CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-312

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #:NDA	21,312	APPLICATION TYPE:	Supplement
SPONSOR:	Schering	PRODUCT/PROPRIETARY NAME:	Clarinex
		USAN Established Name:	Desloratadine
CATEGORY OF DRUG:	Antihistamine	ROUTE OF ADMINISTRATION:	Oral RediTab
MEDICAL REVIEWER:	Nicklas	REVIEW DATE:	29 January 2002

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
21 December 2001	26 December 2001	Response to approvable letter	see overview below

Overview of Application/Review: The NDA for Clarinex RediTabs was submitted on 20 December 2000. An approvable letter was sent to the sponsor on 19 October 2001. In the present submission, the sponsor is responding to comments provided in the approvable letter of 19 October 2001. Comments 1, 2 and 6 pertain to chemistry issues. Comments 3-5 deal with the issue of slow metabolizers of desloratadine and the recommendation that the sponsor attempt to determine the mechanism responsible for this effect and the potential for drug-drug interaction. The sponsor has modified the Metabolism section of the Clinical Pharmacology section to address this issue and has committed to attempting to determine the mechanism and assess the potential for drug-drug interactions. Comment 7 pertains to the labeling, specifically the Clinical Pharmacology section and the Dosage and Administration section. In the approvable letter of 19 October 2001, the Division provided revised wording for these sections. The sponsor has amended the approved labeling to reflect the Division's recommended wording for these sections. Therefore, in terms of the clinical comments in the approvable letter, the sponsor's response is acceptable.

Outstanding Issues: none

Recommended Regulatory Action: none

N drive location:

NDAs:

Efficacy / Label Supp.: ___x___ Approvable _____ Not Approvable

Signed: Medical Reviewer: _____ Date: _____

Medical Team Leader: _____ Date: _____

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/s/

Richard Nicklas
1/30/02 02:19:06 PM
MEDICAL OFFICER

Badrul Chowdhury
2/1/02 05:10:28 PM
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I concur

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MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #:NDA	21,312	APPLICATION TYPE:	Original NDA
SPONSOR:	Schering Corp	PRODUCT/PROPRIETARY NAME:	Clarinex
		USAN Established Name:	Desloratadine
CATEGORY OF DRUG:	Antihsitamine	ROUTE OF ADMINISTRATION:	Reditabs
MEDICAL REVIEWER:	Nicklas	REVIEW DATE:	10 October 2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
20 December 2000; 6 April 2001	21 December 2000; 9 April 2001	Original NDA; 4 month safety update	see overview below

Overview of Application/Review: The sponsor has submitted 2 clinical studies to support the efficacy and safety of Clarinex Reditabs and a 4 month safety update for all Clarinex products that was submitted to the [redacted]. Study 1216 is a pharmacokinetic study that demonstrated that Clarinex Reditabs are bioequivalent to Clarinex tablets and Clarinex[redacted] Study 1419 is a study that showed that the pharmacokinetic profile of Clarinex Reditabs did not change when given with or without water or after a high fat meal. The safety database consisted of the NDA database for Clarinex tablets (NDA 21,165), an integrated summary of safety for the two studies noted above and a 4 month safety update with data from studies of other Clarinex formulations. Study 1216 demonstrated that Clarinex Reditabs are bioequivalent to Clarinex tablets and hence that Clarinex Reditabs are efficacious, since Clarinex tablets were shown to be efficacious. Clarinex Reditabs has also been shown to be safe, based on the database described above in normal metabolizers and in patients without liver disease. However, since the bioavailability of desloratadine in slow metabolizers may be up to 9 times that seen in normal metabolizers, further study in slow metabolizers is needed, over a sufficient period of time and with careful evaluation of cardiac, hepatic and sedative safety parameters before this drug can be approved.

Outstanding Issues: A study with repetitive dose administration of desloratadine in slow metabolizers should be performed, looking carefully at appropriate safety parameters.

Recommended Regulatory Action: This drug product is approvable.

N drive location:

Signed: Medical Reviewer: _____ Date: _____

Medical Team Leader: _____ Date: _____

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Table of Contents

Clarinex Reditabs
NDA 21,312

I. Executive Summary: The sponsor has submitted two studies in support of this application, one demonstrating the bioequivalence of a 5 mg dose of Claritin RediTabs and 5 mg of the tablet and —— formulations, and one demonstrating that neither food nor water had an effect on the bioavailablility of desloratadine.

A. This NDA for Clarinex Reditabs is approvable from a clinical standpoint. However, further study is needed to define the safety of this drug product in slow metabolizers before this drug product can be approved. No phase 4 studies or risk management steps are recommended.

B. The efficacy of Clarinex tablets at a dose of 5 mg per day has been demonstrated for adults (NDA 21,165). In NDA 21,312, the sponsor has demonstrated that Clarinex Reditabs are bioequivalent to Clarinex tablets (see discussion below and Biopharm review). Therefore, by extrapolation from the pharmacokinetic data linking Clarinex tablets and Clarinex Reditabs, Clarinex Reditabs are efficacious.

C. The safety of Clarinex tablets was demonstrated for adults who are normal metabolizers (NDA 21,165). In this NDA, the sponsor has provided data to support the safety of Clarinex Reditabs in normal metabolizers. The safety of Clarinex Reditabs in normal metabolizers is further demonstrated by the data in the integrated summary of safety and the 4 month safety update provided to this NDA (see review below).

D. A dose of 5 mg of Clarinex Reditabs has been shown to be efficacious and safe (in normal metabolizers) and to be bioequivalent to 5 mg of the Clarinex tablet.

E. Clarinex tablets have been shown to produce a comparable degree of efficacy and safety independent of age, race or gender. The bioavailability of Clarinex tablets has been shown to be increased in patients with liver or renal impairment, necessitating labeling for dose adjustment in these patient populations. Therefore, dose adjustment for Clarinex Reditabs will also be necessary when administering this drug product to patients with hepatic or renal impairment.

II. Background: Desloratadine (Clarinex) is the major metabolite of loratadine (Claritin). It is a tricyclic antihistamine with H-1 receptor antagonist activity. Clarinex Reditabs are proposed for the treatment of allergic rhinitis and chronic urticaria at a dose of 5 mg per day for patients 12 years of age and older. Desloratadine is a relatively non-sedating antihistamine when used at the recommended dose and was developed because it appears to have less extensive first-pass metabolism and a longer plasma elimination half life that loratadine.

There are a wide array of therapeutic interventions for allergic rhinitis, including avoidance measures, pharmacotherapy with antihistamines and intranasal corticosteroids, and allergen immunotherapy. The management modalities for chronic urticaria are more limited, and revolve around pharmacology therapy.

An NDA for the treatment of seasonal allergic rhinitis has been submitted and found approvable for the 5 mg tablet formulation of desloratadine (NDA 21,165), [redacted] An NDA for the 5 mg tablet in the treatment of chronic urticaria was submitted on 30 August 2000 (NDA 21,297). The IND for the Reditab formulation of desloratadine was submitted on 12 October 1999 under IND [redacted] An NDA for the Reditab rapidly disintegrating tablet formulation has now been submitted, as well.

The Reditab formulation dissolves on the tongue within several seconds and is then swallowed. It is proposed for use in patients with seasonal allergic rhinitis and chronic urticaria. Studies required to support this application were discussed with the Division at the pre-NDA meeting on 18 January 2000. At this meeting, it was agreed that approvability should be based on a clinical pharmacology program that would link the 5 mg Reditabs formulation with the Clarinex 5 mg tablet formulation. The desloratadine tablet formulation has been approved by the EU.

Claritin (loratadine), Allegra (fexofenadine) and Zyrtec (cetirizine) have been proposed for OTC status, a proposal supported by the Pulmonary-Allergy Drugs Advisory Committee. Clarinex tablets have been and/or are currently being studied in regard to [redacted]

III. Chemistry: CMC issues were discussed at the pre-NDA meeting of 18 January 2000. In this submission, the sponsor has addressed drug substance specifications, stability data, and degradation products (see Chemistry review). Ingredients, in addition to desloratadine, include gelatin, mannitol, aspartame, polacrilin potasium, dye —— red, tutti-fruitti flavor, citric acid ——— —— (see Chemistry review). The formulation proposed for Clarinex Reditabs differs from the formulation used in the marketed Claritin Reditabs, ———

IV. Pharmacology: There are no major pharmacology issues relating to this drug product (see Pharmacology review).

V. Clinical Pharmacology: The primary objective of the clinical program was to demonstrate the bioavailability of 5 mg of the Reditab formulation compared to 5 mg of the tablet ——— formulations and to determine the effect of food on bioavailability. In this regard, study 1216 was an open, crossover study in adults comparing a single dose of 5 mg of desloratadine when administered as the tablet, ——— and Reditab, in regard to pharmacokinetics and safety parameters. Study 1419 was an open crossover study comparing in adults a single dose of the Reditab formulation given fasting, with water and in the fed state.

A. Study 1216: Albert Cohen MD, investigator; objective: to determine the bioavailability/bioequivalency of the Reditab, tablet ——— formulations.

1. Study Characteristics: pages 9-10, volume 1.14

a. number of patients: 30 (7 Caucasian, 2 African-American, 2 Asian, 19 Hispanic)(18 males, 12 females); 28 patients completed the study; one patient was discontinued because of elevated LFTs after treatment with the Reditab formulation; one patient withdrew consent after the first treatment period.
b. age range: 21-45 years
c. patient population: healthy volunteers
d. study design: open, single dose, three way crossover study
e. drug administration: randomized treatment with 5 mg of desloratadine by tablet, Reditab formulation or ——— after a ten hour fast, administered with 180 cc of water in the morning; the tablet was swallowed whole, the Reditab was placed on the patient's tongue and then swallowed, ———

f. periods of study: There were three study days separated by a 14 day washout period; patients were restricted to the study center for 12 hours prior to drug administration on each treatment day and for 120 hours after drug administration

g. parameters evaluated: serial blood samples to measure plasma levels of desloratadine and 3 OH desloratadine up to 120 hours after drug administration for determination of Cmax, Tmax, AUC and terminal phase half-life; 12 lead ECGs at baseline and 3 hours after drug administration on each treatment day and 120 hours after drug administration on the last study day; laboratory tests at screening, baseline, 3 hours after drug administration, and at the last visit; vital signs at all treatment visits at baseline and 3 hours after drug administration

2. study results: pages 11-15, volume 1.14 of initial NDA submission

a. adverse events: 8 patients reported at least one adverse event; 2 patients reported an adverse event after treatment with the tablet formulation, 6 patients reported an adverse event after treatment with the Reditabs formulation and 2 patients reported an adverse event after treatment with the [redacted] formulation. There were 3 patients who developed headache after administration of the Reditab formulation who did not develop headache after administration of the other two formulations.

b. laboratory values: One patient discontinued the study because of elevated liver function tests 14 days after administration of the Reditab formulation, that was considered severe but unrelated to the study drug. This included elevation of LDH, SGOT and SGPT that returned to normal one week after treatment.

c. Pharmacokinetics: Mean plasma concentration-time profiles for the three formulations of desloratadine were almost superimposable for both desloratadine and 3 OH desloratadine (see tables below). There were four patients (3 Hispanic females and one Asian male) who had an AUC for desloratadine about twice the median but AUC for 3-OH desloratadine in these patients was close to the median. [redacted]

Mean Pharmacokinetic Parameters
Desloratadine (tab 2, p 13, v 1.14)

Treatment	Cmax (ng/mL)	Tmax (hours)	AUC (ng.hr/mL)	half-life (hours)
Tablets 5 mg	2.18	2	40.3	21.6
Reditab 5 mg	1.99	3	39.4	22.0
[redacted] 5 mg	2.05	2	38.9	22.2

Mean Pharmacokinetic Parameters
3 OH desloratadine (tab 2, p 13, v 1.14)

treatment	Cmax (ng/mL)	Tmax (hours)	AUC (ng.hr/mL)	half-life (hours)
Tablets 5 mg	1.08	6	29.5	32.6
Reditabs 5 mg	1.03	6	29.0	32.2
[redacted] 5 mg	1.04	4	28.5	34.0

Bioequivalence and 90% confidence intervals

desloratadine
comparison of 5 mg tablet and Reditab formulations (tab 3. P 14, v 1.14)

parameter	Relative Bioavailability (%)	90% confidence interval
AUC (tf)	97.2	92-102
AUC (l)	97.1	92-102
Cmax	91.5	85-99

desloratadine
comparison of Reditab and [redacted] formulations (tab 3, p 14, v 1.14)

Parameter	Relative Bioavailability (%)	90% confidence interval
AUC (tf)	101.2	96-107
AUC (l)	100.9	96-106
Cmax	96.4	90-104

B. Study 1419: Casey Johnson DO principal investigator; study objective was to determine the pharmacokinetic profile of the Reditab 5 mg formulation when given with and without water and after a high fat meal.

1. Study Characteristics: pages 16,17, volume 1.14 of the initial NDA submission

a. number of patients: 30 (22 Caucasian, 8 African-American)(4 males, 26 females)
b. age range: 22-45 years
c. patient population: normal volunteers
d. study design: randomized, open, single dose, three way crossover study
e. drug administration: 5 mg Reditab formulation administered with and without water and with a high fat meal
f. periods of study: washout period of at least 10 days between three study days
g. parameters evaluated: lab tests at screening, baseline and last visit; adverse events; 12 lead ECGs at screening, baseline on each treatment day and 120 hours after drug administration on the last study day; vital signs at all treatment visits

2. Study Results: pages 18-23, volume 1.14 of the initial NDA submission

a. Water and the fed condition had no clinically significant effect on the mean bioavailability of desloratadine or 3 OH desloratadine from the Reditab tablet formulation (see tables below), although T max was one hour and 30 minutes later in fed than in fasting patients. From 4-12 hours after drug administration, the curves for plasma concentrations in the fasting and fed condition were superimposable. This lag time to peak effect in the fed state and the lower AUC under these conditions are not considered clinically relevant differences that require comment in the labeling. One patient, a 25 year old African-American male who had an AUC for desloratadine that was 6 times the median and a very small AUC for 3-OH desloratadine, was probably a slow metabolizer.

Mean Pharmacokinetic Parameters
Desloratadine (tab 5, p 20, v 1.14)

treatment	Cmax (ng/mL)	Tmax (hours)	AUC (ng.hr/mL)	half-life (hours)
Fasting c H2O	1.84	2.50	41.7	23.8
Fasting s H2O	1.93	2.50	43.0	24.7
Fed	1.60	4	41.1	23.6

Mean Pharmacokinetic Parameters
3 OH desloratadine (tab 5, p 20, v 1.14)

treatment	Cmax (ng/mL)	Tmax (hours)	AUC (ng.hr/mL)	half-life (hours)
Fasting c H2O	0.85	4	25.7	42.1
Fasting s H2O	0.85	4	25.9	39.8
Fed	0.79	6	24.7	34.5

Estimates of Bioequivalence and 90% confidence intervals
Comparison of Reditabs with and without water
Desloratadine (tab 6, p 21, v 1.14)

Parameters	relative bioavailability (%)	confidence interval (%)
AUC (ng/hr/mL)	102	98-106
Cmax (ng/mL)	104	97-110

b. adverse events: Eight patients developed at least one adverse event during the study. No clinically significant adverse events occurred and only headache and sneezing occurred in more than one patient (2). One patient developed a severe headache and another patient had a syncopal episode when arising from bed associated with a fall in blood pressure, considered unrelated to the study drug.

c. laboratory tests: screening, baseline and the last visit; no significant changes were noted.

d. 12 lead ECGs: no clinically significant changes in ECGs were noted.

VII. Clinical: There was no clinical data submitted because the efficacy and safety of desloratadine has been demonstrated in adults using the 5 mg tablet formulation and the pharmacokinetic studies link 5 mg of the Reditab to the 5 mg tablet based on the bioequivalence of these two formulations.

A. Clinical Review Methods: The summarized data submitted by the sponsor in the NDA was reviewed in detail, and supported by individual patient data when necessary. Emphasis in review of the data was placed on the safety of the Reditab formulation. This involved some reevaluation of the data submitted under the NDA for the tablet formulation. No review of the literature was necessary for this NDA.

B. Database: The data submitted under this NDA for the Reditab formulation, in conjunction with previous data submitted under NDA 21,165 for the tablet formulation, and the 4 month safety update submitted to the [redacted] served as the database.

C. Data Quality and Integrity: There was no reason, based on a review of the data submitted, to doubt the quality or integrity of the database for this formulation of Clarinex. Therefore, no DSI audit was requested for the studies in this submission.

D. Ethical Standards: There were no ethical issues associated with this NDA.

E. Financial Disclosure: Neither Albert Cohen MD nor Casey Johnson DO, the 2 investigators who performed studies under this NDA had any financial disclosure and no apparent conflict of interest.

F. Integrated Review of Efficacy: none submitted.

G. Integrated Summary of Safety (ISS):

1. Based on the ISS and the 4 month safety update for this drug product, Clarinex Reditabs is safe for administration to patients 12 years of age and older who are normal metabolizers at a dose of 5 mg per day.
2. The ISS is based on the two studies reviewed above, i.e. studies 1216 and 1419 involving 60 healthy volunteers between the ages of 16-45 years, of whom 16 were females and 44 were males. Both studies were open single dose pharamacokinetic studies but because of differences in the design of the two studies, the safety data from these studies was not pooled. In both studies, safety was evaluated by adverse events, ECGs, vital signs and laboratory tests. There were 29 Caucasian, 10 African-American, 2 Asian and 19 Hispanic patients. One patient in study 1216 discontinued because of elevated LFTs 14 days after receiving the study drug and one patient discontinued for personal reasons. All 30 patients in study 1419 completed the study. There were 59 patients who received Claritin Reditabs. In addition, data from 5117 patients are submitted in the 4 month safety update based on use of other formulations. This is an

adequate database upon which to make a determination of the safety of Clarinex Reditabs in normal metabolizers.

A treatment-emergent adverse event was defined as an adverse event that began on or after the initiation of treatment and up to 30 days after the last treatment, or that began prior to starting treatment but worsened after starting treatment. All adverse events were mild-moderate in intensity except for one patient who developed elevation of LFTs 14 days after receiving treatment that resolved in one week and one patient who developed a severe headache. Only one patient who developed headache was considered to have an adverse event possibly related to treatment. One patient in study 1419 had "fainted when rising from bed without loss of consciousness" 24 hours after receiving the Reditab formulation. He had a blood pressure of 63/45 mm Hg and pulse of 72 bpm, which were found to be 106/65 mm Hg and 74 bpm 4 minutes after the episode and were not considered treatment-related. In study 1216, 21% of patients reported an adverse event after administration of the Reditab formulation compared with 7% after administration of the other formulations. In study 1419, 9% of the patients had an adverse event. There was only one adverse event reported by more than one patient in study 1216, headache which was reported by 3 patients after receiving the Reditab formulation and no patients after receiving the other two formulations. It was this difference in the incidence of headache that produced the difference in overall adverse events between the three treatments. There were no cardiovascular adverse events reported, except possibly for the patient who developed syncope as described above.

The patient who developed elevated LFTs 14 days after administration of the Reditab formulation was a 42 year old Caucasian male whose SGOT rose from 23 U/L at baseline to 472 U/L, SGPT rose from 20 U/L at baseline to 124 U/L and LDH rose from 383 U/L at baseline to 2707 U/L after treatment. His GGT and Alkaline Phosphatase remained normal and his SGOT was 45 U/L, SGPT was 77 U/L and LDH was 361 U/L one week later.

No clinically significant changes in laboratory values (with the exception of the patient described above) or vital signs was seen.

ECGs were done at screening, baseline, 3 hours after drug administration in each treatment period and 120 hours after the last treatment in study 1216. In study 1419, ECGs were done at screening, baseline and 120 hours after the last treatment period. QTc intervals were not considered prolonged if they were 450 msec or less for males and 470 msec or less for females. No significant changes in ECGs were noted.

Four month safety update submitted 6 April 2001:

1. Data on an additional 5117 patients, including 3938 who received 5 mg of Clarinex are reported in this update. The data was pooled from 19 multiple dose controlled clinical studies of 2-6 weeks duration in adult and adolescent patients who received 2.5, 5, 7.5, 10 or 20 mg of desloratadine. Data was also provided from [redacted] dies of 2 weeks duration.

2. In the multiple dose studies in adults, ECGs were done at screening and at the end of treatment. In general, vital signs were evaluated at each study visit. All multiple dose studies were randomized, double-blind and active or placebo-controlled studies. The [redacted] studies were randomized, double-blind, placebo-controlled, parallel studies of 2 weeks duration. All treatment groups had more females (approximately 60%) than males. 80% of patients were Caucasian and 86% were 18-65 years of age. Approximately 12% were 12-17 years of age and approximately 2% were > 65 years of age. In contrast, 50-76% of patients in the [redacted] studies were African-American.

a. Adverse events:

number of patients with adverse events in multiple dose studies

Types of AEs	all doses DCL (n=5117)	5 mg DCL (n=3938)	placebo (n=3519)
TE AEs	2060 (40%)	1527 (39%)	1258 (36%)
Related TE AEs	780 (15%)	574 (15%)	398 (11%)
Severe TE AEs	351 (7%)	237 (6%)	205 (6%)
Severe/related AEs	114 (2%)	69 (2%)	59 (2%)
Serious AEs *	10 (0.2%)	10 (0.3%)	5 (0.1%)

- On review, none appeared to be related to treatment

As seen in the table above, the number of adverse events after administration of 5 mg of desloratadine were representative of the number seen after administration of desloratadine as a whole and not significantly different from placebo. The number of adverse events was not dose-related. The most common was headache across all studies and all treatment groups, including 12% of patients who received 5 mg of desloratadine and 13% of patients who received placebo. Other frequently reported adverse events were fatigue, pain, somnolence, dysmenorrhea, and menstrual disorder. Somnolence occurred in 3% of patients receiving 5 mg of desloratadine compared with 2% in those receiving placebo. There were no other specific adverse events that occurred significantly more frequently among patients who received 5 mg of desloratadine than in patients who received placebo. In contrast, somnolence was noted in 13% of the 337 patients who received cetirizine as an active treatment control in studies with desloratadine.

There was no significant difference in the incidence or types of adverse events reported in the age groups of 12-17, 18-65, and > 65 years. Based on a database of 85 patients > 65 years of age, who received 5 mg of desloratadine and 76 patients who received placebo, the table below contains those adverse events that were more frequent in the desloratadine group in this patient population, to a degree that could be considered clinically significant.

Adverse event	5 mg desloratadine	placebo
Dry mouth	4.7%	1.3%
Fatigue	2.4%	None
Arthralgia	2.4%	None
Myalgia	3.5%	None
Insomnia	4.7%	1.3%
Nervousness	3.5%	1.3%
Viral infection	4.7%	1.3%
Asthma aggravated	2.4%	None
Dry eyes	2.4%	None

Comparison of adverse events between patients who received 5 mg desloratadine and patients who received placebo showed no significant differences based on race. The frequency and type of adverse event were similar when compared based on race. Based on a database of 91 Asian patients who received 5 mg of desloratadine and 77 Asian patients who received placebo, 4.4% who received desloratadine developed somnolence compared to none of the placebo group.

The overall incidence of treatment-emergent adverse events was greater in females (45%) compared to males (33%), partly due to an increased incidence of headache in females in both active treatment and placebo groups. In the group that received 5 mg desloratadine, 32% of males and 43% of females had adverse events compared to 29% of males and 40% of females in the placebo group. The percentage of slow metabolizer patients who developed adverse events was 21%, compared to 31% or patients who were normal metabolizers, and 54% in the placebo group.

There were 1-3% of patients who were discontinued after receiving various doses of desloratadine compared to 3% of patients who received placebo.

b. Laboratory Tests:

Changes in hematologic parameters seen in the group that received 5 mg of desloratadine were not substantially different than those seen in the group that received placebo (for example, the percentage of patients who had a decrease in platelets) and were generally in the range seen with other doses of desloratadine. The same pattern was seen for blood chemistries. All studies considered a clinically significant change in lab values to be blood chemistry values 2.6 times or greater the upper limit of the normal reference range, a hemoglobin concentration 9.4 g/dL or less, a platelet count 74,000/uL or less, or a WBC of 2900 or less. There were 2% of patients who received desloratadine and 2% of patients who received placebo who fit these criteria.

c. Vital signs:

There was no significant change from baseline or difference from placebo in regard to mean diastolic blood pressure, systolic blood pressure or heart rate. The percentage of patients who had a change from baseline of 10% or more in systolic blood pressure, diastolic blood pressure and heart rate was not significantly different in the 5 mg of desloratadine and placebo groups.

d. ECGs and assessment of cardiac effect:

The cardiac safety of desloratadine was established in NDA 21,165 including the multiple dose, high dose (9 times the proposed clinical dose) study 357, as well as drug interaction studies with ketoconazole and erythromycin.

Comparison of normal and slow metabolizers of desloratadine showed that the incidence of adverse cardiac events and ECG parameters were similar in both groups of patients, except that the maximum mean change in ventricular rate from baseline in multiple dose pharmacology studies was 14.63 bpm in slow metabolizers, compared to 5.44 bpm in normal metabolizers and 10.22 bpm in the patients who received placebo. QTc prolongation was 7.3 msec slow metabolizers, compared to 1,9 msec in normal metabolizers and 6.5 msec in the placebo group. The 2 patients in these studies who had prolongation of the QTc interval of 61 msec or greater had received placebo. One patient in the slow metabolizer group had an increase in the QTc interval of 34 msec (Fredericia) at endpoint.

A phenotypic polymorphsim in the metabolism of desloratadine has been described, with approximately 7% of 1087 adult patients (15% of pediatric patients) in clinical pharmacology studies being slow metabolizers of desloratadine. It has been shown that 72% of slow metabolizers are African-American. The PK profile of desloratadine in terms of slow or normal metabolizers has been found to be the same whether desloratadine was generated after administration of loratadine or given as desloratadine. Slow metabolizers of desloratadine do not appear to be at increased risk from adverse events or ECG changes based on evaluation of 957 adult and adolescent patients and 130 patients [redacted] years of age.

From a database of 5232 patients in multiple dose studies, two patients had serious AEs related to the cardiovascular system; a 25 year old female who received 5 mg of desloratadine and developed severe chest pain that resolved after treatment with albuterol and epinephrine; and a 69 year old male who developed congestive heart failure due to cardiomyopathy after receiving desloratadine [redacted] There were no reports of syncope in patients who received desloratadine. The incidence of treatment-emergent cardiovascular adverse events was the same in patients who received 5 mg of desloratadine and patients who received placebo (0.4). In one study (study 1430), where desloratadine and cimetidine were given concomitantly, 4 out of 19 patients (21%) had palpitations. In the same study, 2 patients had chest pain and 2 patients had dizziness. In another study (study 1868) where desloratadine and cimetidine were given concomtiantly these types of adverse events did not occur.

There were 262 patients who were discontinued from the multiple dose studies because of adverse events. Of these, 13 discontinued because of a cardiovascular adverse event; 5 patients discontinued because of chest pain, 4 after receiving 5 mg of desloratadine. Patient 464 in study 215, a 25 year old hispanic woman who had a history of anxiety attacks, developed severe chest pain after 8 days of treatment with desloratadine 5 mg which was not felt to be related to the study drug or to be cardiac in etiology. Patient 557 in study 216, a 46 year old hispanic woman developed moderate chest pain on the first day of treatment with 5 mg of desloratadine without ECG change, although this event was considered possibly related to the study drug. Patient

425 in study ~~355~~, a 34 year old African-American woman and patient 112 in study 362, ~~a~~ 20 year old Caucasian woman, developed transient moderately severe chest tightness on day 2 and 15 respectively without change in ECG or vital signs after receiving 5 mg of desloratadine.

Out of a database of 10,487 patients who had had ECGs done at baseline and at the end of treatment, 5 patients (0.1%) that received 5 mg of desloratadine had clinically significantly abnormal ECGs, compared to 0.2% of patients who received placebo. In 3 of these patients, ECG abnormalities were noted only after treatment. Patient 52 in study 001 was a 41 year old African-American female who had a QTc interval of 431 msec at baseline and 465 msec at the conclusion of treatment, using Bazett's correction. This represented a 7% increase in the QTc interval, She had an increase in heart rate from 57 bpm at baseline to 63 bpm after treatment, without experiencing any cardiovascular adverse event. Patient 361 in study 220 was a 68 year old Asian male who had an ECG at baseline that was read as low voltage in the limb leads, and an ECG at endpoint read as a probable inferior wall MI. A follow-up ECG was read as only first degree AV block. He had no cardiovascular adverse event. Patient 451 in study 215, a 51 year old African-American female had a QTc interval of 394 msec at baseline and a QTc interval of 520 msec at endpoint without apparent adverse cardiovascular effect.

The mean change in ventricular rate, QT interval, and QTc interval using both Bazett's and Fredericia's correction was not significantly different in patients who received 5 mg of desloratadine and patients who received placebo. Nor was the percentage of patients who had a 10% or greater change in any ECG parameter significantly different in the groups that received 5 mg of desloratadine and placebo.

d. Hepatic effect:

There were 28 patients (0.3% of the database for the desloratadine tablet formulation) who had adverse events characterized as liver and biliary disorder, 14 of whom received 5 mg of desloratadine, compared to 10 in the placebo group. There were no such adverse events noted in ——— patients. There was not a significant difference between the percentage of patients who had normal alkaline phosphatase, SGPT, SGOT, or total

bilirubin at baseline and a high value after receiving 5 mg of desloratadine and after receiving placebo. There were 16 patients in the 5 mg desloratadine group and 15 patients in the placebo group who had an elevation in LFT that was 2.6 or greater times the upper limit of the normal reference range. There were 14 patients who received 5 mg of desloratadine who had normal baseline values for LFTs but an increase in at least one LFT following treatment. This is in contrast to 5 such patients in the placebo group. Only one patient in the 7.5 mg group, one patient in the 10 mg group, and no patients in the 20 mg group had such changes, but substantially smaller numbers of patients received these doses of desloratadine. A comparison of the increased LFTs in the 5 mg desloratadine and the placebo groups can be seen in the table below. There were no clinical manifestations reported in the patients whose LFTs were elevated.

	5 mg desloratadine				placebo			
Pt # (study)	LFT	baseline	endpoint	Pt number	LFT	baseline	endpoint	normal
178 (225)	SGOT	17 U/L	227 U/L	556 (217)	SGOT	22 U/L	199 U/L	0-41 U/L
118 (219)	SGOT	15 U/L	132 U/L	115 (215)	SGOT	40 U/L	150 U/L	0-41 U/L
37 (219)	SGPT/OT	34/25 U/L	298/117 U/L					
91 (218)	SGPT/AP	37/93 U/L	131/408 U/L					AP 30-115 U/L
192 (214)	SGPT	27 U/L	239 U/L					
258 (216)	SGOT	25 U/L	186 U/L					
781 (362)	SGOT	41 U/L	132 U/L					
747 (362)	SGPT/OT	39/30 U/L	269/135 U/L	128 (214)	SGOT/PT	17/17 U/L	192/348 U/L	
243 (362)	SGOT	22 U/L	123 U/L					
329 (384)	SGOT	25 U/L	119 U/L					
113 (223)	SGPT	25 U/L	138 U/L	423 (223)	SGPT	54 U/L	123 U/L	0-45 U/L
143 (223)	SGPT	31 U/L	125 U/L	189 (224)	SGPT	32 U/L	137 U/L	0-45 U/L
50 (223)	SGPT/OT	73/38 U/L	179/111 U/L					
370 (1434)	SGOT	34 U/L	117 U/L					

COMMENT: There were a significantly greater number of patients who received 5 mg of desloratadine than patients who received placebo who had normal LFTs at baseline but elevated LFTs after treatment. However, the number of patients who had elevated LFTs after administration of 5 mg of desloratadine was a very small percentage of the total number of patients who received this dose of the study drug and more patients received the 5 mg dose

of desloratadine (n=3938) than received placebo (n=3519). Therefore, no clear effect of desloratadine on the liver is supported by this database. Single dose (study 354) and multiple dose (study 272) studies evaluated desloratadine in patients with chronic liver disease (see NDA 21,165) and supported labeling to indicate that patients with hepatic disease may require a smaller dose than patients without hepatic disease.

e. Renal Effect:

Less than 1% of patients who received 5 mg of desloratadine (n=3938) and less than 1% of patients who received placebo (n=3519) had a normal BUN and/or creatinine at baseline that was subsequently elevated above normal after treatment. Treatment-emergent adverse events classified as renal and urinary system disorders occurred in < 0.2% of patients in any treatment group. A single dose PK study (study 355) was performed and reported in NDA 21,165 that showed that there was substantially more systemic availability of desloratadine (up to 2.5 times based on AUC) in patients with some degree of renal impairment, supporting labeling to indicate that lower doses of desloratadine may be required in patients with renal impairment.

f. Drug Interaction:

Studies were done with concomitant administration of desloratadine and fluoxetine (CYP2D6 inhibitor), azithromycin, and cimetidine (CYP3A4 and CYP2D6 inhibitor). The frequency and type of adverse events encountered in these studies was not significantly different than the profile of adverse events noted after administration of desloratadine alone.

XI. Dosing, Regimen and Administration issues: none

XII. Use in special populations:

[redacted] will be evaluated in the future after [redacted]

[redacted] The sponsor is requesting a deferral of [redacted] in patients 2-12 years of age, since studies with this formulation are being conducted in response to a Written Request. The sponsor is also requesting a waiver for study

of patients [redacted] and therefore this formulation would provide no meaningful benefit over existing treatment. These requests by the sponsor are reasonable.

In the two studies submitted with this NDA there was no apparent differences in response based on age, gender or race.

XIII. Conclusions and Recommendations: The sponsor has demonstrated the bioequivalence of the 5 mg tablet of Clarinex and the 5 mg Reditab of Clarinex. The Clarinex tablet has been found to be safe in normal metabolizers and efficacious. Therefore, Clarinex Reditabs are safe in normal metabolizers and effective. This drug product can not be approved, however, until such time as the sponsor has performed repetitive dose studies of sufficient length in either slow metabolizers or in normal metabolizers at a dose at least 9 times the recommended dose. Such studies are needed to support the safe administration of this drug product. In addition, some labeling changes are needed, in particular to insure that the labeling is consistent with the labeling for Clarinex tablets and a statement in the Information for Patients subsection regarding aspartame.

XIV. Labeling:

A. Description section: Acceptable as written, pending review by Chemistry.

B. Clinical Pharmacology section: Mechanism of Action section: needs review by Pharmacology; Pharmacokinetics section: Acceptable as written.

C. Dosage and Administration section: A statement about Clarinex Reditabs, i.e. should be added to this section of the labeling. At the present time, it only indicates the

D. The remainder of the labeling should be consistent with the final labeling for Clarinex tablets, in particular the possible need for lower doses in patients with renal or hepatic impairment.

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

/s/

Richard Nicklas
10/10/01 11:49:56 AM
MEDICAL OFFICER

Badrul Chowdhury
10/10/01 12:11:31 PM
MEDICAL OFFICER
I concur. Also see my team leader memorandum dated October 10, 2001.

APPEARS THIS WAY
ON ORIGINAL

MEDICAL TEAM LEADER MEMORANDUM

DATE: October 10, 2001

TO: NDA 21-312

FROM: Badrul A. Chowdhury, MD, PhD
Clinical Team Leader, Division of Pulmonary and Allergy Drug Products

SUBJECT: Secondary medical review of Claninex™ (desloratadine) Reditabs 5mg

CC: HFD-570: Meyer, Nicklas, Hilfiker

Administrative

NDA 21-312 for Clarinex (desloratadine) Reditabs 5mg was submitted by Schering Corporation on December 20, 2001. The PDUFA action due date on this application is October 20, 2001. Desloratadine (DL) is currently the subject of [redacted] NDAs. NDA 21-165 for use of Clarinex Tablet 5mg in seasonal allergic rhinitis in patients 12 years of age and older, NDA 21-297 for use of Clarinex Tablet 5mg in chronic idiopathic urticaria in patients 12 years of age and older, [redacted] and NDA 21-363 for use of Clarinex Tablet 5mg in perennial allergic rhinitis. Through this application Schering is seeking approval of the Clarinex Reditabs 5mg for seasonal allergic rhinitis and chronic idiopathic urticaria in patients 12 years of age and older.

Schering has submitted results from two clinical pharmacology studies to support the new formulation. The clinical pharmacology studies are: (a) Study 1216, a single dose comparative PK study of three different formulations of desloratadine, (b) Study 1419, a food and water effect study. The studies were done in healthy adult volunteers.

Chemistry and Manufacturing

Clarinex Reditabs 5mg contains 5 mg/tablet desloratadine, and the following inactive ingredients: Gelatin Type B NF [redacted] Mannitol USP [redacted] Aspartame NF [redacted] Polarcrilin Potassium USP [redacted] Dye [redacted] Red [redacted], Flavor Tutti-Frutti [redacted] Citric Acid USP [redacted] The total weight of one tablet is 46.3165mg. Manufacturing, in-process controls, and primary packaging operations (blister packing) will be done at [redacted], and secondary packaging operations and associated controls will be done either at Kenilworth, NJ, or at Miami Lakes, FL (Section 3.D.2, page 31-33). Schering Corporation has not yet resolved the manufacturing problem that is holding up the

marketing of the entire Clarinex line of products, and will also have an impact on the ultimate approvability of this application. Since the drug product contains aspartame, which has implications in patients with Phenylketonuria, the Information for Patients subsection of the label should state the amount of aspartame present per unit dosage.

Pharmacolgoy and Toxicology

The applicant has referenced all preclinical pharmacology and toxicology data to NDA 21-165 for Clarinex Tablet 5mg (Section 3.E, page 58). There are no outstanding preclinical issues.

Clinical Program:

This was primarily a clinical pharmacology program. As mentioned above, the clinical program of Clarinex Reditabs 5mg consists of two clinical pharmacology studies (Table 1). The studies are briefly reviewed in the subsequent sections. Detail reviews of the studies can be found in the primary reviews of Dr. Suarez and Dr. Nicklas.

Table 1. Overview of the clinical studies

Study No.	Type of study	Diagnosis, age of subjects	Clarinex dose mg	Length of treatment	Number All (M,F) (C,B,H,A)*
1216	Clin. pharmacology	Healthy, 21-45 yrs	5 mg	Single dose	30 (18,12) (7,2,19,2)
213	Food effect	Healthy, 22-45 yrs	5 mg	Single dose	30 (26,4) (22,8)
* M=male, F=Female, C=Caucasian, B=Black, H=Hispanic, A=Asian [Source: Item 3.F, page 70)					

Study 1216: Single dose comparative PK study of three different formulations

This was a single-arm, single-dose, single-center, open-label, three-way random sequence crossover study. The primary objective of the study was to determine the bioequivalence of desloratadine (DL) conventional tablet formulation and DL Reditab, and of DL [redacted] formulation and DL Reditab in health adult subjects. The study was conducted by Albert Choen, MD, in a single center in Miami, Florida between December 1999 and January 2000.

A total of 30 subjects, 12 males, and 18 females (mean age 37 years) were enrolled in the study, and 28 completed the study. Subjects were screened within 3 weeks of dosing. Screening included history, physical examination, ECG, and clinical laboratory tests that included blood chemistry, hematology, and urinalysis. Eligible subjects were confined to the study center at least 12 hours prior to dosing (day –1). Upon confinement vital signs, safety laboratory tests, and ECG were repeated. In the morning of day 1, following overnight fast of approximately 10 hours, at approximately 8 AM each subject received a single dose of the study medication. The study medications in the three periods were one 5mg DL tablet, one 5mg DL Reditab, and [redacted] (5mg) [redacted] of DL [redacted] The tablet and Reditab was swallowed whole with 6oz water. The [redacted] was followed by 10ml water to rinse the mouth. The subjects remained awake and ambulatory and continued fasting for the next 4 hours. Drinking water was permitted throughout the fasting period, except for 2 hours postdose. They were confined in the study site for 120 hours for study related procedures.

Each treatment period was separated by at least 14 days washout. The subjects were continually observed and questioned throughout the study period for possible adverse events. They were instructed to report any unusual experiences or discomfort. Safety laboratory tests and ECG were taken 3 hours postdose on day 1. Vital signs were monitored daily during each treatment period. For the pharmacokinetic profile, 5mL of blood were collected just prior to drug administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours after dosing in each period. At completion of the study (after period 3, 120 hour postdose blood collection), the physical examination, safety laboratory tests, and ECGs were repeated.

Mean pharmacokinetic parameters of DL and 3-OH DL after administration of DL 5mg is shown in Table 2. The mean plasma concentration time profiles for DL and 3-OH DL of the three formulations of DL almost superimposable (item 6, study 1216, section 11.4.1, pages 31 and 32 of the submission). The applicant concludes that the Reditab formulation was bioequivalent to both the tablet and ——formulations. The applicant's conclusion is supported by the submitted data.

The drug was well tolerated in this study. No serious or unexpected adverse events were reported. The incidence of adverse events was generally similar among the three treatment groups. Two subjects discontinued participation in the study. Subject no. 14 withdrew consent after period 1, and subject no. 26 discontinued 14 days after dosing with DL Reditab in period 1 due to approximately 4-fold elevation of LDH, AST, and ALT. The liver enzymes returned to normal within one week. The investigator considered these to be unrelated to treatment.

Table 2. Mean pharmacokinetic parameters following single dose of DL 5mg

Parameters	DL			3-OH DL		
	C max (ng/mL)	Tmax (hr)	AUC_{0-t} (ng.hr/mL)	C max (ng/mL)	Tmax (hr)	AUC_{0-t} (ng.hr/mL)
DL 5mg Tablet	2.18	2.00	38.9	1.08	6.00	27.4
DL 5mg Reditab	1.99	3.00	38.0	1.03	6.00	27.0
DL 5 mg ——	2.05	2.00	37.5	1.04	4.00	26.4
Source: Item 6, Study 1216, Section 11.4.1, page 29						

Study 1419: Food and water effect study in healthy adult subjects

This was a single-dose, single-center, open-label, three-way random sequence crossover study. The primary objective of the study was to determine the effect of water and a high-caloric breakfast on the bioavailability of DL 5mg Reditab. The study was conducted by Casey Johnson, DO, in a single center in Laxena, Kansas between February and May 2000.

A total of 30 healthy subjects, 26 males, and 4 females, 22-45 years of age (mean age 32 years) were enrolled and completed the study. Subjects were screened by history, physical examination, ECG, urine drug screen, and clinical laboratory tests that included blood chemistry, hematology, and urinalysis. Eligible subjects were confined to the study center at least 12 hours prior to dosing (day –1). Upon confinement safety laboratory tests and ECG

were repeated. In the morning of day 1, following overnight fast of approximately 10 hours, at approximately 8 AM each subject received a single dose of the study medication. The study medications in the three periods were one 5mg DL Reditab tablet with 6oz of water in fasting state, one 5mg DL Reditab tablet without water in fasting state, and one 5mg Reditab tablet administered within 5 minutes of a standardized high-fat and high-caloric breakfast. The subjects continued fasting for the next 4 hours, at which time lunch was provided. They were confined in the study site for 120 hours for study related procedures. Each treatment period was separated by at least 10 days washout. The subjects were instructed to report any unusual experience or discomfort and questioned for possible adverse events. Vital signs, ECGs, and blood samples were collected at prespecified times for safety and pharmacokinetic evaluations. For the pharmacokinetic profile, approximately 7mL of blood were collected just prior to drug administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours after dosing in each period.

Mean pharmacokinetic parameters of DL and 3-OH DL after administration of DL 5mg is shown in Table 3. The mean pharmacokinetic profile under fasted (with or without water) or fed conditions were similar. The mean plasma concentration time profiles for DL and 3-OH DL of the fasted with water and fasted without water groups were almost superimposable, however, the fed group had a statistically not significant lag time to the peak concentration (item 6, study 1419, section 11.4.1, pages 30 and 31 of the submission).

Two subjects (subject no. 15, a 45-year old Caucasian male; and subject no. 23, a 25-year old black male) appeared to be slow metabolizers of DL evidenced by higher than average plasma concentration of DL and lower than average plasma concentration of 3-OH DL. The AUC of DL in subject no. 15 was approximately 2 fold higher and that subject no. 23 was approximately 4 fold higher than the median value of the group. Safety of DL in slow metabolizers is discussed under a separate heading below.

The drug was well tolerated in this study. No serious or unexpected adverse events were reported. No subjects discontinued participation in the study.

Table 3. Mean pharmacokinetic parameters following single dose of DL 5mg Reditab

Parameters	DL			3-OH DL		
	C max (ng/mL)	Tmax (hr)	AUC_{0-t} (ng.hr/mL)	C max (ng/mL)	Tmax (hr)	AUC_{0-t} (ng.hr/mL)
Fasting with water	1.84	2.50	41.7	0.85	4.00	25.7
Fasting without water	1.93	2.50	43.0	0.85	4.00	25.0
Fed	1.60	4.00	41.1	0.79	6.00	24.7
Source: Item 6, study 1419, Section 11.4.1, page 32						

Efficacy assessment

The applicant has submitted no data to directly establish efficacy of Clarinex Reditabs 5mg. Clinical pharmacology studies, as reviewed above, linked the bioavailability of the Reditab to the tablet and —— formulations. The efficacy of Clarniex Tablets 5mg in adults and adolescents down to 12 years has already been demonstrated in NDA 21-165. In this NDA

the applicant has linked the two formulations adequately and therefore the efficacy of Clarinex Reditabs 5mg can be extrapolated for the same age group. The applicant has also demonstrated that the Clarinex Reditabs 5mg can be taken with or without water.

Safety assessment

The applicant has submitted no new clinical safety data. Safety of Clarinex Tablets 5mg has already been established in NDA 21-165, and the applicant refers to that safety database. Review of the clinical pharmacology studies submitted in this NDA do not show any new safety signals.

The applicant has submitted a four-month safety update on April 6, 2001, to [redacted], and has cross-referenced that safety update to this NDA. The submission includes safety data on additional 2154 adult and adolescent patients in phase-III clinical trials. Review of the safety database does not raise any new concerns. Detail review of the updated safety database can be found in Dr. Nicklas's primary medical review.

Safety of desloratadine is slow metabolizers

During the review of [redacted]

[redacted]

The applicant has addressed the safety of DL in slow metabolizers in the four-month safety update dated April 6, 2001, submitted to [redacted] and has cross-referenced that submission to this NDA. The applicant has summarized data from 38 pharmacology studies and 1 clinical study. The safety of DL in slow metabolziers, in both adults and [redacted] is discussed below.

Clinical Pharmacology Studies

The DL clinical pharmacology studies are listed in Table 4. There were 1087 subjects enrolled in the studies. Most of the studies were single dose. In all studies, excepting two, the proposed therapeutic dose, or a 2-fold higher dose was used. In study C98-357, 45 mg (9-fold of the proposed dose) was given to 24 subjects. In study C98-013, 20 mg (4-fold of the proposed dose) was given to about 10 subjects.

Table 4. Desloratadine (DL) clinical pharmacology studies, as of December 1, 2000

Study	Study description	Study design, DL dosage	Age(yr)	No.(M,F)
DL Tablet				
C98-097	AME	Open-label, single-dose, 10 mg	31-40	6, 0
C98-215	Food effect	Open-label, single-dose, crossover, 7.5 mg	18-43	11, 7
197-24B	Rising single-dose	Parallel-group, single-dose, 0, 2.5, 5, 10, 20 mg	18-45	48, 0

Study	Study description	Study design, DL dosage	Age(yr)	No.(M,F)
C98-013	Rising multiple-dose	Parallel-group, multi-dose, 0, 5, 7.5, 10, 20 mg	24-45	49, 0
C98-214	Dose-proportionality	Open-label, single-dose, crossover, 5, 7.5, 10, 20mg	19-45	20, 0
C98-352	ECG w wo keteconaz	Multi-dose, crossover, 7.5 mg w and wo keto	19-50	12, 12
C98-353	ECG w wo erythro	Multi-dose, crossover, 7.5 mg w and wo erhtyro	19-46	12, 12
C98-356	Gender and race	Open-label, multi-dose, 7.5 mg	19-45	24, 24
P0017	PK of DL, 3OH-DL	Open-label, multi-dose, crossover, 5, 7.5 mg	19-41	18, 7
P0025	PK of DL, 3OH-DL	Open-label, multi-dose, 5 mg	18-70	57, 56
P0031	BA polymorphs	Open-label, crossover, 5 mg	19-41	63, 0
C98-357	ECG	Multi-dose, crossover, 0, 45 mg	19-41	12, 12
C98-577	— PK	Open-label, single-dose, 7.5 mg	—	9, 9
C98-354	PK in liver disease	Open-label, single-dose, parallel-group, 7.5 mg	42-65	16, 4
P00272	PK in liver disease	Open-label, multi-dose, parallel-group, 5 mg	40-66	10, 10
C98-355	PK in renal disease	Open-label, single-dose, parallel-group, 7.5 mg	26-70	26, 11
P01196	Wheal and flare	Double-blind, multi-dose, parallel-group, 0, 5 mg	20-44	25, 3
P01228	Adolescent PK	Open-label, single-dose, parallel-group, 5 mg	12-17	12, 12
P01378	ECG Prozac interact	Open-label, parallel-group, multiple-dose, 5 mg	22-49	38, 16
P01379	Food effect with fexo	Open-label, single-dose, crossover, 5 mg	21-45	12, 12
P01430	ECG Cimetidine inter	Open-label, parallel-group, multiple-dose, 5 mg	18-45	18, 19
P01380	Grapefruit, fexo inter	Open-label, single-dose, crossover, 5 mg	19-44	13, 11
P01381	ECG Azithro, fexo	Placebo-control, multi-dose, crossover, 5 mg	19-46	45, 45
P01868	ECG Cimetidine inter	Open-label, multi-dose, parallel-group, 5 mg	22-45	18, 18
P00213	BA and food effect	Open-label, single-dose, crossover, 5 mg	19-45	24, 6
P00270	— PK	Open-label, single-dose, 5 mg	—	10, 8
P01126	— PK	Open-label, single-dose, 2.5 mg	—	9, 9
P0025	— PK	Open-label, single-dose, 2.5 mg	—	12, 6
P01125	— PK	Open-label, single-dose, 1.25 mg	—	10, 8
P01352	BA, BE of —	Open-label, single-dose, crossover, 2.5 mg	19-42	11, 8
P00230	BA, BE of —	Open-label, single-dose, crossover, 2.5 mg	20-39	17, 0
P00446	BE of DL and —	Open-label, single-dose, crossover, 2.5 mg	19-45	19, 17
P00440	BA, food effect	Open-label, single-dose, crossover, 2.5 mg	18-44	24, 12
P00883	Multi-dose PK	Open-label, Multi-dose, 2.5 mg	21-43	9, 9
P00236	BA, BE of —	Open-label, single-dose, crossover, 2.5 mg	20-40	16, 0
P00439	BE of DL and —	Open-label, single-dose, crossover, 5 mg	31-45	18, 0
P00441	BA, food effect	Open-label, single-dose, crossover, 5 mg	19-44	27, 11
P00884	Multi-dose PK	Open-label, Multi-dose, 5 mg	21-45	15, 3
P01813	Single dose BE	Open-label, single-dose, crossover, 5 mg	19-45	21, 21
P01814	Single dose BE	Open-label, single-dose, crossover, 5 mg	18-45	22, 18
DL Reditabs				
P01216	BA, BE	Open-label, single-dose, crossover, 5 mg	21-45	18, 12
P01419	Food effect	Open-label, single-dose, crossover, 5mg	22-45	26, 4
P01462	— PK	Open-label, single-dose, crossover, 5mg	—	15, 9
Source: April 6, 2001, submission to — Section 1, page 24-26				

Approximately 6% of adults and 15% of — subjects were slow metabolizers in the clinical pharmacology studies. A subject was considered to be a slow metabolizer of DL if their AUC ratio of 3-OH DL to DL was less than 10% in all periods evaluated. If 3-OH DL was not analyzed during the study, then a subject with DL half-life value exceeding 50 hours

was considered to be a slow metabolizer. AUC values for DL is presented for normal and slow metabolizers in Table 5.

Table 5. Median (range) AUC (ng.hr/mL) of DL in normal and slow metabolizers

	Single dose	Multiple dose
Normal metabolizer	37.3 (6.96 – 139)	45.2 (2.28 – 281)
Slow metabolizer	163 (75.9 – 393)	264 (179 – 406)
Source: April 6, 2001, submission to [redacted] Section 13, page 167		

Of the 1087 subjects enrolled in the clinical pharmacology studies, 75 were slow metabolizers. Demographic analyses show that 72% of the slow metabolizers were Black subjects. The higher proportion of slow metabolizers in the [redacted] may reflect increased proportion of black subjects (38%) enrolled in these studies as compared to the proportion of black subjects enrolled in the adult studies (24%). The percentages of subjects reporting adverse events were similar in the slow metabolizers (21%) and normal metabolizers (31%). Curiously 54% of placebo treated subjects reported adverse events. Anticholinergic events and CNS adverse events did not differ between the slow and normal metabolizers. Clinical laboratory adverse events and ECGs were also not different between the groups. The lack of safety signal is not totally reassuring because of the small database (n=75) and because most of the subjects were exposed to a single dose of DL.

The applicant states that the phenomenon of greater DL exposure in some patients was also seen in the loratadine program. Since 3-OH-DL was not identified during the loratadine program, such subjects were considered to be "outliers." On retrospective analyses of loratadine studies the applicant identified that approximately 9.2% of subjects were possibly slow metabolizers.

Clinical Study P01434

Plasma samples from DL treated subjects participating in this study were analyzed for concentrations of DL and 3-OH-DL. In this study blood was collected between 2 and 6 hours after the final morning dose of the study drug. Based on the same definition of slow metabolizer used for the clinical pharmacology studies, 21 subjects were determined to be slow metabolizers and 488 subjects were determined to be normal metabolizers. Status of 101 subjects could not be established either because their plasma levels were too low to be categorized or because plasma samples were not available.

In this study also slow metabolism was more frequent in Blacks. Of the slow metabolizers, 52% were Blacks, and 38% were Caucasian. Of the normal metabolziers, 11% were Blacks, and 79% were Caucasian. As in the clinical pharmacology studies, adverse event reporting, and ECG were not different between the groups. The lack of safety signal is not totally reassuring because of the small database (n=21).

Safety of DL in slow metabolizers

The applicant does not have a large database to substantiate the safety of DL in slow metabolizers. DL is expected to be a widely prescribed drug. Given that approximately 6% of adults and 15% of [redacted] are slow metabolizers of DL (applicant's calculation), the

numbers of slow metabolizers who may receive this drug after marketing are substantial. Based on the comparative DL AUC calculation in adults (Table 5), the slow metabolizers will be exposed to a dose approximately 6-fold of the proposed 5mg/day dose of DL. Comparative exposure ratio [redacted] is unknown, because the applicant does not have any multi-dose pharmacokinetic data [redacted]

Safety of DL in slow metabolizers can be established preferably from a reasonably large database in slow metabolizers exposed to the drug, or secondarily from a reasonably large database in normal metabolizers where a dose that can cover the at least 6-fold higher exposure in slow metabolizers is covered. Unfortunately the applicant does not have such database to support the safety of DL in slow metabolizers. The total safety database in slow metabolizers includes 75 subjects from the clinical pharmacology studies, most of whom received single dose, and 21 subjects from the clinical study P01434. Safety database in subjects with unknown DL metabolism status (presumed normal metabolizers) include the two clinical pharmacology studies mentioned above (C98-357, C98-013), and study C98-001. In study C98-357 (cardiac safety clinical pharmacology study) 24 subjects were treated with DL 45mg for 10 days. In study C98-013 (rising dose study) approximately 10 subjects were treated with DL 20mg. In study C98-001 (dose-ranging submitted to DL SAR NDA 21-65) 169 subjects were treated with DL 20mg for 2 weeks. Although in these studies no safety signals were seen, the lack of safety signal is not reassuring because of the small database. The mechanisms of the slow metabolizer phenotype are also not known. It is possible that there may be yet unidentified drugs or other substances that can convert a normal metabolizer to a slow metabolizer. To gain approval, the applicant will need to establish safety of DL in a large number of slow metabolizers dosed chronically for a long period of time. As an alternate, the applicant may take the route of establishing safety of DL in normal metabolizers given a large dose (at least 6-fold of the proposed dose) to mimic the exposure level that can occur in slow metabolizers.

Financial disclosure and data integrity

The two investigators who conducted the two studies had no conflict of interest on financial disclosure. The applicant has submitted form FDA 3454 with the NDA. There was no reason, based on review of the data submitted, to doubt the quality or integrity of the database. Therefore, DSI audit was not request for this NDA.

Recommendation

The clinical pharmacology studies submitted to this NDA support the efficacy of Clarniex Reditabs 5mg in patients 12 years and older for the same indications that Clarinex Tablets 5mg would be indicated for. However, because of the limited safety data of Clarinex in slow metabolizers the clinical recommendation is for an APPROVABLE action. To gain approval, the applicant will need to establish safety of DL in a large number of slow metabolizers dosed chronically for a long time period. As an alternate, the applicant may take the route of establishing safety of DL in normal metabolizers given a large dose to mimic the exposure level that can occur in slow metabolizers. The applicant should also be encouraged to identify the mechanism of this slow metabolism, and to assess the potential for drug-drug

interactions that might be expected based on the explanatory mechanism. Depending on the safety data seen in slow metabolizers, the label may need to be modified to include a statement that some patients who may not be prospectively identified may be exposed to high level of desloratadine following dosing with the recommended dose of desloratadine.

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/s/

Badrul Chowdhury
10/10/01 12:16:08 PM
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APPEARS THIS WAY
ON ORIGINAL