CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-312/S007

Trade Name: Clarinex RediTabs®

Generic Name: (Desloratadine)

Sponsor: Schering Corporation.

Approval Date: July 14, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-312/S007

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APPLICATION NUMBER:

21-312/S007

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-312/S-007

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Satish Joshi
Senior Manager, CMC Global Regulatory Affairs

Dear Mr. Joshi,

Please refer to your supplemental new drug application dated March 14, 2005, received March 17, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clarinex® (desloratadine) RediTabs® 2.5 mg and 5 mg Orally Disintegrating Tablet.

We acknowledge receipt of your submissions dated March 15, April 14, May 25, and June 15, 2005.

This supplemental new drug application provides for changes to the formulation and the addition of a 2.5 mg strength.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the submitted labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling, copy enclosed (package insert submitted March 14, 2005, immediate container and carton labels submitted June 15, 2005).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-312/S-007**." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Anthony M. Zeccola, Regulatory Management Officer, at (301) 827-1058.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury

7/14/05 01:44:36 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-312/S007

LABELING

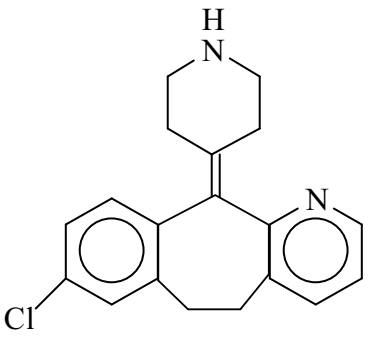
CLARINEX ®
(desloratadine)
TABLETS, SYRUP, REDITABS® TABLETS

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.

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

The **CLARINEX RediTabs®** brand of desloratadine orally-disintegrating tablets are light red, flat-faced, round, speckled tablets with an "A" debossed on one side for the 5 mg tablets and a "K" debossed on one side for the 2.5 mg tablets. Each RediTabs Tablet contains either 5 mg or 2.5 mg of desloratadine. It also contains the following inactive ingredients: mannitol USP, microcrystalline cellulose NF, pregelatinized starch, NF, sodium starch glycolate, USP, magnesium stearate NF, butylated methacrylate copolymer, crospovidone, NF, aspartame NF, citric acid USP, sodium bicarbonate USP, colloidal silicon dioxide, NF, ferric oxide red NF and tutti frutti flavoring.

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: $C_{19}H_{19}ClN_2$ and a molecular weight of 310.8. The chemical name is 8-chloro-6,11-dihydro-11-(4-piperdinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine and has the following structure :



CLINICAL PHARMACOLOGY: Mechanism of Action: Desloratadine is a long-acting tricyclic histamine antagonist with selective H_1-receptor histamine antagonist activity. Receptor binding data indicates that at a concentration of 2 – 3 ng/mL (7 nanomolar), desloratadine shows significant interaction with the human histamine H_1-receptor. Desloratadine inhibited histamine release from human mast cells *in vitro*.

Results of a radiolabeled tissue distribution study in rats and a radioligand H_1-receptor binding study in guinea pigs showed that desloratadine did 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 (T_{max}) occurred at approximately 3 hours post dose and mean steady state peak plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) of 4 ng/mL and 56.9 ng·hr/mL were observed, respectively. Neither food nor grapefruit juice had an effect on the bioavailability (C_{max} and AUC) of desloratadine.

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

The pharmacokinetic profile of CLARINEX RediTabs Tablets was evaluated in a three way crossover study in 24 adult volunteers. A single CLARINEX RediTabs Tablet containing 5 mg of desloratadine was bioequivalent to a single 5 mg CLARINEX Reditabs Tablet (original formulation) for both desloratadine and 3-hydroxydesloratadine. Water had no effect on the bioavailability (AUC and C_{max}) of CLARINEX RediTabs Tablets

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 subjects 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 enzyme(s) responsible for the formation of 3-hydroxydesloratadine have not been identified. Data from clinical trials indicate that a subset of the general population has a decreased ability to form 3-hydroxydesloratadine, and are poor metabolizers of desloratadine. In pharmacokinetic studies (n= 3748), approximately 6% of subjects were poor 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). These pharmacokinetic studies included subjects between the ages of 2 and 70 years, including 977 subjects aged 2-5 years, 1575 subjects aged 6-11 years, and 1196 subjects aged 12-70 years. There was no difference in the prevalence of poor metabolizers across age groups. The frequency of poor metabolizers was higher in Blacks (17%, n=988) as compared to Caucasians (2%, n=1462) and Hispanics (2%, n=1063). The median exposure (AUC) to desloratadine in the poor metabolizers was approximately 6-fold greater than in the subjects who are not poor metabolizers. Subjects who are poor metabolizers of desloratadine cannot be prospectively identified and will be exposed to higher levels of desloratadine following dosing with the recommended dose of desloratadine. In multidose clinical safety studies, where metabolizer status was identified, a total of 94 poor metabolizers and 123 normal metabolizers were enrolled and treated with

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

Elimination: The mean elimination half-life of desloratadine was 27 hours. C_{max} and AUC values increased in a dose proportional manner following single oral doses between 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 87% of the ^{14}C-desloratadine dose, which was equally distributed in urine and feces as metabolic products. Analysis of plasma 3-hydroxydesloratadine showed similar T_{max} 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 C_{max} 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 plasma elimination half-life 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.

Pediatric Subjects: In subjects 6 to 11 years old, a single dose of 5 ml of CLARINEX Syrup containing 2.5 mg of desloratadine, resulted in desloratadine plasma concentrations similar to those achieved in adults administered a single 5 mg CLARINEX Tablet. In subjects 2 to 5 years old, a single dose of 2.5 ml of CLARINEX Syrup containing 1.25 mg of desloratadine, resulted in desloratadine plasma concentrations similar to those achieved in adults administered a single 5 mg CLARINEX Tablet. However, the Cmax and AUCt of the metabolite (3-OH desloratadine) were 1.27 and 1.61 times higher for the 5 mg dose of syrup administered in adults compared to the Cmax and AUCt obtained in children 2-11 years of age receiving 1.25-2.5 mg of Clarinex syrup.

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

The CLARINEX RediTabs Tablet 2.5 mg tablet has not been evaluated in pediatric patients. Bioequivalence of the CLARINEX RediTabs Tablet and the original CLARINEX RediTabs Tablets was established in adults. In conjunction with the dose finding studies in pediatrics described, the pharmacokinetic data for CLARINEX RediTabs Tablets supports the use of the 2.5 mg dose strength in pediatric patients 6-11 years of age.

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 m^2), moderate (n=6; creatinine clearance 34-43 mL/min/1.73 m^2), and severe (n=6; creatinine clearance 5-29 mL/min/1.73 m^2) renal impairment or hemodialysis dependent (n=6) patients. In patients with mild and moderate renal impairment, median C_{max} 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, C_{max} 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 unaltered 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 28% of that in normal subjects, respectively. An increase in the mean elimination half-life of desloratadine in patients with hepatic impairment was observed. For 3-hydroxydesloratadine, the mean C_{max} 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 C_{max} and AUC values, respectively, compared with male subjects. The 3-hydroxydesloratadine C_{max} 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 C_{max} 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 C_{max} and AUC values in Blacks compared to Caucasians. These differences are not likely to be clinically relevant and therefore no dose adjustment is recommended.

Drug Interactions: In two controlled crossover clinical pharmacology studies in healthy male (n=12 in each study) and female (n=12 in each study) volunteers, desloratadine 7.5 mg (1.5 times the daily dose) once daily was coadministered with erythromycin 500 mg every 8 hours or ketoconazole 200 mg every 12 hours for 10 days. In 3 separate controlled, parallel group clinical pharmacology studies, desloratadine at the clinical dose of 5 mg has been coadministered with azithromycin 500 mg followed by 250 mg once daily for 4 days (n=18) or with fluoxetine 20 mg once daily for 7 days after a 23 day pretreatment period with fluoxetine (n=18) or with cimetidine 600 mg every 12 hours for 14 days (n=18) under steady state conditions to normal healthy male and female volunteers. 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

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

	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%

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

Effects on QT_c: Single dose administration of desloratadine did not alter the corrected QT interval (QT_c) 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 QT_c 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 QT_c experience.

Clinical Trials:

Seasonal Allergic Rhinitis: 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- weeks 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 %).

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

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.

Table 2

TOTAL SYMPTOM SCORE (TSS)
Changes in a 2 Week Clinical
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.

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

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

Table 3

TOTAL SYMPTOM SCORE (TSS)
Changes in a 4 Week Clinical
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.

Chronic Idiopathic Urticaria:

The efficacy and safety of CLARINEX Tablets 5 mg once daily was studied in 416 chronic idiopathic urticaria patients 12 to 84 years of age, of whom 211 received CLARINEX. In two double-blind, placebo-controlled, randomized clinical trials of six weeks duration, at the pre-specified one-week primary time point evaluation, CLARINEX Tablets significantly reduced the severity of pruritus when compared to

placebo (Table 4). Secondary endpoints were also evaluated and during the first week of therapy CLARINEX Tablets 5 mg reduced the secondary endpoints, "Number of Hives" and the "Size of the Largest Hive" when compared to placebo.

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.

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

INDICATIONS AND USAGE:

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

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

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

CONTRAINDICATIONS: CLARINEX Tablets 5 mg are contraindicated in patients who are hypersensitive to this medication or to any of its ingredients, or to loratadine.

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

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

In genotoxicity studies with desloratadine, there was no evidence of genotoxic potential in a reverse mutation assay (*Salmonella/E. coli* mammalian microsome

bacterial mutagenicity assay) or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenicity assay and mouse bone marrow micronucleus assay).

There was no effect on female fertility in rats at desloratadine doses up to 24 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 130 times the AUC in humans at the recommended daily oral dose). A male specific decrease in fertility, demonstrated by reduced female conception rates, decreased sperm numbers and motility, and histopathologic testicular changes, occurred at an oral desloratadine dose of 12 mg/kg in rats (estimated desloratadine exposures were approximately 45 times the AUC in humans at the recommended daily oral dose). Desloratadine had no effect on fertility in rats at an oral dose of 3 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 8 times the AUC in humans at the recommended daily oral dose).

Pregnancy Category C: Desloratadine was not teratogenic in rats at doses up to 48 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 210 times the AUC in humans at the recommended daily oral dose) or in rabbits at doses up to 60 mg/kg/day (estimated desloratadine exposures were approximately 230 times the AUC in humans at the recommended daily oral dose). In a separate study, an increase in pre-implantation loss and a decreased number of implantations and fetuses were noted in female rats at 24 mg/kg (estimated desloratadine and desloratadine metabolite exposures were approximately 120 times the AUC in humans at the recommended daily oral dose). Reduced body weight and slow righting reflex were reported in pups at doses of 9 mg/kg/day or greater (estimated desloratadine and desloratadine metabolite exposures were approximately 50 times or greater than the AUC in humans at the recommended daily oral dose). Desloratadine had no effect on pup development at an oral dose of 3 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 7 times the AUC in humans at the recommended daily oral dose). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of

human response, desloratadine should be used during pregnancy only if clearly needed.

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

Pediatric Use: The recommended dose of CLARINEX Syrup in the pediatric population is based on cross-study comparison of the plasma concentration of CLARINEX in adults and pediatric subjects. The safety of CLARINEX Syrup has been established in 246 pediatric subjects aged 6 months to 11 years in three placebo-controlled clinical studies. Since the course of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria and the effects of CLARINEX are sufficiently similar in the pediatric and adult populations, it allows extrapolation from the adult efficacy data to pediatric patients. The effectiveness of CLARINEX Syrup in these age groups is supported by evidence from adequate and well-controlled studies of CLARINEX Tablets in adults. The safety and effectiveness of CLARINEX Tablets or CLARINEX Syrup have not been demonstrated in pediatric patients less than 6 months of age.

The CLARINEX RediTabs Tablet 2.5 mg tablet has not been evaluated in pediatric patients. Bioequivalence of the CLARINEX RediTabs Tablet and the previously marketed RediTabs Tablet was established in adults. In conjunction with the dose finding studies in pediatrics described, the pharmacokinetic data for CLARINEX RediTabs Tablets supports the use of the 2.5 mg dose strength in pediatric patients 6-11 years of age.

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

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

Phenylketonurics: CLARINEX RediTabs Tablets contain phenylalanine 2.55 mg per 5 mg CLARINEX RediTabs tablet or 1.28 mg per 2.5 mg CLARINEX RediTabs tablet.

ADVERSE REACTIONS:

Adults and Adolescents

Allergic Rhinitis: In multiple-dose placebo-controlled trials, 2,834 patients ages 12 years or older received CLARINEX Tablets at doses of 2.5 mg to 20 mg daily, of whom 1,655 patients received the recommended daily dose of 5 mg. In patients receiving 5 mg daily, the rate of adverse events was similar between CLARINEX and placebo-treated patients. The percent of patients who withdrew prematurely due to adverse events was 2.4% in the CLARINEX group and 2.6% in the placebo group. There were no serious adverse events in these trials in patients receiving desloratadine. All adverse events that were reported by greater than or equal to 2% of patients who received the recommended daily dose of CLARINEX Tablets (5.0 mg once-daily), and that were more common with CLARINEX Tablet than placebo, are listed in Table 5.

Table 5

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

Adverse Experience	Clarinex Tablets 5 mg (n=1,655)	Placebo (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%

Adverse Experience	Clarinex Tablets 5 mg (n=1,655)	Placebo (n=1,652)
Dysmenorrhea	2.1%	1.6%

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

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

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

Pediatrics

Two hundred and forty-six pediatric subjects 6 months to 11 years of age received CLARINEX Syrup for 15 days in three placebo-controlled clinical trials. Pediatric subjects aged 6 to 11 years received 2.5 mg once a day, subjects aged 1 to 5 years received 1.25 mg once a day, and subjects 6 to 11 months of age received 1.0 mg once a day. In subjects 6 to 11 years of age, no individual adverse event was reported by 2 percent or more of the subjects. In subjects 2 to 5 years of age, adverse events reported for CLARINEX and placebo in at least 2 percent of subjects receiving CLARINEX Syrup and at a frequency greater than placebo were fever (5.5%, 5.4%), urinary tract infection (3.6%, 0%) and varicella (3.6%, 0%). In subjects 12 months to 23 months of age, adverse events reported for the CLARINEX product and Placebo in at least 2 percent of subjects receiving CLARINEX Syrup and at a frequency greater than placebo were fever (16.9%, 12.9%), diarrhea (15.4% 11.3%), upper respiratory tract infections (10.8%, 9.7%), coughing (10.8%, 6.5%), appetite increased (3.1%, 1.6%), emotional lability (3.1%, 0%), epistaxis (3.1%, 0%), parasitic infection, (3.1%, 0%) pharyngitis (3.1%, 0%), rash

maculopapular (3.1%, 0%). In subjects 6 months to 11 months of age, adverse events reported for CLARINEX and Placebo in at least 2 percent of subjects receiving CLARINEX Syrup and at a frequency greater than placebo were upper respiratory tract infections (21.2%, 12.9%), diarrhea (19.7.% 8.1%), fever (12.1%, 1.6%), irritability (12.1%, 11.3%) coughing (10.6%, 9.7%), somnolence (9.1%, 8.1%), bronchitis (6.1%, 0%), otitis media (6.1%, 1.6%), vomiting (6.1%, 3.2%), anorexia (4.5%, 1.6%), pharyngitis (4.5%, 1.6%), insomnia (4.5%, 0%), rhinorrhea (4.5%, 3.2%), erythema (3.0%, 1.6%), and nausea (3.0%, 0%). There were no clinically meaningful changes in any electrocardiographic parameter, including the QTc interval. Only one of the 246 pediatric subjects receiving CLARINEX Syrup in the clinical trials discontinued treatment because of an adverse event.

Observed During Clinical Practice

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

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

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

Single daily doses of 45 mg were given to normal male and female volunteers for 10 days. All ECGs obtained in this study were manually read in a blinded fashion by a cardiologist. In CLARINEX-treated subjects, there was an increase in mean heart rate of 9.2 bpm relative to placebo. The QT interval was corrected for heart rate (QT_c) by both the Bazett and Fridericia methods. Using the QT_c (Bazett) there was a mean increase of 8.1 msec in CLARINEX-treated subjects relative to placebo.

Using QT_c (Fridericia) there was a mean increase of 0.4 msec in CLARINEX-treated subjects relative to placebo. No clinically relevant adverse events were reported.

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

Lethality occurred in rats at oral doses of 250 mg/kg or greater (estimated desloratadine and desloratadine metabolite exposures were approximately 120 times the AUC in humans at the recommended daily oral dose). The oral median lethal dose in mice was 353 mg/kg (estimated desloratadine exposures were approximately 290 times the human daily oral dose on a mg/m^2 basis). No deaths occurred at oral doses up to 250 mg/kg in monkeys (estimated desloratadine exposures were approximately 810 times the human daily oral dose on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION:

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

Children 6 to 11 years of age: The recommended dose of CLARINEX Syrup is 1 teaspoonful (2.5 mg in 5 ml) once daily or the recommended dose of CLARINEX RediTabs Tablets is one 2.5 mg tablet once daily.

Children 12 months to 5 years of age: The recommended dose of CLARINEX Syrup is $^1/_2$ teaspoonful (1.25 mg in 2.5 ml) once daily.

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

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

In adult patients with liver or renal impairment, a starting dose of one 5 mg tablet every other day is recommended based on pharmacokinetic data. Dosing

recommendation for children with liver or renal impairment cannot be made due to lack of data.

Administration of CLARINEX RediTabs Tablets: Place CLARINEX (desloratadine) RediTabs Tablets on the tongue and allow to disintegrate before swallowing. Tablet disintegration occurs rapidly. Administer with or without water. Take tablet immediately after opening the blister.

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

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

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

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

CLARINEX Syrup: clear orange colored liquid containing 0.5 mg/1ml desloratadine in a 16 ounce Amber glass bottle (NDC 0085-1334-01).

Store syrup at 25° C (77°F); excursions permitted between 15° - 30°C (59°-86°F) [see USP Controlled Room Temperature] Protect from light.

CLARINEX REDITABS (desloratadine orally-disintegrating tablets) 2.5 mg and 5 mg: Light-red, flat-faced, round, speckled tablets with an "A " debossed on one side for the 5 mg tablets and a "K" debossed on one side for the 2.5 mg tablets. One tablet per cavity in peel off foil/foil blisters.

Packs of 30 tablets (containing 5 x 6's) NDC 0085-xxxx

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

Schering

Schering Corporation

Kenilworth, New Jersey 07033 USA

03/05

CLARINEX REDITABS brand of desloratadine orally-disintegrating tablets are manufactured for Schering Corporation by CIMA LABS INC.® Eden Prairie, MN

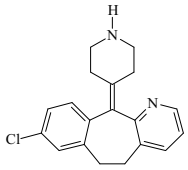
U.S. Patent Nos. 4,659,716; 4,863,931; 5,595,997; 5,178,878; 6,514,520 and 6,100,274

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-312/S007

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #3	1. ORGANIZATION HFD-570 DPDP	2. NDA NUMBER 21-312
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Schering Corporation 2000 Galloping Hill Road Kenilworth, NJ 07033 Contact: Satish Joshi, Senior Manager CMC Global Regulatory Affairs, tel: 908-740-4355		4. AF NUMBER 5. SUPPLEMENT(S) NUMBER(S) DATES(S) SCF-007 17-MAR-2005
6. NAME OF DRUG Clarinex® RediTabs®	7. NONPROPRIETARY NAME desloratadine orally disintegrating tablets	
8. SUPPLEMENT PROVIDED FOR: a complete reformulation of the 5 mg strength and the addition of a new 2.5 mg strength of the product. The reformulation is being done to improve the taste masking of the desloratadine.		9. AMENDMENT(S), REPORT(S), ETC. 15-JUN-2005 05-JUL-2005 *Subject of current review.
10. PHARMACOLOGICAL CATEGORY antihistamine	11. HOW DISPENSED RX _X_ OTC__	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) orally-disintegrating tablets	14. POTENCY 2.5 and 5 mg desloratadine	
15. CHEMICAL NAME AND STRUCTURE 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-benzo[5,6]cylcohepta[1,2-b]pyridine Molecular Formula: $C_{19}H_{19}ClN_2$ Molecular Weight: 310.8  Desloratadine		16. RECORDS AND REPORTS CURRENT YES_x_ NO__ REVIEWED YES NO_X_

17. COMMENTS: See review notes.

cc:
Orig. NDAs 21-312
HFD-570/div. File
HFD-570/CBertha/7/7/05
HFD-570/RLostritto
HFD-570/AZeccola
R/D Init. by:_____
F/T by: CBertha/7/7/05
doc # 05-07-05_rev.doc

18. CONCLUSIONS AND RECOMMENDATIONS: From the CMC perspective the supplement is recommended for **approval (AP)**.

19. REVIEWER NAME:	SIGNATURE	DATE COMPLETED
Craig M. Bertha, Ph.D.		07-JUL-2005

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_____ § 552(b)(5) Deliberative Process

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/s/

Craig Bertha
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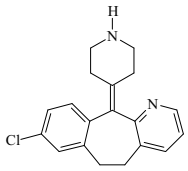
CHEMIST

Richard Lostritto
7/7/05 01:38:23 PM
CHEMIST

CHEMIST'S REVIEW #2	1. ORGANIZATION HFD-570 DPDP	2. NDA NUMBER 21-312
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Schering Corporation 2000 Galloping Hill Road Kenilworth, NJ 07033 Contact: Satish Joshi, Senior Manager CMC Global Regulatory Affairs, tel: 908-740-4355		4. AF NUMBER 5. SUPPLEMENT(S) NUMBER(S) DATES(S) SCF-007 17-MAR-2005
6. NAME OF DRUG Clarinex® RediTabs®	7. NONPROPRIETARY NAME desloratadine orally disintegrating tablets	
8. SUPPLEMENT PROVIDED FOR: a complete reformulation of the 5 mg strength and the addition of a new 2.5 mg strength of the product. The reformulation is being done to improve the taste masking of the desloratadine.		9. AMENDMENT(S), REPORT(S), ETC. 15-JUN-2005* *Subject of current review.
10. PHARMACOLOGICAL CATEGORY antihistamine	11. HOW DISPENSED RX X OTC__	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) orally-disintegrating tablets	14. POTENCY 2.5 and 5 mg desloratadine	
15. CHEMICAL NAME AND STRUCTURE 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-benzo[5,6]cylcohepta[1,2-b]pyridine Molecular Formula: $C_{19}H_{19}ClN_2$ Molecular Weight: 310.8  Desloratadine		16. RECORDS AND REPORTS CURRENT YES x NO__ REVIEWED YES NO_X_

17. COMMENTS: See review notes.

cc:
Orig. NDAs 21-312
HFD-570/div. File
HFD-570/CBertha/6/24/05
HFD-570/RLostritto
HFD-570/AZeccola
R/D Init. by:_____
F/T by: CBertha/6/27/05
doc # 05-06-15 rev.doc

18. CONCLUSIONS AND RECOMMENDATIONS: From the CMC perspective the supplement is considered to be **approvable (AE)**. The PM should send the comments in the attached draft letter to the applicant in a discipline review letter.

19. REVIEWER NAME:	SIGNATURE	DATE COMPLETED
Craig M. Bertha, Ph.D.		27-JUN-2005

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Craig Bertha
6/28/05 02:03:01 PM
CHEMIST

Richard Lostritto
6/28/05 05:48:58 PM
CHEMIST

CHEMIST'S REVIEW #1	1. ORGANIZATION HFD-570 DPDP	2. NDA NUMBER 21-312
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Schering Corporation 2000 Galloping Hill Road Kenilworth, NJ 07033 Contact: Satish Joshi, Senior Manager CMC Global Regulatory Affairs, tel: 908-740-4355		4. AF NUMBER 5. SUPPLEMENT(S) NUMBER(S) DATES(S) SCF-007 17-MAR-2005
6. NAME OF DRUG Clarinex® RediTabs®	7. NONPROPRIETARY NAME desloratadine orally disintegrating tablets	
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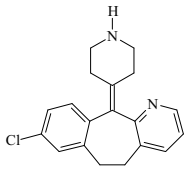
10. PHARMACOLOGICAL CATEGORY antihistamine	11. HOW DISPENSED RX X OTC__	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) orally-disintegrating tablets	14. POTENCY 2.5 and 5 mg desloratadine	
15. CHEMICAL NAME AND STRUCTURE 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-benzo[5,6]cylcohepta[1,2-b]pyridine Molecular Formula: $C_{19}H_{19}ClN_2$ Molecular Weight: 310.8  Desloratadine		16. RECORDS AND REPORTS CURRENT YES x NO__ REVIEWED YES NO_X_

17. COMMENTS: See review notes.

cc:
Orig. NDAs 21-312
HFD-570/div. File
HFD-570/CBertha/5/09/05
HFD-570/RLostritto
HFD-570/AZeccola
R/D Init. by:_____
F/T by: CBertha/5/09/05
doc # 05-03-17 rev.doc

18. CONCLUSIONS AND RECOMMENDATIONS: From the CMC perspective the supplement is considered to be **approvable (AE)**. The PM should send the comments in the attached draft letter to the applicant in a discipline review letter.

19. REVIEWER NAME:	SIGNATURE	DATE COMPLETED
Craig M. Bertha, Ph.D.		09-MAY-2005

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Withheld Track Number: Chemistry-21-312/S007#1

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Craig Bertha
5/24/05 07:32:59 AM
CHEMIST
Dr. Lostritto performed secondary review. Edited review and will sign for him as per his instructions.

Craig Bertha
5/24/05 07:36:26 AM
CHEMIST
for. Richard Lostritto, CMC TL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-312/S007

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-312**
SERIAL NUMBER:	**SCF 007**
DATE RECEIVED BY CENTER:	**March 15, 2005**
PRODUCT:	**Clarinex RediTabs**
INTENDED CLINICAL POPULATION:	**Seasonal allergic rhinitis, Perennial allergic rhinitis, Chronic idiopathic urticaria**
SPONSOR:	**Schering Corporation**
DOCUMENTS REVIEWED:	**Vols. 1 & 8**
REVIEW DIVISION: **(HFD-570)**	**Division of Pulmonary and Allergy Drug Products**
PHARM/TOX REVIEWER:	**Timothy J. McGovern, Ph.D.**
PHARM/TOX SUPERVISOR:	**Timothy J. McGovern, Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Anthony Zecolla**

Date of review submission to Division File System (DFS): June 23, 2005

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
This supplement is recommended for approval from a nonclinical perspective.

B. Recommendation for nonclinical studies
None at this time.

C. Recommendations on labeling
The proposed text is acceptable with the exception of a typographical error in the "Carcinogenesis, Mutagenesis, Impairment of Fertility" section. See OVERALL CONCLUSIONS AND RECOMMENDATIONS for details.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
See original NDA review for information regarding the pharmacologic and toxicologic aspects of SH 34117. To address issues related to local tolerability of the new CIMA formulation, the sponsor initially conducted a study in a hamster cheek pouch model under IND 59,109 which showed enhanced irritant potential when compared to the currently approved formulation. The sponsor was informed that if marketing of the CIMA formulation is pursued, a study of local irritation potential with an assessment of reversibility would be needed in an additional specie (e.g., dog or minipig). The sponsor conducted a local irritation study in dogs to assess the irritation potential of both the CIMA and Cardinal Reditab formulation tablets. Both tablets produced comparable changes indicative of minimal irritation in all dogs sacrificed after the fifth dose which included minimal, multifocal, mixed inflammatory cell infiltration in the submucosa with minimal thickening of the superficial layer of the cheek mucosa. No tablet-related findings were observed after the 14-day recovery period. Thus, the proposed CIMA formulation appears to be no more irritating than the approved formulation in this model.

B. Pharmacologic activity
See original NDA review.

C. Nonclinical safety issues relevant to clinical use
There are no nonclinical safety issues relevant to clinical use.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

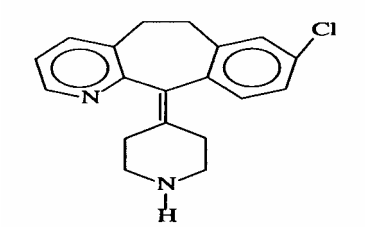
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-312
Review number: 2
Sequence number/date/type of submission: 007/March 15, 2005/SCF
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Schering Corporation, Kenilworth, NJ
Manufacturer for drug substance: Schering Plough

Reviewer name: **Timothy J. McGovern, Ph.D.**
Division name: **Pulmonary and Allergy Drug Products**
HFD #: **570**
Review completion date: June 23, 2005

Drug:

Trade name: CLARINEX RediTabs
Generic name: Descarboethoxyloratadine (DCL)
Code name: SCH 34117
Chemical name: 5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-(4-piperidinyllidene)
CAS registry number: NA
Molecular formula/molecular weight: $C_{19}H_{19}ClN_2$/310.8
Structure:



Relevant INDs/NDAs/DMFs:

IND 55,364 Descarboethoxyloratadine tablets
IND 59,109 Descarboethoxyloratadine RediTabs
NDA 21-165 Clarinex (Seasonal allergic rhinitis)
NDA 21-297 Clarinex (chronic idiopathic urticaria)
NDA 21-300 Clarinex Syrup (Seasonal allergic rhinitis and chronic idiopathic urticaria)
NDA 21-313 Clarinex-D12 (Seasonal allergic rhinitis and congestion)
NDA 21-363 Clarinex (Allergic rhinitis)
DMF (b) (4) Flavor Tutti-Frutti (b) (4)

Drug class: Anti-histamine

Intended clinical population: Clarinex products are approved for treatment of Seasonal Allergic Rhinitis in patients 2 years of age and older; Perennial Allergic Rhinitis in patients 6 months of age and older; Chronic Idiopathic Urticaria in patients 6 months of age and older. The proposed RediTab products are intended for ages 12 years and above (5 mg) and ages 6-11 years old (2.5 mg).

Clinical formulation: The table below compares the currently approved formulation with the new CIMA formulations (2.5 and 5 mg tablets) that are the subject of this supplement. The Desloratadine (b) (4) were developed in partnership with CIMA using their proprietary OraSolv® technology. The (b) (4) are used to manufacture the 2.5 and 5 mg strength of the ODT Clarinex® RediTabs®.

Ingredient	Approved tablet (mg/tablet)	Proposed tablets (mg/tablet)	
Desloratadine (SCH 34117), (b) (4)	5	(b) (4)	
Gelatin type B NF			
Mannitol USP			
Aspartame NF			
Polacrilin potassium USP			
Dye (b) (4) red (b) (4)			
Flavor tutti-frutti (b) (4)			
Citric acid (b) (4), USP			
(b) (4) USP			
(b) (4) mannito (b), USP			
Crospovidone, NF			
Microcrystaline cellulose, NF			
Ferric oxide, red, NF			
Sodium bicarbonate, USP			
Magnesium stearate, NF			
Colloidal silicon dioxide, NF			

* Actual amounts to be used in the batch determined by the assay value of desloratadine (b) (4).

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:
Study # 01355: Mucous membrane irritation of SCH 34117 Reditab (CIMA, Scherer) in the dog cheek (Vol 8)

Studies not reviewed within this submission:
Study # 00480: Mucous membrane irritation of SCH 34117 Reditab (CIMA) Tablets in the hamster cheek pouch (Vol 8; this study was previously reviewed under IND 59,109 (see review # 2 in Appendix)

NDA 21-312 for Clarinex RediTabs was approved in June 2002. This NDA Prior Approval Supplement proposes a complete reformulation of the 5 mg strength and the addition of a new 2.5 mg pediatric strength of the product that is dose-proportional to the 5 mg CIMA formulation. The reformulation is being done to improve the taste masking of the desloratadine. The Agency met with Schering on March 8, 2004 to discuss the reformulation of the 5 mg strength of the orally disintegrating tablet (ODT) product using the Orasolv® technology from CIMA Labs. The original product was manufactured by Cardinal Health (formerly Scherer) in the UK using the (b) (4).

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary
See original NDA review.

2.6.2.2 Primary pharmacodynamics
See original NDA review.

2.6.2.3 Secondary pharmacodynamics
See original NDA review.

2.6.2.4 Safety pharmacology
See original NDA review.

2.6.2.5 Pharmacodynamic drug interactions
See original NDA review.

2.6.3 PHARMACOLOGY TABULATED SUMMARY
Not applicable.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary
See original NDA review.

2.6.4.2 Methods of Analysis
[see under individual study reviews]

2.6.4.3 Absorption
See original NDA review.

2.6.4.4 Distribution
See original NDA review.

2.6.4.5 Metabolism
See original NDA review.

2.6.4.6 Excretion
See original NDA review.

2.6.4.7 Pharmacokinetic drug interactions
See original NDA review.

2.6.4.8 Other Pharmacokinetic Studies
See original NDA review.

2.6.4.9 Discussion and Conclusions
See original NDA review.

2.6.4.10 Tables and figures to include comparative TK summary
Not applicable.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY
Not applicable.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: See original NDA review.

Genetic toxicology: See original NDA review.

Carcinogenicity: See original NDA review.

Reproductive toxicology: See original NDA review.

Special toxicology: A local irritation study was conducted in dogs with both the CIMA and Scherer RediTab formulation tablets. Both tablets produced comparable changes indicative of minimal irritation in all dogs sacrificed after the fifth dose which included minimal, multifocal, mixed inflammatory cell infiltration in the submucosa with minimal thickening of the superficial layer of the cheek mucosa. In one treated dog, minimal, single cell necrosis in both cheeks and focal mucosal erosion in the right cheek was observed. No tablet-related findings were observed after the 14-day recovery period. A previous study reviewed under IND 59,109 (see Appendix) demonstrated a greater response in female Syrian hamsters; very slight to severe mucous membrane irritation was observed in hamsters treated with 5 mg SCH 34117 RediTab (OraSolv formulation) during a 5-day study. Gross findings in the treated group included discoloration, altered surface and abscesses of the cheek pouch and microscopic findings of minimal to

moderate severity included ulceration, necrosis, inflammation and fibroplasia of the oral cavity.

2.6.6.2 Single-dose toxicity
See original NDA review.

2.6.6.3 Repeat-dose toxicity
See original NDA review.

2.6.6.4 Genetic toxicology
See original NDA review.

2.6.6.5 Carcinogenicity
See original NDA review.

2.6.6.6 Reproductive and developmental toxicology
See original NDA review.

2.6.6.7 Local tolerance
See original NDA review.

2.6.6.8 Special toxicology studies

Study title: Mucous membrane irritation study of SCH 34117 Reditab (CIMA, Scherer) in the dog cheek

Key study findings:

- Both the CIMA and Scherer Reditab formulation tablets produced comparable changes indicative of minimal irritation in all dogs sacrificed after the fifth dose which included minimal, multifocal, mixed inflammatory cell infiltration in the submucosa with minimal thickening of the superficial layer of the cheek mucosa.
- In one treated dog, minimal, single cell necrosis in both cheeks and focal mucosal erosion in the right cheek was observed.
- No tablet-related findings were observed after the 14-day recovery period.

Study no.: 01355
Volume #, and page #: 8, Tab 5
Conducting laboratory and location: Safety Evaluation Center, Schering-Plough Research Inst., Lafayette, NJ
Date of study initiation: February, 2004
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: SCH 34117 OraSolv Reditab (5 mg tablet manufactured by CIMA), 78012-122, 98.4%; Comparative control SCH 34117 Reditab (5 mg tablet manufactured by Scherer), 2-MCR-2, COA not provided

Formulation/vehicle: detailed formulation information not provided for either tablet; assumed to be identical to proposed clinical tablet and approved tablet.

Methods

Doses: Dose groups included a sham control and a test group. The sham control group underwent physical manipulation of the cheek only. The test groups were dosed with both the test article (CIMA 5 mg RediTab in the right cheek) and the comparative control article (Scherer 5 mg RediTab in the left cheek).

Study design: Dose groups included 4 beagle dogs/sex, animals were 8-27 months old. Animals were dosed for once daily for 5 days. Two dogs per sex were sacrificed after the 5th dose and the other two per sex were sacrificed after 14 days observation. Prior to manipulation or dosing, each dog was anesthetized with an i.m. injection of 10 mg/kg ketamine/1 mg/kg xylazine. A small amount of sterile water was added to the dosed cheek pouch just prior to insertion of the tablet in each cheek pouch (between molars and cheek) on each day. Both cheeks were examines for the presence of tablet remains after a 10 minute (target time) exposure period. Both cheeks of sham control dogs were physically manipulated to simulate dosing and observation for tablet remains.

Observations and measurements included viability and clinical observations, body weight, mucous membrane irritation (twice daily – prior to and 10 minutes after dosing – on the basis of the following criteria:
0 – no reaction; 1 – very slight redness, usually nonconfluent; 2 – slight redness, usually confluent; 3 – moderate redness; 4 – severe redness, with or without edema, necrosis or scab formation.

Both cheeks of each dog were dissected free from surrounding tissues, examined and fixed. A section of each cheek was processed to slides and stained with H&E. All processed tissues were examined by a pathologist with a peer review.

Results: No clinical observations related to treatment with the SCH 34117 RediTab tablets were noted. No evidence of mucous membrane irritation was observed macroscopically. Microscopically, both tablets produced changes indicative of minimal irritation in all dogs sacrificed on day 4 (after the fifth dose). The change consisted of a minimal, multifocal, mixed inflammatory cell infiltration (primarily mononuclear cells and occasional neutrophils and eosinophils) in the submucosa with minimal thickening of the superficial layer of the cheek mucosa. In one treated dog, minimal, single cell necrosis in both cheeks and focal mucosal erosion in the right cheek was observed. These findings were not observed at the day 18 sacrifice.

2.6.6.9 Discussion and Conclusions

This NDA supplement proposes a change in the product formulation from the approved tablet manufactured by Cardinal (formerly Scherer) to a new formulation manufactured by CIMA Labs; in addition, a new 2.5 mg tablet is proposed. A previous study reviewed

under IND 59,109 (see Appendix) demonstrated a severe local irritation response and gross and microscopic changes (necrosis, ulceration, inflammation and fibroplasias, minimal to moderate severity) in female Syrian hamsters administered a 5 mg CIMA Labs SCH 34117 RediTab (OraSolv formulation) tablet; the response was enhanced when compared to the Scherer formulation.

The sponsor's position regarding the above findings is that the results in hamsters are not representative of the expected response in humans. The sponsor suggests that the salivary flow in hamsters was restricted and the tablet was still not fully dissolved in the cheek pouch 24 hours after placement. Further, findings in hamster are not relevant given methodological limitations of the model (usually used for sublingual tablets with prolonged contact, sensitive since clinical dose form is applied regardless of animal-to-human dose multiple, high dose of DCL could have had anti-cholinergic effects that could have affected salivary flow (in clinical setting, action of human saliva would have had a greater flushing effect), residual tablet residue persisted overnight indicating that the RediTab was not operative in this model).

Based on the results of the hamster study, the Division concluded that the sponsor would "… need to conduct additional studies in other animal species to further characterize the local irritation effect, and demonstrate reversibility of these findings. In addition, you may need to further evaluate this effect in humans to determine the clinical relevance of the animal findings." The General Correspondence of May 22, 2001 should be consulted for further detail.

The sponsor subsequently conducted a 5-day local irritation study in dogs to assess the irritation potential of both the CIMA and Cardinal Reditab formulation tablets. Both tablets produced comparable changes indicative of minimal irritation in all dogs sacrificed after the fifth dose which included minimal, multifocal, mixed inflammatory cell infiltration in the submucosa with minimal thickening of the superficial layer of the cheek mucosa. In one treated dog, minimal, single cell necrosis in both cheeks and focal mucosal erosion in the right cheek was observed. No tablet-related findings were observed after the 14-day recovery period. Thus, the proposed formulation appears to be no more irritating than the approved formulation in this model.

2.6.6.10 Tables and Figures

Not applicable.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: NDA 21-312 for Clarinex RediTabs was approved in June 2002. This NDA Prior Approval Supplement proposes a complete reformulation of the 5 mg strength and

the addition of a new 2.5 mg pediatric strength of the product that is dose-proportional to the 5 mg CIMA formulation. The reformulation is being done to improve the taste masking of the desloratadine. The Agency met with Schering in March 2004 to discuss the reformulation of the 5 mg strength of the orally disintegrating tablet (ODT) product using the Orasolv® technology from CIMA Labs. The original product was manufactured by Cardinal Health (formerly Scherer) in the UK using the (b) (4) technology. The only issues to be addressed from the nonclinical standpoint are the local tolerability of the newly formulated tablet and proposed revisions to the nonclinical sections of the product label.

To address the local tolerability, the sponsor initially conducted a tolerability study in a hamster cheek pouch model which showed enhanced irritant potential when compared to the currently approved formulation. This study was reviewed in 2000 under IND 59,109 (see review attached in Appendix). The sponsor's position at the time of the initial study submission and in the current NDA submission is that the observed irritation is not relevant to humans given methodological limitations of the model (usually used for sublingual tablets with prolonged contact, overly sensitive since the clinical dose form is applied regardless of animal-to-human dose multiple, a high dose of SCH 34117 could have had anti-cholinergic effects that could have affected salivary flow (in clinical setting, action of human saliva would have had a greater flushing effect), and residual tablet residue persisted overnight indicating that the RediTab was not operative in this model).

After reviewing this data, the Division allowed single dose and 14-day clinical trials to proceed to assess the bioequivalence and buccal irritation of the OraSolve RediTab tablet since buccal irritation is easily monitored. However, the sponsor was informed in a fax of May 22, 2001 that if marketing of this formulation is pursued, a study of local irritation potential with an assessment of reversibility would be needed in an additional specie (e.g., dog or minipig).

The sponsor conducted a local irritation study in dogs to assess the irritation potential of both the CIMA and Cardinal Reditab formulation tablets. This study was submitted to the current NDA supplement and is reviewed above. Both tablets produced comparable changes indicative of minimal irritation in all dogs sacrificed after the fifth dose which included minimal, multifocal, mixed inflammatory cell infiltration in the submucosa with minimal thickening of the superficial layer of the cheek mucosa. In one treated dog, minimal, single cell necrosis in both cheeks and focal mucosal erosion in the right cheek was observed. No tablet-related findings were observed after the 14-day recovery period. Thus, the proposed formulation appears to be no more irritating than the approved formulation in this model.

In regard to product labeling, the only changes relevant to nonclinical text are the incorporation of the results of a carcinogenicity study in mice with desloratadine that was done as a post-approval commitment for NDA 21-165 (Clarinex tablet). The study was recently reviewed under that NDA and the Agency and Sponsor agreed on acceptable revisions to the "Carcinogenesis, Mutagenesis, Impairment of Fertility" section of the

product label under NDA 21-605 (Clarinex D-24). The sponsor's proposed revision for the current NDA supplement differs slightly from that agreed upon previously and is reviewed below.

Unresolved toxicology issues (if any): None.

Recommendations: This NDA supplement is approvable from a nonclinical perspective pending incorporation of recommended changes to the product label.

Suggested labeling:

The sponsor's proposed text for nonclinical sections is identical to that currently approved with the exception of the "Carcinogenesis, Mutagenesis, Impairment of Fertility" section. The only changes are the incorporation of the results of a carcinogenicity study in mice with desloratadine that was done as a post-approval commitment for NDA 21-165 (Clarinex tablet). The study was recently reviewed under that NDA by Dr. Luqi Pei and the Agency and Sponsor agreed on acceptable revisions to the "Carcinogenesis, Mutagenesis, Impairment of Fertility" section of the product label in March 2005 under NDA 21-605 (Clarinex D-24). The sponsor's proposed text for the current NDA supplement is shown below:

> **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility:** The carcinogenic potential of desloratadine was assessed using a loratadine study in rats and a desloratadine study in mice. In a 2-year study in rats, loratadine was administered in the diet at doses up to 25 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 30 times the AUC in humans at the recommended daily oral dose). A significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg/day of loratadine and in males and females given 25 mg/kg/day of loratadine. The estimated desloratadine and desloratadine metabolite exposures in rats given 10 mg/kg of loratadine were approximately 7 times the AUC in humans at the recommended daily oral dose. The clinical significance of these findings during long-term use of desloratadine is not known.
>
> In a 2-year dietary study in mice, males and females given up to 16 mg/kg/ay and 32 mg/kg/day desloratadine, respectively, did not show significant increases in the incidence of any tumors. The estimated desloratadine and metabolite exposures in mice at these doses were 12 and 27 times, respectively, the AUC in humans at the recommended daily oral dose.

The proposed text is essentially identical to that approved in March 2005 with the exception of one typographical error (line 308 from the full label text). The error should be corrected as follows (edit marked by underlined text):

In a 2-year dietary study in mice, males and females given up to 16 mg/kg/day and 32 mg/kg/day desloratadine, respectively, did not show significant increases in the incidence of any tumors.

The sponsor's proposal for the labeling changes is, therefore, acceptable pending inclusion of the above-recommended revision to the text.

APPENDIX/ATTACHMENTS

PHARMACOLOGY / TOXICOLOGY REVIEW AND EVALUATION

IND number: 59,109
Review number: 2
Sequence number/date/type of submission: 021/15 DEC 2000/Info Tox
023/18 APR 2001/Info Tox
024/20 APR 2001/Info Tox

Information to sponsor: Yes ( ), No (X)
Sponsor and/or agent: Schering-Plough Corp., Kenilworth, NJ
Manufacturer for drug substance: Scherer DDS, Ltd., Wiltshire, UK

Reviewer name: Timothy J. McGovern, Ph.D.
Division name: Pulmonary and Allergy Drug Products
HFD #: 570
Review completion date: August 30, 2001

Drug:

Trade name: Clarinex rapidly disintegrating tablets
Generic name: NA
Code name: SCH 34117
Chemical name: 5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-(4-piperidinylidene)
CAS registry number: NA
Mole file number: NA
Molecular formula/molecular weight: $C_{19}H_{19}ClN_2$/310.82

Relevant INDs/NDAs/DMFs: IND 55,364 (Desloratadine Tablet), IND 57,960 (Desloratadine Syrup), NDA 19-658 (Loratadine Tablet), NDA 20-704 (Loratadine RediTabs), IND 21,249 (Loratadine Tablet), IND 28,015 (Loratadine Syrup)

Drug Class: **Antihistamine**

Indication: Seasonal allergic rhinitis and chronic idiopathic urticaria

Clinical Formulation:

Ingredient	**mg/tablet**
SCH 37114	5
Gelatin Type B NF/Ph./Eur.	(b) (4)
Mannitol USP	(b) (4)
Aspartame	(b) (4)
Polacrilin potassium	(b) (4)
Dye (b) (4) Red (b) (4)	(b) (4)
Flavor Tutti-Frutti (b) (4)	(b) (4)

Citric acid USP	(b) (4)
(b) (4)	)

Route of administration: Oral
Proposed clinical protocol: None. Two protocol concept sheets were submitted for review.

Previous Clinical Experience: SCH 34117 has been assessed in numerous clinical trials using various formulations including the rapidly disintegrating tablet.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Preclinical studies reviewed in these submissions:
SN 99290: Mucous membrane irritation study of SCH 34117 (desloratadine) RediTab Tablets in the hamster cheek pouch. Submission 021

SN 00479: Mucous membrane irritation of SCH 34117 RediTab (Scherer) Tablets in the hamster cheek pouch. Submission 023

SN 00480: Mucous membrane irritation of SCH 34117 RediTab (CIMA) Tablets in the hamster cheek pouch. Submission 024

Preclinical studies <u>not</u> reviewed in these submissions: None

Introduction and drug history: Desloratadine (SCH 34117) is the active metabolite of loratadine and has an antihistaminic potency of 2.5-20 times that of loratadine. Tablet, syrup and rapidly disintegrating tablet formulations have all been approved for loratadine.

The sponsor submitted two oral mucosa irritation studies in hamsters using a formulation referred to as R.P. Scherer (021 and 023) in order to assess the irritancy potential of the SCH 34117 RediTab tablet. It is unclear if the formulations were similar in both studies.

The sponsor also submitted a hamster oral mucosa irritation study using CIMA Labs Inc. OraSolv technology (024). The study was performed to investigate one formulation found to taste better than the RediTab formulation that is the subject of NDA 21-312. The sponsor plans to assess the effects of 5 mg desloratadine OraSolv formulation in humans through two clinical pharmacology studies (protocol concept sheets for protocols P02393 and P02430) to evaluate the bioequivalence of 5 mg desloratadine OraSolv formulation and a 5 mg CLARINEX tablet and the potential irritation of the 5 mg desloratadine OraSolv formulation during 14 days of treatment. The sponsor plans to develop a 2.5 mg and a (b) (4) formulation for use in children.

SPECIAL TOXICOLOGY STUDIES:

Study title: Mucous membrane irritation of SCH 34117 (desloratadine) reditab tablets in the hamster cheek pouch

Key study findings: Drug-related observations during this 5-day study included very slight to slight redness in all hamsters treated with 5 mg SCH 34117 RediTab from the first day of dosing onward. Severity did not increase with dosing duration. Death in one drug-treated animal was attributed to a possible toxic effect of the drug with the isoflurane anesthesia.

Study no: SN 99290
Volume #, and page #: 4.1, 1
Conducting laboratory and location: Schering Plough, Lafayette, NJ
Date of study initiation: July 1999
GLP compliance: The report included a signed GLP report
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: SCH 34117 reditab tablet, batch # 39554-152, purity not reported
Formulation/vehicle: not stated, assumed to correspond to above noted clinical formulation

Methods: Prior to dosing, each hamster was anesthetized with isoflurane for one-hour prior to and during dosing. Anesthesia was maintained for at least 10 minutes after dosing for observation of the cheek pouch. A small amount of sterile water was added to the dosed cheek pouch just prior to insertion of the tablet. Tablets were inserted in the left cheek pouch. The contralateral cheek pouch served as an untreated control.

Dosing:

Species/strain: Golden Syrian Hamsters ((b) (4))
#/sex/group or time point (main study): 6 females
Satellite groups used for toxicokinetics or recovery: NA
Age: 10-11 weeks
Weight: 115.8-141 g
Doses in administered units: 6 females were treated as sham controls and underwent physical manipulation of the cheek pouch. Hamsters received four 5-mg SCH 34117 tablets on day 0 at 10 minute intervals, two tablets on day 1 and one tablet thereafter for the remaining 3 dosing days. The sponsor states that the initial dose of 4 tablets was reduced due to a possible toxic effect of SCH 34117 in combination with isoflurane anesthesia as indicated by a longer recovery time from anesthesia compared with controls.
Route, form, volume, and infusion rate: transmucosal, tablet for 5 consecutive days

Observations and times:

Clinical signs:	Not assessed
Body weights:	Day 0
Gross pathology:	Day 5 following observation period. Both cheek pouches of each hamster were dissected free from the surrounding tissues, opened longitudinally, examined and fixed in buffered formalin.
Organs weighed:	Not assessed
Histopathology:	Day 5 following observation period. Six transverse sections of each cheek pouch, 3 from proximal end and 3 from distal end were processed and examined microscopically.

Other: Mucous membrane irritation, 2x daily (immediately prior to and 10 minutes after dosing)

Results:

Mortality: One SCH 34117-dosed hamster was found dead on day 3. Cause of death was not determined but was attributed to a possible toxic effect of the drug with the isoflurane anesthesia.

Mucous membrane irritation: Results are summarized in the table below. No findings were noted prior to dosing on Days 0 through 3 of dosing. One SCH 34117-treated animal displayed very slight redness prior to dosing on Day 4. At 10 minutes after dosing, very slight redness was noted on Day 0 in SCH 34117-treated cheek pouches of all hamsters; on Day 1 very slight (5/6) to slight redness (1/6) was noted. Five of six SCH 34117-treated animals demonstrated very slight redness on Day 2 and five of five animals demonstrated very slight to slight redness on Days 3 and 4. No irritation was observed in sham animals while one SCH 34117-treated animal demonstrated very slight redness in the untreated cheek pouch on days 2 and 4 (animals 8 and 10, respectively).

Gross pathology: No significant drug-related findings were noted.

Histopathology: No significant drug-related findings were noted.

Summary of individual study findings: Drug-related observations included very slight to slight redness in all female Syrian hamsters treated with the proposed clinical dose of 5 mg SCH 34117 RediTab from the first day of dosing onward. Severity did not increase with dosing duration. One drug-treated animal died and the death was attributed to a possible toxic effect of the drug with the isoflurane anesthesia; doses were 385-1541 times the human dose on a mg/kg basis. No drug-related gross or microscopic findings were noted.

Table 1 Individual Mucous Membrane Irritation Scores[a]

	Day of Dosing[b]																			
	0				1				2				3				4			
	Predose		Postdose		Predose		Postdose		Predose		Postdose		Predose		Postdose		Predose		Postdose	
Hamster No.	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
Sham Control																				
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SCH 34117 Reditab Tablet (5 mg)																				
7	0	0	±	0	0	0	±	0	0	0	±	0	0	0	±	0	0	0	1	0
8	0	0	±	0	0	0	±	0	0	0	±	±	0	0	±	0	±	0	±	0
9	0	0	±	0	0	0	±	0	0	0	0	0	0	0	1	0	0	0	±	0
10	0	0	±	0	0	0	1	0	0	0	±	0	0	0	1	0	0	0	±	±
11	0	0	±	0	0	0	±	0	0	0	±	0	0	0	1	0	0	0	±	0
12	0	0	±	0	0	0	±	0	0	0	±	0	FD	---	---	---	---	---	---	---

L = Left cheek pouch R = Right cheek pouch FD =Found Dead

a: Grading Scale for Mucous Membrane Irritation

0 = No reaction

± = Very slight (barely perceptible) redness, usually nonconfluent

1 = Slight (well defined) redness, usually confluent

2 = Moderate redness

3 = Severe redness, with or without edema, necrosis or scab formation

b: SCH 34117-dosed hamsters received four tablets on Day 0, two tablets on Day 1, and one tablet thereafter. The initial dose of four tablets was reduced due to a possible toxic effect of SCH 34117 in combination with isoflurane anesthesia; this was indicated by a longer recovery time from anesthesia compared with controls.

Study title: Mucous membrane irritation of SCH 34117 reditab (R.P. Scherer) tablets in the hamster cheek pouch

Key study findings: Very slight redness of the mucous membrane was observed in 4 of 6 female Syrian hamsters treated with 5 mg SCH 34117 RediTab with the R.P. Scherer formulation during the course of the 5-day study. Incidence diminished as the study progressed.

Study no: SN 00479
Volume #, and page #: 1, 1
Conducting laboratory and location: Schering Plough, Lafayette, NJ
Date of study initiation: November, 2000
GLP compliance: The report included a signed GLP report
QA report: yes (✓) no ( )
Drug, lot #, radiolabel, and % purity: SCH 34117 (Scherer), batch # 24180J917, purity not reported
Formulation/vehicle: Cover letter states that the objective of this study was to assess the irritation potential of flavor enhanced SCH 34117 RediTab tablets (R.P. Scherer). Although this statement implies that the formulation differs from the originally proposed formulation, the sponsor did not provide formulation data for this batch.

Methods: Prior to dosing, each hamster was anesthetized with isoflurane for one-hour prior to and during dosing. Anesthesia was maintained for at least 10 minutes after dosing for observation of the cheek pouch. A small amount of sterile water was added to the dosed cheek pouch just prior to insertion of the tablet. Tablets were inserted in the left cheek pouch. The contralateral cheek pouch served as an untreated control.

Dosing:
Species/strain: Golden Syrian Hamsters (b) (4)
#/sex/group or time point (main study): 6 females
Satellite groups used for toxicokinetics or recovery: NA
Age: 8 weeks
Weight: 113-127 g
Doses in administered units: 6 females were treated as sham controls and underwent physical manipulation of the cheek pouch. 5 mg (39-44 mg/kg) was administered daily
Route, form, volume, and infusion rate: transmucosal, 1 tablet for 5 consecutive days

Observations and times:

Clinical signs:	1 time daily
Body weights:	Day 0
Gross pathology:	Day 5 following observation period. Both cheek pouches of each hamster were dissected free from the surrounding tissues, opened longitudinally, examined and fixed in buffered formalin.

Histopathology:	Day 5. Six transverse sections of each cheek pouch, 3 from proximal end and 3 from distal end, were processed and examined microscopically.
Other:	Mucous membrane irritation, 2x daily (immediately prior to and 10 minutes after dosing)

Results:

Mortality: All hamsters survived dosing procedure.

Clinical signs: No significant observations were noted.

Mucous membrane Irritation: Results are summarized in the table below. No findings were noted before dosing on Days 0 through 4 of dosing or 10 minutes after dosing on Days 0 and 1. Very slight redness was noted in SCH 34117-treated cheek pouches 10 minutes after dosing in 3 hamsters on Day 2 in 2 hamsters on Day 3 and 1 hamster on day 4. No irritation was observed in sham animals or in the untreated cheek pouches of treated hamsters.

Gross pathology: No significant drug-related findings were noted.

Histopathology: No significant drug-related findings were noted.

Summary of individual study findings: Very slight redness of the mucous membrane was observed in 4 of 6 female Syrian hamsters treated with the proposed clinical dose of 5 mg SCH 34117 RediTab with the R.P. Scherer formulation during the course of the 5-day study. Incidence diminished as the study progressed. No drug-related gross or microscopic findings were noted.

Table 1 Individual Mucous Membrane Irritation Scores[a]

Hamster No. / Sex	Day 0				Day 1				Day 2				Day 3				Day 4			
	Predose		Postdose		Predose		Postdose		Predose		Postdose		Predose		Postdose		Predose		Postdose	
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
Sham Control																				
1F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SCH 34117 Reditab Tablet (5 mg)																				
7F	0	0	0	0	0	0	0	0	0	0	±	0	0	0	0	0	0	0	0	0
8F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	±	0	0	0	0	0
10F	0	0	0	0	0	0	0	0	0	0	±	0	0	0	±	0	0	0	0	0
11F	0	0	0	0	0	0	0	0	0	0	±	0	0	0	0	0	0	0	±	0
12F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

L = Left cheek pouch, R = Right cheek pouch

a: Grading Scale for Mucous Membrane Irritation
0 = No reaction
± = Very slight (barely perceptible) redness, usually nonconfluent
1 = Slight (well defined) redness, usually confluent
2 = Moderate redness
3 = Severe redness, with or without edema, necrosis or scab formation

Study title: Mucous membrane irritation of SCH 34117 reditab (CIMA) tablets in the hamster cheek pouch

Key study findings: Very slight to severe mucous membrane irritation was observed in female Syrian hamsters treated with 5 mg SCH 34117 RediTab (OraSolv formulation) during the 5-day study. Gross findings in the treated group included discoloration, altered surface and abscesses of the cheek pouch and microscopic findings of minimal to moderate severity included ulceration, necrosis, inflammation and fibroplasia of the oral cavity.

Study no: SN 00480
Volume #, and page #: 1, 4
Conducting laboratory and location: Schering Plough, Lafayette, NJ
Date of study initiation: November, 2000
GLP compliance: The report included a signed GLP report
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: SCH 34117 (CIMA), batch # LB760-10, purity not reported
Formulation/vehicle:
OraSolv formulation

	mg/tablet
SCh 34117	(b) (4)
Mannitol USP	(b) (4)
Aspartame NF	(b) (4)
Tutti frutti flavor	(b) (4)
Citric acid (b) (4)	(b) (4)
Crospovidone NF	(b) (4)
Microcrystalline cellulose	(b) (4)
Sodium bicarbonate (b) (4) USP	(b) (4)
Magnesium stearate NF	(b) (4)
Colloidal silicon dioxide	(b) (4)
NF Red (b) (4) oxide	(b) (4)

Methods: Prior to dosing, each hamster was anesthetized prior to and during dosing. Anesthesia was maintained for at least 10 minutes after dosing for observation of the cheek pouch. A small amount of sterile water was added to the dosed cheek pouch just prior to insertion of the tablet. Tablets were inserted in the left cheek pouch. The contralateral cheek pouch served as an untreated control.

Dosing:

Species/strain: Golden Syrian Hamsters (b) (4)
#/sex/group or time point (main study): 6 females
Satellite groups used for toxicokinetics or recovery: NA
Age: 11 weeks
Weight: 107-135 g
Doses in administered units: 5 mg (37-46 mg/kg)

Route, form, volume, and infusion rate: transmucosal, 1 tablet for 5 consecutive days

Observations and times:

Clinical signs:	1 time daily
Body weights:	Day 0
Gross pathology:	Day 5 following observation period. Both cheek pouches of each hamster were dissected free from the surrounding tissues, opened longitudinally, examined and fixed in buffered formalin.
Histopathology:	Day 5. Six transverse sections of each cheek pouch, 3 from proximal end and 3 from distal end, were processed and examined microscopically.
Other:	Mucous membrane irritation, 2x daily (immediately prior to and 10 minutes after dosing)

Results:

Mortality: All hamsters survived dosing procedure.

Clinical signs: No significant observations were noted.

Mucous membrane Irritation: Results are summarized in the table below. No findings were noted on Day 0 of dosing. On day 1 pre-dose, one animal demonstrated slight irritation with pale, raised areas in the drug-treated cheek. At 10 minutes after dosing on day 1, 4 of 6 treated animals displayed very slight to slight irritation in the drug-treated pouches. Two had blister-like and pale, raised areas. By day 2, 5 of 6 had very slight to moderate irritation with pale, raised areas and/or blister-like raised areas in drug-treated pouches. The degree of irritation had increased to slight to severe by day 3 with blisters in 4 of 6 animals. Two animals had thickened, abraded areas in the left corner of the mouth. By day 4, irritation was moderate to severe in 4 of 6 animals. No irritation was observed in sham animals or in the untreated cheek pouches of treated hamsters.

Table 1 Individual Mucous Membrane Irritation Scores[a]

Hamster No./ Sex	Day of Dosing																			
	0				1				2				3				4			
	Predose		Postdose		Predose		Postdose		Predose		Postdose		Predose		Postdose		Predose		Postdose	
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
Sham Control																				
1F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SCH 34117 Reditab (CIMA) Tablet (5 mg)																				
7F	0	0	0	0	0	0	0	0	0	0	±	0	0	0	0	0	0	0	0	0
8F	0	0	0	0	0	0	$1^{b,c}$	0	$\pm^{c}$	0	1^{c}	0	3^{c}	0	3^{c}	0	3^{c}	0	3^{c}	0
9F	0	0	0	0	0	0	±	0	0	0	±	0	2^{c}	0	2^{c}	0	3^{c}	0	3^{c}	0
10F	0	0	0	0	0	0	0	0	$\pm^{c}$	0	$\pm^{c}$	0	$1^{c,d}$	0	$1^{c,d}$	0	2^{c}	0	$2^{c,d}$	0
11F	0	0	0	0	1^{b}	0	$1^{b,c}$	0	$\pm^{b,c}$	0	$2^{b,c}$	0	3^{c}	0	$3^{c,d}$	0	3^{c}	0	$3^{c,d}$	0
12F	0	0	0	0	0	0	±	0	0	0	0	0	0^{d}	0	0^{d}	0	0	0	0	0

L = Left cheek pouch R = Right cheek pouch

a: Grading Scale for Mucous Membrane Irritation
- 0 = No reaction
- ± = Very slight (barely perceptible), redness usually nonconfluent
- 1 = Slight (well defined) redness, usually confluent
- 2 = Moderate redness
- 3 = Severe redness, with or without edema, necrosis or scab formation

b: Pale, raised areas

c: Blister-like areas (with or without abrasions)

d: Corner of mouth thickened and abraded

Gross pathology: The treated cheek pouches contained pink material interpreted by the sponsor as undissolved Reditab tablet (see Table below). Discoloration of the cheek pouch was noted in 2 hamsters.

Histopathology: Microscopic changes in the SCH 34117-treated group included ulceration, necrosis, inflammation and fibroplasia of the oral cavity (see Table below). Findings were of minimal to moderate severity.

Gross/microscopic changes following 5 day administration of SCH 34117 RediTabs (OraSolv).

I. Observed signs	Dose group (mg)	
	0	5
Gross changes n=	6	6
Oral cavity		
Not remarkable	6	0
Alt. content, cheek pouch, unilateral	0	6
Alt. surface, cheek pouch, MF, unilateral	0	4
Discoloration, cheek pouch, proximal, red	0	1
Discoloration, cheek pouch, red, unilateral	0	1
Abscess(es), cheek pouch, focal, unilateral	0	1
Microscopic changes n=	6	6
Oral cavity		
Ulcer, proximal and distal, left		
Mild	0	2
Moderate	0	3
Necrosis, proximal, left		
Minimal	0	1
Inflamm., subacute, prox. & distal, left		
Minimal	0	2
Mild	0	3
Inflamm., neutrophilic, prox. & distal, left		
Minimal	0	1
Mild	0	3
Moderate	0	1
Fibroplasia, cheek pouch, prox. & distal, left		
Minimal	0	2
Mild	0	2

Summary of individual study findings: Observations related to mucous membrane irritation were observed in female Syrian hamsters treated with the proposed clinical dose of 5 mg SCH 34117 RediTab with the OraSolv formulation. The findings were judged as very slight to severe. Gross findings in the treated group included discoloration, altered surface and abscesses and microscopic findings of minimal to moderate severity included ulceration, necrosis, inflammation and fibroplasia.

OVERALL SUMMARY AND EVALUATION:

Introduction: The sponsor is developing a rapidly disintegrating desloratadine tablet (RediTab) product for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria. The tablets are designed for rapid disintegration in the mouth upon administration to allow ease of swallowing. The sponsor submitted three *in vivo* cheek pouch mucous membrane irritation studies performed in Syrian golden hamsters. In the first study using a Scherer formulation, the tablets were comprised of SCH 34117, gelatin Type B NF, mannitol USP, aspartame NF, Polacrilin Potassium USP, dye (b) (4) red (b) (4), tutti frutti flavor (b) (4) citric acid USP and (b) (4). Dosing began with four 5 mg tablets on day 1 followed by two tablets on day 2 and one tablet on the following 3 days. The second study was performed using a "flavor enhanced" desloratadine Reditab (Scherer) formulation (one 5 mg tablet per day) although the changes to the formulation, if any, were not provided. In the third study, an OraSolv formulation (SCH 34117, mannitol USP, aspartame NF, tutti frutti flavor, crospovidone NF, microcrystalline cellulose, sodium bicarbonate (b) (4) USP, magnesium stearate NF, citric acid (b) (4) USP, Red (b) (4) oxide, colloidal silicon dioxide NF) was utilized (one 5 mg tablet per day). The OraSolv formulation is under development to improve the taste of the tablet.

Safety evaluation: One death of a SCH 34117-treated animal occurred with the Scherer formulation in which animals were dosed with 4, 2, and 1 tablet(s) on days 1, 2, and 3, respectively. Cause of death was considered to be due to an interaction with the anesthetic and dosing was 385-1540 times the human dose on a mg/kg basis. Very slight to slight irritation of the hamster cheek pouch was reported in the two studies performed with the Scherer formulations. These findings either diminished or plateaued with increased dosing. No drug-related gross or microscopic findings were noted in either study. The studies were performed using 5 mg desloratadine tablets which were comparable to those used clinically. The findings of these studies indicate that the SCH 34117 RediTab Scherer formulations do not pose a significant irritancy risk in the intended population.

In the study performed with the OraSolv formulation (5 mg desloratadine), severe irritation was noted in treated animals as well as gross and microscopic findings (necrosis, ulceration, inflammation and fibroplasia; minimal to moderate severity). The sponsor states that the findings may not be relevant to human risk assessment due to methodological limitations of the assay. The model has historically been used for evaluation of formulations that will have prolonged contact with the oral mucosa, but most specifically has been applied to the evaluation of sublingual tablets intended for local delivery of drug through the oral mucosa. It is an extremely sensitive model since the clinical dose form is applied to the cheek pouch regardless of the animal to human dose ratio. The sponsor explains that the high dose of desloratadine could have resulted in anticholinergic effects that could have affected normal salivary flow. In the clinical setting the action of human salivary flow may have a greater flushing action than would have been operative in hamsters. Residual testing material remained overnight in the cheek pouch indicating that the expected rapid disintegration of the OraSolv tablet was

not operative under the test conditions. The tablet is expected to disintegrate rapidly and be swallowed (based on their experience with OraSolv) and residual tablet material in contact with the oral mucosa would not be expected to persist under normal clinical test conditions. Regular flushing action and rapid disintegration would act to reduce residency time and likely remove irritation liability.

Although the sponsor is correct in the historical use of the assay, the claim of a high animal to human dose ratio is not valid since the findings are a local toxicity and are more related to surface area effect than on a body weight effect. The animal dose to human dose ratio is comparable based on buccal mucosa surface area and is equivalent based upon drug concentration at the site of irritation. In addition, a potential toxic effect of desloratadine due to anticholinergic activity on normal salivary flow is not likely since this assay was performed twice using a different formulation but with equivalent or greater daily doses of desloratadine resulting in only very slight to slight irritation.

In regards to the observed toxicity of the OraSolv formulation of the RediTab tablet being a result of residual testing material remaining in the cheek pouch, the Agency currently has no information as to the actual rate of disintegration of this new formulation in clinical studies. OraSolv formulations are currently marketed in OTC products including Tempra and Triaminic and in a prescription brand anti-migraine prodcut (Zomig, marketed in Europe) and there is no data to suggest OraSolv based products have irritation liability. However, the OraSolv formulation for desloratadine RediTabs includes four new components: red (b) (4) oxide, tutti frutti flavor, pregelatinized starch, sodium starch glycolate. Although none of these new components are expected to have a significant irritation liability individually, the potential exists that the combination of some or all components may produce the observed cheek pouch toxicity.

The sponsor feels that a human clinical oral irritation study should be conducted to evaluate human irritation liability of the OraSolv formulation and has submitted two Protocol Concept Sheets (PCS) proposing a single dose bioequivalence trial with a 5 mg OraSolv formulation RediTab tablet and a 5 mg tablet and a 14-day open label study to assess buccal irritation of the 5 mg OraSolv RediTab tablet. The review team discussed these protocols in an internal meeting on May 18, 2001 and decided that the proposed protocols could proceed since the desloratadine doses are acceptable and the potential for buccal irritation is easily monitored. However, if the sponsor wishes to pursue development of this formulation for marketing, additional animal studies in other species (e.g., dog or minipig) will be needed to further characterize the local irritation potential and demonstrate reversibility of the findings. These comments were communicated to the sponsor in a fax dated May 22, 2001.

RECOMMENDATIONS:

Internal comments: The trials proposed in the Protocol Concept Sheets are considered to be reasonably safe to proceed with careful monitoring for oral irritation.

External recommendations (to sponsor): None at this time.

Future development or NDA issues: Should the sponsor pursue development of the OraSolv formulation for RediTab tablets, qualification studies may be necessary for the certain inactive ingredients. In addition, the sponsor will need to conduct additional preclinical studies to assess the potential for buccal irritation and reversibility of the findings.

Reviewer signature:

Timothy J. McGovern, Ph.D.

Team leader signature:

C. Joseph Sun, Ph.D.

Original IND 59,190
CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/D. Hilfiker
HFD-570/T.J. McGovern

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/s/

Timothy McGovern
6/23/05 08:33:14 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-312/S007

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-312
Proprietary Drug Name:	Clarinex-Reditabs®
Generic Name:	Desloratadine
Indication:	Treatment of Seasonal Allergic Rhinitis (SAR), Perennial Allergic Rhinitis (PAR) and Chronic Idiopathic Urticaria (CIU)
Dosage Form:	Tablet
Strength:	2.5- and 5 mg
Route of Administration:	Oral
Dosage and administration:	**Adults and children (age 12 and older):** 5 mg tablet (b) (4) daily **Children 6 to 11 years of age:** 2.5 mg once daily
Applicant:	Schering Corporation
Clinical Division:	DPADP (HFD-570)
Submission Date:	March 14, 2005
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader:	Emmanuel Fadiran, Ph. D.

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1. EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceuticals / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed this application submitted to NDAs 21-312 on March 14, 2004 to support the use of CIMA Clarinex Reditabs for the treatment of PAR, SAR and CIU. The present report provides information on the BE of a new formulation of Clarinex Reditabs (CIMA Reditabs tablets) and the currently marketed formulation of Reditabs tablets. It also provides information on the dissolution method and specifications for these tablets. The NDA's Human Pharmacokinetics and Bioavailability Section is acceptable to OCPB.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Desloratadine (DL, Clarinex®), the major active metabolite of loratadine (Claritin®), is a long-acting tricyclic antihistamine with selective peripheral histamine H1-receptor antagonistic activity. Desloratadine is currently approved in a 5-mg tablet formulation, a 5-mg RediTabs formulation, and a 0.5 mg/mL syrup formulation for the relief of the symptoms of allergic rhinitis (AR) and chronic idiopathic urticaria (CIU). In the USA, the 5-mg QD dose is approved for adults and adolescents 12 years and over. In addition, DL Syrup is approved at 2.5 mg QD for children 6 to 11 years of age, 1.25 mg QD for children 12 months to 5 years of age, and 1.00 mg QD for infants 6 to 11 months of age (DL is not approved for use in SAR below 2 years of age).

In the present submission the sponsor, Schering-Plough, is seeking approval to market a new formulation of DL RediTabs manufactured in partnership with CIMA Labs Inc. in replacement for the currently marketed RediTabs formulation manufactured by Cardinal Health. CIMA DL RediTabs Tablets would be available in a 5-mg dose for use in adults and children 12 years and over, and in a 2.5-mg dose for use in children 6 to 11 years old. The application for the 5-mg dose is based on the bioequivalence of the CIMA DL 5-mg RediTabs Tablet to the currently marketed Cardinal DL 5-mg RediTabs Tablet. The application for the 2.5-mg dose is based on a waiver of BE granted based on the existence of dose-proportionality between the CIMA RediTabs 2.5- and 5 mg formulations and comparative in vitro dissolution profiles. The F2 value for the comparison of the dissolution profiles of these 2 strengths was not calculated because more than (b) (4) of the drug was dissolved in less than (b) (4) for both strengths.

In support of this application, the sponsor submitted the results of one pivotal bioequivalence study (Study P02721) using the final formulation, and two pilot studies (P02393 and P02340) using a prototype formulation. Study P02340 was not reviewed since it did not add relevant information to support the approval of this submission.

The CIMA DL 5-mg RediTabs Tablet was bioequivalent to the marketed Cardinal DL 5-mg RediTabs Tablet, and the oral bioavailability of the CIMA DL 5-mg RediTabs Tablet was not affected by the presence of water (Table 1.3.1).

Table 1.3.1. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of DL and 3-OH DL following single administration of the treatments

Comparison	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer' findings	Sponsor's findings	This reviewer' findings
	Desloratadine				
CIMA with water/cardinal with water	AUCinf Cmax	103 106	102.9 105.6	98-109 98-114	97.6-108.4 98-113.8
CIMA without water/CIMA with water	AUCinf Cmax	94 99	106.6 101.1	89-99 92-107	101-112 93.8-108.9
	3-OH DL				
CIMA with water/cardinal with water	AUCinf Cmax	101 105	101.4 105.3	97-105 99-111	97.4-105.6 99.5-111
CIMA without water/CIMA with water	AUCinf Cmax	98 101	99.3 101.1	94-102 95-108	95.4-103.6 95.5-109.2

The proposed dissolution specification is Q (b) (4) in 10 minutes. The dissolution method and specification are acceptable from a CPB standpoint.

1.4 COMMENTS TO THE MEDICAL OFFICER

- Results from Study P02721 indicated that 2 out 24 subjects (subject numbers 23 and 24) presented high DL AUCinf values. None of these subjects showed a % ratio of 3-OH DL AUC/ DL AUC less than 10, and therefore, there were NO poor metabolizers.

Reviewer
Sandra Suarez-Sharp, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader

cc :
NDAs: 21-312
HFD-870: Malinowski, Hunt
HFD-570: Fadiran, Nicklas, Chowdhury, Zeccola, Suarez-Sharp

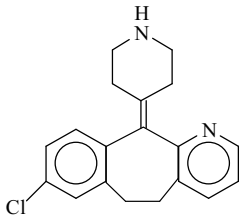
2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

DL Chemical name:. The chemical name is 8-chloro-6,11-dihydro-11-(4-piperdinylidene)-5H-benzo[5,6] cyclohepta [1,2-b]pyridine and has the following structural formula:

Structural formula:



Molecular formula: $C_{19}H_{19}ClN_2$

Molecular weight: 310.8

Solubility: DL is a white to off-white powder that is slightly soluble in water, but very soluble in ethanol and propylene glycol.

FORMULATION

The CLARINEX RediTabs® brand of desloratadine orally-disintegrating tablets are light red, flat-faced, round, speckled tablets with an "A" debossed on one side for the 5 mg tablets and a "K" debossed on one side for the 2.5 mg tablets. Each RediTabs Tablet contains either 5 mg or 2.5 mg of desloratadine with the compositions of the formulations shown in Table 2.1.1.

Table 2.1.1. Composition of Clarinex RediTabs (CIMA) 2.5 mg and 5 mg tablets

Component	mg/2.5 mg Tablet	mg/5 mg Tablet	Function
Desloratadine	(b) (4)	(b)	(b) (4)
Mannitol	(b)		(b) (4)
(b) (4)Mannito	(b)	(b)	(b) (4)
Crospovidone	(b)		(b) (4)
Microcrystalline Cellulose[b]	(b)		(b) (4)
Aspartame	(b)		(b) (4)
Tutti Frutti	(b) (4)	(b)	(b)
Ferric Oxide, Red	(b)		(b) (4)
Sodium bicarbonate	(b)		(b) (4)
Citric Acid	(b) (4)	(b)	(b) (4)
Magnesium Stearate	(b)		(b) (4)
Colloidal Silicon Dioxide	(b)		(b) (4)
Total Theoretical Tablet Weight	(b)		

a: Actual amounts to be used in the batch are determined by the assay value of desloratadine (b) (b) (4); b: (b) (4); c: The quantitative composition of the flavor is incorporated by reference from (b) (4), which was submitted in January 2001.

The orally disintegrating desloratadine tablets were developed in partnership with CIMA LABS INC.® using CIMA's patented OraSolv® technology. The main objectives of

the formulation development were to achieve acceptable taste masking, fast disintegration times and minimum grittiness for the orally disintegrating tablets. Consequently, efforts were also directed towards optimizing the tablet content uniformity, without compromising the taste masking or disintegration time of the formulation.

These orally disintegrating tablets require that the (b) (4) be taste masked (b) (4) was selected as the (b) (4) component (b) (4) is a (b) (4) which is insoluble in human saliva (pH=6-7) but soluble in gastric fluid (pH=1-3). During the prototype development a suitable (b) (4) was identified for (b) (4). Following the pilot pharmacokinetic (PK) batch, the amount of (b) (4) to address any environmental or safety concerns. In addition, the formulation of the (b) (4) to optimize the tablet content uniformity. Following these formulation improvements, the registration stability batches (including the pivotal clinical batch) were manufactured at (b) (4) No formulation changes were made between the registration stability batches and the intended commercial product.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?
Mechanism of Action:

Desloratadine, the major active metabolite of loratadine (Claritin), is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic activity that possesses peripheral antihistaminic effects with no sedative or other central nervous system effects at clinically recommended doses.

INDICATION (as per proposed label)
Seasonal Allergic Rhinitis: CLARINEX is indicated for the relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis in patients 2 years of age and older.
Perennial Allergic Rhinitis: CLARINEX is indicated for the relief of the nasal and non-nasal symptoms of perennial allergic rhinitis in patients 6 months of age and older.
Chronic Idiopathic Urticaria: CLARINEX is indicated for the symptomatic relief of pruritus, reduction in the number of hives, and size of hives, in patients with chronic idiopathic urticaria 6 months of age and older.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed route of administration is by oral administration.

DOSAGE AND ADMINISTRATION (as per proposed label)
Adults and children 12 years of age and over: the recommended dose of CLARINEX Tablets or CLARINEX RediTabs Tablets is one 5 mg tablet once daily or the recommended dose of CLARINEX Syrup is 2 teaspoonfuls (5 mg in 10 ml) once daily.
Children 6 to 11 years of age: The recommended dose of CLARINEX Syrup is 1 teaspoonful (2.5 mg in 5 ml) once daily or the recommended dose of CLARINEX RediTabs Tablets is one 2.5 mg tablet once daily.

2.2 General Clinical Pharmacology

2.2.1 What are the PK characteristics of the drug and its major metabolite?

The following pharmacokinetics of desloratadine were presented in previous NDAs.

Absorption: Following oral administration of desloratadine 5 mg once daily for 10 days to normal healthy volunteers, the mean time to maximum plasma concentrations (T_{max}) occurred at approximately 3 hours post dose and mean steady state peak plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) of 4 ng/mL and 56.9 ng·hr/mL were observed, respectively. Neither food nor grapefruit juice had an effect on the bioavailability (C_{max} 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 subjects 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 enzyme(s) responsible for the formation of 3-hydroxydesloratadine have not been identified. Data from clinical trials indicate that a subset of the general population has a decreased ability to form 3-hydroxydesloratadine, and are poor metabolizers of desloratadine. In pharmacokinetic studies (n= 3748), approximately 6% of subjects were poor 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). These pharmacokinetic studies included subjects between the ages of 2 and 70 years, including 977 subjects aged 2-5 years, 1575 subjects aged 6-11 years, and 1196 subjects aged 12-70 years. There was no difference in the prevalence of poor metabolizers across age groups. The frequency of poor metabolizers was higher in Blacks (17%, n=988) as compared to Caucasians (2%, n=1462) and Hispanics (2%, n=1063). The median exposure (AUC) to desloratadine in the poor metabolizers was approximately 6-fold greater than in the subjects who are not poor metabolizers. Subjects who are poor metabolizers of desloratadine cannot be prospectively identified and will be exposed to higher levels of desloratadine following dosing with the recommended dose of desloratadine. In multidose clinical safety studies, where metabolizer status was identified, a total of 94 poor metabolizers and 123 normal metabolizers were enrolled and treated with CLARINEX Syrup for 15-35 days. In these studies, no overall differences in safety were observed between poor metabolizers and normal metabolizers. Although not seen in these studies, an increased risk of exposure-related adverse events in patients who are poor metabolizers cannot be ruled out.

Elimination: The mean elimination half-life of desloratadine was 27 hours. C_{max} and AUC values increased in a dose proportional manner following single oral doses between 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 87% of the ^{14}C-desloratadine dose, which was equally distributed in urine and feces as metabolic products. Analysis of plasma 3-hydroxydesloratadine showed similar T_{max} and half-life values compared to desloratadine.

2.3 Intrinsic Factors

2.3.1 Does age affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

The following pharmacokinetic information of desloratadine was presented in previous NDAs.

Special Populations: Geriatric: In older subjects (≥ 65 years old; n=17) following multiple-dose administration of CLARINEX Tablets, the mean C_{max} 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 plasma elimination half-life 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.

Pediatric Subjects: In subjects 6 to 11 years old, a single dose of 5 ml of CLARINEX Syrup containing 2.5 mg of desloratadine, resulted in desloratadine plasma concentrations similar to those achieved in adults administered a single 5 mg CLARINEX Tablet. In subjects 2 to 5 years old, a single dose of 2.5 ml of CLARINEX Syrup containing 1.25 mg of desloratadine, resulted in desloratadine plasma concentrations similar to those achieved in adults administered a single 5 mg CLARINEX Tablet. However, the Cmax and AUCt of the metabolite (3-OH desloratadine) were 1.27 and 1.61 times higher for the 5 mg dose of syrup administered in adults compared to the Cmax and AUCt obtained in children 2-11 years of age receiving 1.25-2.5 mg of Clarinex syrup.

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

The CLARINEX RediTabs Tablet 2.5 mg tablet has not been evaluated in pediatric patients. Bioequivalence of the CLARINEX RediTabs Tablet and the original CLARINEX RediTabs Tablets was established in adults. In conjunction with the dose finding studies in pediatrics described, the pharmacokinetic data for CLARINEX RediTabs Tablets supports the use of the 2.5 mg dose strength in pediatric patients 6-11 years of age.

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 m^2), moderate (n=6; creatinine clearance 34-43 mL/min/1.73 m^2), and severe (n=6; creatinine clearance 5-29 mL/min/1.73 m^2) renal impairment or hemodialysis dependent (n=6) patients. In patients with mild and moderate renal impairment, median C_{max} 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, C_{max} 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 unaltered by renal impairment. Dosage adjustment for patients with renal impairment is recommended.

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 28% of that in normal subjects, respectively. An increase in the mean elimination half-life of desloratadine in patients with hepatic impairment was observed. For 3-hydroxydesloratadine, the mean C_{max} 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.

Gender: Female subjects treated for 14 days with CLARINEX Tablets had 10% and 3% higher desloratadine C_{max} and AUC values, respectively, compared with male subjects. The 3-hydroxydesloratadine C_{max} 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 C_{max} 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 C_{max} and AUC values in Blacks compared to Caucasians. These differences are not likely to be clinically relevant and therefore no dose adjustment is recommended.

2.4 Extrinsic Factors
2.4.1 Drug Interactions

The following information of desloratadine was presented in previous NDAs.
In two controlled crossover clinical pharmacology studies in healthy male (n=12 in each study) and female (n=12 in each study) volunteers, desloratadine 7.5 mg (1.5 times the daily dose) once daily was coadministered with erythromycin 500 mg every 8 hours or ketoconazole 200 mg every 12 hours for 10 days. In 3 separate controlled, parallel group clinical pharmacology studies, desloratadine at the clinical dose of 5 mg has been coadministered with azithromycin 500 mg followed by 250 mg once daily for 4 days (n=18) or with fluoxetine 20 mg once daily for 7 days after a 23 day pretreatment period with fluoxetine (n=18) or with cimetidine 600 mg every 12 hours for 14 days (n=18) under steady state conditions to normal healthy male and female volunteers. 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.

2.5 General Biopharmaceutics

2.5.1 Was the Cima Clarinex Reditab formulation bioequivalent to the Cardinal Clarinex Reditab and Clarinex tablet formulations?

The Cls for the ratio of the geometric means of Cmax and AUC(I) of DL and 3-OH DL for CIMA Reditab relative to the Cardinal Reditab (Study P02721) formulation met the 80-125 bioequivalence guideline criteria. This indicates that the CIMA Reditab formulation IS bioequivalent to the Cardinal Reditab formulation

Study P02721 was a Phase I, open-label, single-dose, randomized, 3-way crossover study in 24 healthy male and female with at least a 10-day washout period between each treatment. This study evaluated the bioequivalence of the CIMA DL 5 mg orally-disintegrating tablet and the currently marketed Cardinal DL 5 mg orally-disintegrating tablet under standard conditions (ie, administered with 240 mL of water). Also, it evaluated the effect of water on the bioavailability of the CIMA DL 5 mg orally disintegrating tablet. The formula of CIMA reditabs used in this study was the same as the to-be marketed formulation and the batch size was more than (b) (4) units (b) (4) units).

The mean PK parameters for DL and its metabolite are presented in Table 2.5.1.1. The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for DL and its metabolite are presented in Table 2.5.1.2.

Table 2.5.1.1 Mean (%CV) pharmacokinetic parameters of DL and 3-OH following single administration of the treatments

	Pharmacokinetic Parameters		
Treatment	**Cmax (ng/mL)**	**Tmax**	**AUC inf (ng*hr/mL)**
	Desloratadine (n=22)		
A: Cardinal DL reditabs	2.83 (47)	3 (1.5-6)	52.8 (51)
B: CIMA DL with water	2.92 (39)	2.5 (1.5-6)	54.7 (154)
	3-OH Desloratadine		
A: Cardinal DL reditabs	1.22 (28)	6 (2-8)	34.5 (23)
B: CIMA DL with water	1.26 (20)	6 (3-8)	34.9 (23)

Table 2.5.1.2. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of DL and 3-OH DL following single administration of the treatments

Comparison	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer' findings	Sponsor's findings	This reviewer' findings
	Desloratadine				
CIMA with water/cardinal with water	AUCinf Cmax	103 106	102.89 105.6	98-109 98-114	97.6-108.4 98-113.8
	3-OH DL				
CIMA with water/cardinal with water	AUCinf Cmax	101 105	101.4 105.3	97-105 99-111	97.4-105.6 99.5-111

2.5.2 Was the bioavailability of DL from the CIMA DL reditab tablet affected by the presence of water?

The Cls for the ratio of the geometric means of Cmax and AUC(I) of DL and 3-OH DL for CIMA Reditab without water relative to CIMA Reditab with water met the 80-125 bioequivalence guideline criteria. *This indicates that water does not affect the BA of desloratadine or its metabolites when delivered from the CIMA Reditab formulation*

Study P02721 was a Phase I, open-label, single-dose, randomized, 3-way crossover study in 24 healthy male and female with at least a 10-day washout period between each treatment. This study, as indicated before evaluated not only the BE of the CIMA DL 5 mg orally-disintegrating tablet and the currently marketed Cardinal DL 5 my orally-disintegrating tablet under standard, but also evaluated the effect of water on the bioavailability of the CIMA DL 5 my orally disintegrating tablet.

The mean PK parameters for DL and its metabolite are presented in Table 2.5.2.1. The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for DL and its metabolite are presented in Table 2.5.2.2.

Table 2.5.2.1. Mean (%CV) pharmacokinetic parameters of DL and 3-OH following single administration of the treatments

	Pharmacokinetic Parameters		
Treatment	**Cmax (ng/mL)**	**Tmax**	**AUC inf (ng*hr/mL)**
	Desloratadine (n=22)		
B: CIMA DL with water	2.92 (39)	2.5 (1.5-6)	54.7 (154)
C: CIMA DL without water	2.90 (38)	3 (1-6)	51.8 (56)
	3-OH Desloratadine		
B: CIMA DL with water	1.26 (20)	6 (3-8)	34.9 (23)
C: CIMA DL without water	1.29 (27)	6 (2-6)	34.3 (24)

Table 2.5.2.2. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of DL and 3-OH DL following single administration of the treatments

Comparison	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer' findings	Sponsor's findings	This reviewer' findings
	Desloratadine				
CIMA without water/CIMA with water	AUCinf Cmax	94 99	106.56 101.1	89-99 92-107	101-112 93.8-108.9
	3-OH DL				
CIMA without water/CIMA with water	AUCinf Cmax	98 101	99.3 101.1	94-102 95-108	95.4-103.6 95.5-109.2

Figure 2.5.2.1 shows that 2 out 24 subjects presented high DL AUCinf values. None of these subjects showed a % ratio of 3-OH DL AUC/ DL AUC less than 10, and therefore, there were NO poor metabolizers. The clinical relevance of these outliers on the safety of Clarinex should be evaluated by the medical reviewer.

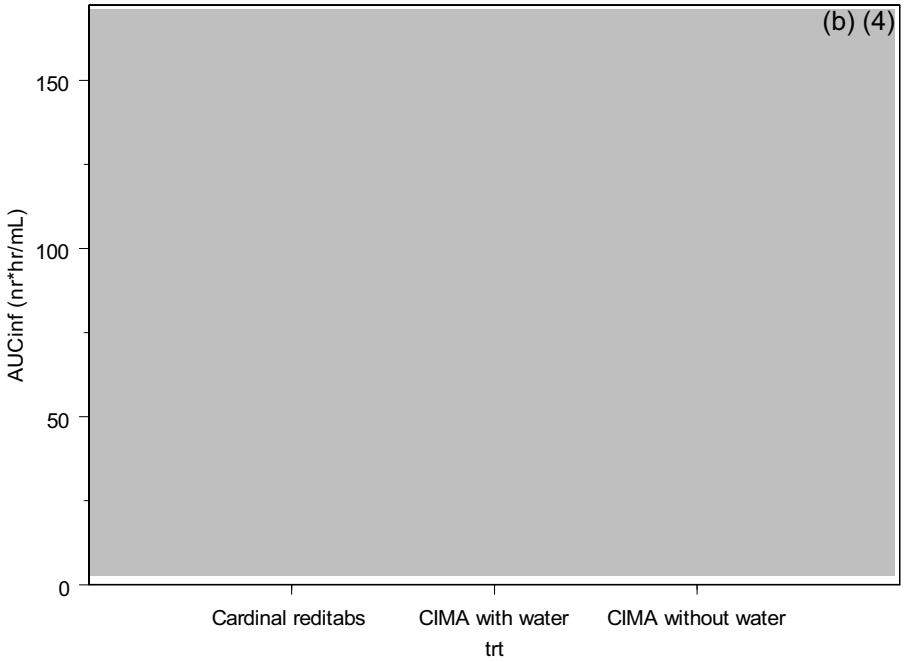


Figure 2.5.2.1. Individual DL AUCinf values following single administration of CIMA reditabs 5mg with and without water and cardinal DL clarinex tablets 5mg.

2.5.3 What data support or do not support a waiver of in vivo BE data

The 2.5-mg and 5-mg tablets are dose proportional, and a waiver of bioequivalence testing of the 2.5-mg CIMA RediTabs Tablet was requested at a March 8, 2004 meeting with FDA, based on the Agency's Guidance to industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products. The F2 value for the

comparison of the dissolution profiles of these 2 strengths was not calculated because higher than (b) (4) was dissolved in less than (b) (4) for both strengths. Based on these finding and on the fact that the formulations have a proportional composition (see Table 2.1), the 2.5-mg and the 5 mg tablets are considered bioequivalent.

2.5.4 Are the proposed dissolution method and specifications supported by the data provided by the sponsor

The CIMA Clarinex Reditab dissolution method and specifications proposed by the sponsor are listed in Table. Figures 2.5.4.1 and 2.5.4.2 and Tables 2.5.4.1, 2.5.4.2, and 2.5.4.3 show the dissolution profiles for the Reditabs used in the pivotal PK study. These method and specifications are acceptable from a CPB standpoint.

Table 2.5.4.1. Proposed dissolution method for Clarinex Reditabs

Method	
Apparatus:	USP apparatus II (paddle)
Detection:	UV at 280 nm
Speed:	50 rpm
Temperature:	37 °C ± 0.5 °C
Medium:	900 mL of 0.1N HCL
Specification:	Q (b) (4) in 10 minutes

Table 2.5.4.2. Dissolution data for CIMA Clarinex Reditabs 5 mg

Time (min)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**average**	**SD**
						Percent DL dissolved/dosage form								
3	(b) (4)												**85**	**15.17**
6	(b) (4)												**95**	**6.22**
10	(b) (4)												**98**	**5.23**
15	(b) (4)												**98**	**5.24**

Table 2.5.4.3. Dissolution data for CIMA Clarinex Reditabs 2.5 mg

Time (min)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**average**	**SD**
						Percent DL dissolved/dosage form								
3	(b) (4)												**89**	**12**
6	(b) (4)												**96**	**4.96**
10	(b) (4)												**97**	**4.79**
15	(b) (4)												**97**	**4.54**

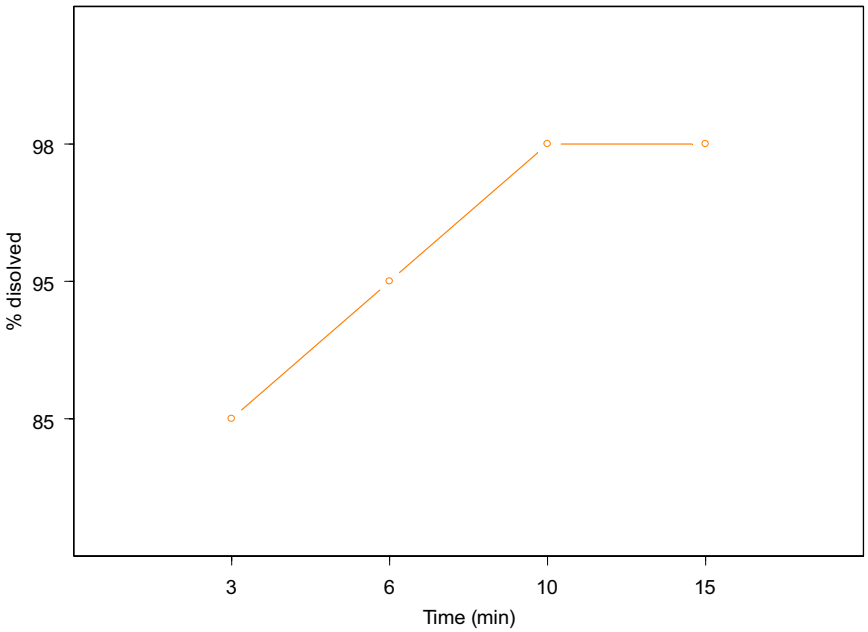
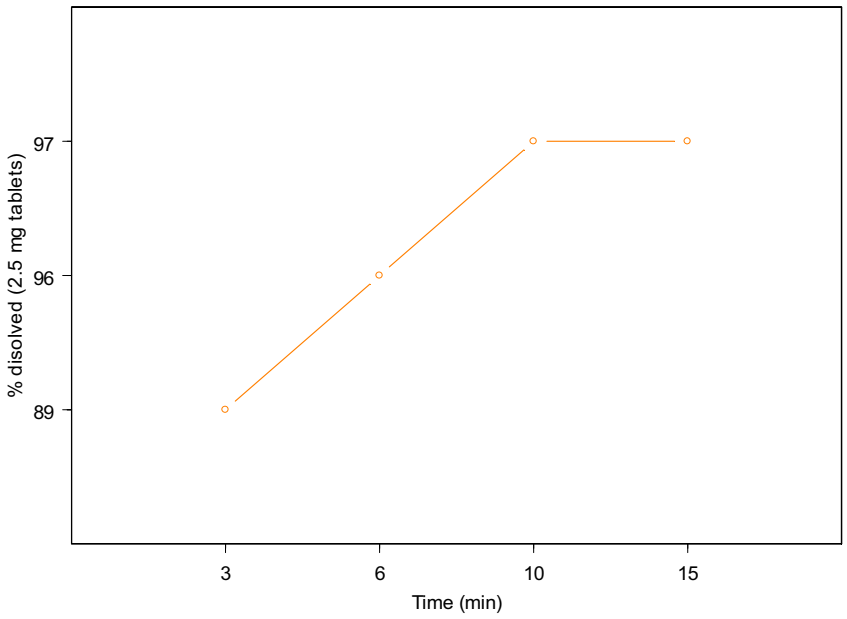


Figure 2.5.4.1 Average dissolution-time profile for CIMA Clarinex Reditabs 5 mg.



2.5.4.2 Average dissolution-time profile for CIMA Clarinex Reditabs 2.5 mg

2.5.5 What is the effect of food on the BA of the drug from the dosage form?

According to what is establish on Appendix 4 (Review Considerations for Orally Disintegrating Tablets), if food has not affected the BA of the active drug in the conventional oral dosage form (COD), similar lack of food effect may be expected with an ODT, if BE has been established between the COD and the ODT. In this case, no food

effect study is necessary. Neither food nor grapefruit juice had an effect on the bioavailability (C_{max} and AUC) of desloratadine from the conventional tablet, therefore, the effect of food on the BA of DL from the CIMA reditab was not necessary.

2.6 Analytical Section

2.6.1 Was the suitability of the analytical method supported by the submitted information?

The sponsor did not mention if free, bound or total drug was measured. Therefore, it is assumed that total drug was measured. The analysis of the plasma concentrations of DL (desloratadine) and 3-OH DL (major metabolite) were performed using validated liquid chromatography with tandem mass spectrometric method (LC/MS/MS). The calibration range for both the analytes ranged from 0.025 to 10.0 ng/mL. The method was validated for specificity, sensitivity, accuracy and precision and met the acceptance criteria for all validation parameters over the concentration range of 0.025 to 10.0 ng/mL.

The lower limit of quantification was set at 25 pg/ml for both analytes. The upper calibration limit for both analytes was 10 ng/mL. Calibration curve range from 25- to 10000 pg/mL for both analytes. The calibration curves for DL an its metabolite were linear with a coefficient of correlation equal or better than 0.993.

The accuracy, intra- and inter-day precision were acceptable for all the methods (<10% Bias or %CV) for in-study validation information

3. LABELING COMMENTS

There are not CPB labeling comments at this time.

___10___ Page (s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__✓___ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clinical Pharm/Bio-_____

"THE BIOEQUIVALENCE OF TWO DL 5 MG ORALLY-DISINTEGRATING TABLET FORMULATIONS (REDITABS®) AND THE EFFECT OF WATER ON THE CIMA REDITABS® BIOAVAILABILITY: A THREE-WAY CROSSOVER STUDY"

Name of Sponsor:	Schering-Plough Corporation
Included Protocols:	P02721
Development Phase of Study:	I
Study Initiation Date:	29 Jan 2004
Study Completion Date:	04 Mar 2004
Sponsor's Project Physician:	Suzanne Khalilieh, PharmD.
Date of the Report:	19 Oct 2004

OBJECTIVE

Primary

- to evaluate the bioequivalence of the CIMA DL 5 mg orally-disintegrating tablet and the currently marketed Cardinal DL 5 my orally-disintegrating tablet under standard conditions (ie, administered with 240 mL of water);
- to evaluate the effect of water on the bioavailability of the CIMA DL 5 my orally disintegrating tablet.

SUBJECTS

Twenty four subjects (12 male and 12 female) were enrolled and 22 of them completed the study. They were between the ages of 18 and 45 years inclusive (mean=31 years) weighing between 54.2 and 96.5 kg (mean=71.4 kg) and with BMIs between 19 and 27 kg/m^2 (mean=24.7 kg/m). Twenty two subjects were Hispanic and two were black.

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a Phase I, open-label, single-dose, randomized, 3-way crossover study with at least a 10-day washout period between each treatment. A total of 24 healthy male and female subjects were enrolled in the study. Subjects received the following treatments in the order assigned by a computer-generated random code:

Treatment A:	Cardinal DL 5 mg oral tablet CIMA Reditab administered with 240 ml of temperature tap water following a 10-hour fast.
Treatment B:	Cima DL 5 mg orally-disintegrating tablet with 240 ml of temperature tap water following a 10-hour fast.
Treatment C:	Cima DL 5 mg orally-disintegrating tablet following a 10-hour fast without water.

FORMULATION

The CIMA DL REDITABS® (SCH 34117) tablets were manufactured by CIMA Labs Inc., Eden Prairie, Minnesota, USA, and the Cardinal REDITABS® tablets were obtained through a commercial source (Table 1).

Table 1. Formulation for clarinex 5mg Tablets

Formulation	DL 5 mg CIMA Reditab®	Cardinal 5 mg
Formula No.	3843	
Batch No.	78012-122	2-MCR-12
Batch size	(b) (4)	
Manufacturing date	19 FEB 2003	

Formula 3843 is the same as the to-be marketed formulation.

PHARMACOKINETIC MEASUREMENTS

Blood Sampling

Serial blood samples (approximately 6 mL) for determination of DL and 3-OH DL concentrations were collected into tubes containing heparin as an anticoagulant at the following time points: 0 (pre-dose), 0.5,1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96 and 120 hr post-dose.

Analytical Method

Plasma concentrations of DL and 3-OH DL were determined using a validated liquid chromatography-tandem mass spectrometric (LC/MS/MS) method with a lower limit of quantitation (LOQ) of 0.025 ng/mL, and calibration curve range of 0.025-10 ng/mL for each analyte.

SAFETY MEASUREMENTS

Safety was assessed by monitoring adverse events, laboratory safety tests (CBC, blood chemistries and urinalysis), pre and poststudy physical examinations, vital signs and electrocardiograms.

DATA ANALYSIS

Pharmacokinetic Data Analysis

The mean and %CV were calculated for plasma concentrations of DL, its metabolite. Concentration values less than the assay LOQ were reported as and set to zero in the tables and calculations. The plasma concentration-time data for DL and its metabolite were subjected to pharmacokinetic analysis by non-compartmental methods using WinNonlin computer program.

For the determination of slow metabolizers of DL, the AUC ratio was calculated as follows:

$$\text{Ratio}(\%) = \frac{\text{AUC (I) SCH45581}}{\text{AUC(I) SCH 34117}} \times 100\%$$

A subject with a ratio of <10% was considered to be a slow metabolizer. None of the subjects in this study could be classified as slow metabolizers.

Statistical Analysis

The derived pharmacokinetic parameters were statistically analyzed using a crossover analysis of variance mode. The effects due to sequence, subject nested in sequence, period and treatment were extracted.

The bioavailability of DL and 3-OH DL from the CIMA DL REDITABS® formulation given with water compared to Cardinal DL REDITABS® formulation with water as well as the bioequivalence of the CIMA DL REDITABS® administered with and without water were expressed as the ratio of each pair of treatments. The analysis was based on log-transformed AUC and Cmax values. Ninety percent confidence intervals (CIs) for these estimates were calculated. The pooled residual error and associated degrees of freedom from the analyses of variance were used in the calculation of the confidence interval.

Bioequivalence was concluded if the 90% Cl for the ratio of means based on log-transformed data fell within 80% to 125% for AUC and Cmax. Gender effect on bioequivalence was analyzed to assess consistency with the overall study inference.

Preliminary analysis included examining the pharmacokinetic parameters for extreme values by reviewing the studentized ranges of deviations from the expected value derived from the analysis of variance to see if any value exceeds 3. The impact of any outliers on the results of the analyses was evaluated.

Reviewer's remarks

This reviewer used WinNonlin program to calculate 90% confidence intervals for the ratio of the means (Cmax and AUCinf) between treatments (A vs. B); see Table 4).

RESULTS

Analytical Method

In study Validation Results

Table 2. In-study validation information for DL and 3-OH DL

	DL	3-OH DL
Linearity	Satisfactory: Standard curve range from 0.025 to 10.0 ng/mL; $r^2 \geq 0.993$	Satisfactory: Standard curve range from 0.025-10 ng/mL; $r^2 \geq 0.9932$
Accuracy	Satisfactory: -2.1% (% Bias) at 0.075 ng/mL; 2% at 1 ng/mL; 1.1% at 7.5 ng/mL.	Satisfactory: -1.2% (% Bias) at 0.075 ng/mL; 2% at 1 ng/mL; 1.2 at 7.5 ng/mL.
Precision	Satisfactory: (%CV) 7.3 at 0.075 ng/mL; 3.7 at 1 ng/mL; 7.9 at 7.5 ng/mL.	Satisfactory: 6.8 % at 0.075 ng/mL; 3.6% at 1 ng/mL; 9.5% at 7.5 ng/mL.
Specificity	Satisfactory: Chromatograms submitted	Satisfactory: Chromatograms submitted

Pharmacokinetic Results

The mean plasma concentration-time profiles for DL and its metabolite following single administration of CIMA reditabs 5mg and clarinex tablets are shown in Figures 1 and 2, respectively. The mean pharmacokinetic parameters for DL and its metabolite are summarized in Table 3. Individual DL Cmax and AUC(inf) values following the administration of the treatments are shown in Figures 3 and 4, respectively.

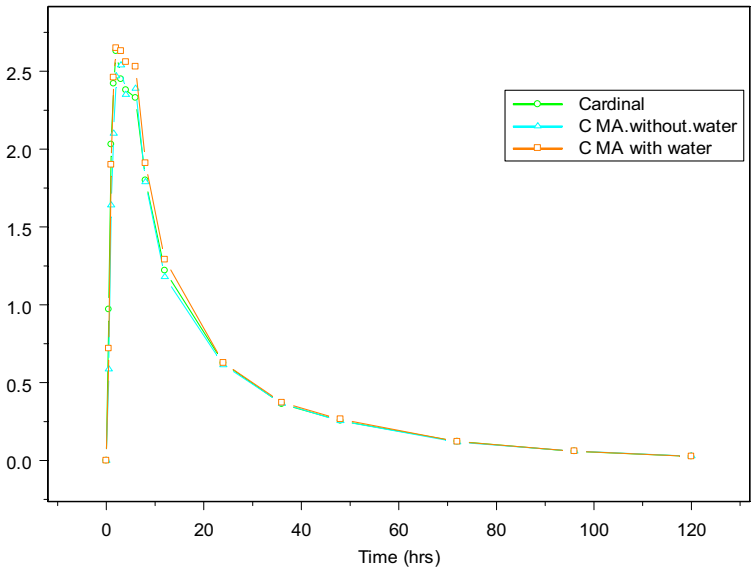


Figure 1. Mean DL plasma concentration-time profiles following single administration of CIMA reditabs 5mg with and without water and clarinex tablets 5mg.

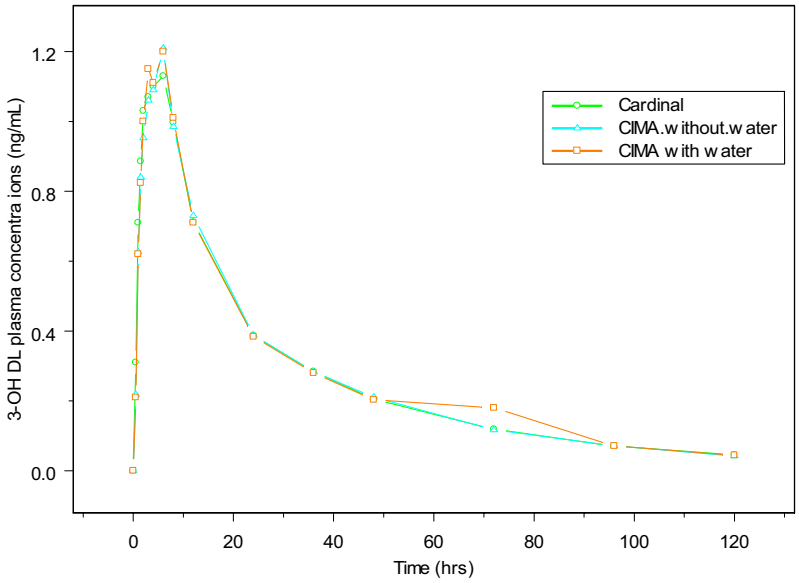


Figure 2. Mean 3-OH DL and plasma concentration-time profiles following single administration of the treatments.

Table 3. Mean (%CV) pharmacokinetic parameters of DL and 3-OH following single administration of the treatments

	Pharmacokinetic Parameters		
Treatment	**Cmax (ng/mL)**	**Tmax**	**AUC inf (ng*hr/mL)**
	Desloratadine (n=22)		
A: Cardinal DL reditabs	2.83 (47)	3 (1.5-6)	52.8 (51)
B: CIMA DL with water	2.92 (39)	2.5 (1.5-6)	54.7 (154)
C: CIMA DL without water	2.90 (38)	3 (1-6)	51.8 (56)
	3-OH Desloratadine		
A: Cardinal DL reditabs	1.22 (28)	6 (2-8)	34.5 (23)
B: CIMA DL with water	1.26 (20)	6 (3-8)	34.9 (23)
C: CIMA DL without water	1.29 (27)	6 (2-6)	34.3 (24)

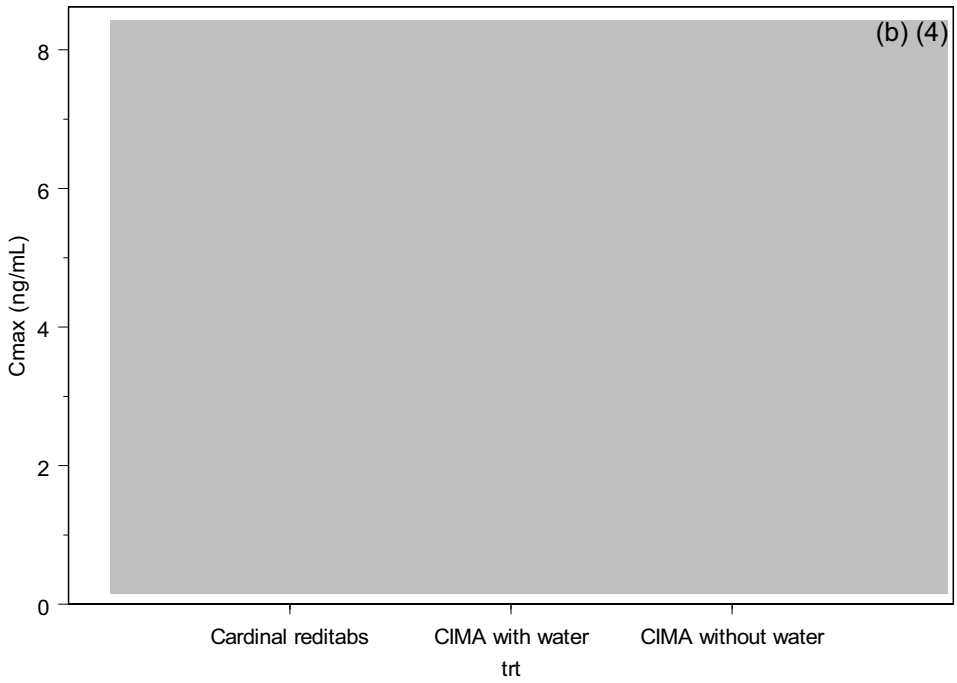


Figure 3. Individual DL Cmax values following single administration of CIMA reditabs 5mg with and without water and cardinal DL clarinex tablets 5mg.

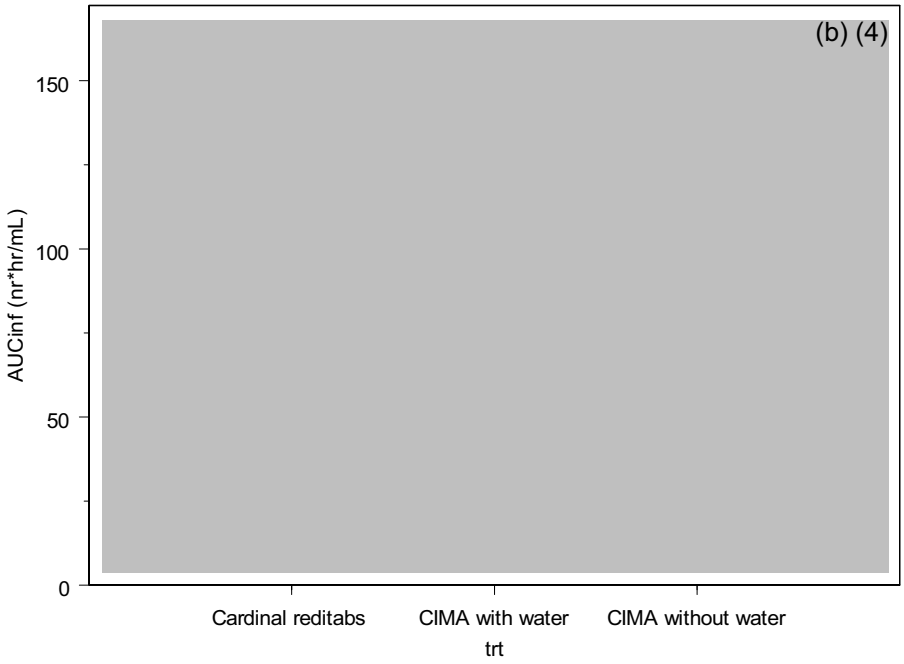


Figure 4. Individual DL AUCinf values following single administration of CIMA reditabs 5mg with and without water and cardinal DL clarinex tablets 5mg.

The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for DL and its metabolite are presented in Table 4. The Cls of Cmax and AUC(I) of DL and 3-OH DL for Treatment B (CIMA Reditab with water) relative to Treatment A (Cardinal tablet) and for Treatment C (CIMA Reditab without water) relative to Treatment B (CIMA with water), met the 80-125 bioequivalence guideline. *This indicates that the CIMA Reditab formulation was bioequivalent to the conventional tablet and that water does not affect the PK of the drug and its metabolite*

Table 4. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of DL and 3-OH DL following single administration of the treatments

Comparison	**PK parameter**	**Point estimates**		**90% confidence intervals**	
		Sponsor's findings	This reviewer' findings	Sponsor's findings	This reviewer' findings
	Desloratadine				
CIMA with water/cardinal with water	AUCinf Cmax	103 106	102.89 105.6	98-109 98-114	97.6-108.4 98-113.8
CIMA without water/CIMA with water	AUCinf Cmax	94 99	106.56 101.1	89-99 92-107	101-112 93.8-108.9
	3-OH DL				
CIMA with water/cardinal with water	AUCinf Cmax	101 105	101.4 105.3	97-105 99-111	97.4-105.6 99.5-111
CIMA without water/CIMA with water	AUCinf Cmax	98 101	99.3 101.1	94-102 95-108	95.4-103.6 95.5-109.2

CONCLUSIONS

- The CIMA DL REDITABS® tablet was bioequivalent to the Cardinal DL REDITABS® tablet.

- The CIMA DL REDITABS® tablet administered with water was bioequivalent to the CIMA DL REDITABS® tablet administered without water.

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/s/

Sandra Suarez
6/20/05 02:01:54 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
6/20/05 02:33:56 PM
BIOPHARMACEUTICS
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-312/S007

OTHER REVIEW(S)

Division of Pulmonary and Allergy Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-312/S-007

Name of Drug: Clarinex® (desloratadine) Reditabs Tablets

Applicant: Schering-Plough

Material Reviewed:

Submission Date(s): July 16, 2007

Receipt Date(s): July 17, 2007

Background and Summary

This submission contains final printed labeling as requested in the approval letter dated July 14, 2005.

Review

I compared the package insert, carton, and container labeling dated July 16, 2007, to the approved labeling dated July 14 2005. The submitted labeling contained the following differences, not outlined in the approved label:

HOW SUPPLIED:

1. CLARINEX Syrup subsection includes the addition of a (b) ounce Amber glass bottle.
2. CLARINEX REDITABS (desloratadine orally-disintegrating tablets) subsection includes the language in *italics:* Packs of 30 tablets (containing 5 x6's) *5 mg … and 2.5 mg*

PRECAUTIONS: Information for Patients:

> Phenylketonurics section reads " CLARINEX RediTabs Tablets contain phenylalanine *2.9* mg per 5 mg CLARINEX RediTabs tablet or *1.4* mg per 2.5 mg CLARINEX RediTabs tablet" instead of the approved …. *2.55* mg per 5 mg CLARINEX RediTabs tablet or *1.28* mg per 2.5 mg …

The changes to the HOW SUPPLIED Section of the label reflect additional product sizes, thus these changes are acceptable.

In a CMC discipline review letter dated May 26, 2005, the Agency requested revised carton labels to include the amount of phenylalanine in each dosage strength. Schering submitted a response dated June 15, 2005, indicating that the amount of phenyalanine for the 2.5 mg and the 5 mg tablet was 1.4 mg and 2.9 mg, respectively. The CMC review dated June 28, 2005, concluded that the above change to the PRECAUTIONS: Information for Patients: Phenylketonurics was acceptable.

Conclusions

The final printed labeling dated July 16, 2007, should be retained. No further action is needed.

Philantha Bowen, MPH, RN
Senior Regulatory Management Officer

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: Bowen/January 20, 2010
Initialed: Barnes/January 29, 2010
Finalized: Bowen/February 1, 2010

CSO LABELING REVIEW

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21312	SUPPL-7	SCHERING CORP	CLARINEX (DESLORATADINE) REDITABS 5MG

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/s/

PHILANTHA M BOWEN
02/01/2010

SANDRA L BARNES
02/04/2010

Division of Pulmonary and Allergy Drug Products
CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 21-312/S-007

Name of Drug: Clarinex RediTabs® (deloratadine orally-disintegrating tablets) Tablets

Sponsor: Schering Corporation

Additional Submissions Dated: March 15, April 14, May 25, and June 15, 2005

Material Reviewed:

CMC Reviews Dated: May 25, June 28 and July 7, 2005
CMC DR Date May 26, 2005
FPL Submitted February 3, 2003 (Current Package Insert)
Biopharmaceutics Review dated June 20, 2005
Pharmacology/Toxicology Review dated June 23, 2005

Background

On April 14, 2005, Schering submitted a Prior Approval Supplement for the reformulation of Clarinex RediTabs, this product was originally approved on June 26, 2002. This Supplement New Drug Application (sNDA) provides for changes to the formulation of the product and the addion of the 2.5 mg product. This includes changes to the method of manufacturing, site of manufacturing, testing methods and specification, preclinical toxicology study results report and pivotal bioequivalence study report. This review incorporates the items noted above, including submissions made by the applicant and the associated FDA reviews. Because there were no changes to the clinical sections of the label and no clinical data or clinical studies were submitted, it was determined that a clinical review would not be necessary.

Discussion

The Pharmacology/Toxicology and Clinical Pharmacology/Biopharmaceutics review recommended approval and did not contain labeling comments. The CMC Discipline Review Letter dated May 26, 2005, contained 2 labeling comments (items 24 and 25) which the Applicant addressed adequately in their amendment dated June 15, 2005, (see CMC Review date June 28, 2005, pages 19 and 20 for details). The Applicant's June 15, 2005, amendment also included an additional modification to the carton label to distinguish between the 2.5 mg and 5 mg products, which was deemed acceptable in the June 28, 2005, CMC review (see page 20).

A line by line comparison with the most recently approved labeling revealed no changes other than those submitted with this sNDA or other pending sNDAs. It should be noted that the label for this sNDA incorporated the changes provided for in the following pending sNDAs:

NDA 21-165/SLR-007 – Phase IV Mouse Carcinogenicity Study Results
NDA 21-300/SLR-004 – Phase IV Mouse Carcinogenicity Study Results
NDA 21-312/SLR-008 – Phase IV Mouse Carcinogenicity Study Results

NDA 21-300/SLR-003 – Modifications to the Observed During Clinical Practice Subsection of the Adverse Reaction Secion
NDA 21-312/SLR-006 – Modifications to the Observed During Clinical Practice Subsection of the Adverse Reaction Secion

NDA 21-312/SCF-007 included wording in the Precautions: Carcinogenesis, Mutagenesis, Impairment of Fertility section of the package insert that was subject of NDA 21-312/SLR-008. The Pharmacology/Toxicology review dated February 16, 2005, recommended approval of this same language, this language is acceptable for RediTabs. . The Medical Officer review dated July 6, 2005, recommended approval of the revisions regarding the Observed During Clinical Practice subsection of the Adverse Reactions. Therefore NDA 21- 312 S-006 and S-008 should acknowledged and retained.

Conclusions

All appropriate changes have been implemented as discussed above, labeling is acceptable. NDA 21-312/S-007 should be approved. Following approval of NDA 21-312/S-007, NDA 21-312/S-006 and S-008 will be acknowledged and retained. NDA 21-165/S-007, NDA 21-300/S003 and S-004 should be approved.

Anthony M. Zeccola
Regulatory Management Officer

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/s/

Anthony Zeccola
7/14/05 09:55:34 AM
CSO

Sandra Barnes
7/14/05 10:15:43 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-312/S007

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 30, 2005

To: Satish Joshi	**From: Anthony Zeccola**
Company: Schering Corporation	Division of Pulmonary and Allergy Drug Products
Fax number: 908-740-5100	**Fax number:** 301-827-1271
Phone number:	**Phone number:** 301-827-1058

Subject: NDA 21-312/S-007

Total no. of pages including cover: 3 (Including electronic signature page)

Comments: As Discussued

Document to be mailed: YES ☑NO

Satish,

As discussed during our telephone conversation on June 28, 2005, here are the Agency's suggested revised acceptance criteria for Clarinex RediTabs:

Revise the acceptance criterion for disintegration time such that the two individual orally-disintegrating tablets (ODTs) that have a disintegration (b) (4) both have a disintegration time not more than (b) (4) An allowance of (b) (4) of the ODTs to have a disintegration time substantially larger than the bulk of the tested units is not acceptable.

Tony

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/s/

Anthony Zeccola
6/30/05 12:35:57 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-312/S-007 **DISCIPLINE REVIEW LETTER**

Schering Corporation
Vice President, Worldwide Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Satish Joshi.

Dear Mr. Joshi:

Please refer to your March 14, 2005 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clarinex (desloratadine) RediTabs 2.5mg and 5 mg.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Revise the acceptance specifications for the Desloratadine (b) (4) to include a specific test for identification of the (b) (4) used in the (b) (4) process.

2. Identify the (b) (4) used (b) (4) of the Desloratadine (b) (4).

3. Provide a specific method to be used for the estimation of the Desloratadine (b) (4) The current procedure (b) (4) does not include specific parameters to be used for testing of the (b) (4)

4. Tighten the acceptance criteria for the (b) (4) that can be present in the Desloratadine (b) (4), to reflect the batch analyses data (b) (4) For example, your current limit of NMT (b) (4) when batch analyses show data ranging from only (b) (4)

5. Tighten your acceptance criterion for the assay of the Desloratadine (b) (4) to reflect the release and stability data, e.g., (b) (4).

6. Tighten your acceptance criterion for the dissolution of the Desloratadine (b) (4), e.g., the average of (b) (4). The acceptance criterion should not be based on low results from the pilot batches that you speculate are due to

sampling or methodological problems as opposed to a stability trend. The confirmation of the low values as a stability trend in dissolution would most likely limit your (b) (4)

7. Tighten your acceptance criterion for the moisture content of the Desloratadine (b) (4) to reflect the release and stability data, e.g., NMT (b) (4)

8. Provide an explanation for the low recovery of desloratadine in the excipient screening studies performed on the Desloratadine (b) (4) when stored for (b) weeks at (b) (4) with (b) (4).

9. Provide a flagged copy of the master batch record that includes the appropriate (b) (4) instructions to prevent occurrences of high assay values at the (b) (4) batch, such as that which occurred for demonstration batch 740451.

10. Provide an explanation for why the (b) (4) high assay result for batch 740451 was only observed for this particular batch and not for the other demonstration batches prepared on the same equipment and with the same process.

11. Provide data obtained from simulated shipping studies that demonstrate the tablets have an acceptable level of friability, considering the relatively low hardness.

12. Specify the environmental conditions that are in place during the manufacturing of the drug product considering the moisture sensitive nature of the (b) (4) formulation. Also specify the maximum allowable hold time (b) (4) in blisters.

13. Provide a description of the seal integrity testing performed on the blister packages and the acceptance criteria that are applied to this in-process test.

14. Revise the acceptance specifications for the Tutti Frutti flavor such that there is more assurance of correct identity. The acceptance specifications for the alternate Tutti Frutti flavoring used for the original formulation were acceptable, i.e., including a flavor and odor comparison to a standard, a determination of the density and refractive index.

15. Revise the drug product release specifications for each strength to include the parameter of hardness. Reference to in-process testing can be included in the specification. The acceptance criteria should be reflective of acceptable batch data.

16. Provide an explanation for why the 2.5 mg strength batch 920016 used in the validation of the disintegration method (b) (4) had an anomalous slow average disintegration time of (b) seconds when compared to all other batches presented in the supplement, where average disintegration times for the remaining 2.5 mg batches and the 5 mg batches ranged from (b) (4) If not intentional, whatever identified factors led to the slow disintegration time for this batch should have adequate controls such that future batches will be more in line with the remainder of the batches.

17. Provide a more detailed description and drawing of the (b) (4) in the method for determination of the disintegration of the drug product so that Agency laboratories will be able to replicate the procedure.

18. Provide the (b) (4) that is used to confirm the absence of *Pseudomonadaceae* and *Enterobacteriaceae* in the drug product.

19. Provide comparative moisture permeation data for the two similar blister packages. Identify which of these types was used for the batches supporting the supplement.

20. DMFs (b) (4) were reviewed and were found to be inadequate to support your supplemental application. The holders have been sent deficiency letters. Once the holders respond completely to the deficiency letters by amendment of their respective DMFs, provide the Agency with the dates of those complete responses. Separate and complete responses specific to each deficiency should be included in the amendments to the DMFs.

21. Tighten the disintegration acceptance criteria for both the 2.5 and 5 mg strength of the product. As indicated at the March 8, 2004, meeting, an orally-disintegrating tablet (ODT) dosage unit should disintegrate within 30 seconds. Revise the acceptance criteria for individual units such that it is not more than this time period. Your drug product batch analyses and stability data are clearly supportive of a tighter limit that coincides with the disintegration standard for an ODT.

22. As (b) (4) is a trending parameter, and the stability consequences of approaching your current proposed limit of NMT (b) (4) are not addressed by the data provided, tighten the acceptance criterion for (b) (4) to reflect the levels reported, e.g., NMT (b) (4)

23. Once drug product specifications and methods are finalized, revise and resubmit four copies of the methods validation package for the (b) (4) and drug product methods.

24. Revise the carton labels for both strengths of the product to indicate the usual dosage as per 21 CFR 201.55, as it is clear that such instructions can be set forth in an informative and realistic manner.

25. Revise the carton labels to include the amount of phenylalanine in each dosage strength as per 21 CFR 201.21(c).

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Anthony Zeccola, Regulatory Management Officer, at 301-827-1058.

Sincerely,

Rik Lostritto, Ph.D.
Chemistry Team Leader for the
Division of Pulmonary and Allergy Drug Products, HFD-570
DNDC DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Craig Bertha
5/26/05 10:21:09 AM
for R. Lostritto