CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-312

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-312
Type of submission:	Answers to comments in approvable letter
Proprietary Drug Name:	Clarinex-Reditabs©
Generic Name:	Desloratadine
Indication:	Treatment of Seasonal Allergic Rhinitis (SAR) and Chronic Idiopathic Urticaria (CIU)
Dosage Form:	Tablet
Strength:	5 mg
Route of Administration:	Oral
Applicant:	Schering Corporation
Submission Date:	December 21, 2001
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader:	Emmanuel Fadiran, Ph. D.

BACKGROUND

A Clarinex (DL) RediTab (rapidly-disintegrating tablet) formulation was developed by Schering Corporation for the treatment of seasonal allergic rhinitis (SAR) and chronic idiopathic Urticaria (CIU) in adult patients. According to the sponsor the DL Reditab formulation is a rapidly dissolving oral tablet dosage form that is designed to desintegrate in the mouth within several seconds of ingestion. The dosage form is not a ——— tablet.

In support of this NDA, the sponsor submitted on December 20, 2000, two studies to assess the safety and pharmacokinetics of the reditab in 60 healthy subjects. Since different formulations of DL (tablet, —— Reditab) are intended to be used interchangeably, one PK study in this report was designed to determine the bioavailability/bioequivalence of DL reditab to the conventional to-be-marketed tablet formulation and to the —— formulation in healthy adult subjects. In the second study, the effect of food and water on the pharmacokinetics of the Reditab formulation was determined. Both pharmacokinetic studies utilized single doses in adult subjects.

The results from these pharmacokinetic studies showed that the exposure (AUC and Cmax) to DL from the Reditab was equivalent to the exposure to DL from both the 5 mg DL tablet and 5 mg of DL : —— There was no significant effect of food or water on the pharmacokinetics of the Reditab formulation. The following comments were sent to the sponsor via the approvable letter on October 19, 2001:

COMMENTS TO SPONSOR

1) Please consider the assessment of dissolution rate using a paddle speed of — rpm instead of 50 rpm.

COMMENTS 3 TO 5

3) From the overall desloratadine pharmacokinetic database, it appears that a substantial subset of patients had a significantly higher exposure to desloratadine (AUC) than most patients. These patients had very low levels of 3-hydroxydesloratatine. The exposure to

desloratadine resulting from repetitive dosing in such patients is estimated to be six to nine times greater than the exposure in adult patients as a whole. There are no data to identify the mechanism for these high exposure levels, and there are no means of prospectively Identifying those patients who may have such high exposure. If these patients are inherently slow metabolizers of desloratadine, then the number of patients who experience these high exposure levels in clinical use may be much greater with actual use, particularly if there is a deficient metabolic pathway involved that may be inhibited by concomitant medications.

4) You should attempt to determine the mechanism accounting for higher levels of drug exposure in some patients, and to assess the potential for drug-drug interactions that might be expected depending on the outcome of these investigations.

5) Comments 3 and 4 are pertinent to other NDAs for desloratadine products with adult indications (NDAs 21-165, 21-297, ——— and 21-363).

Comments 3 and 4 are pertinent to other NDAs for desloratadine products with adult indications (NDAs 21 -1 65, 21 -297, ——— , and 21 -363)..

In the present submission (dated December 21, 2001) the sponsor included the following answers for the above questions:

Answer to question 1: We commit to evaluate the Desloratadine Reditab dissolution method using a paddle speed of — RPM. Results of these experiments will be submitted to the agency during June 2002.

If the —— paddle speed proves to be more discriminating and reproducible, three commercial batches will be tested up to the six-month time point to establish a new dissolution specification. The new method and specification will be amended to our NDA nine months after the start of the stability program on these three batches.

Until the above experiments are completed, we request our current (50 RPM) method for the ongoing research product release testing. Furthermore, dispersion data testing are an additional control of the reditabs fast seconds. These two control methods will insure the product.

REVIEWER'S REMARKS

The CPB team agrees with this proposal.

Answer to Question 2-4. Reference is made to a submission dated October 15, 2001 to this NDA and the approved Metabolism section of the CLINICAL PHARMACOLOGY section of the product information. The following text was added to the product information to address these comments for the approval of NDA 21 -1 65 (CLARINEX Tablets).

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 patient population has a decreased ability to form 3-hydroxydesloratadine, and are slow metabolizers of desloratadine. In pharmacokinetic studies (n=1087), approximately 7% of subjects were slow metabolizers of desloratadine (defined as a subject with an AUC ratio of 3-hydroxydesloratadine to desloratadine less than 0.1, or a subject with a desloratadine half-life exceeding 50 hours). The frequency of slow metabolizers is higher in blacks (approximately 20% of blacks were slow metabolizers in pharmacokinetic studies, n=276). The median exposure (AUC) to desloratadine in the slow metabolizers was approximately 6-fold greater than the subjects who are not slow metabolizers. Subjects who are slow metaboiizers of desloratadine cannot be prospectively identified and will be exposed to higher levels of desloratadine following dosing with the recommended dose of desloratadine. Although not seen in these pharmacokinetic studies, patients who are slow metabolizers may be more susceptible to dose-related adverse events.

REVIEWER'S REMARKS

This reviewer acknowledges the effort made by the sponsor to elucidate the metabolic pathway of the drug and encouraged the sponsor to continue with this effort.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed answers to comments sent by sponsor on December 21, 2001 for NDA 21-312. This reviewer agrees with the sponsor's proposal related to dissolution. In addition, we acknowledge the efforts that the sponsor has made in elucidating the mechanisms behind the metabolic pathway of desloratadine and encouraged the sponsor to continue with this effort.

Reviewer

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

Emmanuel Fadiran, Ph.D., Team leader

cc

NDA 21-312/N-000:	Division File
HFD-870:	Malinowski, Hunt
HFD-570:	Fadiran, Nicklas, Zeccola, Suarez-Sharp
CDR:	Barbara Murphy

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/s/

Sandra Suarez
6/7/02 10:24:35 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
6/7/02 10:30:33 AM
BIOPHARMACEUTICS
I concur

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-312
Proprietary Drug Name:	Clarinex-Reditabs®
Generic Name:	Desloratadine
Indication:	Treatment of Seasonal Allergic Rhinitis (SAR) and Chronic Idiopathic Urticaria (CIU)
Dosage Form:	Tablet
Strength:	5 mg
Route of Administration:	Oral
Dosage and administration:	**Adults and children (age 12 and older):** One tablet
Applicant:	Schering Corporation
Clinical Division:	DPADP (HFD-570)
Submission Date:	December 20, 2000
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader:	Emmanuel Fadiran, Ph. D.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

A Clarinex (DL) RediTab (rapidly-disintegrating tablet) formulation was developed by Schering Corporation for the treatment of seasonal allergic rhinitis (SAR) and chronic idiopathic Urticaria (CIU) in adult patients. According to the sponsor the DL Reditab formulation is a rapidly dissolving oral tablet dosage form that is designed to dissolve in the mouth within several seconds of ingestion. The dosage form is not a ——— tablet.

In support of this NDA, the sponsor conducted two studies to assess the safety and pharmacokinetics of the reditab in 60 healthy subjects. The integrated summary of safety focuses on the results of these two phase I, randomized, open-label, single-center, crossover studies in adults.

Since different formulations of DL (tablet, ——, Reditab) are intended to be used interchangeably, one PK study in this report was designed to determine the bioavailability bioequivalence of DL reditab to the conventional to-be-marketed tablet formulation and to the ———formulation in healthy adult subjects. In the second study, the effect of food and water on the pharmacokinetics of the Reditab formulation was determined. Both pharmacokinetic studies utilized single doses in adult subjects.

The results from these pharmacokinetic studies showed that the exposure (AUC and Cmax) to DL from the Reditab was equivalent to the exposure to DL from both the 5 mg DL tablet and 5 mg of DL——— There was no significant effect of food or water on the pharmacokinetics of the Reditab formulation.

2. COMMENTS TO SPONSOR

- Please consider the assessment of dissolution rate using a paddle speed of — rpm instead of 50 rpm.
- The sponsor is encouraged to identify the enzyme (s) responsible for the presence of slow metabolism of DL observed in some subjects.

3. COMMENTS TO THE MEDICAL OFFICER

- The Reditab formulation was bioequivalent to both the conventional tablet and ——— formulations.
- Water and a high-fat and high-caloric meal had no effect on the bioavailability (AUC, Cmax) of DL and 3-OH DL from the Redi-Tab tablet (when fasted with water conditions used as a reference). However, the ratio of DL Cmax under fed/fasted without water conditions resulted in a 90% CI of 79-90. This 21% decrease on the DL Cmax under fed compared to fasted without water conditions may not be clinically relevant.
- Food increased the median (min-max) DL Tmax from 2.5 — to 4 — It is our recommendation that this finding should be reflected in the label (see comments to proposed label).
- The batches of reditab tablets used in the PK studies correspond to the to-be-marketed formulation and were within the proposed reditab dissolution specifications of Q= ———
- There was one potential subject identified as slow metabolizer. This subject had an AUCinf % ratio of 3-OH DL/DL of 5. The DL AUCinf for this subject was more than

4-fold higher (181 ng*hr/mL) than the observed mean value (41 ng*hr/mL) and the 3-OH DL AUCinf value was more than two-fold lower (9.7 ng*hr/mL) than the observed mean value (24.7 ng*hr/mL). Low AUC % ratios of 3-OH DL/DL have been identified in previous Clarinex [redacted] suggesting the existence of DL slow metabolizers. The clinical relevance of these observations on the safety of Clarinex should be evaluated by the medical reviewer.

4. LABELING COMMENTS

Pharmacokinetics:

Absorption:

Following oral administrations of desloratadine dosed 5 mg once daily for 10 days to normal healthy volunteers, the mean time to maximum plasma concentrations (Tmax) occurred at approximately 3 hours post dose and mean steady state peak plasma concentrations (Cmax) and area under the concentration-time curve (AUC) of 4 ng/mL and 56.9 ng×hr/ml were observed, respectively. [redacted]

([redacted]).

The pharmacokinetic profile of CLARINEX Reditabs [redacted] was evaluated in a three way crossover study in 30 adult volunteers. [redacted]

[redacted]

DOSAGE AND ADMINISTRATION:

Adults and children 12 years of age and over: The recommended dose of CLARINEX Tablets is 5 mg once daily. [redacted] In patients with liver [redacted] or renal [redacted], a starting dose of one 5 mg tablet every other day is recommended based on pharmacokinetic data. [redacted]

[redacted]

Note: Underlined text represents new addition to the label made by the sponsor. The red underlined text is this reviewer's comments to the label.

5. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-312 submitted on December 20, 2000. The NDA's Human Pharmacokinetics and Bioavailability Section is acceptable to OCPB. However, the clinical relevance of the existence of desloratadine slow metabolizers on the Clarinex safety should be evaluated by the medical reviewer.

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
NDA 21-312/N-000: Division File
HFD-870: Malinowski, Hunt
HFD-570: Fadiran, Nicklas, Trout, Suarez-Sharp

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The present review has been focused on the following issues.

6. QUESTION BASED REVIEW

Q1. Was the to-be-marketed formulation used in the pharmacokinetic studies?

Yes. The sponsor used formula 3566 (see Table 1.1) to conduct both PK studies. The batch size used was —— of the proposed to be marketed batch size.

Table 1.1. Components for formula number 3566 (Clarinex Reditabs)

Ingredients	mg/tablet
SCH 34117 (Desloratadine) ——	5.0
Gelatin EP/USNF	
Mannitol EP/USP	
Aspartame EP/USNF	
Polacrilin Potassium USP	
Dye — Red ——	
Flavor Tutti-Frutti ——	
Citric Acid USP	
——	
Approximate tablet weight	**48.07**

Table 1.2. Formulation for Clarinex Reditabs 5 mg

Strength	5 mg
Formula. No.	3566
Batch No.	76728-001
FMR No.	——
Manf. Date	6/2/99
Manf. Site	——
Batch Size (tablets)	——

Q2.Was the Clarinex Reditab formulation bioequivalent to the Clarinex —— and tablet formulations?

Yes. The sponsor conducted a phase I, open-label, single-dose, randomized, 3-way crossover study (P01216) with a 14-day washout period between each treatment. A total of 30 healthy male and female subjects were enrolled in the study.

Figure 2.1 shows the plasma concentration-time profile for DL and its metabolite following single administration of the treatments. The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for DL and its metabolite are presented in Table 2.1. The CIs of Cmax AUC(tf) and AUC(I) of DL and 3-OH DL for Treatment B (Reditab) relative to Treatment A (conventional tablet), and Treatment B (Reditab) relative to Treatment C (—— met the —— bioequivalence guideline criteria.

This indicates that the Reditab formulation was bioequivalent to both the conventional tablet and —— formulations.

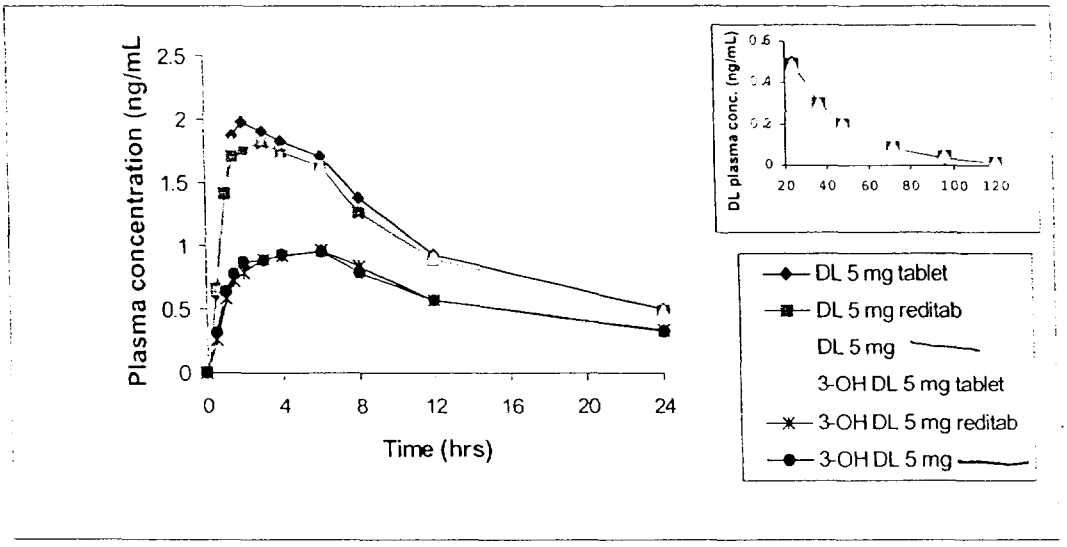

Figure 2.1. Mean DL and 3-OH DL plasma concentration-time profiles following single administration of Clarinex Reditabs 5mg, Clarinex tablets 5mg and Clarinex —— 5 mg. Insert represents the terminal phase of the profiles.

Table 2.1. 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				
5mg Reditab/5mg Tablet	AUCtf	97.2	101.25	92-102	96.1-106.7
	AUCinf	97.1		92-102	
	Cmax	91.1	91.25	85-99	84.7-98.3
5 mg Reditab/5mg ——	AUCtf	101.2	101.0	96-107	95.9-106.4
	AUCinf	100.9		96-106	
	Cmax	96.4	96.22	90-104	89.3-103.6
	3-OH DL				
5mg Reditab/5mg Tablet	AUCtf	97.1	98.3	94-101	93.5-102.3
	AUCinf	97		93-101	
	Cmax	93.5	92.1	87-100	87.9-102.5
5 mg Reditab/5mg ——	AUCtf	101.2	101.8	98-105	96.9-104.3
	AUCinf	100.8		97-105	
	Cmax	99	100.1	93-106	93.2-106.1

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Q3.Was the bioavailability of DL from the DL reditab tablet affected by the presence of food and/or water?

NO. The sponsor conducted study P01419 to evaluate the effect of water and high caloric breakfast (total calories: 841; 31.6g protein; 53.8g fat; 57.4g carbohydrates) on the oral bioavailability of desloratadine (DL) Redi-Tab tablet. This was a phase I, randomized, open-label, single-dose, 3-way crossover study in 30 male and female healthy subjects with at least a 10-day washout period between each treatment. Each subject received one 5-mg tablet of DL Redi- orally under either a fasted (with or without water) or fed conditions.

The mean plasma concentration-time profiles for DL and its metabolite following single administration of Clarinex Reditabs 5mg under fasted (with and without water) and fed conditions are shown in Figure 3.1.

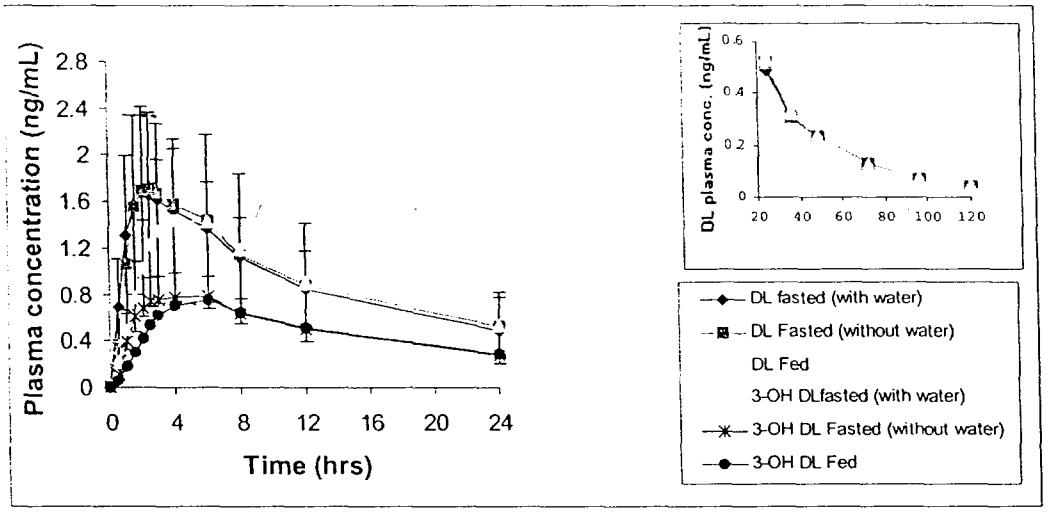

Figure 3.1. Mean DL and 3-OH DL plasma concentration-time profiles following single administration of Clarinex Reditabs 5 mg under fasted conditions (with and without water) ,and under fed conditions. The insert represents the terminal phase profile for DL.

The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) DL and 3-OH DL are presented in Table 3.1. For both DL and 3-OH DL, the CIs of AUC(I) and Cmax for fed relative to fasted conditions (with and without water) and fasted (without water) relative to fasted (with water) met the ——— bioequivalence guideline criteria.

This indicates that water and a high-fat and high-caloric meal had no effect on the bioavailability of DL and 3-OH DL from the Redi-Tab tablet. However, as it is observed in Figure 3.2, food did increase DL median Tmax from 2.5 to 4 hours. The clinical relevance of this shift has been discussed with the medical reviewer and the conclusion reached is that this finding needs to be reflected in the label. The ratio of DL Cmax under fed/fasted without water conditions resulted in a 90% CI of 79-90. This 21%

decrease on the DL Cmax under fed compared to fasted without water conditions may not be clinically relevant.

Table 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 Clarinex Reditabs 5 mg under fasted conditions (with and without water) and under fed conditions.

Comparison	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's findings
	Desloratadine				
Trt C Trt A	AUCinf	99.4	99.4	96-1.3	95.7-103.3
	Cmax	87.4	87.4	82-93	82-93
Trt C Trt B	AUCinf	97.3	97.3	94-101	93.7-101.1
	Cmax	84.3	84.3	79-90	79.12-89.7
Trt B Trt A	AUCinf	102	102.19	98-106	98.4-106.2
	Cmax	104	103.7	97-110	97.4-110.4
	3-OH DL				
Trt C Trt A	AUCinf	95.4	93.9	92-99	89.1-98.9
	Cmax	93.9	95.4	89-99	92.1-98.8
Trt C Trt B	AUCinf	94	93.6	91-97	90.7-97.3
	Cmax	92.6	92.7	88-98	87.9-97.6
Trt B Trt A	AUCinf	101	101.6	98-105	98-105.2
	Cmax	101	101.3	96-107	96.2-106.7

A: fasted with water; B: fasted without water; C: fed conditions

Figure 3.2 shows that 3 out 30 subjects presented high DL AUCinf values. One of these subjects showed a % ratio of 3-OH DL AUC/ DL AUC less than 10, suggesting slow metabolism. The presence of slow metabolism for DL has been observed in previous Clarinex [redacted]. The clinical relevance of these outliers on the safety of Clarinex should be evaluated by the medical reviewer.

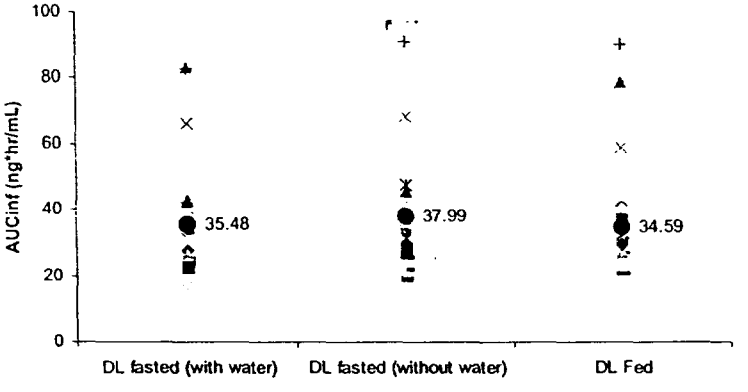

Figure 3.2 Individual DL AUCinf values following single administration of Clarinex Reditabs 5mg fasted (with water; without water), and under fed conditions.

Q4. Are the proposed dissolution method and specifications supported by the data provided by the sponsor?

Yes. The Clarinex Reditab dissolution method and specifications proposed by the sponsor are listed in Table 4.1 Figure 4.1 and Table 4.2 show the dissolution profiles for the Reditabs used in the PK studies.

Table 4.1. Proposed dissolution method for Clarinex Reditabs

Method	
Apparatus:	USP apparatus II (paddle)
Detection:	[redacted]
Speed:	50 rpm
Temperature:	37 °C ± 0.5 °C
Medium:	500 mL of 0.1N HCL
Specification:	Q= [redacted] in 4 minutes

Table 4.2. Dissolution data for Clarinex Reditabs

Time (min)	1	2	3	4	5	6	7	8	9	10	11	12	average
	Percent DL dissolved/dosage form												
2	102	103	102	100	101	101	101	87	96	102	101	101	**99.8**
4	102	104	103	101	102	102	102	100	102	103	101	102	**102**
6	102	104	103	101	101	102	102	101	103	103	101	102	**102**
8	102	104	103	101	102	102	102	102	103	103	101	102	**102**
10	102	104	103	101	102	102	102	102	103	103	101	102	**102**

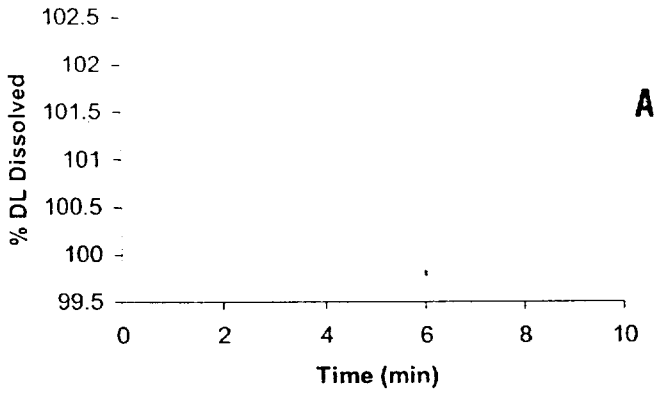

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Figure 4.1 Average dissolution-time profile for Clarinex Reditabs.

7. BACKGROUND AND RATIONALE

Desloratadine (DL, SCH 34117; formerly known as descarboethoxyloratadine, DCL) is an active metabolite of loratadine (SCH 29851, Claritin) which possesses qualitatively similar pharmacodynamic activity with a relative oral potency 2 to 4 times that of loratadine. Like loratadine, DL is a selective, oral, peripheral H1-receptor antagonist. Pharmacokinetic studies have shown that administration of the proposed therapeutic dose of 5.0-mg DL gives the same systemic exposure (plasma AUC) of DL as

administration of the marketed dose of 10-mg loratadine (NDA 21-165). Loratadine is also marketed in the United States and internationally as loratadine D-12 and loratadine D-24 tablets containing loratadine plus sustained-release pseudoephedrine (PSE) for the treatment of SAR.

The safety and efficacy data obtained for desloratadine in adolescents and adults during clinical trials revealed that it is effective in the treatment of SAR or CIU, well tolerated, and characterized by an adverse event profile similar to that previously observed with loratadine.

A RediTab (rapidly-disintegrating tablet) formulation was developed for the treatment of adult patients. According to the sponsor the DL Reditab formulation is a rapidly dissolving oral tablet dosage form that is designed to dissolve in the mouth within several seconds of ingestion. The dosage form is not a ——— tablet.

In support of this NDA, the sponsor conducted two studies to assess the safety and pharmacokinetics of the reditab in 60 healthy subjects. The integrated summary of safety focuses on the results of these two phase I, randomized, open-label, single-center, crossover studies in adults. The safety profile of the DL Reditab, the DL tablet and the DL ——— formulation were examined using the following parameters: adverse events, electrocardiograms (ECGs), vital signs, and clinical laboratory results. Vital signs, including diastolic and systolic blood pressure (mm Hg), pulse (beats/minute), respiration rate (breaths/minute), and body temperature (°F), were assessed throughout the studies (refer to medical reviewer's report).

Since different formulations of DL (tablet ——— Reditab) are intended to be used interchangeably, one PK study in this report was designed to determine the bioavailability/bioequivalence of DL Reditab to the conventional to-be-marketed tablet formulation and to the ——— formulation in healthy adult subjects. In the second study, the effect of food on the pharmacokinetics of the Reditab formulation was determined. Both pharmacokinetic studies utilized single doses in adult subjects.

The results from these pharmacokinetic studies showed that the exposure (AUC and Cmax) to DL from the Reditab was equivalent to the exposure to DL from both the 5 mg DL tablet and 5 mg of DL ——— There was no significant effect of food and water on the pharmacokinetics of the Reditab formulation.

Clinical Safety and PK Studies

Study P01216. BIOAVAILABILITY/BIOEQUIVALENCE OF A RAPIDLY DISSOLVING TABLET FORMULATION OF DESLORATADINE IN HEALTHY VOLUNTEERS.

Study P01419. INFLUENCE OF FED AND FASTED CONDITIONS, WITH AND WITHOUT WATER ON THE ORAL BIOAVAILABILITY OF DESLORATADINE ADMINISTERED TO HEALTHY SUBJECTS: A THREE-WAY CROSSOVER STUDY

7.1 INTRODUCTION

7.1.1 PHARMACOKINETICS

The pharmacokinetics of DL and its metabolite have been presented in detail in a previous NDA for Clarinex (21-165).

Pharmacokinetic/Pharmacodynamic Correlation. No studies have been conducted.

7.1.2 CHEMISTRY OVERVIEW

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:

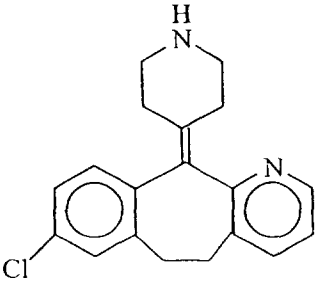

Figure 1. Structural formula of DL.

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.

7.1.3 FORMULATION

The CLARINEX Reditabs product is a pink colored round tablet shaped units with a "C" debossed on one side. Each Reditab unit contains 5 mg of desloratadine. It also contains the following inactive ingredients: gelatin Type B NF, mannitol USP, aspartame NF, polarcrillin potassium NF, citric acid USP, red dye and tutti frutti flavoring (see table below).

Components for formula number 3566 (Clarinex Reditabs)

Ingredients	mg/tablet
SCH 34117 (Desloratadine),	5.0
Gelatin EP/USNF	
Mannitol EP/USP	
Aspartame EP/USNF	
Polacrilin Potassium USP	
Dye Red	
Flavor Tutti-Frutti	
Citric Acid USP	
Approximate tablet weight	**48.07**

7.1.4 INDICATION (as per proposed label)

CLARINEX is indicated for the relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria in patients 12 years of age and older. Symptoms treated in chronic idiopathic urticaria were pruritus, number of hives and the size of the largest hive.

7.1.5 DOSAGE AND ADMINISTRATION (as per proposed label)

Adults and children 12 years of age and over: The recommended dose of CLARINEX Tablets is 5 mg once daily. In patients with liver ——— or renal ——— a starting dose of one 5 mg tablet every other day is recommended based on pharmacokinetic data.

8. SAFETY

The sponsor has submitted two studies in support of this application, one demonstrating the bioequivalence of Claritin Reditabs and the 5 mg tablet and ——— formulations to the tablet formulation, and one demonstrating the neither food nor water had an effect on the bioavailability of desloratadine. According to the medical reviewer:

A. This NDA for Clarinex Reditabs is approvable from a clinical standpoint. 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 (NDA 21,165). In this NDA, the sponsor has provided data to support the safety of Clarinex Reditabs. The safety of Clarinex Reditabs is 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 and to be bioequivalent to 5 mg of the Clarinex tablet.
E. Clarinex tablets have been 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.

"BIOAVAILABILITY/BIOEQUIVALENCE OF A RAPIDLY DISSOLVING TABLET FORMULATION OF DESLORATADINE IN HEALTHY VOLUNTEERS"

Name of Sponsor:	Schering-Plough Corporation
Included Protocols:	P01216
Development Phase of Study:	I
Study Initiation Date:	03 DEC 1999
Study Completion Date:	25 JAN 2000
Sponsor's Project Physician:	Mark Marino, M.D.
Sponsor's Project Director:	Christopher Banfield, Ph.D.
Date of the Report:	31 JUL 2000

OBJECTIVE

- to determine the bioequivalence following single oral dose administration of: 1) a desloratadine conventional tablet formulation and a desloratadine rapidly dissolving tablet formulation (Reditab), and 2) a rapidly dissolving desloratadine tablet formulation (Reditab) and the desloratadine —— formulation.

SUBJECTS

Thirty healthy volunteers, 18 male and 12 female, between the ages of 21 and 45 years inclusive (mean=37 years) with BMIs ranging from 19 to 29 kg/m^2 and weighing between 50 and 88 kg (mean=71 kg) were enrolled into the study. Nineteen subjects were Hispanic (63%), 7 were Caucasian (23%), 2 were Black (7%), and 2 were Asian (7%).

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a Phase I, open-label, single-dose, randomized, 3-way crossover study with at least a 14-day washout period between each treatment. A total of 30 healthy male and female subjects were enrolled in the study and 28 successfully completed all three treatment periods. Subjects received the following treatments in the order assigned by a computer-generated random code:

Treatment A:	One 5 mg SCH 34117 tablet administered after a 10-hr fast.
Treatment B:	One 5 mg SCH 34117 rapidly dissolving tablet (Reditab) administered after a 10-hr fast.
Treatment C:	—— SCH 34117 — formulation —— administered after a 10-hr fast.

Each treatment was administered with 180 mL (6 fl oz) of non-carbonated room temperature water. A washout period of at least 14 days separated each period of the study.

FORMULATION

The Clarinex — tablets and DL — tablets were manufactured by SPRI, Kenilworth, NJ, USA. The following formulations (Table 1) were used:

Table 1. Formulation for Clarinex 5mg Tablets

Strength	5 mg
Formula. No.	3408
Batch No.	38833-142
FMR No.	98564D02
Manf. Date	3/23/98
Manf. Site	Las Piedras. PR
Batch Size (tablets)	—

Table 2. Formulation for Clarinex — 5 mg

Strength	—
Formula. No.	3518
Batch No.	75882-024-B
FMR No.	99610D02
Manf. Date	5/4/99
Manf. Site	Kenilworth. NJ
Batch Size	—

Table 3. Formulation for Clarinex Reditabs 5 mg

Strength	5 mg
Formula. No.	3566
Batch No.	39554-152
FMR No.	—
Manf. Date	6/2/99
Manf. Site	—
Batch Size (tablets)	—

Formula 3566 is the same as the to-be marketed formulation. Refer to the end of this study review for information regarding Reditabs tablet formulation, dissolution method and dissolution data.

PHARMACOKINETIC MEASUREMENTS

Blood Sampling

Serial blood samples (approximately 10 mL) 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. During each treatment phase, all subjects were confined at the study site until the 120-hr blood sample was collected.

Analytical Method

Plasma concentrations of SCH 34117 and SCH 45581 were determined using a ——— method with a lower limit of quantitation (LOQ) of — ng/mL, and calibration curve range of — — 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 SCH 34117 and SCH 45581 were subjected to pharmacokinetic analysis by non-compartmental methods.

Statistical Analysis

Summary statistics (mean and %CV) were calculated for the concentration data at each sampling time and for the derived pharmacokinetic parameters. The pharmacokinetic parameters were then subjected to statistical analysis by using a cross-over analysis of variance (ANOVA) model. The effects due to sequence, subject within sequence, period, and treatment were extracted. Cmax and AUC values were log-transformed, and 90% confidence intervals (CI) for the mean difference between the treatments expressed as a percent of each treatment mean were calculated. The primary statistical comparisons were Treatment B (Reditab) relative to Treatment A (tablet); and Treatment B (Reditab) to Treatment C ——.

Reviewer's remarks

This reviewer used —— program to calculate 90% confidence intervals for the ratio of the means (Cmax and AUCinf) between treatments (A vs. B and A vs.C); see Table 5).

RESULTS

Analytical Method

In study Validation Results

Table 4. In-study validation information for DL and 3-OH DL

	DL	3-OH DL
Linearity	Satisfactory: Standard curve range from ——	Satisfactory: Standard curve range from ——
Accuracy	Satisfactory: ——	Satisfactory: ——
Precision	Satisfactory: (%CV) ——	Satisfactory: ——
Specificity	Satisfactory: —— submitted	Satisfactory: —— submitted

Pharmacokinetic Results

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

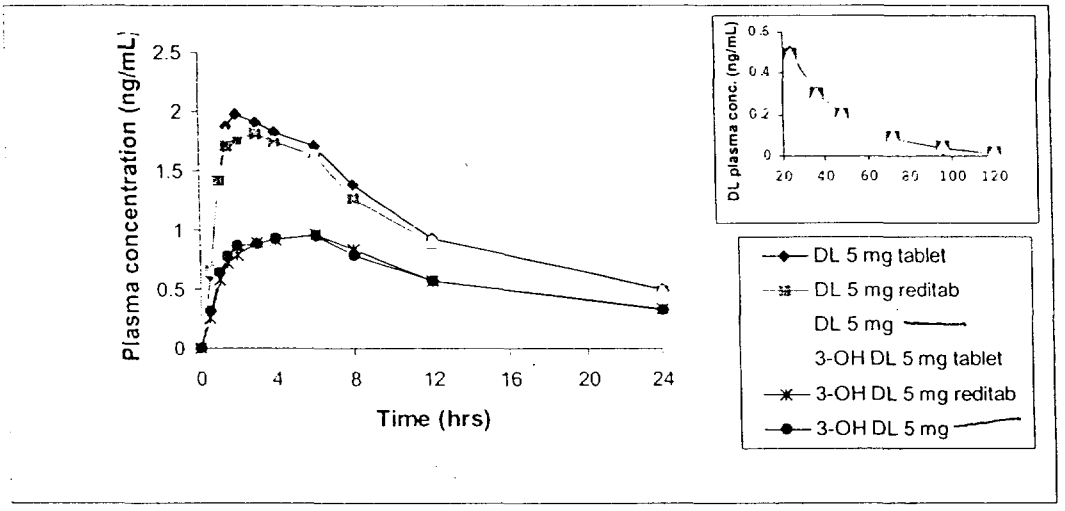

Figure 1. Mean DL and 3-OH DL and plasma concentration-time profiles following single administration of Clarinex Reditabs 5mg, Clarinex tablets 5mg and Clarinex ——— 5 mg.

Table 5. Mean (%CV) pharmacokinetic parameters of DL and 3-OH following single administration of Clarinex Reditabs 5mg, Clarinex tablets 5mg and Clarinex ——— 5 mg.

	Pharmacokinetic Parameters		
Treatment	**Cmax (ng/mL)**	**AUC (ng*hr/mL)**	**AUC inf (ng*hr/mL)**
	Desloratadine		
5 mg Tablets	2.18 (35)	38.9 (45)	40.3 (45)
5 mg Reditabs	1.99 (30)	38 (44)	39.4 (43)
5 mg ———	2.05 (33)	37.5 (47)	38.9 (47)
	3-OH Desloratadine		
5 mg Tablets	1.08 (27)	27.4 (27)	29.5 (27)
5 mg Reditabs	1.03 (28)	27 (29)	29 (29)
5 mg ———	1.04 (33)	26.4 (25)	28.5 (24)

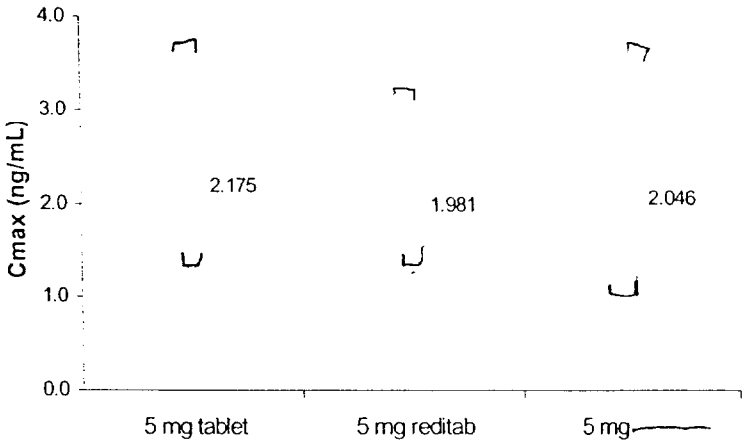

Figure 2. Individual DL Cmax values following single administration of Clarinex Reditabs 5mg, Clarinex tablets 5mg and Clarinex ——— 5 mg.

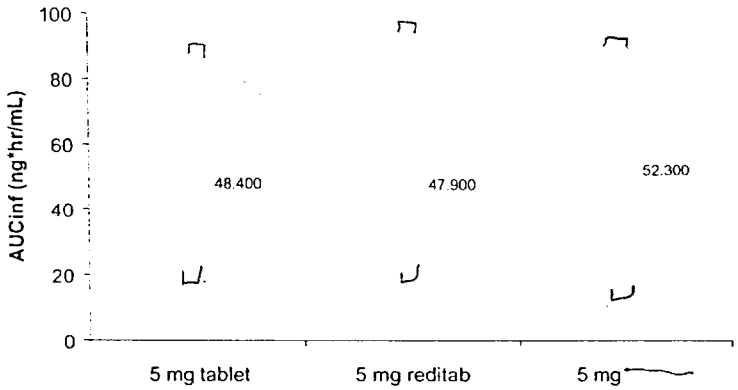

Figure 3. Individual DL AUCinf values following single administration of Clarinex Reditabs 5mg, Clarinex tablets 5mg and Clarinex ——— 5 mg.

The blood sample at 0-hr time point for Subject 11 in Period 1 (Reditab treatment) contained SCH 45581 at a concentration of ——— ng/mL; this concentration was considered to have no impact on the overall results of the study and is included in all calculations. Preliminary statistical analysis was performed to examine the extreme pharmacokinetic values and the impact of outliers on the overall results. It was found that exclusion of outliers did not change the overall bioequivalence conclusion of the study. Therefore, all subjects were included in the final statistical analysis.

The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for DL and its metabolite are presented in Table 6. The CIs of Cmax AUC(tf) and AUC(I) of DL and 3-OH DL for Treatment B (Reditab) relative to Treatment A (conventional tablet), and Treatment B (Reditab) relative to Treatment C ——— met the ——— bioequivalence guideline criteria.

Table 6. 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				
5mg Reditab/5mg Tablet	AUCtf	97.2	101.25	92-102	96.1-106.7
	AUCinf	971		92-102	
	Cmax	91.1	91.25	85-99	84.7-98.3
5 mg Reditab/5mg [redacted]	AUCtf	101.2	101.0	96-107	95.9-106.4
	AUCinf	100.9		96-106	
	Cmax	96.4	96.22	90-104	89.3-103.6
	3-OH DL				
5mg Reditab/5mg Tablet	AUCtf	97.1	98.3	94-101	93.5-102.3
	AUCinf	97		93-101	
	Cmax	93.5	92.1	87-100	87.9-102.5
5 mg Reditab/5mg [redacted]	AUCtf	101.2	101.8	98-105	96.9-104.3
	AUCinf	100.8		97-105	
	Cmax	99	100.1	93-106	93.2-106.1

CONCLUSION

The results presented above indicate that the Reditab formulation was bioequivalent to both the conventional tablet and [redacted] formulations.

Dissolution

The Clarinex Reditabs tablet formulation used in this study, proposed dissolution method and specifications are listed below.

Table D1. Proposed dissolution method for Clarinex Reditabs

Method	
Apparatus:	USP apparatus II (paddle)
Detection:	[redacted]
Speed:	50 rpm
Temperature:	37 °C ± 0.5 °C
Medium:	500 mL of 0.1N HCL
Specification:	Q= [redacted] in 4 minutes

Table D2. Components for formula number 3566 (Clarinex Reditabs)

Ingredients	mg/tablet
SCH 34117 (Desloratadine), [redacted]	5.0
Gelatin EP/USNF	[redacted]
Mannitol EP/USP	
Aspartame EP/USNF	
Polacrilin Potassium USP	
Dye [redacted] Red [redacted]	
Flavor Tutti-Frutti [redacted]	
Citric Acid USP	
[redacted]	
Approximate tablet weight	**48.07**

Table D3. Dissolution data for Clarinex Reditabs

Time (min)	1	2	3	4	5	6	7	8	9	10	11	12	average
	3 Percent DL dissolved/dosage form												
2	102	103	102	100	101	101	101	87	96	102	101	101	**99.8**
4	102	104	103	101	102	102	102	100	102	103	101	102	**102**
6	102	104	103	101	101	102	102	101	103	103	101	102	**102**
8	102	104	103	101	102	102	102	102	103	103	101	102	**102**
10	102	104	103	101	102	102	102	102	103	103	101	102	**102**

COMMENTS

The batch used in this PK study was within the proposed dissolution specifications.

"INFLUENCE OF FED AND FASTED CONDITIONS, WITH AND WITHOUT WATER, ON THE ORAL BIOAVAILABILITY OF DESLORATADINE ADMINISTERED TO HEALTHY SUBJECTS: A THREE-WAY CROSSOVER STUDY"

Name of Sponsor:	Schering-Plough Corporation
Included Protocols:	P01419
Development Phase of Study:	I
Study Initiation Date:	25 FEB 2000
Study Completion Date:	05 MAY 2000
Sponsor's Project Physician:	Mark Marino M.D.
Sponsor's Project Director:	Christopher Banfield, Ph.D.
Date of the Report:	20 SEP 2000
Report Number: 1	584488

OBJECTIVE

- to evaluate the effect of water and high caloric breakfast on the oral bioavailability of desloratadine (DL) Redi-Tab® tablet.

SUBJECTS

Thirty healthy volunteers (26 males and 4 females) between the ages of 22 and 45 years inclusive (mean=32 years) weighing between 60 and 108 kg (mean=79.9 kg) with a BMI range of 19.2-28.4 kg/m^2 (mean=24.9 kg/m^2) were enrolled into the study. Twenty-two (73%) subjects were Caucasian and 8 (27%) were Black.

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a Phase I, randomized, open-label, single-dose, 3-way crossover study in 30 male and female healthy subjects with at least a 10-day washout period between each treatment. Each subject received one 5-mg tablet of DL Redi-Tab (a rapidly dissolving oral tablet dosage form) orally under either a fasted (with or without water) or fed condition in the order assigned by a computer-generated random code:

Treatment A:	One DL 5-mg Redi-Tab tablet administered with 180 mL of ambient temperature tap water on an empty stomach following an overnight fast.
Treatment B:	One DL 5-mg Redi-Tab tablet administered without water on an empty stomach following an overnight fast.
Treatment C:	One DL 5-mg Redi-Tab tablet administered with 180 mL of ambient temperature tap water within 5 min following a standardized high-fat, high-caloric breakfast.

For Treatment C, subjects consumed the standardized high-fat, high-caloric breakfast (total calories: 841; 31.6g protein; 53.8g fat; 57.4g carbohydrates) over a 20-min period, and then received Redi-Tab tablet within 5 min after breakfast.

FORMULATION

The Clarinex — tablets and DL — tablets were manufactured by SPRI, Kenilworth, NJ, USA. The following formulations (Table 1) were used:

Table 1 . Formulation for Clarinex Reditabs 5 mg

Strength	5 mg
Formula. No.	3566
Batch No.	76728-001
FMR No.	—
Manf. Date	6/2/99
Manf. Site	—
Batch Size (tablets)	—

Formula 3566 is the same as the to-be marketed formulation. Refer to the end of this study review for information regarding Reditabs tablet formulation, dissolution method and dissolution data.

PHARMACOKINETIC MEASUREMENTS

Blood Sampling

Serial blood samples (approximately 10 mL) 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 SCH 34117 and SCH 45581 were determined using a) method with a lower limit of quantitation (LOQ) of — ng/mL, and calibration curve range of — 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 SCH 34117 and SCH 45581 were subjected to pharmacokinetic analysis by non-compartmental methods.

Statistical Analysis

Summary statistics (mean and %CV) were calculated for the concentration data at each sampling time and for the derived pharmacokinetic parameters. The pharmacokinetic parameters were then subjected to statistical analysis by using a cross-over analysis of variance (ANOVA) model. The effects due to sequence, subject within sequence, period, and treatment were extracted. Cmax and AUC values were log-transformed, and 90% confidence intervals (CI) for the mean difference between the treatments expressed as a percent of each treatment mean were calculated. The primary statistical comparison were Treatment C (Fed) relative to Treatments A (Fasted, with water) and B (Fasted, without water); and Treatment B (Fasted without water) relative to Treatment A (Fasted, with water).

Reviewer's remarks

This reviewer used [redacted] program to calculate 90% confidence intervals for the ratio of the means (Cmax and AUCinf) between treatments (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 [redacted]	Satisfactory: Standard curve range from [redacted]
Accuracy	Satisfactory: [redacted]	Satisfactory: [redacted]
Precision	Satisfactory: (%CV) [redacted]	Satisfactory: [redacted]
Specificity	Satisfactory: [redacted] submitted	Satisfactory: [redacted] submitted

Pharmacokinetic Results

The mean plasma concentration-time profiles for DL and its metabolite following single administration of Clarinex Reditabs 5mg under fasted (with and without water) and fed conditions are shown in Figure 1. 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 2 and 3, respectively. The blood samples at 0-hr time point for subjects 6, 15 and 23 contained either DL or 3-OH DL at low concentrations ([redacted]. The reason for this is unknown; however, these concentrations were considered by the sponsor to have no impact on the overall results of the study. This reviewer is of the opinion that the low concentration at time 0hr may be to the presence of slow metabolism in these subjects as is shown by the higher values of AUC and Cmax (3 to 4 fold higher than the mean) and lower values of 3-

OH DL (see Figures 2 and 3). Thus, the metabolic rate of DL to 3-OH appeared to be slow in Subject 23 with AUC ratio <10% (DL AUCinf=185 ng*hr/mL; 3-OH DL AUCinf= 17 ng*hr/mL)). This subject was identified as a slow metabolizer.

Figure 3 shows that 3 out 30 subjects presented high DL AUCinf values. One of these subjects showed a ratio of 3-OH DL AUC/ DL AUC less than 10 suggesting slow metabolism. The presence of slow metabolism for DL has been observed in previous Clarinex [redacted]. The clinical relevance of these outliers on the safety of Clarinex should be evaluated by the medical reviewer.

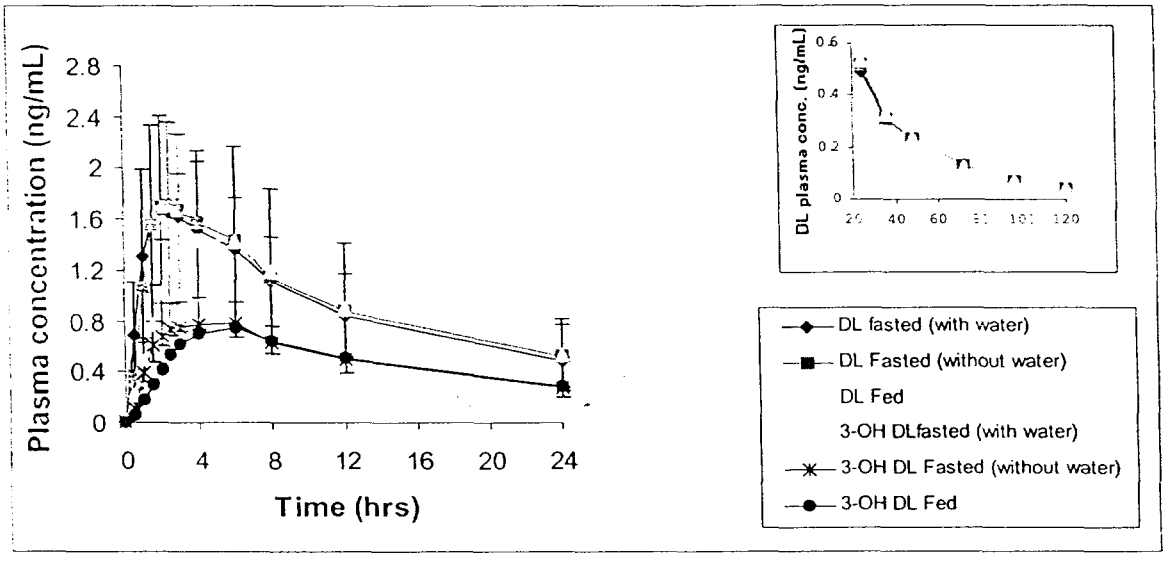

Figure 1. Mean DL and 3-OH DL and plasma concentration-time profiles following single administration of Clarinex Reditabs 5 mg under fasted conditions (with and without water) and under fed conditions.

Table 3. Mean (%CV) pharmacokinetic parameters of DL and 3-OH following single administration of Clarinex Reditabs 5 mg under fasted conditions (with and without water) and under fed conditions.

	Pharmacokinetic Parameters				
Treatment	**Cmax (ng/mL)**	**Tmax (hr)**	**AUCt (ng*hr/mL)**	**AUC inf (ng*hr/mL)**	**T1/2 (hr)**
	Desloratadine				
fasted with water	1.84 (38)	2.5 [redacted]	38.4 (62)	41.7 (76)	23.8 (36)
fasted without water	1.93 (41)	2.5 [redacted]	39.5 (63)	43 (77)	24.7 (45)
fed	1.6 (38)	4 [redacted]	38.1 (61)	41.1 (75)	23.6 (35)
	3-OH Desloratadine				
fasted with water	0.85 (34)	4 [redacted]	23.1 (30)	25.7 (25)	42.1 (107)
fasted without water	0.85 (31)	4 [redacted]	23.3 (27)	25.9 (24)	39.8 (69)
fed	0.79 (34)	6 [redacted]	22.5 (29)	24.7 (27)	34.5 (39)

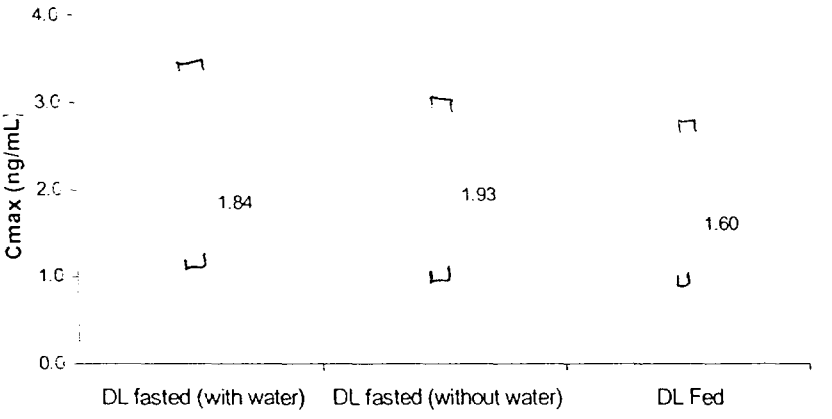

Figure 2. Individual DL Cmax values following single administration of: Clarinex Reditabs 5mg fasted (with water; without water), and under fed conditions.

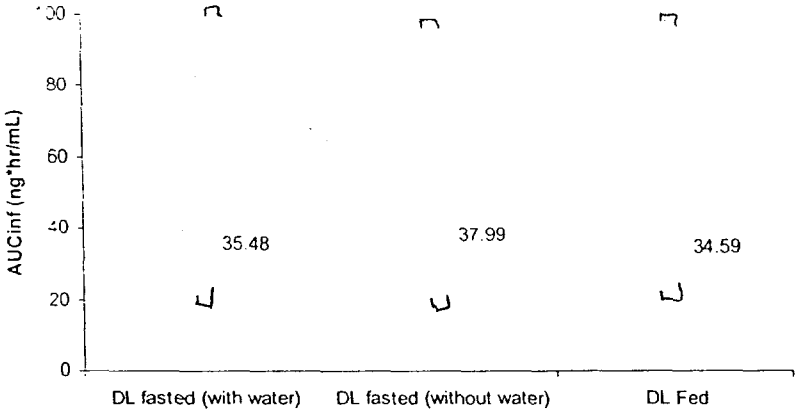

Figure 3. Individual DL AUCinf values following single administration of Clarinex Reditabs 5mg fasted (with water; without water), and under fed conditions.

Preliminary statistical analysis was performed to examine the extreme pharmacokinetic values and the impact of outliers on the overall results. It was found that exclusion of outliers did not change the overall bioequivalence conclusion of the study. Therefore, all subjects were included in the final statistical analysis.

Statistical comparisons of Cmax and AUC(I) values between treatments were performed. No statistically significant differences among treatments were observed for AUC(I) ($p>0.05$). However, statistically significant differences among treatments were observed ($p = 0.001$) for Cmax. The Cmax value for Treatment C was statistically less than that for Treatments A and B ($p<0.05$); however, the differences were small (<16%) and according to the sponsor, are considered not to be clinically relevant. This reviewer agrees with this statement. For the metabolite, although statistically significant differences were observed among some treatments, the differences were small (~ 7%) and are also considered not to be clinically relevant.

Overall, the results suggested that the bioavailability of DL under fasted (with and without water) and fed conditions was similar. Water and high-fat and high-caloric meal had no effect on the bioavailability of DL from the Redi-Tab tablet. The relative bioavailability and the 90% CIs for the log-transformed Cmax and AUC(I) DL and 3-OH DL are presented in Table 4.

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 Clarinex Reditabs 5 mg under fasted conditions (with and without water) and under fed conditions.

Comparison	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's findings
	Desloratadine				
Trt C TrtA	AUCinf	99.4	99.4	96-1.3	95.7-103.3
	Cmax	87.4	87.4	82-93	82-93
Trt C TrtB	AUCinf	97.3	97.3	94-101	93.7-101.1
	Cmax	84.3	84.3	79-90	79.12-89.7
Trt B Trt A	AUCinf	102	102.19	98-106	98.4-106.2
	Cmax	104	103.7	97-110	97.4-110.4
	3-OH DL				
Trt C TrtA	AUCinf	95.4	93.9	92-99	89.1-98.9
	Cmax	93.9	95.4	89-99	92.1-98.8
Trt C TrtB	AUCinf	94	93.6	91-97	90.7-97.3
	Cmax	92.6	92.7	88-98	87.9-97.6
Trt B Trt A	AUCinf	101	101.6	98-105	98-105.2
	Cmax	101	101.3	96-107	96.2-106.7

For both DL and 3-OH DL, the CIs of AUC(I) and Cmax for fed relative to fasted conditions (with and without water) and fasted (without water) relative to fasted (with water) met the ——— bioequivalence guideline criteria.

CONCLUSION AND DISCUSION

The results presented above indicate that water and a high-fat and high-caloric meal had no effect on the bioavailability of SCH 34117 and SCH 45581 from the Redi-Tab tablet. However, as it is observed in Table 3, food did increase DL median Tmax from 2.5 to 4 hours. The clinical relevance of this shift has been discussed with the medical reviewer and the conclusion reached is that this variation needs to be reflected in the label.

The ratio of DL Cmax under fed/fasted without water conditions resulted in a 90% CI of 79-90. This 21% decrease on the DL Cmax under fed compared to fasted without water conditions may not be clinically relevant.

Three out 30 subjects presented high DL AUCinf values. One of these subjects showed a ratio of 3-OH DL AUC/ DL AUC less than 10 suggesting slow metabolism. The presence of slow metabolism for DL has been observed in previous Clarinex ——→ ——————. The clinical relevance of these outliers on the safety of Clarinex should be evaluated by the medical reviewer. The sponsor will be requested to identify the enzymes responsible for the presence of slow metabolism observed in some

subjects.

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ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Dissolution

The Clarinex Reditabs tablet formulation used in this study, proposed dissolution method and specifications are listed below.

Table D1. Proposed dissolution method for Clarinex Reditabs

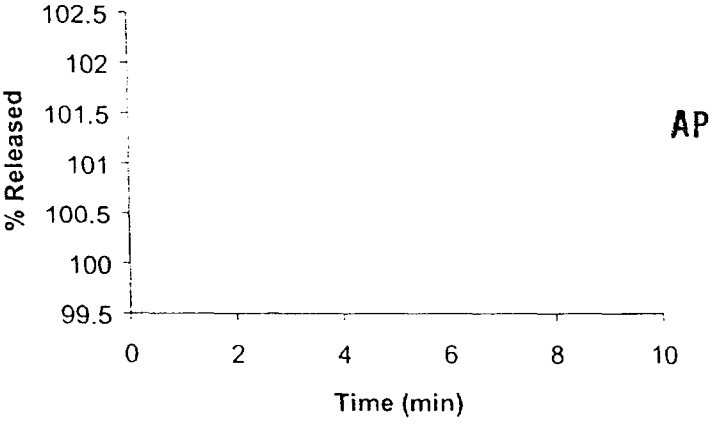
Method	
Apparatus:	USP apparatus II (paddle)
Detection:	[redacted]
Speed:	50 rpm
Temperature:	37 °C ± 0.5 °C
Medium:	500 mL of 0.1N HCL
Specification:	Q= [redacted] in 4 minutes

Table D2. Components for formula number 3566 (Clarinex Reditabs)

Ingredients	mg/tablet
SCH 34117 (Desloratadine), [redacted]	5.0
Gelatin EP/USNF	[redacted]
Mannitol EP/USP	
Aspartame EP/USNF	
Polacrilin Potassium USP	
Dye [redacted] Red [redacted]	
Flavor Tutti-Frutti [redacted]	
Citric Acid USP	
[redacted]	
Approximate tablet weight	**48.07**

Table D3. Dissolution data for Clarinex Reditabs

Time (min)	1	2	3	4	5	6	7	8	9	10	11	12	average
	Percent DL dissolved/dosage form												
2	102	103	102	100	101	101	101	87	96	102	101	101	**99.8**
4	102	104	103	101	102	102	102	100	102	103	101	102	**102**
6	102	104	103	101	101	102	102	101	103	103	101	102	**102**
8	102	104	103	101	102	102	102	102	103	103	101	102	**102**
10	102	104	103	101	102	102	102	102	103	103	101	102	**102**



COMMENTS

Batch number 39554-152 for Clarinex Redi-tab meets dissolution specifications. However, the sponsor will be requested to assess dissolution using a more discriminative method such as [redacted] rpm instead of 50 rpm.

APPEARS THIS WAY
ON ORIGINAL

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-312	Brand Name	Clarinex Reditabs 5 mg
OCPB Division (I, II, III)	II	Generic Name	Desloratadine, DL
Medical Division	DPADP	Drug Class	Antihistamine
OCPB Reviewer	Sandra Suarez-Sharp	Indication(s)	SAR, CIU
OCPB Team Leader	Young Moon Choi (acting)	Dosage Form	Rapidly disintegrating tablets
		Dosing Regimen	5mg QD
Date of Submission	December 20, 2000	Route of Administration	Oral
Estimated Due Date of OCPB Review	September 2001	Sponsor	Schering Corp.
PDUFA Due Date	October 21, 2001	Priority Classification	Standard
Division Due Date	October 01, 2001		

4 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	[redacted]	[redacted]	[redacted]	[redacted]
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	[redacted]	[redacted]	
Tabular Listing of All Human Studies	X	[redacted]	[redacted]	
HPK Summary	X	[redacted]	[redacted]	
Labeling	X	[redacted]	[redacted]	
Reference Bioanalytical and Analytical Methods	X	[redacted]	[redacted]	
I. Clinical Pharmacology	[redacted]	[redacted]	[redacted]	[redacted]
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	[redacted]	[redacted]	[redacted]	[redacted]
Healthy Volunteers-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:	X	2	2	
multiple dose:				
Patients-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:				
multiple dose:				
Dose proportionality -	[redacted]	[redacted]	[redacted]	[redacted]
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	[redacted]	[redacted]	[redacted]	[redacted]
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -	[redacted]	[redacted]	[redacted]	[redacted]
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

Population Analyses -		[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics		[redacted]	[redacted]	[redacted]
Absolute bioavailability:				
Relative bioavailability -		[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -		[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:	X	SINGLE	1	
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X	1	1	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies		[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X			
Literature References	X			
Total Number of Studies		2	2	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. • **Please submit in-study validation information for the analysis of DL and its metabolite in protocol P01216.**
QBR questions (key issues to be considered)		**1. Was the to-be-marketed formulation used in the pharmacokinetic studies?** **2. Was the Clarinex Reditab formulation bioequivalent to the Clarinex [redacted] and tablet formulations?** **3. Was the bioavailability of DL from the DL Reditab tablet affected by the presence of food and/or water?** **4. Are the proposed dissolution method and specifications supported by the data provided by the sponsor?**
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-312, HFD-850 (Electronic Entry or Lee), HFD-570 (Trout), HFD-870 (Fadiran, Hunt, Malinowski) CDR (B. Murphy)

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/s/

Sandra Suarez
10/10/01 05:55:44 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
10/11/01 04:21:18 PM
BIOPHARMACEUTICS
I concur

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-312	Brand Name	Clarinex RediTabs 5 mg
OCPB Division (I, II, III)	II	Generic Name	Desloratadine, DL
Medical Division	DPADP	Drug Class	Antihistamine
OCPB Reviewer	Sandra Suarez-Sharp	Indication(s)	SAR, CIU
OCPB Team Leader	Young Moon Choi (acting)	Dosage Form	Rapidly disintegrating tablets
		Dosing Regimen	5mg QD
Date of Submission	December 20, 2000	Route of Administration	Oral
Estimated Due Date of OCPB Review	September 2001	Sponsor	Schering Corp.
PDUFA Due Date	October 21, 2001	Priority Classification	Standard
Division Due Date	October 01, 2001		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:	X	SINGLE		
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X			
Literature References	X			
Total Number of Studies	[redacted]	2		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. • **Please submit in-study validation information for the analysis of DL and its metabolite in protocol P01216.**
QBR questions (key issues to be considered)		1. **Is the DL RediTab formulation bioequivalent to the DL tablet and [redacted] formulations?** 2. **Do water and high fat meal affect the PK of desloratidine and its metabolite?**
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-312, HFD-850 (Electronic Entry or Lee), HFD-570 (Trout), HFD-870 (Choi, Hunt, Malinowski)
CDR (B. Murphy)

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

/s/

Sandra Suarez
4/26/01 12:07:22 PM
BIOPHARMACEUTICS

Young-Moon Choi
4/26/01 02:39:03 PM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL