped, blue and white bilayer tablets with "D12" embossed in the blue layer, containing 2.5 mg desloratadine in the blue immediate-release layer and 120 mg of pseudoephedrine sulfate USP in the white extended-release layer. CLARINEX-D 12 HOUR Extended Release Tablets are supplied in high-density polyethylene bottles of 100 (NDC 0085-1322-01).

Storage: Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Avoid exposure at or above 30°C (86°F). Protect from excessive moisture. Protect from light.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

17.1 Cardiovascular and Central Nervous System Effects

Patients should be informed that pseudoephedrine, one of the active ingredients in CLARINEX-D 12 HOUR Extended Release Tablets may cause cardiovascular or central nervous system effects such as insomnia, dizziness, tremor, or arrhythmia.

17.2 Dosing

Patients should be advised not to increase the dose or dosing frequency of CLARINEX-D 12 HOUR Extended Release Tablets.

17.3 Additional Antihistamines and/or Decongestants

Patients should be advised against the concurrent use of CLARINEX-D 12 HOUR Extended Release Tablets with other antihistamines and/or decongestants.

17.4 Monoamine Oxidase (MAO) Inhibitors


Patients should be informed that due to its pseudoephedrine component, they should not use CLARINEX-D 12 HOUR with a monoamine oxidase (MAO) inhibitor or within 14 days of stopping use of an MAO inhibitor.

17.5 Coexisting Conditions

Patients with severe hypertension or severe coronary artery disease, narrow-angle glaucoma, or urinary retention should be advised not to use CLARINEX-D 12 HOUR Extended Release Tablets.

17.6 Instructions for Use

Patients should be instructed not to break, crush, or chew the tablet; the tablet should be swallowed whole, and can be taken without regard to meals.

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