

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 a histamine-1 (H1) receptor antagonist and an alpha adrenergic agonist 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 Organon LLC, a subsidiary of Organon & Co., at 1-844-674-3200 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.

Revised: 6/2021

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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 (12.3)*].

5.6 Hepatic Impairment

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

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)*]
- Severe Skin Reactions

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:

Cardiac disorders: tachycardia, palpitations

Respiratory, thoracic and mediastinal disorders: dyspnea

Skin and subcutaneous tissue disorders: rash, pruritus

In addition to these events, the following spontaneous adverse events have been reported during the marketing of desloratadine as a single ingredient product:

Nervous system disorders: headache, somnolence, dizziness, psychomotor hyperactivity, movement disorders (including dystonia, tics, and extrapyramidal symptoms), seizures (reported in patients with and without a known seizure disorder)

Immune system disorders: hypersensitivity reactions (such as urticaria, edema and anaphylaxis)

Investigations: elevated liver enzymes including bilirubin

Hepatobiliary disorders: hepatitis

Metabolism and nutrition disorders: increased appetite

Cases of severe skin reactions such as acute generalized exanthematous pustulosis (AGEP) have been reported with pseudoephedrine-containing products.

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

Risk Summary

The limited available data with CLARINEX-D 12 HOUR in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. 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 or pseudoephedrine alone. Desloratadine given during organogenesis to pregnant rats was not teratogenic at the summed area under the concentration-time curve (AUC)-based exposures of desloratadine and its metabolite approximately 320 times that at the recommended human daily oral dose (RHD) of 5 mg/day. Desloratadine given during organogenesis to pregnant rabbits was not teratogenic at the AUC-based exposures of desloratadine approximately 230 times that at the RHD. Desloratadine given to pregnant rats during organogenesis through lactation resulted in reduced body weight and slow righting reflex of F₁ pups at the summed AUC-based exposures of desloratadine and its metabolite approximately 70 times or greater than that at the RHD [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

Pseudoephedrine

The majority of studies examining the use of pseudoephedrine in pregnancy did not find an association with an increased risk of congenital anomalies. A few case-control studies conducted reported potential associations with isolated congenital disorders. However, several similar studies did not find statistically significant associations. Methodological limitations of these studies included small sample size, selection bias, recall bias, inadequate adjustment for risk factors, residual confounding, exposure misclassification, and lack of information regarding dose and timing of exposure.

Animal Data

No animal reproduction studies were conducted with the combination of desloratadine and pseudoephedrine or pseudoephedrine alone.

Desloratadine

Desloratadine was given orally during organogenesis to pregnant rats at doses of 6, 24 and 48 mg/kg/day (approximately 50, 200 and 320 times the summed AUC-based exposure of desloratadine and its metabolite at the RHD). No fetal malformations were present. Reduced fetal weights and skeletal variations noted at doses of 24 and 48 mg/kg/day were likely secondary to the maternal toxicities of reduced body weight gain and food consumption observed at the same doses. Desloratadine was also given orally during organogenesis to pregnant rabbits at doses of 15, 30 and 60 mg/kg/day (approximately 30, 70 and 230 times the AUC-based exposure of desloratadine at the RHD). No adverse effects to the fetus were noted. Reduced maternal body weight gain was noted in rabbits at 60 mg/kg/day. In a peri- and post-natal development study, desloratadine was given to rats orally during the peri-natal (Gestation Day 6) through lactation periods (Postpartum Day 21) at doses of 3, 9 and 18 mg/kg/day. Reduced body weight and slow righting reflex were reported in F₁ pups at doses of 9 mg/kg/day or greater (approximately 70 times or greater than the summed AUC-based exposure of desloratadine and its metabolite at the RHD). Desloratadine had no effect on F₁ pup development at 3 mg/kg/day (approximately 10 times the summed AUC-based exposure of desloratadine and its metabolite at the RHD). Maternal toxicities including reduced body weight gain and food consumption were noted at 18 mg/kg/day for F₀ dams. F₁ offspring were subsequently mated and there was no developmental toxicity for F₂ pups observed.

8.2 Lactation

Risk Summary

Desloratadine and pseudoephedrine both pass into breast milk. There are not sufficient data on the effects of desloratadine on the breastfed infant or the effects of desloratadine on milk production. Pseudoephedrine has been reported to decrease milk production [see *Data*]. Pseudoephedrine has been reported to cause irritability in breastfed infants. The decision should be made whether to discontinue nursing or to discontinue CLARINEX-D 12 HOUR Extended Release Tablets, taking into account the developmental and health benefits of breastfeeding, the nursing mother's clinical need, and any potential adverse effects on the breastfed infant from desloratadine and pseudoephedrine or from the underlying maternal condition.

Data

Human Data

Pseudoephedrine

In a study of eight lactating women, who were 8 to 76 weeks postpartum and received a single dose of 60 mg of pseudoephedrine, the mean 24-hour milk production was reduced by 24%. In the same study, the estimated mean relative infant dose from breast milk (assuming mean milk consumption of 150 mL/kg/day and a maternal dosing regimen of 60 mg pseudoephedrine four times per day) was calculated to be 4.3% of the weight-adjusted maternal dose.

8.3 Females and Males of Reproductive Potential

Infertility

There are no data available on human infertility associated with desloratadine, pseudoephedrine, or the combination. There are no animal fertility studies with the combination or pseudoephedrine alone.

There were no clinically relevant effects of desloratadine on female fertility in rats. A male specific decrease in fertility occurred at an oral desloratadine dose of 12 mg/kg or greater in rats (approximately 65 times the summed AUC-based exposure of desloratadine and its metabolite at the

RHD). Male fertility was unaffected at a desloratadine dose of 3 mg/kg (approximately 10 times the summed AUC-based exposure of desloratadine and its metabolite at the RHD). [See *Nonclinical Toxicology* (13.1).]

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)].

10.2 Sympathomimetics

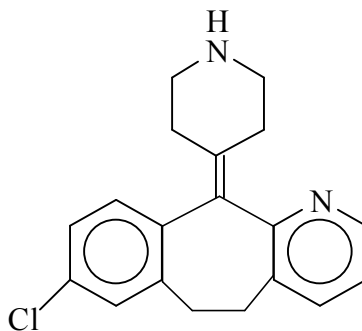
In large doses, sympathomimetics such as pseudoephedrine may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscle weakness and tenseness, anxiety, restlessness, and insomnia. Many patients can present a toxic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

11 DESCRIPTION

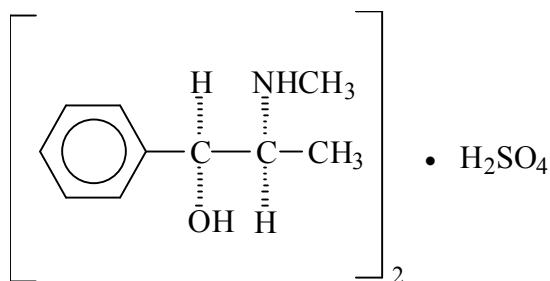
CLARINEX-D 12 HOUR Extended Release Tablets are oval-shaped blue and white bilayer tablets containing 2.5 mg desloratadine in the blue immediate-release layer and 120 mg of pseudoephedrine sulfate USP in the white extended-release layer which is released slowly, allowing for twice-daily administration.

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: C₁₉H₁₉ClN₂ 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 ^{14}C -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 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

	Desloratadine		3-hydroxydesloratadine	
	C_{max}	AUC_{0-24hrs}	C_{max}	AUC_{0-24hrs}
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 or pseudoephedrine alone to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

Carcinogenicity Studies:

Desloratadine

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 (approximately 45 times the summed AUC-based exposure of desloratadine and its metabolite at the RHD). A significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg/day of loratadine (approximately 10 times the summed AUC-based exposure of desloratadine and its metabolite at the RHD) and in males and females given 25 mg/kg/day of loratadine. 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 (approximately 30 and 70 times the summed AUC-based exposure of desloratadine and its metabolite at the RHD, respectively), did not show significant increases in the incidence of any tumors.

Pseudoephedrine

The carcinogenic potential of pseudoephedrine was assessed using ephedrine sulfate studies in F344/N rats and B6C3F1 mice conducted under the National Toxicology Program (NTP). In a 2-year dietary study in rats, male and female rats given up to 9 and 11 mg/kg/day ephedrine sulfate (approximately 0.4 and 0.5 times the RHD of 240 mg/day on a mg/m² basis, respectively) did not show any evidence of tumorigenicity. In a 2-year dietary study in mice, male and female mice given up to 29 and 25 mg/kg/day ephedrine sulfate (approximately 0.7 and 0.6 times the RHD of pseudoephedrine on a mg/m² basis, respectively) did not show any evidence of tumorigenicity.

Genotoxicity Studies:

Desloratadine

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).

Pseudoephedrine

Mutagenicity studies with pseudoephedrine have not been conducted.

Impairment of Fertility:

Desloratadine

In a female fertility study, desloratadine was given to female rats orally 14 days prior to and throughout mating until Gestation Day 7 at doses of 6, 12 and 24 mg/kg/day. An increase in preimplantation loss and a decrease in number of implantations and fetuses noted at 24 mg/kg (approximately 200 times the summed AUC-based exposure of desloratadine and its metabolite at the RHD) was likely due to maternal toxicities including reduced body weight gain and food consumption. In a male fertility study in rats, desloratadine was given orally to male rats for 70 days prior to mating and throughout the mating period (total dosing period 106-108 days) at doses of 3, 12 and 40 mg/kg/day. Reduced body weight gain, food consumption, and absolute organ weights of testes, epididymis, and cauda epididymis were noted at 40 mg/kg/day. A male-specific decrease in fertility, demonstrated by reduced female conception rates, decreased sperm numbers and motility, and histopathologic changes in testes and epididymis, occurred at a dose of 12 mg/kg or greater (approximately 65 times or greater than the summed AUC-based exposure of desloratadine and its metabolite at the RHD). Desloratadine had no effect on male fertility in rats at 3 mg/kg/day (approximately 10 times the summed AUC-based exposure of desloratadine and its metabolite at the RHD).

Pseudoephedrine

Fertility studies with pseudoephedrine have not been conducted.

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 78206-120-01).

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

Advise the patient to read the 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, convulsions 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.

Manufactured for: Organon LLC, a subsidiary of
 ORGANON & Co.,
Jersey City, NJ 07302, USA

For patent information: www.organon.com/our-solutions/patent/

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