

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-605

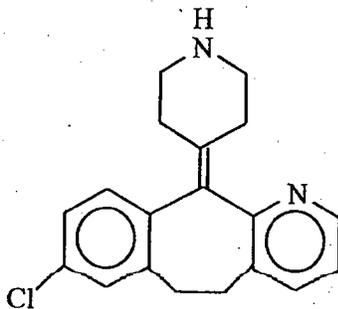
APPROVED LABELING

1 **CLARINEX-D® 24 HOUR**
2 **(desloratadine 5 mg and pseudoephedrine sulfate, USP 240 mg) Extended**
3 **Release Tablets**

4
5 **DESCRIPTION:** CLARINEX-D® 24 HOUR Extended Release Tablets are light blue
6 oval shaped tablets containing 5 mg desloratadine in the tablet coating for
7 immediate release and 240 mg pseudoephedrine sulfate, USP in the tablet core for
8 extended release.

9 The inactive ingredients contained in CLARINEX-D® 24 HOUR Extended
10 Release Tablets are hypromellose USP, ethylcellulose NF, dibasic calcium
11 phosphate dihydrate USP, magnesium stearate NF, povidone USP, silicone dioxide
12 NF, talc USP, polyacrylate dispersion, polyethylene glycol NF, simethicone USP,
13 Blue Lake Blend 50726 (FD&C Blue No. 2 Lake, titanium dioxide USP and edetate
14 disodium USP), and ink (Opacode® S-1-17746 or Opacode® S-1-4159).

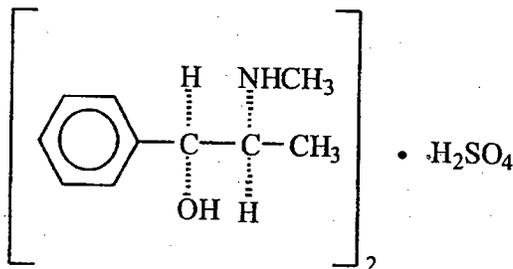
15 Desloratadine, one of the two active ingredients of CLARINEX-D® 24 HOUR
16 Extended-Release Tablets, is a white to off-white powder that is slightly soluble in
17 water, but very soluble in ethanol and propylene glycol. It has an empirical formula:
18 $C_{19}H_{19}ClN_2$ and a molecular weight of 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 :



22
23



24 Pseudoephedrine sulfate, the other active ingredient of CLARINEX-D® 24 HOUR
25 Extended-Release Tablets, is the synthetic salt of one of the naturally occurring
26 dextrorotatory diastereomers of ephedrine and is classified as an indirect
27 sympathomimetic amine. Pseudoephedrine sulfate is a colorless hygroscopic
28 crystals 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:



40 **CLINICAL PHARMACOLOGY: Mechanism of Action:** Desloratadine is a long-
41 acting tricyclic histamine antagonist with selective H₁-receptor histamine antagonist
42 activity. Receptor binding data indicate that at a concentration of 2 – 3 ng/mL (7
43 nanomolar), desloratadine shows significant interaction with the human histamine
44 H₁-receptor. Desloratadine inhibited histamine release from human mast cells *in*
45 *vitro*. Results of a radiolabeled tissue distribution study in rats and a radioligand H₁-
46 receptor binding study in guinea pigs showed that desloratadine did not readily cross
47 the blood brain barrier.

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



54 Pharmacokinetics: Absorption:

55 A bioequivalence study that compared CLARINEX-D[®] 24 HOUR Extended Release
56 Tablets to the monotherapy (desloratadine 5 mg, and pseudoephedrine 240 mg)
57 showed that CLARINEX-D[®] 24 HOUR Extended Release Tablets was not
58 bioequivalent to the monotherapy (desloratadine 5 mg tablet). The systemic
59 exposure to desloratadine and 3-hydroxydesloratadine was 15-20% lower from
60 CLARINEX-D[®] 24 HOUR Extended Release Tablets than those from desloratadine 5
61 mg tablet. Clinical trials were therefore necessary to support efficacy of CLARINEX-
62 D[®] 24 HOUR Extended Release Tablets (see **Clinical Trials** section).

63 In the above single dose pharmacokinetic study the mean time to maximum
64 plasma concentrations (T_{max}) for desloratadine occurred at approximately 6-7 hours
65 post dose and mean peak plasma concentrations (C_{max}) and area under the
66 concentration-time curve (AUC(tf)) of approximately 1.79 ng/mL and 61.1 ng•hr/mL,
67 respectively, were observed. In another pharmacokinetic study, food and grapefruit
68 juice had no effect on the bioavailability (C_{max} and AUC) of desloratadine. For
69 pseudoephedrine the mean T_{max} occurred at 8-9 hours post dose and mean peak
70 plasma concentrations (C_{max}) and AUC(tf) of 328 ng/mL and 6438 ng•hr/mL,
71 respectively, were observed. The ingestion of food did not affect the absorption of
72 pseudoephedrine from CLARINEX-D[®] 24 HOUR Extended Release Tablets.

73 Following oral administrations of CLARINEX-D[®] 24 HOUR Extended Release
74 Tablets once daily for 14 days to healthy volunteers steady-state conditions were
75 reached on day 12 for desloratadine and day 10 for pseudoephedrine. For
76 desloratadine, mean steady-state C_{max} and AUC (0-24h) of approximately 2.44
77 ng/mL and 34.8 ng•hr/mL, respectively were observed. For pseudoephedrine, mean
78 steady-state peak plasma concentrations (C_{max}) and AUC (0-24h) of 523 ng/mL and
79 8795 ng•hr/mL, respectively were observed.

80 **Distribution:** Desloratadine and 3-hydroxydesloratadine are approximately 82% to
81 87% and 85% to 89%, bound to plasma proteins, respectively. Protein binding of
82 desloratadine and 3-hydroxydesloratadine was unaltered in subjects with impaired
83 renal function.



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

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

113 **Elimination:** Following single dose administration of CLARINEX-D® 24 HOUR
114 Extended Release Tablets, the mean plasma elimination half-life of desloratadine



115 was similar to the desloratadine 5 mg tablet, approximately 24 and 27 hours,
116 respectively.

117 In another study, following administration of single oral doses of desloratadine
118 5 mg, C_{max} and AUC values increased in a dose proportional manner between 5 and
119 20 mg. The degree of accumulation after 14 days of dosing was consistent with the
120 half-life and dosing frequency. A human mass balance study documented a recovery
121 of approximately 87% of the ^{14}C -desloratadine dose, which was equally distributed in
122 urine and feces as metabolic products. Analysis of plasma 3-hydroxydesloratadine
123 showed similar T_{max} and half-life values compared to desloratadine.

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

127 **Special Populations: Geriatric:** The number of patients (n=8) \geq 65 years old treated
128 with CLARINEX-D® 24 HOUR Extended Release Tablets was too limited to make
129 any clinically relevant judgment regarding the efficacy or safety of this drug product
130 in this age group. Following multiple-dose administration of CLARINEX Tablets, the
131 mean C_{max} and AUC values for desloratadine were 20% greater than in younger
132 subjects (< 65 years old). The oral total body clearance (CL/F) when normalized for
133 body weight was similar between the two age groups. The mean plasma elimination
134 half-life of desloratadine was 33.7 hr in subjects \geq 65 years old. The
135 pharmacokinetics for 3-hydroxydesloratadine appeared unchanged in older versus
136 younger subjects. These age-related differences are unlikely to be clinically relevant
137 and no dosage adjustment is recommended in elderly subjects.

138 **Pediatric Subjects:** CLARINEX-D® 24 HOUR Extended Release Tablets are not an
139 appropriate dosage form for use in pediatric patients below 12 years of age.

140 **Renally Impaired:** No studies with CLARINEX-D® 24 HOUR Extended Release
141 Tablets have been conducted in patients with renal insufficiency. Following a single
142 dose of desloratadine 7.5 mg, pharmacokinetics were characterized in patients with
143 mild (n=7; creatinine clearance 51-69 mL/min/1.73 m²), moderate (n=6; creatinine
144 clearance 34-43 mL/min/1.73 m²), and severe (n=6; creatinine clearance 5-29



145 mL/min/1.73 m²) renal impairment or hemodialysis dependent (n=6) patients. In
146 patients with mild and moderate renal impairment, median C_{max} and AUC values
147 increased by approximately 1.2- and 1.9-fold, respectively, relative to subjects with
148 normal renal function. In patients with severe renal impairment or who were
149 hemodialysis dependent, C_{max} and AUC values increased by approximately 1.7- and
150 2.5-fold, respectively. Minimal changes in 3-hydroxydesloratadine concentrations
151 were observed. Desloratadine and 3-hydroxydesloratadine were poorly removed by
152 hemodialysis. Plasma protein binding of desloratadine and 3-hydroxydesloratadine
153 was unaltered by renal impairment.

154 Pseudoephedrine is primarily excreted unchanged in the urine as unchanged
155 drug, the remainder is apparently metabolized in the liver. Therefore,
156 pseudoephedrine may accumulate in patients with renal insufficiency.

157 Dosage adjustment for patients with renal impairment is recommended (see
158 **PRECAUTIONS and DOSAGE AND ADMINISTRATION** section).

159 **Hepatically Impaired:** No studies with CLARINEX-D[®] 24 HOUR Extended Release
160 Tablets or pseudoephedrine have been conducted in patients with hepatic
161 impairment. Following a single oral dose of desloratadine, pharmacokinetics were
162 characterized in patients with mild (n=4), moderate (n=4), and severe (n=4) hepatic
163 impairment as defined by the Child-Pugh classification of hepatic function and 8
164 subjects with normal hepatic function. Patients with hepatic impairment, regardless
165 of severity, had approximately a 2.4-fold increase in AUC as compared with normal
166 subjects. The apparent oral clearance of desloratadine in patients with mild,
167 moderate, and severe hepatic impairment was 37%, 36%, and 28% of that in normal
168 subjects, respectively. An increase in the mean elimination half-life of desloratadine
169 in patients with hepatic impairment was observed. For 3-hydroxydesloratadine, the
170 mean C_{max} and AUC values for patients with hepatic impairment were not statistically
171 significantly different from subjects with normal hepatic function. CLARINEX-D[®] 24
172 HOUR Extended Release Tablets should generally be avoided in patients with
173 hepatic insufficiency (see **PRECAUTIONS and DOSAGE AND ADMINISTRATION**).

174 **Gender:** No clinically significant gender-related differences were observed in the
175 pharmacokinetic parameters of desloratadine, 3-hydroxydesloratadine, or



176 pseudoephedrine following administration of CLARINEX-D® 24 HOUR Extended
177 Release Tablets. Female subjects treated for 14 days with CLARINEX Tablets had
178 10% and 3% higher desloratadine C_{max} and AUC values, respectively, compared
179 with male subjects. The 3-hydroxydesloratadine C_{max} and AUC values were also
180 increased by 45% and 48%, respectively, in females compared with males.
181 However, these apparent differences are not likely to be clinically relevant and
182 therefore no dosage adjustment is recommended.

183 **Race:** No studies have been conducted to evaluate the effect of race on the
184 pharmacokinetics of CLARINEX-D® 24 HOUR Extended Release Tablets. Following
185 14 days of treatment with CLARINEX Tablets, the C_{max} and AUC values for
186 desloratadine were 18% and 32% higher, respectively, in Blacks compared with
187 Caucasians. For 3-hydroxydesloratadine there was a corresponding 10% reduction
188 in C_{max} and AUC values in Blacks compared to Caucasians. These differences are
189 not likely to be clinically relevant and therefore no dose adjustment is recommended.

190 **Drug Interactions:** No specific interaction studies have been conducted with
191 CLARINEX-D® 24 HOUR Extended Release Tablets. However, in two controlled
192 crossover clinical pharmacology studies in healthy male (n=12 in each study) and
193 female (n=12 in each study) subjects, desloratadine 7.5 mg (1.5 times the daily
194 dose) once daily was coadministered with erythromycin 500 mg every 8 hours or
195 ketoconazole 200 mg every 12 hours for 10 days. In 3 separate controlled, parallel
196 group clinical pharmacology studies, desloratadine at the clinical dose of 5 mg has
197 been coadministered with azithromycin 500 mg followed by 250 mg once daily for 4
198 days (n=18) or with fluoxetine 20 mg once daily for 7 days after a 23 day
199 pretreatment period with fluoxetine (n=18) or with cimetidine 600 mg every 12 hours
200 for 14 days (n=18) under steady state conditions to healthy male and female
201 subjects. Although increased plasma concentrations (C_{max} and AUC 0-24 hrs) of
202 desloratadine and 3-hydroxydesloratadine were observed (see Table 1), there were
203 no clinically relevant changes in the safety profile of desloratadine, as assessed by
204 electrocardiographic parameters (including the corrected QT interval), clinical
205 laboratory tests, vital signs, and adverse events.

206



207

Table 1208
209

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%

210

211 Due to the pseudoephedrine component, CLARINEX-D[®] 24 HOUR Extended
212 Release Tablets should not be used by patients taking monoamine oxidase
213 inhibitors or within 14 days after stopping such treatment. The antihypertensive
214 effects of beta-adrenergic blocking agents, methyldopa, mecamylamine, reserpine,
215 and veratrum alkaloids may be reduced by sympathomimetics. Increased ectopic
216 pacemaker activity can occur when pseudoephedrine is used concomitantly with
217 digitalis.

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

224 **Effects on QT_c:** In clinical trials for CLARINEX-D[®] 24 HOUR Extended Release
225 Tablet, ECGs were recorded at baseline and after two weeks of treatment within 1 to



226 3 hours after dosing. No clinically meaningful changes were observed following
227 treatment with CLARINEX-D[®] 24 HOUR Extended Release Tablet for any ECG
228 parameter, including the QT_c interval. An increase in the ventricular rate of 6.7 and
229 5.4 bpm was observed in the CLARINEX-D[®] 24 HOUR Extended Release Tablet
230 and pseudoephedrine groups, respectively, compared to an increase of 2.8 bpm in
231 patients receiving desloratadine alone.

232 Single dose administration of desloratadine did not alter the corrected QT
233 interval (QT_c) in rats (up to 12 mg/kg, oral), or guinea pigs (25 mg/kg, intravenous).
234 Repeated oral administration at doses up to 24 mg/kg for durations up to 3 months
235 in monkeys did not alter the QT_c at an estimated desloratadine exposure (AUC) that
236 was approximately 955 times the mean AUC in humans at the recommended daily
237 oral dose. See **OVERDOSAGE** section for information on human QT_c experience.

238

239 **CLINICAL TRIALS:**

240 The clinical efficacy and safety of CLARINEX-D[®] 24 HOUR Extended Release
241 Tablets was evaluated in two 2-week multicenter, randomized parallel group clinical
242 trials involving 2852 patients 12 to 78 years of age with seasonal allergic rhinitis, 708
243 of whom received CLARINEX-D[®] 24 HOUR Extended Release Tablets. In the two
244 trials patients were randomized to receive CLARINEX-D[®] 24 HOUR Extended
245 Release Tablets once daily, CLARINEX Tablets 5 mg once daily, and sustained-
246 release pseudoephedrine tablet 240 mg once daily for two weeks. Primary efficacy
247 variable was twice-daily reflective patient scoring of four nasal symptoms
248 (rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing) and four non-
249 nasal symptoms (itching/burning eyes, tearing/watering eyes, redness of eyes, and
250 itching of ears/palate) on a four point scale (0=none, 1=mild, 2=moderate, and
251 3=severe). In both trials, the antihistaminic efficacy of CLARINEX-D[®] 24 HOUR
252 Extended Release Tablets, as measured by total symptom score excluding nasal
253 congestion, was significantly greater than pseudoephedrine alone over the 2-week
254 treatment period; and the decongestant efficacy of CLARINEX-D[®] 24 HOUR
255 Extended Release Tablets, as measured by nasal stuffiness/congestion, was



256 significantly greater than desloratadine alone over the 2-week treatment period.

257 Primary efficacy variable results from one of two trials are shown in Table 2.

258

259

260

261

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® 24 HOUR Comparison to components*** (P- value)
Total Symptom Score (Excluding Nasal Congestion)			
CLARINEX-D® 24 HOUR Extended Release Tablets (333)	14.84 (0.15)	-5.71 (-37.4) (0.22)	-
Pseudoephedrine tablet 240 mg (337)	15.03 (0.15)	-4.95 (-32.0) (0.22)	p=0.015
CLARINEX 5 mg Tablets (337)	15.06 (0.15)	-4.78 (-30.8) (0.22)	p=0.003
Nasal Stuffiness/Congestion			
CLARINEX-D® 24 HOUR Extended Release Tablets (333)	2.56 (0.020)	-0.85 (-32.3) (0.034)	-
Pseudoephedrine tablet 240 mg (337)	2.54 (0.020)	-0.70 (-27.1) (0.034)	p=0.002
CLARINEX 5 mg Tablets (337)	2.57 (0.020)	-0.65 (-24.8) (0.034)	p<0.001
<p>* 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).</p> <p>** Mean reduction in score averaged over the 2-week treatment period.</p> <p>*** The comparison of interest is shown bolded.</p>			

262



263 There were no significant differences in the efficacy of CLARINEX-D® 24 HOUR
264 Extended Release Tablets across subgroups of patients defined by gender, age, or
265 race.

266

267 **INDICATIONS AND USAGE:**

268 CLARINEX-D® 24 HOUR Extended Release Tablets is indicated for the relief of the
269 nasal and non-nasal symptoms of seasonal allergic rhinitis, including nasal
270 congestion, in patients 12 years of age and older. CLARINEX-D® 24 HOUR
271 Extended Release Tablets should be administered when the antihistaminic
272 properties of desloratadine and the nasal decongestant properties of
273 pseudoephedrine are desired (see **CLINICAL PHARMACOLOGY**).

274

275 **CONTRAINDICATIONS:** CLARINEX-D® 24 HOUR Extended Release Tablets is
276 contraindicated in patients who are hypersensitive to this medication or to any of its
277 ingredients, or to loratadine. Due to its pseudoephedrine component, it is
278 contraindicated in patients with narrow-angle glaucoma or urinary retention, and in
279 patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen
280 (14) days of stopping such treatment (see **Drug Interactions** section). It is also
281 contraindicated in patients with severe hypertension, severe coronary artery
282 disease, and in those who have shown hypersensitivity or idiosyncrasy to its
283 components, to adrenergic agents, or to other drugs of similar chemical structures.
284 Manifestations of patient idiosyncrasy to adrenergic agents include insomnia,
285 dizziness, weakness, tremor, or arrhythmias.

286

287 **WARNINGS:** CLARINEX-D® 24 HOUR Extended Release Tablets should be used
288 with caution in patients with hypertension, diabetes mellitus, ischemic heart disease,
289 increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic
290 hypertrophy. Central nervous system stimulation with convulsions or cardiovascular
291 collapse with accompanying hypotension may be produced by sympathomimetic
292 amines.



293

294 **PRECAUTIONS:**

295 **General:** Patients with decrease renal function should be dosed with CLARINEX-D®
296 24 HOUR Extended Release Tablets once every other day because they have
297 reduced elimination of desloratadine and pseudoephedrine. CLARINEX-D® 24
298 HOUR Extended Release Tablets should generally be avoided in patients with
299 hepatic insufficiency (see **CLINICAL PHARMACOLOGY**, and **DOSAGE AND**
300 **ADMINISTRATION**).

301 **Information for Patients:** Patients should be instructed to use CLARINEX-D® 24
302 HOUR Extended Release Tablets as directed. As there are no food effects on
303 bioavailability, patients can be instructed that CLARINEX-D® 24 HOUR Extended
304 Release Tablets may be taken without regard to meals. Patients should be advised
305 not to increase the dose or dosing frequency as studies have not demonstrated
306 increased effectiveness and at higher doses somnolence may occur. Patients should
307 also be advised against the concurrent use of CLARINEX-D® 24 HOUR Extended
308 Release Tablets with over-the-counter antihistamines and decongestants.

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

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

316 CLARINEX-D® 24 HOUR Extended Release Tablets should generally be
317 avoided in patients with hepatic insufficiency. Patients who have renal impairment
318 should modify the dosing to every other day.

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



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

326 The carcinogenic potential of desloratadine was assessed using a loratadine
327 study in rats and a desloratadine study in mice. In a 2-year study in rats, loratadine
328 was administered in the diet at doses up to 25 mg/kg/day (estimated desloratadine
329 and desloratadine metabolite exposures were approximately 30 times the AUC in
330 humans at the recommended daily oral dose). A significantly higher incidence of
331 hepatocellular tumors (combined adenomas and carcinomas) was observed in
332 males given 10 mg/kg/day of loratadine and in males and females given
333 25 mg/kg/day of loratadine. The estimated desloratadine and desloratadine
334 metabolite exposures in rats given 10 mg/kg of loratadine were approximately 7
335 times the AUC in humans at the recommended daily oral dose. The clinical
336 significance of these findings during long-term use of desloratadine is not known.

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

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

347 There was no effect on female fertility in rats at desloratadine doses up to 24
348 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were
349 approximately 130 times the AUC in humans at the recommended daily oral dose).
350 A male specific decrease in fertility, demonstrated by reduced female conception
351 rates, decreased sperm numbers and motility, and histopathologic testicular



352 changes, occurred at an oral desloratadine dose of 12 mg/kg in rats (estimated
353 desloratadine exposures were approximately 45 times the AUC in humans at the
354 recommended daily oral dose). Desloratadine had no effect on fertility in rats at an
355 oral dose of 3 mg/kg/day (estimated desloratadine and desloratadine metabolite
356 exposures were approximately 8 times the AUC in humans at the recommended
357 daily oral dose).

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

378 **Nursing Mothers:** Desloratadine passes into breast milk, therefore a decision
379 should be made whether to discontinue nursing or to discontinue CLARINEX-D® 24
380 HOUR Extended Release Tablets, taking into account the importance of the drug to
381 the mother. Caution should be exercised when CLARINEX-D® 24 HOUR Extended
382 Release Tablets are administered to a nursing woman.



383 **Pediatric Use:** CLARINEX-D® 24 HOUR Extended Release Tablets is not an
384 appropriate formulation for use in pediatric patients under 12 years of age.

385 **Geriatric Use:** Clinical studies of CLARINEX-D® 24 HOUR Extended Release
386 Tablets did not include sufficient numbers of subjects aged 65 and over to determine
387 whether they respond differently from younger subjects. Other reported clinical
388 experience has not identified differences between the elderly and younger patients,
389 although the elderly are more likely to have adverse reactions to sympathomimetic
390 amines. In general, dose selection for an elderly patient should be cautious,
391 reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and
392 of concomitant disease or other drug therapy (see **CLINICAL PHARMACOLOGY-**
393 **Special Populations**).

394 Pseudoephedrine, desloratadine, and their metabolites are known to be
395 substantially excreted by the kidney, and the risk of adverse reactions may be
396 greater in patients with impaired renal function. Because elderly patients are more
397 likely to have decreased renal function, care should be taken in dose selection, and
398 it may be useful to monitor the patient for adverse events (see **CLINICAL**
399 **PHARMACOLOGY- Special Populations**).

400

401 **ADVERSE REACTIONS:**

402 **Adults and Adolescents**

403 The clinical trials with CLARINEX-D® 24 HOUR Extended Release Tablets included
404 2852 patients, of which 708 patients received CLARINEX-D® 24 HOUR Extended
405 Release Tablets daily for up to 15 days. The percentage of patients receiving
406 CLARINEX-D® 24 HOUR Extended Release Tablets, and who discontinued from the
407 study because of an adverse event was 3.4%. Adverse events that were reported by
408 = 2% of patients receiving CLARINEX-D® 24 HOUR Extended Release Tablets,
409 regardless of relationship to study drugs, are shown in Table 3.



410

TABLE 3

411

Incidence of Adverse Events Reported by = 2% of Patients Receiving
CLARINEX-D® 24 HOUR Extended Release Tablets

412

413

Adverse Reaction	CLARINEX-D® 24 HOUR (N = 708)	Desloratadine 5 mg (N = 712)	Pseudoephedrine 240 mg (N = 719)
Mouth Dry	8%	2%	11%
Headache	6%	5%	7%
Insomnia	5%	1%	8%
Fatigue	3%	3%	2%
Pharyngitis	3%	2%	3%
Somnolence	3%	2%	3%
Nausea	2%	1%	3%
Dizziness	2%	1%	2%
Nervousness	2%	1%	1%
Hyperactivity	2%	0%	2%
Anorexia	2%	0%	2%

414

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

417 **Observed During Clinical Practice**

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

423

424 **DRUG ABUSE AND DEPENDENCE:** There is no information to indicate that abuse
425 or dependency occurs with CLARINEX or the combination of the CLARINEX product
426 with pseudoephedrine.

427

428 **OVERDOSAGE:** Information regarding acute overdosage with desloratadine is
429 limited to experience from post-marketing adverse event reports and from clinical



430 trials conducted during the development of the CLARINEX product. In the reported
431 cases of overdose, there were no significant adverse events that were attributed to
432 desloratadine. In a dose ranging trial, at doses of 10 mg and 20 mg/day somnolence
433 was reported.

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

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

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

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

460



461 **DOSAGE AND ADMINISTRATION:**

462 **Adults and children 12 years of age and over:** The recommended dose of
463 CLARINEX-D[®] 24 HOUR Extended Release Tablets is one tablet once daily,
464 administered with or without a meal. A dose of one tablet every other day is
465 recommended in patients with renal impairment. CLARINEX-D[®] 24 HOUR Extended
466 Release tablets should generally be avoided in patients with hepatic insufficiency.

467
468 **CAUTION:** Do not break or crush the tablet; swallow whole.
469

470 **HOW SUPPLIED:** CLARINEX-D[®] 24 HOUR Extended Release Tablets contain 5
471 mg desloratadine in the tablet coating for immediate release and 240 mg
472 pseudoephedrine sulfate, USP in an extended release core. CLARINEX-D[®] 24
473 HOUR Extended Release Tablets are light blue oval shaped coated tablets with "D
474 24" branded in black on one side; high-density polyethylene bottles of 100 (NDC
475 0085-1317-01).

476 **Protect from excessive moisture.**

477

478 **Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP**
479 **Controlled Room Temperature] Heat Sensitive. Avoid exposure at or above**
480 **30°C (86°F).**

481

482



Schering Corporation

483

Kenilworth, New Jersey 07033 USA

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485 03/05

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487 U.S. Patent Nos. 4,659,716; 4,731,447; 5,595,997; and 6,100,274

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Badrul Chowdhury
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