

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-300

APPROVED LABELING

1 **CLARINEX®**
2 **(desloratadine)**
3 **TABLETS, SYRUP, REDITABS® TABLETS**
4

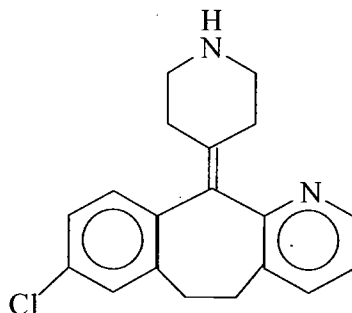
5 **DESCRIPTION: CLARINEX (desloratadine) Tablets** are light blue, round, film
6 coated tablets containing 5 mg desloratadine, an antihistamine, to be administered
7 orally. It also contains the following excipients: dibasic calcium phosphate dihydrate
8 USP, microcrystalline cellulose NF, corn starch NF, talc USP, carnauba wax NF,
9 white wax NF, coating material consisting of lactose monohydrate, hydroxypropyl
10 methylcellulose, titanium dioxide, polyethylene glycol, and FD&C Blue # 2 Aluminum
11 Lake.

12 **CLARINEX Syrup** is a clear orange colored liquid containing 0.5 mg/1ml
13 desloratadine. The syrup contains the following inactive ingredients: propylene glycol
14 USP, sorbitol solution USP, citric acid (anhydrous) USP, sodium citrate dihydrate
15 USP, sodium benzoate NF, disodium edetate USP, purified water USP. It also
16 contains granulated sugar, natural and artificial flavor for bubble gum and FDC
17 Yellow #6 dye.

18 The **CLARINEX RediTabs®** brand of desloratadine orally-disintegrating
19 tablets is a pink colored round tablet shaped units with a "C" debossed on one side.
20 Each RediTabs unit contains 5 mg of desloratadine. It also contains the following
21 inactive ingredients: gelatin Type B NF, mannitol USP, aspartame NF, polacrillin
22 potassium NF, citric acid USP, red dye and tutti frutti flavoring.

23 Desloratadine is a white to off-white powder that is slightly soluble in water,
24 but very soluble in ethanol and propylene glycol. It has an empirical formula:
25 C₁₉H₁₉ClN₂ and a molecular weight of 310.8. The chemical name is 8-chloro-6,11-
26 dihydro-11-(4-piperdinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine and has the
27 following structure :





32

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

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

42 **Pharmacokinetics: Absorption:** Following oral administration of
43 desloratadine 5 mg once daily for 10 days to normal healthy volunteers, the mean
44 time to maximum plasma concentrations (T_{max}) occurred at approximately 3 hours
45 post dose and mean steady state peak plasma concentrations (C_{max}) and area under
46 the concentration-time curve (AUC) of 4 ng/mL and 56.9 ng·hr/mL were observed,
47 respectively. Neither food nor grapefruit juice had an effect on the bioavailability
48 (C_{max} and AUC) of desloratadine.

49 The pharmacokinetic profile of CLARINEX Syrup was evaluated in a three-
50 way crossover study in 30 adult volunteers. A single dose of 10 ml of CLARINEX
51 Syrup containing 5 mg of desloratadine was bioequivalent to a single dose of 5 mg
52 CLARINEX Tablet. Food had no effect on the bioavailability (AUC and C_{max}) of
53 CLARINEX Syrup.

54 The pharmacokinetic profile of CLARINEX RediTabs Tablets was evaluated
55 in a three way crossover study in 30 adult volunteers. A single CLARINEX



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56 RediTabs Tablet containing 5 mg of desloratadine was bioequivalent to a single 5
57 mg CLARINEX tablet and was bioequivalent to 10 mL of CLARINEX Syrup
58 containing 5 mg of desloratadine for both desloratadine and 3-hydroxydesloratadine.
59 In a separate study with 30 adult volunteers, food or water had no effect on the
60 bioavailability (AUC and C_{max}) of CLARINEX RediTabs Tablets however, food shifted
61 the desloratadine median T_{max} value from 2.5 to 4 hr.

62 **Distribution:** Desloratadine and 3-hydroxydesloratadine are approximately 82% to
63 87% and 85% to 89%, bound to plasma proteins, respectively. Protein binding of
64 desloratadine and 3-hydroxydesloratadine was unaltered in subjects with impaired
65 renal function.

66 **Metabolism:** Desloratadine (a major metabolite of loratadine) is extensively
67 metabolized to 3-hydroxydesloratadine, an active metabolite, which is subsequently
68 glucuronidated. The enzyme(s) responsible for the formation of 3-
69 hydroxydesloratadine have not been identified. Data from clinical trials indicate that
70 a subset of the general population has a decreased ability to form 3-
71 hydroxydesloratadine, and are poor metabolizers of desloratadine. In
72 pharmacokinetic studies (n=3748), approximately 6% of subjects were poor
73 metabolizers of desloratadine (defined as a subject with an AUC ratio of 3-
74 hydroxydesloratadine to desloratadine less than 0.1, or a subject with a
75 desloratadine half-life exceeding 50 hours). These pharmacokinetic studies included
76 subjects between the ages of 2 and 70 years, including 977 subjects aged 2-5 years,
77 1575 subjects aged 6-11 years, and 1196 subjects aged 12-70 years. There was no
78 difference in the prevalence of poor metabolizers across age groups. The frequency
79 of poor metabolizers was higher in Blacks (17%, n=988) as compared to Caucasians
80 (2%, n=1462) and Hispanics(2%, n=1063). The median exposure (AUC) to
81 desloratadine in the poor metabolizers was approximately 6-fold greater than the
82 subjects who are not poor metabolizers. Subjects who are poor metabolizers of
83 desloratadine cannot be prospectively identified and will be exposed to higher levels
84 of desloratadine following dosing with the recommended dose of desloratadine. In
85 multidose clinical safety studies, where metabolizer status was identified, a total of
86 94 poor metabolizers and 123 normal metabolizers were enrolled and treated with



87 Clarinex for 15 to 35 days. In these studies, no overall differences in safety were
88 observed between poor metabolizers and normal metabolizers. Although not seen
89 in these studies, an increased risk of exposure-related adverse events in patients
90 who are poor metabolizers cannot be ruled out.

91 **Elimination:** The mean elimination half-life of desloratadine was 27 hours. C_{max} and
92 AUC values increased in a dose proportional manner following single oral doses
93 between 5 and 20 mg. The degree of accumulation after 14 days of dosing was
94 consistent with the half-life and dosing frequency. A human mass balance study
95 documented a recovery of approximately 87% of the ^{14}C -desloratadine dose, which
96 was equally distributed in urine and feces as metabolic products. Analysis of plasma
97 3-hydroxydesloratadine showed similar T_{max} and half-life values compared to
98 desloratadine.

99 **Special Populations: Geriatric:** In older subjects (≥ 65 years old; $n=17$) following
100 multiple-dose administration of CLARINEX Tablets, the mean C_{max} and AUC values
101 for desloratadine were 20% greater than in younger subjects (< 65 years old). The
102 oral total body clearance (CL/F) when normalized for body weight was similar
103 between the two age groups. The mean plasma elimination half-life of desloratadine
104 was 33.7 hr in subjects ≥ 65 years old. The pharmacokinetics for 3-
105 hydroxydesloratadine appeared unchanged in older versus younger subjects. These
106 age-related differences are unlikely to be clinically relevant and no dosage
107 adjustment is recommended in elderly subjects.

108 **Pediatric Subjects:** In subjects 6 to 11 years old, a single dose of 5 ml of
109 CLARINEX Syrup containing 2.5 mg of desloratadine, resulted in desloratadine
110 plasma concentrations similar to those achieved in adults administered a single 5
111 mg CLARINEX Tablet. In subjects 2 to 5 years old, a single dose of 2.5 ml of
112 CLARINEX Syrup containing 1.25 mg of desloratadine, resulted in a desloratadine
113 plasma concentrations similar to those achieved in adults administered a single 5
114 mg CLARINEX Tablet. However, the C_{max} and AUCt of the metabolite (3-OH
115 desloratadine) were 1.27 and 1.61 times higher for the 5 mg dose of syrup
116 administered in adults compared to the C_{max} and AUCt obtained in children 2-11
117 years of age receiving 1.25-2.5mg of Clarinex syrup.



118 A single dose of either 2.5 ml or 1.25 ml of CLARINEX Syrup containing 1.25 mg or
119 0.625 mg, respectively, of desloratadine was administered to subjects 6 to 11
120 months of age and 12 to 23 months of age. The results of a population
121 pharmacokinetic analysis indicated that a dose of 1 mg for subjects aged 6 to 11
122 months and 1.25 mg for subjects 12 to 23 months of age is required to obtain
123 desloratadine plasma concentrations similar to those achieved in adults
124 administered a single 5 mg dose of CLARINEX Syrup.

125 **Renally Impaired:** Desloratadine pharmacokinetics following a single dose of 7.5
126 mg were characterized in patients with mild (n=7; creatinine clearance 51-69
127 mL/min/1.73 m²), moderate (n=6; creatinine clearance 34-43 mL/min/1.73 m²), and
128 severe (n=6; creatinine clearance 5-29 mL/min/1.73 m²) renal impairment or
129 hemodialysis dependent (n=6) patients. In patients with mild and moderate renal
130 impairment, median C_{max} and AUC values increased by approximately 1.2 and 1.9
131 fold, respectively, relative to subjects with normal renal function. In patients with
132 severe renal impairment or who were hemodialysis dependent, C_{max} and AUC
133 values increased by approximately 1.7 and 2.5 fold, respectively. Minimal changes in
134 3-hydroxydesloratadine concentrations were observed. Desloratadine and 3-
135 hydroxydesloratadine were poorly removed by hemodialysis. Plasma protein
136 binding of desloratadine and 3-hydroxydesloratadine was unaltered by renal
137 impairment. Dosage adjustment for patients with renal impairment is recommended
138 (see **DOSAGE AND ADMINISTRATION** section).

139 **Hepatically Impaired:** Desloratadine pharmacokinetics were characterized following
140 a single oral dose in patients with mild (n=4), moderate (n=4), and severe (n=4)
141 hepatic impairment as defined by the Child-Pugh classification of hepatic function
142 and 8 subjects with normal hepatic function. Patients with hepatic impairment,
143 regardless of severity, had approximately a 2.4 fold increase in AUC as compared
144 with normal subjects. The apparent oral clearance of desloratadine in patients with
145 mild, moderate, and severe hepatic impairment was 37%, 36%, and 28% of that in
146 normal subjects, respectively. An increase in the mean elimination half-life of
147 desloratadine in patients with hepatic impairment was observed. For 3-
148 hydroxydesloratadine, the mean C_{max} and AUC values for patients with hepatic



149 impairment were not statistically significantly different from subjects with normal
150 hepatic function. Dosage adjustment for patients with hepatic impairment is
151 recommended (see **DOSAGE AND ADMINISTRATION** section).

152 **Gender:** Female subjects treated for 14 days with CLARINEX Tablets had 10% and
153 3% higher desloratadine C_{max} and AUC values, respectively, compared with male
154 subjects. The 3-hydroxydesloratadine C_{max} and AUC values were also increased by
155 45% and 48%, respectively, in females compared with males. However, these
156 apparent differences are not likely to be clinically relevant and therefore no dosage
157 adjustment is recommended.

158 **Race:** Following 14 days of treatment with CLARINEX Tablets, the C_{max} and AUC
159 values for desloratadine were 18% and 32% higher, respectively in Blacks compared
160 with Caucasians. For 3-hydroxydesloratadine there was a corresponding 10%
161 reduction in C_{max} and AUC values in Blacks compared to Caucasians. These
162 differences are not likely to be clinically relevant and therefore no dose adjustment is
163 recommended.

164 **Drug Interactions:** In two controlled crossover clinical pharmacology studies in
165 healthy male (n=12 in each study) and female (n=12 in each study) volunteers,
166 desloratadine 7.5 mg (1.5 times the daily dose) once daily was coadministered with
167 erythromycin 500 mg every 8 hours or ketoconazole 200 mg every 12 hours for 10
168 days. In 3 separate controlled, parallel group clinical pharmacology studies,
169 desloratadine at the clinical dose of 5 mg has been coadministered with
170 azithromycin 500 mg followed by 250 mg once daily for 4 days (n=18) or with
171 fluoxetine 20 mg once daily for 7 days after a 23 day pretreatment period with
172 fluoxetine (n=18) or with cimetidine 600 mg every 12 hours for 14 days (n=18) under
173 steady state conditions to normal healthy male and female volunteers. Although
174 increased plasma concentrations (C_{max} and AUC 0-24 hrs) of desloratadine and 3-
175 hydroxydesloratadine were observed (see **Table 1**), there were no clinically relevant
176 changes in the safety profile of desloratadine, as assessed by electrocardiographic
177 parameters (including the corrected QT interval), clinical laboratory tests, vital signs,
178 and adverse events.



179

Table 1

180

Changes in Desloratadine and 3-Hydroxydesloratadine Pharmacokinetics in Healthy
181 Male and Female Volunteers

	<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%

182

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

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



196 **Clinical Trials:**

197 **Seasonal Allergic Rhinitis:** The clinical efficacy and safety of CLARINEX Tablets
 198 were evaluated in over 2,300 patients 12 to 75 years of age with seasonal allergic
 199 rhinitis. A total of 1,838 patients received 2.5 – 20 mg/day of CLARINEX in 4 double-
 200 blind, randomized, placebo-controlled clinical trials of 2 to 4 weeks duration
 201 conducted in the United States. The results of these studies demonstrated the
 202 efficacy and safety of CLARINEX 5 mg in the treatment of adult and adolescent
 203 patients with seasonal allergic rhinitis. In a dose ranging trial, CLARINEX 2.5-20
 204 mg/day was studied. Doses of 5, 7.5, 10, and 20 mg/day were superior to placebo;
 205 and no additional benefit was seen at doses above 5.0 mg. In the same study, an
 206 increase in the incidence of somnolence was observed at doses of 10 mg/day and
 207 20 mg/day (5.2% and 7.6%, respectively), compared to placebo (2.3 %).

208 In 2 four-week studies of 924 patients (aged 15 to 75 years) with seasonal
 209 allergic rhinitis and concomitant asthma, CLARINEX Tablets 5 mg once daily
 210 improved rhinitis symptoms, with no decrease in pulmonary function. This supports
 211 the safety of administering CLARINEX Tablets to adult patients with seasonal
 212 allergic rhinitis with mild to moderate asthma.

213 CLARINEX Tablets 5 mg once daily significantly reduced the Total Symptom
 214 Scores (the sum of individual scores of nasal and non-nasal symptoms) in patients
 215 with seasonal allergic rhinitis. See **Table 2**.

216 **Table 2**
 217 TOTAL SYMPTOM SCORE (TSS)
 218 Changes in a 2 Week Clinical
 219 Trial in Patients with Seasonal Allergic Rhinitis

Treatment Group (n)	Mean Baseline* (sem)	Change from Baseline** (sem)	Placebo Comparison (P- value)
CLARINEX 5.0 mg (171)	14.2 (0.3)	-4.3 (0.3)	P=<0.01
Placebo (173)	13.7 (0.3)	-2.5 (0.3)	

*At baseline, a total nasal symptom score (sum of 4 individual symptoms) of at least 6 and a total non-nasal symptom score (sum of 4 individual symptoms) of at least 5 (each symptom scored 0 to 3 where 0=no symptom and 3=severe symptoms) was required for trial eligibility. TSS ranges from 0=no symptoms to 24=maximal symptoms.
 **Mean reduction in TSS averaged over the 2-week treatment period.

220 There were no significant differences in the effectiveness of CLARINEX
221 Tablets 5 mg across subgroups of patients defined by gender, age, or race.

222 **Perennial Allergic Rhinitis:** The clinical efficacy and safety of CLARINEX Tablets 5
223 mg were evaluated in over 1,300 patients 12 to 80 years of age with perennial
224 allergic rhinitis. A total of 685 patients received 5 mg/day of CLARINEX in 2 double
225 blind, randomized, placebo controlled clinical trials of 4 weeks duration conducted in
226 the United States and internationally. In one of these studies CLARINEX Tablets 5
227 mg once daily was shown to significantly reduce symptoms of perennial allergic
228 rhinitis (**Table 3**).

229 **Table 3**
230 TOTAL SYMPTOM SCORE (TSS)
231 Changes in a 4 Week Clinical
232 Trial in Patients with Perennial Allergic Rhinitis

Treatment Group (n)	Mean Baseline* (sem)	Change from Baseline** (sem)	Placebo Comparison (P- value)
CLARINEX 5.0 mg (337)	12.37 (0.18)	-4.06 (0.21)	P=<0.01
Placebo (337)	12.30 (0.18)	-3.27 (0.21)	

*At baseline, average of total symptom score (sum of 5 individual nasal symptoms and 3 non-nasal symptoms, each symptom scored 0 to 3 where 0=no symptom and 3=severe symptoms) of at least 10 was required for trial eligibility. TSS ranges from 0=no symptoms to 24=maximal symptoms.

**Mean reduction in TSS averaged over the 4-week treatment period.

233

234 **Chronic Idiopathic Urticaria:**

235 The efficacy and safety of CLARINEX Tablets 5 mg once daily was studied in 416
236 chronic idiopathic urticaria patients 12 to 84 years of age, of whom 211 received
237 CLARINEX. In two double-blind, placebo-controlled, randomized clinical trials of six
238 weeks duration, at the pre-specified one-week primary time point evaluation,
239 CLARINEX Tablets significantly reduced the severity of pruritus when compared to
240 placebo (**Table 4**). Secondary endpoints were also evaluated and during the first
241 week of therapy CLARINEX Tablets 5 mg reduced the secondary endpoints,
242 "Number of Hives" and the "Size of the Largest Hive" when compared to placebo.



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Table 4
PRURITUS SYMPTOM SCORE
Changes in the First Week of a Clinical
Trial in Patients with Chronic Idiopathic Urticaria

Treatment Group (n)	Mean Baseline (sem)	Change from Baseline* (sem)	Placebo Comparison (P- value)
CLARINEX 5.0 mg (115)	2.19 (0.04)	-1.05 (0.07)	P=<0.01
Placebo (110)	2.21 (0.04)	-0.52 (0.07)	

Pruritus scored 0 to 3 where 0 = no symptom to 3 = maximal symptom

*Mean reduction in pruritus averaged over the first week of treatment.

247

248 The clinical safety of CLARINEX Syrup was documented in three, 15-day,
249 double-blind, placebo-controlled safety studies in pediatric subjects with a
250 documented history of allergic rhinitis, chronic idiopathic urticaria, or subjects who
251 were candidates for antihistamine therapy. In the first study, 2.5 mg of CLARINEX
252 Syrup was administered to 60 pediatric subjects 6 to 11 years of age. The second
253 study evaluated 1.25 mg of CLARINEX Syrup administered to 55 pediatric subjects
254 2 to 5 years of age. In the third study, 1.25 mg of CLARINEX Syrup was
255 administered to 65 pediatric subjects 12 to 23 months of age and 1.0 mg of
256 CLARINEX Syrup was administered to 66 pediatric subjects 6 to 11 months of age.
257 The results of these studies demonstrated the safety of CLARINEX Syrup in
258 pediatric subjects 6 months to 11 years of age.

259 **INDICATIONS AND USAGE:**

260 **Seasonal Allergic Rhinitis:** CLARINEX is indicated for the relief of the nasal and
261 non-nasal symptoms of seasonal allergic rhinitis in patients 2 years of age and older.

262 **Perennial Allergic Rhinitis:** CLARINEX is indicated for the relief of the nasal and
263 non-nasal symptoms of perennial allergic rhinitis in patients 6 months of age and
264 older.



265 **Chronic Idiopathic Urticaria:** CLARINEX is indicated for the symptomatic relief of
266 pruritus, reduction in the number of hives, and size of hives, in patients with chronic
267 idiopathic urticaria 6 months of age and older.

268 **CONTRAINDICATIONS:** CLARINEX is contraindicated in patients who are
269 hypersensitive to this medication or to any of its ingredients, or to loratadine.

270

271 **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility:** The
272 carcinogenic potential of desloratadine was assessed using loratadine studies. In an
273 18-month study in mice and a 2-year study in rats, loratadine was administered in
274 the diet at doses up to 40 mg/kg/day in mice (estimated desloratadine and
275 desloratadine metabolite exposures were approximately 3 times the AUC in humans
276 at the recommended daily oral dose) and 25 mg/kg/day in rats (estimated
277 desloratadine and desloratadine metabolite exposures were approximately 30 times
278 the AUC in humans at the recommended daily oral dose). Male mice given 40
279 mg/kg/day loratadine had a significantly higher incidence of hepatocellular tumors
280 (combined adenomas and carcinomas) than concurrent controls. In rats, a
281 significantly higher incidence of hepatocellular tumors (combined adenomas and
282 carcinomas) was observed in males given 10 mg/kg/day and in males and females
283 given 25 mg/kg/day. The estimated desloratadine and desloratadine metabolite
284 exposures of rats given 10 mg/kg of loratadine were approximately 7 times the AUC
285 in humans at the recommended daily oral dose. The clinical significance of these
286 findings during long-term use of desloratadine is not known.

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

292 There was no effect on female fertility in rats at desloratadine doses up to 24
293 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were
294 approximately 130 times the AUC in humans at the recommended daily oral dose).
295 A male specific decrease in fertility, demonstrated by reduced female conception



296 rates, decreased sperm numbers and motility, and histopathologic testicular
297 changes, occurred at an oral desloratadine dose of 12 mg/kg in rats (estimated
298 desloratadine exposures were approximately 45 times the AUC in humans at the
299 recommended daily oral dose). Desloratadine had no effect on fertility in rats at an
300 oral dose of 3 mg/kg/day (estimated desloratadine and desloratadine metabolite
301 exposures were approximately 8 times the AUC in humans at the recommended
302 daily oral dose).

303 **Pregnancy Category C:** Desloratadine was not teratogenic in rats at doses up to
304 48 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures
305 were approximately 210 times the AUC in humans at the recommended daily oral
306 dose) or in rabbits at doses up to 60 mg/kg/day (estimated desloratadine exposures
307 were approximately 230 times the AUC in humans at the recommended daily oral
308 dose). In a separate study, an increase in pre-implantation loss and a decreased
309 number of implantations and fetuses were noted in female rats at 24 mg/kg
310 (estimated desloratadine and desloratadine metabolite exposures were
311 approximately 120 times the AUC in humans at the recommended daily oral dose).
312 Reduced body weight and slow righting reflex were reported in pups at doses of 9
313 mg/kg/day or greater (estimated desloratadine and desloratadine metabolite
314 exposures were approximately 50 times or greater than the AUC in humans at the
315 recommended daily oral dose). Desloratadine had no effect on pup development at
316 an oral dose of 3 mg/kg/day (estimated desloratadine and desloratadine metabolite
317 exposures were approximately 7 times the AUC in humans at the recommended
318 daily oral dose). There are, however, no adequate and well-controlled studies in
319 pregnant women. Because animal reproduction studies are not always predictive of
320 human response, desloratadine should be used during pregnancy only if clearly
321 needed.

322 **Nursing Mothers:** Desloratadine passes into breast milk, therefore a decision
323 should be made whether to discontinue nursing or to discontinue desloratadine,
324 taking into account the importance of the drug to the mother.

325 **Pediatric Use:** The recommended dose of CLARINEX Syrup in the pediatric
326 population is based on cross-study comparison of the plasma concentration of



327 CLARINEX in adults and pediatric subjects. The safety of CLARINEX Syrup has
328 been established in 246 pediatric subjects aged 6 months to 11 years in three
329 placebo-controlled clinical studies. Since the course of seasonal and perennial
330 allergic rhinitis and chronic idiopathic urticaria and the effects of CLARINEX are
331 sufficiently similar in the pediatric and adult populations, it allows extrapolation from
332 the adult efficacy data to pediatric patients. The effectiveness of CLARINEX Syrup
333 in these age groups is supported by evidence from adequate and well-controlled
334 studies of CLARINEX Tablets in adults. The safety and effectiveness of CLARINEX
335 Tablets or CLARINEX Syrup has not been demonstrated in pediatric patients less
336 than 6 months of age.

337 **Geriatric Use:** Clinical studies of desloratadine did not include sufficient numbers of
338 subjects aged 65 and over to determine whether they respond differently from
339 younger subjects. Other reported clinical experience has not identified differences
340 between the elderly and younger patients. In general, dose selection for an elderly
341 patient should be cautious, reflecting the greater frequency of decreased hepatic,
342 renal, or cardiac function, and of concomitant disease or other drug therapy. (see
343 **CLINICAL PHARMACOLOGY- Special Populations**).

344 **Information for Patients:** Patients should be instructed to use CLARINEX Tablets
345 as directed. As there are no food effects on bioavailability, patients can be instructed
346 that CLARINEX Tablets may be taken without regard to meals. Patients should be
347 advised not to increase the dose or dosing frequency as studies have not
348 demonstrated increased effectiveness at higher doses and somnolence may occur.

349 **Phenylketonurics:** CLARINEX RediTabs Tablets contain phenylalanine 1.75 mg per
350 tablet.

351 **ADVERSE REACTIONS:**

352 **Adults and Adolescents**

353 **Allergic Rhinitis:** In multiple-dose placebo-controlled trials, 2,834 patients ages 12
354 years or older received CLARINEX Tablets at doses of 2.5 mg to 20 mg daily, of
355 whom 1,655 patients received the recommended daily dose of 5 mg. In patients
356 receiving 5 mg daily, the rate of adverse events was similar between CLARINEX and



357 placebo-treated patients. The percent of patients who withdrew prematurely due to
358 adverse events was 2.4% in the CLARINEX group and 2.6% in the placebo group.
359 There were no serious adverse events in these trials in patients receiving
360 desloratadine. All adverse events that were reported by greater than or equal to 2%
361 of patients who received the recommended daily dose of CLARINEX Tablets (5.0
362 mg once-daily), and that were more common with CLARINEX Tablet than placebo,
363 are listed in **Table 5**.

364 **Table 5**

365 Incidence of Adverse Events Reported by 2% or More of Adult and Adolescent
366 Allergic Rhinitis Patients in Placebo-Controlled, Multiple-Dose Clinical Trials
367 with the Tablet Formulation of CLARINEX

Adverse Experience	Clarinet Tablets	Placebo
	5 mg (n=1,655)	(n=1,652)
Pharyngitis	4.1%	2.0%
Dry Mouth	3.0%	1.9%
Myalgia	2.1%	1.8%
Fatigue	2.1%	1.2%
Somnolence	2.1%	1.8%
Dysmenorrhea	2.1%	1.6%

368

369 The frequency and magnitude of laboratory and electrocardiographic
370 abnormalities were similar in CLARINEX and placebo-treated patients.

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

373 **Chronic Idiopathic Urticaria:** In multiple-dose, placebo-controlled trials of chronic
374 idiopathic urticaria, 211 patients ages 12 years or older received CLARINEX Tablets
375 and 205 received placebo. Adverse events that were reported by greater than or
376 equal to 2% of patients who received CLARINEX Tablets and that were more
377 common with CLARINEX than placebo were (rates for CLARINEX and placebo,
378 respectively): headache (14%, 13%), nausea (5%, 2%), fatigue (5%, 1%), dizziness
379 (4%, 3%), pharyngitis (3%, 2%), dyspepsia (3%, 1%), and myalgia (3%, 1%).

380 **Pediatrics**

381 Two hundred and forty-six pediatric subjects 6 months to 11 years of age
382 received CLARINEX Syrup for 15 days in three placebo-controlled clinical trials.



383 Pediatric subjects aged 6 to 11 years received 2.5 mg once a day, subjects aged 1
384 to 5 years received 1.25 mg once a day, and subjects 6 to 11 months of age
385 received 1.0 mg once a day. In subjects 6 to 11 years of age, no individual adverse
386 event was reported by 2 percent or more of the subjects. In subjects 2 to 5 years of
387 age, adverse events reported for CLARINEX and placebo in at least 2 percent of
388 subjects receiving CLARINEX Syrup and at a frequency greater than placebo were
389 fever (5.5%, 5.4%), urinary tract infection (3.6%, 0%) and varicella (3.6%, 0%). In
390 subjects 12 months to 23 months of age, adverse events reported for the CLARINEX
391 product and Placebo in at least 2 percent of subjects receiving CLARINEX Syrup
392 and at a frequency greater than placebo were fever (16.9%, 12.9%), diarrhea
393 (15.4% 11.3%), upper respiratory tract infections (10.8%, 9.7%), coughing (10.8%,
394 6.5%), appetite increased (3.1%, 1.6%), emotional lability (3.1%, 0%), epistaxis
395 (3.1%, 0%), parasitic infection, (3.1%, 0%) pharyngitis (3.1%, 0%), rash
396 maculopapular (3.1%, 0%). In subjects 6 months to 11 months of age, adverse
397 events reported for CLARINEX and Placebo in at least 2 percent of subjects
398 receiving CLARINEX Syrup and at a frequency greater than placebo were upper
399 respiratory tract infections (21.2%, 12.9%), diarrhea (19.7.% 8.1%), fever (12.1%,
400 1.6%), irritability (12.%, 11.3%) coughing (10.6%, 9.7%), somnolence (9.1%, 8.1%),
401 bronchitis (6.1%, 0%), otitis media (6.1%, 1.6%), vomiting (6.1%, 3.2%), anorexia
402 (4.5%, 1.6%), pharyngitis (4.5%, 1.6%), insomnia (4.5%, 0%), rhinorrhea (4.5%,
403 3.2%), erythema (3.0%, 1.6%), and nausea (3.0%, 0%). There were no clinically
404 meaningful changes in any electrocardiographic parameter, including the QTc
405 interval. Only one of the 246 pediatric subjects receiving CLARINEX Syrup in the
406 clinical trials discontinued treatment because of an adverse event.

407 **Observed During Clinical Practice**

408 The following spontaneous adverse events have been reported during the marketing
409 of desloratadine: tachycardia, and rarely hypersensitivity reactions (such as rash,
410 pruritus, urticaria, edema, dyspnea, and anaphylaxis), and elevated liver enzymes
411 including bilirubin.

412



413 **DRUG ABUSE AND DEPENDENCE:** There is no information to indicate that abuse
414 or dependency occurs with CLARINEX.

415

416 **OVERDOSAGE:** Information regarding acute overdosage is limited to experience
417 from clinical trials conducted during the development of the CLARINEX product. In a
418 dose ranging trial, at doses of 10 mg and 20 mg/day somnolence was reported.

419 Single daily doses of 45 mg were given to normal male and female volunteers
420 for 10 days. All ECGs obtained in this study were manually read in a blinded fashion
421 by a cardiologist. In CLARINEX-treated subjects, there was an increase in mean
422 heart rate of 9.2 bpm relative to placebo. The QT interval was corrected for heart
423 rate (QT_c) by both the Bazett and Fridericia methods. Using the QT_c (Bazett) there
424 was a mean increase of 8.1 msec in CLARINEX-treated subjects relative to placebo.
425 Using QT_c (Fridericia) there was a mean increase of 0.4 msec in CLARINEX-treated
426 subjects relative to placebo. No clinically relevant adverse events were reported.

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

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

438 **DOSAGE AND ADMINISTRATION:**

439 **Adults and children 12 years of age and over:** the recommended dose of
440 CLARINEX Tablets or CLARINEX RediTab Tablets is one 5 mg tablet once daily or
441 the recommended dose of CLARINEX Syrup is 2 teaspoonfuls (5 mg in 10 ml) once
442 daily.



443 **Children 6 to 11 years of age:** The recommended dose of CLARINEX Syrup is 1
444 teaspoonful (2.5 mg in 5 ml) once daily.

445 **Children 12 months to 5 years of age:** The recommended dose of CLARINEX
446 Syrup is $\frac{1}{2}$ teaspoonful (1.25 mg in 2.5 ml) once daily.

447 **Children 6 to 11 months of age:** The recommended dose of CLARINEX Syrup is 2
448 ml (1.0 mg) once daily.

449 The age-appropriate dose of CLARINEX Syrup should be administered with a
450 commercially available measuring dropper or syringe that is calibrated to deliver 2
451 mL and 2.5 mL (1/2 teaspoon).

452 In adult patients with liver or renal impairment, a starting dose of one 5 mg
453 tablet every other day is recommended based on pharmacokinetic data. Dosing
454 recommendation for children with liver or renal impairment cannot be made due to
455 lack of data.

456 **Administration of CLARINEX RediTabs Tablets:** Place CLARINEX
457 (desloratadine) RediTabs Tablets on the tongue. Tablet disintegration occurs
458 rapidly. Administer with or without water. Take tablet immediately after opening the
459 blister.

460 **HOW SUPPLIED: CLARINEX Tablets:** Embossed "C5", light blue film coated
461 tablets; that are packaged in high-density polyethylene plastic bottles of 100 (NDC
462 0085-1264-01) and 500 (NDC 0085-1264-02). Also available, CLARINEX Unit-of-
463 Use package of 30 tablets (3 x 10; 10 blisters per card) (NDC 0085-1264-04); and
464 Unit Dose-Hospital Pack of 100 Tablets (10 x 10; 10 blisters per card) (NDC 0085-
465 1264-03).

466

467 **Protect Unit-of-Use packaging and Unit Dose-Hospital Pack from**
468 **excessive moisture.**

469

470 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP**
471 **Controlled Temperature]**

472

Heat Sensitive. Avoid exposure at or above 30°C (86°F).



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473

474 **CLARINEX Syrup:** clear orange colored liquid containing 0.5 mg/1ml desloratadine
475 in a 16 ounce Amber glass bottle (NDC 0085-xxxx).

476

477 **Store syrup at 25° C (77°F); excursions permitted between 15° - 30°C**
478 **(59°-86°F) [see USP Controlled Temperature]**

479 **Protect from light.**

480

481 **CLARINEX REDITABS (desloratadine orally-disintegrating tablets) 5 mg: "C"**
482 **debossed, pink tablets in foil/foil blisters.**

483 **Packs of 30 tablets (containing 3 x 10's) NDC 0085-xxxx**

484

485 **Store REDITABS TABLETS at 25° C (77°F); excursions permitted**
486 **between 15° - 30° C (59°-86°F) [See USP Controlled Room Temperature].**

487

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490 *Schering*®

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Schering Corporation

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Kenilworth, New Jersey 07033 USA

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497 CLARINEX REDITABS brand of desloratadine orally-disintegrating tablets are
498 manufactured for Schering Corporation by Cardinal Health UK. 416 Limited,
499 England.

500 U.S. Patent Nos. 4,659,716; 4,863,931; 4,804,666; 5,595,997; and 6,100,274



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/s/

Badrul Chowdhury
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