

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-313

LABELING

1 **CLARINEX-D[®] 12 HOUR** **PRODUCT**
2 **(desloratadine 2.5 mg and pseudoephedrine sulfate, USP 120 mg) INFORMATION**
3 **EXTENDED RELEASE TABLETS**

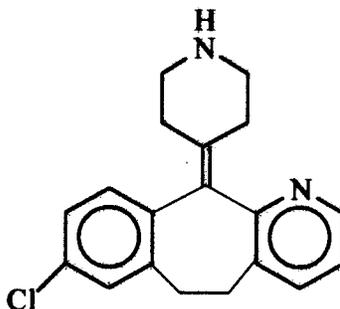
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5 **DESCRIPTION: CLARINEX-D[®] 12 HOUR Extended Release Tablets are oval**
6 **shaped blue and white bilayer tablets containing 2.5 mg desloratadine in the blue**
7 **immediate-release layer and 120 mg of pseudoephedrine sulfate, USP in the white**
8 **extended-release layer which is released slowly, allowing for twice-daily**
9 **administration.**

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

15 Desloratadine, one of the two active ingredients of CLARINEX-D[®] 12 HOUR
16 Extended Release Tablets, is a white to off-white powder that is slightly soluble in
17 water, but very soluble in ethanol and propylene glycol. It has an empirical formula:
18 C₁₉H₁₉ClN₂ and molecular weight of 310.8. The chemical name is 8-chloro-6,11-
19 dihydro-11-(4-piperidinylidene)-5H-benzo[5,6]cyclohepta [1,2-*b*]pyridine and has the
20 following structure:

21



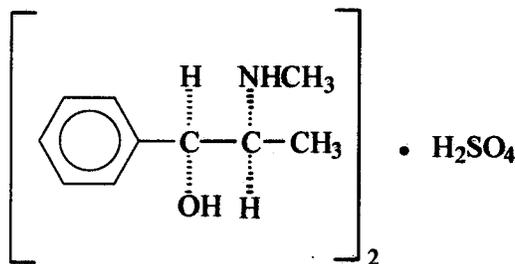
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24 Pseudoephedrine sulfate, the other active ingredient of CLARINEX-D[®] 12
25 HOUR Extended Release Tablets, is the synthetic salt of one of the naturally
26 occurring dextrorotatory diastereomer of ephedrine and is classified as an indirect
27 sympathomimetic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



35 **CLINICAL PHARMACOLOGY: Mechanism of Action:** Desloratadine is a long
36 acting tricyclic histamine antagonist with selective H₁-receptor histamine antagonist
37 activity. Receptor binding data indicate that at a concentration of 2-3 ng/mL (7
38 nanomolar), desloratadine shows significant interaction with the human histamine H₁
39 receptor. Desloratadine inhibited histamine release from human mast cells *in vitro*.

40 Results of a radiolabeled tissue distribution study in rats and a radioligand H₁-
41 receptor binding study in guinea pigs showed that desloratadine does not readily
42 cross the blood brain barrier.

43 Pseudoephedrine sulfate is an orally active sympathomimetic amine and
44 exerts a decongestant action on the nasal mucosa. Pseudoephedrine sulfate is
45 recognized as an effective agent for the relief of nasal congestion due to allergic
46 rhinitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine



47 and central effects similar to, but less intense than, amphetamines. It has the
48 potential for excitatory side effects.

49

50 **Pharmacokinetics: Absorption:** In a single dose pharmacokinetic study, the mean
51 time to maximum plasma concentrations (T_{max}) for desloratadine occurred at
52 approximately 4-5 hours post dose and mean peak plasma concentrations (C_{max})
53 and area under the concentration-time curve (AUC) of approximately 1.09 ng/mL
54 and 31.6 ng•hr/mL, respectively, were observed. In another pharmacokinetic study,
55 food and grapefruit juice had no effect on the bioavailability (C_{max} and AUC) of
56 desloratadine. For pseudoephedrine, the mean T_{max} occurred at 6-7 hours post
57 dose and mean peak plasma concentrations (C_{max}) and area under the
58 concentration-time curve (AUC) of approximately 263 ng/mL and 4588 ng•hr/mL,
59 respectively, were observed. Food had no effect on the bioavailability (C_{max} and
60 AUC) of desloratadine or pseudoephedrine.

61 Following oral administrations of CLARINEX-D[®] 12 HOUR Extended Release
62 Tablets twice daily for 14 days in normal healthy volunteers, steady-state conditions
63 were reached on day 10 for desloratadine, 3-hydroxydesloratadine and
64 pseudoephedrine. For desloratadine, mean steady state peak plasma
65 concentrations (C_{max}) and area under the concentration-time curve (AUC 0-12 h) of
66 approximately 1.7 ng/mL and 16 ng•hr/mL were observed, respectively. For
67 pseudoephedrine, mean steady state peak plasma concentrations (C_{max}) and AUC
68 (0-12 h) of 459 ng/mL and 4658 ng•hr/mL were observed.

69

70 **Distribution:** Desloratadine and 3-hydroxydesloratadine are approximately 82% to
71 87% and 85% to 89%, bound to plasma proteins, respectively. Protein binding of
72 desloratadine and 3-hydroxydesloratadine was unaltered in subjects with impaired
73 renal function.

74

75 **Metabolism:** Desloratadine (a major metabolite of loratadine) is extensively
76 metabolized to 3-hydroxydesloratadine, an active metabolite, which is subsequently



77 glucuronidated. The enzyme(s) responsible for the formation of 3-
78 hydroxydesloratadine have not been identified. Data from clinical trials with
79 desloratadine indicate that a subset of the general population has a decreased
80 ability to form 3-hydroxydesloratadine, and are poor metabolizers of desloratadine.
81 In pharmacokinetic studies (n=3748), approximately 6% of subjects were poor
82 metabolizers of desloratadine (defined as a subject with an AUC ratio of 3-
83 hydroxydesloratadine to desloratadine less than 0.1, or a subject with a
84 desloratadine half-life exceeding 50 hours). These pharmacokinetic studies included
85 subjects between the ages of 2 and 70 years, including 977 subjects aged 2-5 years,
86 1575 subjects aged 6-11 years, and 1196 subjects aged 12-70 years. There was no
87 difference in the prevalence of poor metabolizers across age groups. The frequency
88 of poor metabolizers was higher in Blacks (17%, n=988) as compared to Caucasians
89 (2%, n=1462) and Hispanics (2%, n=1063). The median exposure (AUC) to
90 desloratadine in the poor metabolizers was approximately 6-fold greater than in the
91 subjects who are not poor metabolizers. Subjects who are poor metabolizers of
92 desloratadine cannot be prospectively identified and will be exposed to higher levels
93 of desloratadine following dosing with the recommended dose of desloratadine. In
94 multidose clinical safety studies, where metabolizer status was prospectively
95 identified, a total of 94 poor metabolizers and 123 normal metabolizers were enrolled
96 and treated with CLARINEX® Syrup for 15-35 days. In these studies, no overall
97 differences in safety were observed between poor metabolizers and normal
98 metabolizers. Although not seen in these studies, an increased risk of exposure-
99 related adverse events in patients who are poor metabolizers cannot be ruled out.

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

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105 **Elimination:** Following single dose administration of CLARINEX-D[®] 12 HOUR
106 Extended Release Tablets, the mean plasma elimination half-life of desloratadine
107 was approximately 27 hours.

108 In another study, following administration of single oral doses of desloratadine
109 5 mg, C_{max} and AUC values increased in a dose proportional manner following single
110 oral doses between 5 and 20 mg. The degree of accumulation after 14 days of
111 dosing was consistent with the half-life and dosing frequency. A human mass
112 balance study documented a recovery of approximately 87% of the ¹⁴C-
113 desloratadine dose, which was equally distributed in urine and feces as metabolic
114 products. Analysis of plasma 3-hydroxydesloratadine showed similar T_{max} and half-
115 life values compared to desloratadine.

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

119 **Special Populations: Geriatric:** The number of patients (n=10) ≥ 65 years old
120 treated with CLARINEX-D[®] 12 HOUR Extended Release Tablets was too limited to
121 make any clinically relevant judgment regarding the efficacy or safety of this drug
122 product in this age group. Following multiple-dose administration of CLARINEX[®]
123 Tablets, the mean C_{max} and AUC values for desloratadine were 20% greater than in
124 younger subjects (< 65 years old). The oral total body clearance (CL/F) when
125 normalized for body weight was similar between the two age groups. The mean
126 plasma elimination half-life of desloratadine was 33.7 hr in subjects ≥ 65 years old.
127 The pharmacokinetics for 3-hydroxydesloratadine appeared unchanged in older
128 versus younger subjects. These age-related differences are unlikely to be clinically
129 relevant and no dosage adjustment is recommended in elderly subjects.

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

132 **Renally Impaired:** No studies with CLARINEX-D[®] 12 HOUR Extended Release
133 Tablets were conducted in patients with renal impairment. Following a single dose
134 of desloratadine 7.5 mg pharmacokinetics were characterized in patients with mild



135 (n=7; creatinine clearance 51-69 mL/min/1.73m²), moderate (n=6; creatinine
136 clearance 34-43 mL/min/1.73m²) and severe (n=6; creatinine clearance 5-29
137 mL/min/1.73m²) renal impairment or hemodialysis dependent (n=6) patients. In
138 subjects with mild and moderate impairment, median C_{max} and AUC values
139 increased by approximately 1.2 and 1.9-fold, respectively, relative to subjects with
140 normal renal function. In patients with severe renal impairment or who were
141 hemodialysis dependent, C_{max} and AUC values increased by approximately 1.7- and
142 2.5-fold, respectively. Minimal changes in 3-hydroxydesloratadine concentrations
143 were observed. Desloratadine and 3-hydroxydesloratadine were poorly removed by
144 hemodialysis. Plasma protein binding of desloratadine and 3-hydroxydesloratadine
145 was unaltered by renal impairment.

146 Pseudoephedrine is primarily excreted unchanged in the urine as unchanged
147 drug with the remainder apparently being metabolized in the liver. Therefore,
148 pseudoephedrine may accumulate in patients with renal impairment. CLARINEX-D[®]
149 12 HOUR Extended Release Tablets should generally be avoided in patients with
150 renal impairment (see **PRECAUTIONS** and **DOSAGE** and **ADMINISTRATION**
151 section).

152

153 **Hepatically Impaired:** No studies with CLARINEX-D[®] 12 HOUR Extended Release
154 Tablets or pseudoephedrine were conducted in patients with hepatic impairment.
155 Following a single oral dose of desloratadine, pharmacokinetics were characterized
156 in patients with mild (n=4), moderate (n=4) and severe (n=4) hepatic impairment as
157 defined by the Child-Pugh classification of hepatic impairment and 8 subjects with
158 normal hepatic function. Patients with hepatic impairment, regardless of severity,
159 had approximately a 2.4-fold increase in AUC as compared with normal subjects.
160 The apparent oral clearance of desloratadine in subjects with mild, moderate, and
161 severe hepatic impairment was 37%, 36%, and 28% of that in normal subjects,
162 respectively. An increase in the mean elimination half-life of desloratadine in
163 patients with hepatic impairment was observed. For 3-hydroxydesloratadine, the
164 mean C_{max} and AUC values for subjects with hepatic impairment combined were not



165 statistically significantly different from subjects with normal hepatic function.
166 CLARINEX-D[®] 12 HOUR Extended Release Tablets should generally be avoided in
167 patients with hepatic impairment (see PRECAUTIONS and DOSAGE AND
168 ADMINISTRATION).

169

170 **Effect of Gender:** No clinically significant gender-related differences were observed
171 in the pharmacokinetic parameters of desloratadine, 3-hydroxydesloratadine or
172 pseudoephedrine following administration of CLARINEX-D[®] 12 HOUR Extended
173 Release Tablets. Female subjects treated for 14 days with CLARINEX[®] Tablets had
174 10% and 3% higher desloratadine C_{max} and AUC values, respectively, compared
175 with male subjects. The 3-hydroxydesloratadine C_{max} and AUC values were also
176 increased by 45% and 48%, respectively, in females compared with males.
177 However, these apparent differences are not considered clinically relevant and
178 therefore no dosage adjustment is recommended.

179 **Effect of Race:** No studies have been conducted to evaluate the effect of race on
180 the pharmacokinetics of CLARINEX-D[®] 12 HOUR Extended Release Tablets.
181 Following 14 days of treatment with CLARINEX[®] Tablets, the C_{max} and AUC values
182 for desloratadine were 18% and 32% higher, respectively in Blacks compared with
183 Caucasians. For 3-hydroxydesloratadine there was a corresponding 10% reduction
184 in C_{max} and AUC values in Blacks compared to Caucasians. These differences are
185 not considered to be clinically relevant and therefore no dose adjustment is
186 recommended.

187 **Drug Interactions:** No specific interaction studies have been conducted with
188 CLARINEX-D[®] 12 HOUR Extended Release Tablets. However, in two controlled
189 crossover clinical pharmacology studies in healthy male (n=12 in each study) and
190 female (n=12 in each study) subjects, desloratadine 7.5 mg (1.5 times the daily
191 dose) once daily was coadministered with erythromycin 500 mg every 8 hours or
192 ketoconazole 200 mg every 12 hours for 10 days. In 3 separate controlled, parallel
193 group clinical pharmacology studies, desloratadine at the clinical dose of 5 mg has
194 been coadministered with azithromycin 500 mg followed by 250 mg once daily for 4



195 days (n=18) or with fluoxetine 20 mg once daily for 7 days after a 23-day
196 pretreatment period with fluoxetine (n=18) or with cimetidine 600 mg every 12 hours
197 for 14 days (n=18) under steady state conditions to healthy male and female
198 subjects. Although increased plasma concentrations (C_{max} and AUC 0-24 hrs) of
199 desloratadine and 3-hydroxydesloratadine were observed (see Table 1), there were
200 no clinically relevant changes in the safety profile of desloratadine, as assessed by
201 electrocardiographic parameters (including the corrected QT interval), clinical
202 laboratory tests, vital signs, and adverse events.

203 **Table 1**

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

	<u>Desloratadine</u>		<u>3-hydroxydesloratadine</u>	
	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%

206

207 Due to the pseudoephedrine component, CLARINEX-D[®] 12 HOUR Extended
208 Release Tablets should not be used by patients taking monoamine oxidase
209 inhibitors or within 14 days after stopping such treatment. The antihypertensive
210 effects of beta-adrenergic blocking agents, methyldopa, mecamlamine, reserpine,
211 and veratrum alkaloids may be reduced by sympathomimetics. Increased ectopic
212 pacemaker activity can occur when pseudoephedrine is used concomitantly with
213 digitalis.



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

220 **Effects on QTc:** In clinical trials for CLARINEX-D[®] 12 HOUR Extended Release
221 Tablets, ECGs were recorded at baseline and endpoint within 1 to 3 hours after the
222 last dose. The majority of ECGs were normal at both baseline and endpoint. No
223 clinically meaningful changes were observed following treatment with CLARINEX-D[®]
224 12 HOUR Extended Release Tablets for any ECG parameter, including the QTc
225 interval. An increase in the ventricular rate of 7.1 and 6.4 bpm was observed in the
226 CLARINEX-D[®] 12 HOUR Extended Release Tablets and pseudoephedrine groups,
227 respectively, compared to an increase of 3.2 bpm in patients receiving desloratadine
228 alone.

229 Single dose administration of desloratadine did not alter the corrected QT
230 interval (QTc) in rats (up to 12 mg/kg, oral), or guinea pigs (25 mg/kg, intravenous).
231 Repeated oral administration (up to 24 mg/kg, 1 and 3 months) to monkeys did not
232 alter the QTc at an estimated desloratadine exposure (AUC) that was approximately
233 955 times the mean area under the plasma concentration versus time curve (AUC)
234 in humans at the recommended daily oral dose. See OVERDOSAGE section for
235 information on human QTc experience.

236 **CLINICAL TRIALS:** The clinical efficacy and safety of CLARINEX-D[®] 12 HOUR
237 Extended Release Tablets was evaluated in two 2-week multicenter, randomized
238 parallel group clinical trials involving 1248 patients 12 to 78 years of age with
239 seasonal allergic rhinitis, 414 of whom received CLARINEX-D[®] 12 HOUR Extended
240 Release Tablets. In the two trials patients were randomized to receive CLARINEX-
241 D[®] 12 HOUR Extended Release Tablets twice daily, CLARINEX[®] Tablets 5 mg once
242 daily, and sustained-release pseudoephedrine tablet 120 mg twice daily for two
243 weeks. Primary efficacy variable was twice-daily reflective patient scoring of four



244 nasal symptoms (rhinorrhea, nasal stuffiness/congestion, nasal itching, and
245 sneezing) and four non-nasal symptoms (itching/burning eyes, tearing/watering
246 eyes, redness of eyes, and itching of ears/palate) on a four point scale (0=none,
247 1=mild, 2=moderate, and 3=severe). In both trials, the antihistaminic efficacy of
248 CLARINEX-D® 12 HOUR Extended Release Tablets, as measured by total symptom
249 score excluding nasal congestion, was significantly greater than pseudoephedrine
250 alone over the 2-week treatment period; and the decongestant efficacy of
251 CLARINEX-D® 12 HOUR Extended Release Tablets, as measured by nasal
252 stuffiness/congestion, was significantly greater than desloratadine alone over the 2-
253 week treatment period. Primary efficacy variable results from one of two trials are
254 shown in Table 2.

255
256
257

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.

258

259 There were no significant differences in the efficacy of CLARINEX-D[®] 12 HOUR
260 Extended Release Tablets across subgroups of patients defined by gender, age, or
261 race.

262 **INDICATIONS AND USAGE:** CLARINEX-D[®] 12 HOUR Extended Release Tablets
263 is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic
264 rhinitis including nasal congestion, in adults and children 12 years of age and older.
265 CLARINEX-D[®] 12 HOUR Extended Release Tablets should be administered when
266 the antihistaminic properties of desloratadine and the nasal decongestant activity of
267 pseudoephedrine are desired (see **CLINICAL PHARMACOLOGY**).

268 **CONTRAINDICATIONS:** CLARINEX-D[®] 12 HOUR Extended Release Tablets are
269 contraindicated in patients who are hypersensitive to this medication or to any of its
270 ingredients, or to loratadine. Due to its pseudoephedrine component, it is
271 contraindicated in patients with narrow-angle glaucoma or urinary retention, and in
272 patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen
273 (14) days of stopping such treatment (see **Drug Interactions** section). It is also
274 contraindicated in patients with severe hypertension, severe coronary artery
275 disease, and in those who have shown hypersensitivity or idiosyncrasy to its
276 components, to adrenergic agents, or to other drugs of similar chemical structures.
277 Manifestations of patient idiosyncrasy to adrenergic agents include: insomnia,
278 dizziness, weakness, tremor, or arrhythmias.

279

280 **WARNINGS:** CLARINEX-D[®] 12 HOUR Extended Release Tablets should be used
281 with caution in patients with hypertension, diabetes mellitus, ischemic heart disease,
282 increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic
283 hypertrophy. Central nervous system stimulation with convulsions or cardiovascular



284 collapse with accompanying hypotension may be produced by sympathomimetic
285 amines.

286

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

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

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

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

306 CLARINEX-D[®] 12 HOUR Extended Release Tablets should generally be
307 avoided in patients with hepatic impairment. Patients who have renal impairment
308 should modify the dosing to one tablet daily.

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

312 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** There are no animal or
313 laboratory studies on the combination product of desloratadine and



314 pseudoephedrine sulfate to evaluate carcinogenesis, mutagenesis, or impairment of
315 fertility.

316 The carcinogenic potential of desloratadine was assessed using a loratadine
317 study in rats and a desloratadine study in mice. In a 2-year study in rats, loratadine
318 was administered in the diet at doses up to 25 mg/kg/day (estimated desloratadine
319 and desloratadine metabolite exposures were approximately 30 times the AUC in
320 humans at the recommended daily oral dose). A significantly higher incidence of
321 hepatocellular tumors (combined adenomas and carcinomas) was observed in
322 males given 10 mg/kg/day of loratadine and in males and females given
323 25 mg/kg/day of loratadine. The estimated desloratadine and desloratadine
324 metabolite exposures in rats given 10 mg/kg of loratadine were approximately 7
325 times the AUC in humans at the recommended daily oral dose. The clinical
326 significance of these findings during long-term use of desloratadine is not known.

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

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

337 There was no effect on female fertility in rats at doses up to 24 mg/kg/day
338 (estimated desloratadine and desloratadine metabolite exposures were
339 approximately 130 times the AUC in humans at the recommended daily oral dose).
340 A male specific decrease in fertility, demonstrated by reduced female conception
341 rates, decreased sperm numbers and motility, and histopathologic testicular
342 changes, occurred at an oral dose of 12 mg/kg (estimated desloratadine and
343 desloratadine metabolite exposures were approximately 45 times the AUC in



344 humans at the recommended daily oral dose). Desloratadine had no effect on
345 fertility in rats at an oral dose of 3 mg/kg/day (estimated desloratadine and
346 desloratadine metabolite exposures were approximately 8 times the AUC in humans
347 at the recommended daily oral dose).

348 **Pregnancy Category C:** There have been no reproduction studies conducted with
349 the combination of desloratadine and pseudoephedrine. Desloratadine was not
350 teratogenic in rats at doses up to 48 mg/kg/day (estimated desloratadine and
351 desloratadine metabolite exposures were approximately 210 times the AUC in
352 humans at the recommended daily oral dose) or in rabbits at doses up to 60
353 mg/kg/day (estimated desloratadine exposure was approximately 230 times the AUC
354 in humans at the recommended daily oral dose). In a separate study, an increase in
355 pre-implantation loss and a decreased number of implantations and fetuses were
356 noted in female rats at 24 mg/kg (estimated desloratadine and desloratadine
357 metabolite exposures were approximately 120 times the AUC in humans at the
358 recommended daily oral dose). Reduced body weight and slow righting reflex were
359 reported in pups at doses of 9 mg/kg/day or greater (estimated desloratadine and
360 desloratadine metabolite exposures were approximately 50 times or greater than the
361 AUC in humans at the recommended daily oral dose). Desloratadine had no effect
362 on pup development at an oral dose of 3 mg/kg/day (estimated desloratadine and
363 desloratadine metabolite exposures were approximately 7 times the AUC in humans
364 at the recommended daily oral dose). There are, however, no adequate and well-
365 controlled studies in pregnant women. Because animal reproduction studies are not
366 always predictive of human response, CLARINEX-D[®] 12 HOUR Extended Release
367 Tablets should be used during pregnancy only if clearly needed.

368 **Nursing Mothers:** Desloratadine passes into breast milk, therefore a decision
369 should be made whether to discontinue nursing or to discontinue CLARINEX-D[®] 12
370 HOUR Extended Release Tablets, taking into account the importance of the drug to
371 the mother. Caution should be exercised when CLARINEX-D[®] 12 HOUR Extended
372 Release Tablets are administered to a nursing woman.



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

375 **Geriatric Use:** Clinical studies of CLARINEX-D[®] 12 HOUR Extended Release
376 Tablets did not include sufficient numbers of subjects aged 65 and over to determine
377 whether they respond differently from younger subjects. Other reported clinical
378 experience has not identified differences between the elderly and younger patients,
379 although the elderly are more likely to have adverse reactions to sympathomimetic
380 amines. In general, dose selection for an elderly patient should be cautious,
381 reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and
382 of concomitant disease or other drug therapy (see **CLINICAL PHARMACOLOGY -**
383 **Special Populations**).

384 Pseudoephedrine, desloratadine, and their metabolites are known to be
385 substantially excreted by the kidney, and the risk of adverse reactions may be
386 greater in patients with renal impairment. Because elderly patients are more likely to
387 have decreased renal function, care should be taken in dose selection, and it may
388 be useful to monitor the patient for adverse events (see **CLINICAL**
389 **PHARMACOLOGY- Special Populations**).

390

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

399

400

Table 3

401

Incidence of Adverse Events Reported by $\geq 2\%$ of Patients Receiving

402

CLARINEX-D[®] 12 HOUR Extended Release Tablets



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403

Adverse Reaction	CLARINEX-D [®] 12 HOUR BID (N = 414)	Desloratadine 5 mg QD (N = 412)	Pseudoephedrine 120 mg BID (N = 422)
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407	Insomnia	10%	3%	13%
408	Headache	8%	8%	9%
409	Mouth Dry	8%	2%	8%
410	Fatigue	4%	2%	2%
411	Somnolence	3%	4%	2%
412	Pharyngitis	3%	3%	3%
413	Dizziness	3%	2%	2%
414	Infection, viral	2%	2%	2%
415	Nausea	2%	1%	3%
416	Anorexia	2%	0%	2%

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

419

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

426

427 **DRUG ABUSE AND DEPENDENCE:** There is no information to indicate that abuse
428 or dependency occurs with CLARINEX[®] or CLARINEX-D[®] 12 HOUR Extended
429 Release Tablets.

430

431 **OVERDOSAGE:** Information regarding acute overdose with desloratadine is
432 limited to experience from post-marketing adverse event reports and from clinical
433 trials conducted during the development of the CLARINEX[®] product. In the reported
434 cases of overdose, there were no significant adverse events that were attributed to



435 desloratadine. In a dose ranging trial, at doses of 10 mg and 20 mg/day,
436 somnolence was reported.

437 Single daily doses of 45 mg were given to normal male and female volunteers
438 for 10 days. All ECGs obtained in this study were manually read in a blinded fashion
439 by a cardiologist. In the CLARINEX[®]-treated subjects, there was a mean increase
440 in the maximum heart rate of 9.2 bpm relative to placebo. The QT interval was
441 corrected for heart rate (QTc) by both the Bazett and Fridericia methods. Using the
442 QTc (Bazett), there was a mean increase of 8.1 msec in the CLARINEX[®]-treated
443 subjects relative to placebo. Using QTc (Fridericia) there was a mean increase of
444 0.4 msec in CLARINEX[®]-treated subjects relative to placebo. No clinically relevant
445 adverse events were reported.

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

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

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

463



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

470

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

472

473 **HOW SUPPLIED:** CLARINEX-D[®] 12 HOUR Extended Release Tablets contain 2.5
474 mg desloratadine in the blue immediate-release layer and 120 mg of
475 pseudoephedrine sulfate, USP in the white extended-release layer. CLARINEX-D[®]
476 12 HOUR Extended-Release Tablets are oval shaped, blue and white bilayer tablets
477 with "D12" embossed in the blue layer; supplied in high-density polyethylene bottles
478 of 100 (NDC 0085-1322-01).

479

480 **Protect from excessive moisture. Protect from light.**

481

482 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP**
483 **Controlled Room Temperature]. Avoid exposure at or above 30°C (86°F).**

484

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Kenilworth, New Jersey 07033 USA

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/s/

Badrul Chowdhury
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