CLARINEX®
(desloratadine)
TABLETS

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

Desloratadine is a white to off-white powder that is slightly soluble in water, but very soluble in ethanol and propylene glycol. It has an empirical formula: C_{22}H_{27}ClN_{2}O_{4}, and a molecular weight of 310.8. The chemical name is 8-chloro-6,11-dihydro-11-(4-piperdinylidene)-5H-indeno[1,2-b]pyridine and has the following structure:

![Chemical Structure of Desloratadine](image)

CLINICAL PHARMACOLOGY: Mechanism of Action: Desloratadine is a long-acting triacyclic histamine antagonist with selective H₁-receptor histamine antagonist activity. Receptor binding data indicates that at a concentration of 2-3 nM (7 nanomolar), desloratadine shows significant interaction with the human histamine H₁ receptor. Desloratadine inhibited histamine release from human mast cells in vitro.

Results of a radiolabeled tissue distribution study in rats and a radiolabeled H₁-receptor binding study in guinea pigs showed that desloratadine does not readily cross the blood brain barrier. Pharmacokinetics: Absorption: Following oral administration of desloratadine 5 mg once daily for 10 days to normal healthy volunteers, the mean time to maximum plasma concentrations (Tₘₐₓ) occurred at approximately 3 hours post dose and mean steady state peak plasma concentrations (Cmax) and area under the concentration-time curve (AUC) of 4 mg/mL and 56.9 ng·h/mL were observed, respectively. Food had no effect on the bioavailability (Cmax and AUC of desloratadine).

Distribution: Desloratadine and 3-hydroxydesloratadine are approximately 82 to 87% and 85 to 89%, bound to plasma proteins, respectively. Protein binding of desloratadine and 3-hydroxydesloratadine was unaltered in patients with impaired renal function. Metabolism: Desloratadine (a major metabolite of loratadine) is extensively metabolized to 3-hydroxydesloratadine, an active metabolite, which is subsequently glucuronidated. The enzymes responsible for the formation of 3-hydroxydesloratadine have not been identified. Data from clinical trials indicate that a subset of the general patient population has a decreased ability to form 3-hydroxydesloratadine, and are slow metabolizers of desloratadine. In pharmacokinetic studies (n=1087), approximately 7% of subjects were slow metabolizers of desloratadine (defined as a subject with an AUC ratio of 3-hydroxydesloratadine to desloratadine less than 0.1, or a subject with a desloratadine half-life exceeding 50 hours). The frequency of slow metabolizers is higher in blacks (approximately 20% of blacks were slow metabolizers) and in the elderly.

Elimination: The mean elimination half-life of desloratadine was 27 hours. Cmax and AUC values increased in a dose proportional manner following single oral doses of 5 and 20 mg. The degree of accumulation after 14 days of dosing was consistent with the half-life and dosing frequency. A human mass balance study documented a recovery of approximately 85% of the dose excreted in the urine and feces as metabolic products. Analysis of plasma 3-hydroxydesloratadine showed similar Tₘₐₓ and half-life values compared to desloratadine.

Special Populations: Geriatric: In older subjects (>65 years old; n=17) following multiple-dose administration of CLARINEX Tablets, the mean Cₘₐₓ and AUC values for desloratadine were 20% greater than in younger subjects (<65 years old). The oral total body clearance (CL/F) when normalized for body weight was similar between the two age groups. The mean oral clearance of desloratadine was 33.7 hr in subjects ≥65 years old. The pharmacokinetics for 3-hydroxydesloratadine appeared unchanged in older versus younger subjects. These age-related differences are unlikely to be clinically relevant and no dosage adjustment is recommended in elderly subjects.

Renally Impaired: Desloratadine pharmacokinetics following a single dose of 7.5 mg were characterized in patients with mild (n=7), creatinine clearance 51-69 mL/min/1.73 m², moderate (n=4), creatinine clearance 34-49 mL/min/1.73 m², and severe (n=6), creatinine clearance 5-29 mL/min/1.73 m² renal impairment or hemodialysis dependent (n=6) patients. In patients with mild and moderate renal impairment, median Cₘₐₓ and AUC values increased by approximately 1.2 and 1.9-fold, respectively, relative to subjects with normal renal function. In patients with severe renal impairment or who were hemodialysis dependent, Cₘₐₓ and AUC values increased by approximately 1.7- and 2.5-fold, respectively. Minimal changes in 3-hydroxydesloratadine concentrations were observed. Desloratadine and 3-hydroxydesloratadine were poorly removed by hemodialysis. Plasma protein binding of desloratadine and 3-hydroxydesloratadine was unaffected by renal impairment. Dosage adjustment for patients with renal impairment is recommended (see DOSAGE AND ADMINISTRATION section).

Hepatically Impaired: Desloratadine pharmacokinetics were characterized following a single oral dose in patients with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment as defined by the Child-Pugh classification of hepatic function and 8 subjects with normal hepatic function. Patients with hepatic impairment, regardless of severity, had approximately a 2.4-fold increase in AUC as compared with normal subjects. The apparent oral clearance of desloratadine in patients with mild, moderate, and severe hepatic impairment was 37, 36, and 26%, respectively. An increase in the mean elimination half-life of desloratadine in patients with hepatic impairment was observed. For 3-hydroxydesloratadine, the mean Cₘₐₓ and AUC values for patients with hepatic impairment were not statistically significantly different from subjects with normal hepatic function. Dosage adjustment for patients with hepatic impairment is recommended (see DOSAGE AND ADMINISTRATION section).

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

Race: Following 14 days of treatment with CLARINEX Tablets, the Cₘₐₓ and AUC values for desloratadine were 18 and 32% higher, respectively, in Blacks compared with Caucasians. For 3-hydroxydesloratadine there was a corresponding 10% reduction in Cₘₐₓ and AUC values in Blacks compared to Caucasians. These differences are not likely to be clinically relevant and therefore no dosage adjustment is recommended.

Drug Interactions: In two controlled clinical pharmacology studies in healthy male (n=12 in each study) and female (n=12 in each study) volunteers, desloratadine 7.5 mg once daily was coadministered with erythromycin 500 mg every 8 hours or ketoconazole 200 mg every 12 hours for 10 days. Although increased plasma concentrations (Cₘₐₓ and AUC 0-24 hrs) of desloratadine and 3-hydroxydesloratadine were observed (see Table 1), there were no clinically relevant changes in the safety profile of desloratadine, as assessed by electrocardiographic parameters (including the corrected QT interval), clinical laboratory tests, vital signs, and adverse events.

Table 1

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>Cₘₐₓ</th>
<th>AUC 0-24 hrs</th>
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<tbody>
<tr>
<td>Erythromycin (500 mg Q8h)</td>
<td>+24%</td>
<td>+14%</td>
</tr>
<tr>
<td>Ketoconazole (200 mg Q12h)</td>
<td>+45%</td>
<td>+39%</td>
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</tbody>
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Pharmacodynamics: Effects on QTc: Single dose administration of desloratadine did not alter the corrected QT interval (QTc) in rats (up to 12 mg/kg, oral), or guinea pigs (25 mg/kg, intravenous). Repeated oral administration at doses up to 24 mg/kg for durations up to 3 months in monkeys did not alter the QTc, at an estimated desloratadine exposure (AUC) that was approximately 955 times the mean AUC in humans at the recommended daily oral dose. See OVERDOSAGE section for information on human QTc experience.

Clinical Trials: The clinical efficacy and safety of CLARINEX Tablets were evaluated in over 2,300 patients 12 to 75 years of age with seasonal allergic rhinitis. A total of 1,838 patients received 2.5-20 mg/day of CLARINEX in 4 double-blind, randomized, placebo-controlled clinical trials of 2- to 4- week duration conducted in the United States. The results of these studies demonstrated the efficacy and safety of CLARINEX 5 mg in the treatment of adult and adolescent patients with seasonal allergic rhinitis. In a dose ranging trial, CLARINEX 2.5-20 mg/day was studied. Doses of 5, 7.5, 10, and 20 mg/day were superior to placebo; and no additional benefit was seen at doses above 5.0 mg. In the same study, an increase in the incidence of somnolence was observed at doses of 10 mg/day and 20 mg/day (5.2% and 7.6%, respectively), compared to placebo (2.3%). CLARINEX Tablets 5 mg once daily significantly reduced the Total Symptom Scores (the sum of individual scores of nasal and non-nasal symptoms) in patients with seasonal allergic rhinitis. See Table 2.
Desloratadine was not teratogenic in rats at doses up to 25 mg/kg/day. In multiple-dose placebo-controlled trials, 1,838 patients received desloratadine 5 mg once daily. In patients with liver or renal impairment, the starting dose of one 5 mg tablet every other day is recommended based on pharmacokinetic data.

**DOSAGE AND ADMINISTRATION:** In adults and children 12 years of age and over, the recommended dose of CLARINEX Tablets is 5 mg once daily. In patients with liver or renal impairment, a starting dose of one 5 mg tablet every other day is recommended based on pharmacokinetic data.

**HOW SUPPLIED:** CLARINEX Tablets: Embossed “CS”, light blue film-coated tablets; that are supplied in bottles of 100 (NDC 0085-1247-01), and 500 (NDC 0085-1248-02). Also available, CLARINEX Unit-of-Use package of 30 tablets (3 x 10; 10 blisters per card) (NDC 0085-1244-04); and Unit Dose-Hospital Pack of 100 Tablets (10 x 10; 10 blisters per card) (NDC 0085-1243-04). Protect Unit-of-Use packaging and Unit-Dose Hospital Pack from excessive moisture. Store between 2° and 25°C (36° and 77°F). Heat sensitive. Avoid exposure to or above 30°C (86°F).
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/s/

Robert Meyer
12/21/01 05:00:43 PM
For Dr. Jenkins