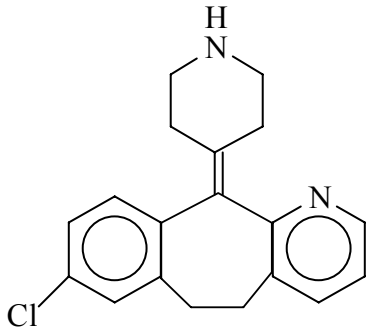
CLARINEX-D® 12 HOUR PRODUCT
(desloratadine 2.5 mg and pseudoephedrine sulfate, USP 120 mg) INFORMATION
EXTENDED RELEASE TABLETS

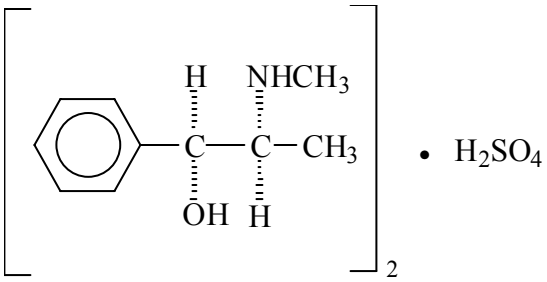
DESCRIPTION: CLARINEX-D® 12 HOUR Extended Release Tablets are oval shaped blue and white bilayer tablets containing 2.5 mg desloratadine in the blue immediate-release layer and 120 mg of pseudoephedrine sulfate, USP in the white extended-release layer which is released slowly, allowing for twice-daily 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, one of the two 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 molecular weight of 310.8. The chemical name is 8-chloro-6,11-dihydro-11-(4-piperdinylidene)-5*H*-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 diastereomer 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 $(C_{10}H_{15}NO)_2 \bullet H_2SO_4$; the chemical name is benzenemethanol, α-[1-(methylamino) ethyl]-,[*S*-(*R**,*R**)]-, sulfate (2:1)(salt); and the chemical structure is:



CLINICAL PHARMACOLOGY: 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 2-3 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.

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.

Pharmacokinetics: Absorption: In a single dose pharmacokinetic study, the mean time to maximum plasma concentrations (T_{max}) for desloratadine occurred at approximately 4-5 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 6-7 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 desloratadine or pseudoephedrine.

Following oral administrations of CLARINEX-D® 12 HOUR Extended Release Tablets twice daily for 14 days in normal 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 h) 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 h) 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 2-5 years, 1575 subjects aged 6-11 years, and 1196 subjects aged 12-70 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 15-35 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 55-96% 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 3-6 or 9-16 hours when the urinary pH is 5 or 8, respectively.

Special Populations: Geriatric: The number of patients (n=10) ≥ 65 years old treated with CLARINEX-D® 12 HOUR Extended Release Tablets was too limited to make any clinically relevant judgment regarding the efficacy or safety of this drug product in this age group. 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 two 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 versus younger subjects. These age-related differences are unlikely to be clinically relevant and no dosage adjustment is recommended in elderly subjects.

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: No studies with CLARINEX-D® 12 HOUR Extended Release Tablets were conducted in patients with renal impairment. Following a single dose of desloratadine 7.5 mg pharmacokinetics were characterized in patients with mild

(n=7; creatinine clearance 51-69 mL/min/1.73m^2), moderate (n=6; creatinine clearance 34-43 mL/min/1.73m^2) and severe (n=6; creatinine clearance 5-29 mL/min/1.73m^2) renal impairment or hemodialysis dependent (n=6) patients. In subjects with mild and moderate 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 patients 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. CLARINEX-D® 12 HOUR Extended Release Tablets should generally be avoided in patients with renal impairment (see **PRECAUTIONS** and **DOSAGE and ADMINISTRATION** section).

Hepatically Impaired: No studies with CLARINEX-D® 12 HOUR Extended Release Tablets or pseudoephedrine were conducted in patients with hepatic impairment. Following a single oral dose of desloratadine, pharmacokinetics were characterized in patients 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. Patients 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 patients 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. CLARINEX-D® 12 HOUR Extended Release Tablets should generally be avoided in patients with hepatic impairment (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Effect of 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. 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 clinically relevant and therefore no dosage adjustment is recommended.

Effect of Race: No studies have been conducted to evaluate the effect of race on the pharmacokinetics of CLARINEX-D® 12 HOUR Extended Release Tablets. 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 and therefore no dose adjustment is recommended.

Drug Interactions: No specific interaction studies have been conducted with CLARINEX-D® 12 HOUR Extended Release Tablets. However, in two 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 coadministered 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 coadministered 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 1), 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 1

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

	Desloratadine		3-hydroxydesloratadine	
	C_{max}	AUC 0-24 hrs	C_{max}	AUC 0-24 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%

Due to the pseudoephedrine component, CLARINEX-D® 12 HOUR Extended Release Tablets should not be used by patients taking monoamine oxidase inhibitors or within 14 days after stopping such treatment. 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.

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 QTc: 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 QTc 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 patients receiving desloratadine alone.

Single dose administration of desloratadine did not alter the corrected QT interval (QTc) in rats (up to 12 mg/kg, oral), or guinea pigs (25 mg/kg, intravenous). Repeated oral administration (up to 24 mg/kg, 1 and 3 months) to monkeys did not alter the QTc at an estimated desloratadine exposure (AUC) that was approximately 955 times the mean area under the plasma concentration versus time curve (AUC) in humans at the recommended daily oral dose. See **OVERDOSAGE** section for information on human QTc experience.

CLINICAL TRIALS: 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 patients 12 to 78 years of age with seasonal allergic rhinitis, 414 of whom received CLARINEX-D® 12 HOUR Extended Release Tablets. In the two trials patients were randomized to receive CLARINEX-D® 12 HOUR Extended Release Tablets twice daily, CLARINEX® Tablets 5 mg once daily, and sustained-release pseudoephedrine tablet 120 mg twice daily for two weeks. Primary efficacy variable was twice-daily reflective patient scoring of four

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 four 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 desloratadine alone over the 2-week treatment period. Primary efficacy variable results from one of two trials are shown in Table 2.

Table 2

Changes in Symptoms in a 2-Week Clinical Trial in Patients 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**

* To qualify at Baseline, the sum of the twice-daily diary reflective scores for the three 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 patients defined by gender, age, or race.

INDICATIONS AND USAGE: CLARINEX-D® 12 HOUR Extended Release Tablets is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion, in adults and children 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 activity of pseudoephedrine are desired (see **CLINICAL PHARMACOLOGY**).

CONTRAINDICATIONS: CLARINEX-D® 12 HOUR Extended Release Tablets are contraindicated in patients who are hypersensitive to this medication or to any of its ingredients, or to loratadine. Due to its pseudoephedrine component, it 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: CLARINEX-D® 12 HOUR Extended Release Tablets should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, or prostatic hypertrophy. Central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension may be produced by sympathomimetic amines.

PRECAUTIONS: General: CLARINEX-D® 12 HOUR Extended Release Tablets should generally be avoided in patients with hepatic impairment and patients with renal impairment (see **CLINICAL PHARMACOLOGY**, and **DOSAGE AND ADMINISTRATION**).

Information for Patients: Patients should be instructed to use CLARINEX-D® 12 HOUR Extended Release Tablets as directed. As there are no food effects on bioavailability, patients can be instructed that CLARINEX-D® 12 HOUR Extended Release Tablets may be taken without regard to meals. Patients should be advised not to increase the dose or dosing frequency as studies have not demonstrated increased effectiveness and at higher doses, somnolence may occur. Patients should also be advised against the concurrent use of CLARINEX-D® 12 HOUR Extended Release Tablets with over-the-counter antihistamines and decongestants.

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

Patients who are hypersensitive to this product or to any of its ingredients should not use this product. 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.

CLARINEX-D® 12 HOUR Extended Release Tablets should generally be avoided in patients with hepatic impairment and in patients with renal impairment.

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.

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.

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 metabolite exposures in mice at these doses were 12 and 27 times, respectively, the AUC in humans at the recommended daily oral dose.

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 two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenicity assay and mouse bone marrow micronucleus assay).

There was no effect on female fertility in rats at 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 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).

Pregnancy Category C: There have been no reproduction studies conducted with the combination of desloratadine and pseudoephedrine. 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 exposure was 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). There are, however, no adequate and well-controlled studies in pregnant women. 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.

Nursing Mothers: Desloratadine passes 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 importance of the drug to the mother. Caution should be exercised when CLARINEX-D® 12 HOUR Extended Release Tablets are administered to a nursing woman.

Pediatric Use: CLARINEX-D® 12 HOUR Extended Release Tablets is not an appropriate formulation for use in pediatric patients under 12 years of age.

Geriatric Use: Clinical studies of CLARINEX-D® 12 HOUR Extended Release Tablets did not include sufficient numbers of subjects aged 65 and over 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 - Special Populations**).

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- Special Populations**).

ADVERSE REACTIONS: The clinical trials with CLARINEX-D® 12 HOUR Extended Release Tablets included 1248 patients, of which 414 patients received CLARINEX-D® 12 HOUR Extended Release Tablets twice daily for up to 2 weeks. The percentage of patients receiving CLARINEX-D® 12 HOUR Extended Release Tablets, and who discontinued from the clinical trials because of an adverse event was 3.6%. Adverse events that were reported by ≥ 2% of patients receiving CLARINEX-D® 12 HOUR Extended Release Tablets, regardless of relationship to study drugs, are shown in Table 3.

Table 3

Incidence of Adverse Events Reported by ≥ 2% of Patients 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)
Insomnia	10%	3%	13%
Headache	8%	8%	9%
Mouth Dry	8%	2%	8%
Fatigue	4%	2%	2%
Somnolence	3%	4%	2%
Pharyngitis	3%	3%	3%
Dizziness	3%	2%	2%
Infection, viral	2%	2%	2%
Nausea	2%	1%	3%
Anorexia	2%	0%	2%

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

Observed During Clinical Practice: The following spontaneous adverse events have been reported during the marketing of desloratadine as a single ingredient product: headache, somnolence, dizziness, tachycardia, palpitations and rarely hypersensitivity reactions (such as rash, pruritus, urticaria, edema, dyspnea, and anaphylaxis), and elevated liver enzymes including bilirubin and very rarely, hepatitis.

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.

OVERDOSAGE: 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.

Single daily doses of 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 (QTc) by both the Bazett and Fridericia methods. Using the QTc (Bazett), there was a mean increase of 8.1 msec in the CLARINEX®-treated subjects relative to placebo. Using QTc (Fridericia) there was a mean increase of 0.4 msec in CLARINEX®-treated subjects relative to placebo. No clinically relevant adverse events were reported.

In large doses, sympathomimetics 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.

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.

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 a mg/m^2 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 a mg/m^2 basis).

DOSAGE AND ADMINISTRATION: Adults and children 12 years of age and over: The recommended dose of CLARINEX-D® 12 HOUR Extended Release Tablets is one tablet twice a day, administered approximately 12 hours apart and with or without a meal. CLARINEX-D® 12 HOUR Extended Release Tablets should generally be avoided in patients with hepatic impairment and patients with renal impairment.

CAUTION: Do not to break or chew the tablet; swallow whole.

HOW SUPPLIED: CLARINEX-D® 12 HOUR Extended Release Tablets contain 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 oval shaped, blue and white bilayer tablets with "D12" embossed in the blue layer; supplied in high-density polyethylene bottles of 100 (NDC 0085-1322-01).

Protect from excessive moisture. Protect from light.

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).

(*Schering logo)*

Manufactured for Schering Corporation
Kenilworth, New Jersey 07033 USA

02/06 29307601T

U.S. Patent Nos. 4,659,716; 4,863,931; 5,595,997; and 6,100,274