

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-563**

**APPROVED LABELING**

1 **CLARINEX<sup>®</sup>**  
2 **(desloratadine)**  
3 **TABLETS, SYRUP, REDITABS<sup>®</sup> 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<sup>®</sup>** 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 C<sub>19</sub>H<sub>19</sub>ClN<sub>2</sub> 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 :

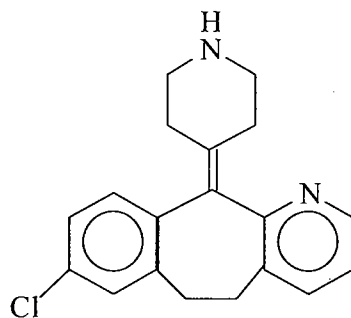
28

29

30

31





32

33 **CLINICAL PHARMACOLOGY: Mechanism of Action:** Desloratadine is a long-  
34 acting tricyclic histamine antagonist with selective H<sub>1</sub>-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 H<sub>1</sub>-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 H<sub>1</sub>-  
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<sub>max</sub>) occurred at approximately 3 hours  
45 post dose and mean steady state peak plasma concentrations (C<sub>max</sub>) 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<sub>max</sub> 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<sub>max</sub>) 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



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 ( $\geq 65$  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  $\geq 65$  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 m<sup>2</sup>), moderate (n=6; creatinine clearance 34-43 mL/min/1.73 m<sup>2</sup>), and  
128 severe (n=6; creatinine clearance 5-29 mL/min/1.73 m<sup>2</sup>) renal impairment or  
129 hemodialysis dependent (n=6) patients. In patients with mild and moderate renal  
130 impairment, median C<sub>max</sub> 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<sub>max</sub> 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<sub>max</sub> 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<sub>c</sub>:** Single dose administration of desloratadine did not alter the  
190 corrected QT interval (QT<sub>c</sub>) 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<sub>c</sub> 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<sub>c</sub> 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.



243  
244  
245  
246

**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 overdose 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<sub>c</sub>) by both the Bazett and Fridericia methods. Using the QT<sub>c</sub> (Bazett) there  
424 was a mean increase of 8.1 msec in CLARINEX-treated subjects relative to placebo.  
425 Using QT<sub>c</sub> (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/m<sup>2</sup> 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/m<sup>2</sup>  
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 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).**



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

488

489

*Schering*®

490

Schering Corporation

491

Kenilworth, New Jersey 07033 USA

492

493

494

495 08/04

XXXXXXXXXXT

496

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



SCHERING-PLOUGH RESEARCH INSTITUTE

501 Copyright© 2004, Schering Corporation. All rights reserved.

502

503



SCHERING-PLOUGH RESEARCH INSTITUTE