

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-952

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA:	21-952
Generic Name:	Loratadine
Proprietary Drug Name:	Claritin 10 mg LiquiGels
Indication:	Antihistamine
Dosage Form:	capsules
Strengths:	10 mg
Route of Administration:	Oral
Applicant:	Schering-Plough
Clinical Division:	DPAP (HFD-570)
Type of Submission:	Resubmission
Submission Date:	December 20, 2007
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader (acting):	Wei Qiu, Ph. D.

TABLE OF CONTENTS

ITEM	PAGE NUMBER
1. Executive Summary	2
1.1 Recommendation	2
1.2 Phase IV Commitments	2
1.3 Summary of Clinical Pharmacology Findings	2
2. Question-Based Review	3
2.1 General Attributes	3
2.2 General Biopharmaceutics	5
• Fed BE study	5
4. Appendices	7
4.1 Individual Study Reviews	7
• Study Protocol CL2006-09: Fed BE Study	7

1. EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology II (OCP / DCP-2) has reviewed the complete response to NDA 21-952 submitted on December 20, 2007. We found the complete response acceptable from an OCP standpoint. There are no labeling comments to the proposed labeling for this product.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Claritin® 10 mg liquiGel capsules contain loratadine, an antihistamine. The proposed dose in adults and children 6 years and older is one capsule (10 mg) QD. The recommended Claritin dose of 10 mg in the pediatric population (6 years and older) was based on a cross-study comparison of the PK of Claritin in adults and pediatrics subjects and on the safety profile of loratadine in both adults and pediatric patients at doses equal to or higher than the recommended doses. The clinical pharmacology of loratadine has been reported in previous submissions. This review will focus on the findings related to food effect comparison between Claritin Tablets and Claritin LiquiGels.

The present submission is a complete response to the approvable letter issued on January 12, 2007. It contains the results of a fed BE study entitled: "A Single-Dose, Comparative, Randomized, Crossover Bioequivalence Study of Two Dosage Forms of Loratadine: 10 mg Soft Gelatin Capsule and 10 mg Claritin Tablet under Fed Conditions".

The Claritin LiquiGel capsule was not bioequivalent to the Claritin 10 mg tablet in the presence of food since the loratadine C_{max} 90% CI (94.4-143.8) was out of BE acceptance criteria. In the presence of high fat meal, the mean C_{max} (geometric mean) of loratadine was about 16% greater for the Liqui-Gel formulation compared to the tablet formulation (Table 1.3.1).

Table 1.3.1. Geometric means, point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of loratadine and desloratadine following single administration of the treatments

Parameter	Test	Reference	% ratio	90% CI
Loratadine				
AUCt	10421	10318.84	100.99	90.11, 113.19
AUCinf	11102.52	11097.47	100.05	89.3, 112.08
Cmax	3338.16	2864.8	116.52	94.42, 143.8
Desloratadine				
AUCt	43569.34	44347.17	98.25	(93.35, 103.4)
AUCinf	44593.38	45408.58	98.20	(93.37, 103.29)
Cmax	3946.90	3697.23	106.75	(95.89, 118.85)

Based on the package insert for the prescribed Claritin Tablets, drowsiness is observed after doses of Claritin tablets of 20 mg and higher. Although the Claritin tablet and liquiGel formulations for claritin were not bioequivalent, the 16% higher loratadine Cmax observed for the liquiGel formulation in the presence of food compared to that for the Claritin tablet in the presence of food may not be clinically relevant for the reasons listed below:

- There were two subjects taking Claritin Tablet with food whose Cmax values were higher than the highest value of Cmax observed for the subject taking the liquiGel formulation with food.
- Loratadine is classified as a highly variable drug. For this kind of drugs, bioequivalence is usually assessed using a replicated design. The study design used to evaluate the comparative effect of food between the tablet and liquiGel formulation of Claritin was a non-replicate cross-over design. This suggests that if a replicate design would have been used for this drug, the tablet and the liquiGel formulations may have been bioequivalent in the presence of food.

Therefore, this reviewer believes that no additional directions (such as "take on an empty stomach. Taking with food may cause drowsiness") are required to advise consumers of the safe and effective use of this product when taking with food.

2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Claritin® 10 mg liquiGel capsules contain loratadine, an antihistamine. The proposed dose in adults and children 6 years and older is one capsule (10 mg) QD for the temporarily relieves of symptoms due to hay fever or other upper respiratory allergies. Claritin® 10 mg tablets was approved by the Agency on April 12, 1993 under NDA 19-658 for the temporarily relieves of symptoms due to hay fever or other upper respiratory allergies in children (>6 years of age), adolescent and adults. Claritin is also available as Claritin-D 12 hrs (loratadine 5 mg/pseudoephedrine 120 mg) (approved for adults and adolescents 12 years and older); Claritin-D 24 hrs (loratadine 10 mg/pseudoephedrine 240 mg) (approved for adults and adolescents 12 years and older); Claritin Reditabs (10 mg) (approved for adults and children 6 years and older); Claritin Chewable tablet (5 mg); and Claritin Syrup (1mg/mL) (approved for adults and children 2 years and older). Claritin became available as OTC drug in the above formulations in December 2002. Since coming into the OTC market, many generic formulations of loratadine are now available.

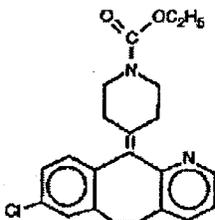
Claritin® liquiGels received an approvable action under NDA 21-952 on January 12, 2007. The approvable letter requested that the sponsor add an additional new statement in the Directions Section of the Drug Facts labeling as follows: "take on an empty stomach. Taking with food may cause drowsiness". These recommendations were based on the findings (Study CL205-17) of an increased exposure to loratadine (C_{max} and AUC) observed when Claritin® liquiGels were administered with food. The administration of Claritin® Liqui-Gels™ with food increased the loratadine C_{max} by 53%, AUC_{0-t} by 121%, and AUC_{0-∞} by 118%. No significant change in desloratadine PK.

The sponsor believes that there is no reason to conclude that this increased exposure signified anything more than the known variability of loratadine data. In addition, there was no significant food effect for the active metabolite desloratadine. Therefore, in previous communications the sponsor proposed with the Agency to undertake a comparison of the LiquiGels capsules to the Claritin® 10 mg tablets under fed conditions. If these products exhibit similar bioavailability under fed condition, there would be no requirement to include a new statement in the Drugs Facts labeling as proposed by the Agency. The Agency agreed with this proposal on a teleconference dated November 30, 2006 (refer to meeting minutes dated December 15, 2006).

The present submission is a complete response to the approvable letter issued to the sponsor on January 12, 2007. It contains the results of a fed BE study entitled: "A Single-Dose, Comparative, Randomized, Crossover Bioequivalence Study of Two Dosage Forms of Loratadine: 10 mg Soft Gelatin Capsule and 10 mg Claritin Tablet under Fed Conditions".

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

Drug Substance: The active pharmaceutical ingredient in Claritin® Liqui- Gels™ capsules is Loratadine USP. Loratadine is a white to off-white powder not soluble in water, but very soluble in acetone, alcohol, and chloroform. It has a molecular weight of 382.89, and empirical formula of C₂₂H₂₃ClN₂O₂. Its chemical name is ethyl 4-(8-chloro-5, 6-dihydro- 11 H-benzo[5,6]cyclohepta [1,2- b]pyridin-11- ylidene)-1-piperidinecarboxylate. It has the following formula:



Drug Product: Claritin® Liqui- Gels™ is an oval, clear blue liquid filled (soft gel) capsules. Each capsule contains 10 mg loratadine. The components and composition of the formulation are provided in Table 2.1.1.

Table 2.1.1. Target composition: Claritin Liqui- Gels™ Capsules.

		Drug Substance	10
Loratadine USP	USP and in-house		
Caprylic/Capric Acids	Vendor		
Povidone USP	USP		
Polysorbate 80 NF/FCC	NF		
	NF		
Gelatin NF	NF		
Sorbitol Glycerin	Vendor		
Dye, Blue # I, FD&C	Vendor		
Water, Purified USP	USP		

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2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

Loratadine is an antihistamine, and is available in several approved products as OTC medications.

INDICATION, DOSAGE AND ADMINISTRATION (as per proposed labeling for the carton)

The sponsor's proposed indication for Claritin® Liqui-Gels™ capsules is to treat temporarily relief symptoms due to hay fever or other upper respiratory allergies, such as runny nose, itchy and watery eyes, sneezing, and itching of the nose or throat for adults and children 6 years and over, 1 capsule daily.

2.2 General Biopharmaceutics

2.2.1 What is the relative bioavailability of Claritin liquiGel formulation compared to Claritin Tablet under fed condition?

The PK of loratadine and desloratadine from the liquiGel versus the tablet Claritin formulations was evaluated in a two-way crossover design, single dose study under fed condition. In this study (CL2006-09) female and male volunteers (36) received the following treatment in a randomized fashion:

TEST PRODUCT: Claritin Liqui -Gels™ Capsules (loratadine 10 mg)

REFERENCE PRODUCT: Claritin 10 mg 24 hour TABLETS

Each dose was separated by a 14-day washout interval. The FDA standardized high fat breakfast was served to each subject. Blood samples were collected at pre-dose (0 hour) and post-dose at study hours 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 120 for loratadine and desloratadine determination. Loratadine and desloratadine were analyzed using a LC-MS/MS method.

The Claritin Liqui-Gel capsule was not bioequivalent in the presence of food to the Claritin 10 mg tablet since the loratadine C_{max} 90% CI (94.4-143.8) were out of BE acceptance criteria. Under fed condition, the mean C_{max} (geometric mean) of loratadine was about 16% greater from the Liqui-Gel formulation compared to the tablet formulation (Table 2.2.1.1).

Table 2.2.1.1. Geometric means, point estimates and 90% confidence intervals for the log-transformed C_{max} and AUC_{inf} values of loratadine and desloratadine following single administration of the treatments

Parameter	Test	Reference	% ratio	90% CI
Loratadine				
AUC _t	10421	10318.84	100.99	90.11, 113.19
AUC _{inf}	11102.52	11097.47	100.05	89.3, 112.08
C _{max}	3338.16	2864.8	116.52	94.42, 143.8
Desloratadine				
AUC _t	43569.34	44347.17	98.25	(93.35, 103.4)
AUC _{inf}	44593.38	45408.58	98.20	(93.37, 103.29)
C _{max}	3946.90	3697.23	106.75	(95.89, 118.85)

Based to the package insert for the prescribed Claritin Tablets, drowsiness is observed after doses of Claritin tablets of 20 mg and higher. Although the tablet and liquiGel formulations for Claritin were not bioequivalent, the 16% higher C_{max} observed in the presence of food for the liquiGel formulation compared to the tablet may not be clinically relevant for the reasons listed below:

- There were two subjects taking Claritin Tablet whose C_{max} was higher than the highest value of C_{max} observed for the liquiGel formulation (Figure 2.2.1.1).
- Loratadine is classified as highly variable drug. For this kind of drugs, bioequivalence is usually assessed using a replicated design. This suggests that if the replicate design would have been used for this drug, the tablet and the liquiGel formulation may have been bioequivalent in the presence of food.

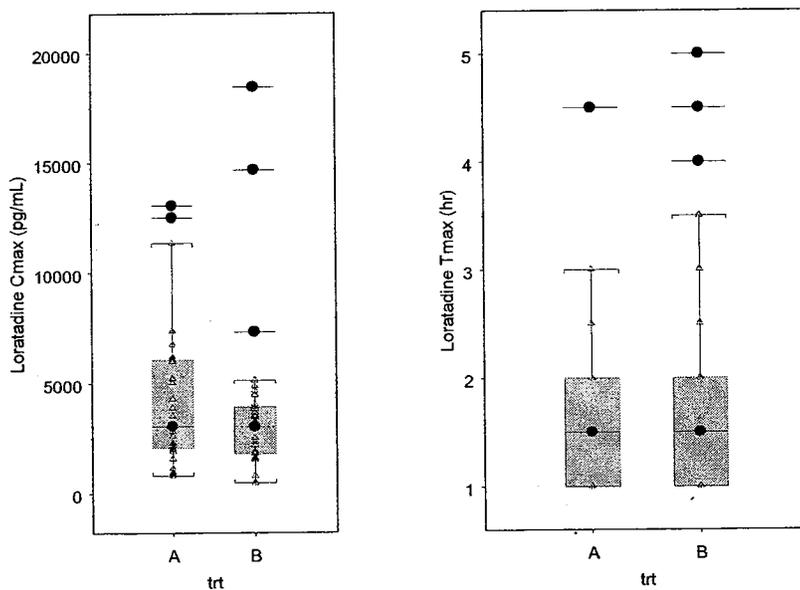


Figure 2.2.1.1. Individual loratadine C_{max} and T_{max} values following single administration of the treatments: **TRT A:** Claritin Liqui-Gels capsules 10 mg and **TRT B:** Claritin 10 mg tablets to 33 male/female healthy volunteers.

Therefore, this reviewer believes that no additional directions (such as "take on an empty stomach. Taking with food may cause drowsiness") are required to advise consumers of the safe and effective use of this product when taking with food.

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4. APPENDIX

4.1 Individual Study Reports

"A Single-Dose, Comparative, Randomized, Crossover Bioequivalence Study of Two Dosage Forms of Loratadine: 10 mg Soft Gelatin Capsule and 10 mg Claritin® Tablet under Fed Conditions"

Study no.: CL2006-09
Development Phase of Study: Phase I
Principal investigator: Alan K. Copa, Pharm. D.
625 De Mers Avenue
East Grand Forks, MN 56721

Study Dates: February 26, 2007- March 17, 2007

Objectives

Primary:

- to compare the relative bioavailability of Claritin Liqui-Gels™ Capsules (loratadine 10 mg) with Claritin 10 mg 24 hour Tablets in healthy adult non-smoking subjects under non-fasting conditions (after a standardized high fat breakfast).

Study Population

The mean demographic data for subjects included in the study, including standard deviations, subjects, and for all subjects grouped by gender is shown in Table 1.

Table 1. Summary of Mean Demographic Data (±SD)

	All Subjects (N=36)	Males (N=25)	Females (N=11)
Age	26.2 (:17.5)	25.4 (:17.5)	28.0 (:17.6)
Weight (lbs)	170.3 (:127.5)	178.2 (:125.9)	152.4 (:122.9)
Height (in.)	68.5 (:14.0)	70.4 (:12.9)	64.3 (:12.6)
BMI	25.4 (:12.8)	25.2 (:12.6)	25.9 (:13.2)

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This single dose, randomized, two-period, two-treatment, two-sequence, crossover study was conducted to compare the relative bioavailability of two formulations of Claritin (Liqui-Gels™ Capsules (loratadine 10 mg) or 10 mg 24 hour tablets) under non-fasting conditions after a standardized high fat breakfast. In each study period, a single 10 mg dose was administered to all subjects following an overnight fast of at least 10 hours and following the completion of an FDA standardized high fat breakfast 30 minutes prior to dosing. Subjects received the following treatments:

TEST PRODUCT: Claritin Liqui -Gels™ Capsules (loratadine 10 mg)
Manufactured for Schering-Plough Health Care Products, Inc.

Lot 250747; Exp. N/A

REFERENCE PRODUCT: Claritin 10 mg 24 hour TABLETS
Distributed by Schering-Plough HealthCare Products, Inc.
Lot 6-RXF-34; EXP DEC 08

Each dose was separated by a 14-day washout interval. The FDA standardized high fat breakfast served to each subject consisted of the following:

- two eggs fried in butter
- two slices of toast with butter
- two strips of bacon
- four ounces of hash brown potatoes
- 8 fluid ounces (240 mL) of whole milk

At 4 and 9 hours after dose administration, standardized meals and beverages were provided to each subject. In addition, a standardized snack was served at approximately 14.5 hours postdose. All meals were free from grapefruit, xanthine-, and caffeine-containing products. Subjects refrained from engaging in strenuous activities at any time during the confinement period.

PHARMACOKINETIC MEASUREMENTS

In each study period, blood samples were collected at pre-dose (0 hour) and post-dose at study hours 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 120 for loratadine and desloratadine determination.

Analytical Method

An automated extraction procedure using solid phase extraction and analysis of the extract by LC-MS/MS was developed and validated for the determination of Loratadine and Descarboethoxy Loratadine in human plasma containing Sodium - Heparin as the anticoagulant. The standard curve ranged from _____

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_____ was used to monitor the precursor and product ions for both the analytes, Loratadine and Descarboethoxy Loratadine (Desloratadine), and internal standards, Loratadine-ds and Descarboethoxy Loratadine-d4 (Desloratadine-d4). Samples were analyzed by _____ on April 11, 2007 to May 6, 2007.

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SAFETY MEASUREMENTS

Safety was evaluated from the results of spontaneously reported signs and symptoms, scheduled physical examinations, measurements of vital signs, 12-lead ECGs, and clinical laboratory evaluations. All adverse events were recorded.

Concomitant therapy

Subjects were not allowed to use prescription medications during the 14 days preceding the study and throughout the study. Subjects were also not allowed to use non-prescription medications (except acetaminophen) during the 14 days preceding the study and throughout the study. All

subjects were queried regarding concomitant medication prior to each study period and at each ambulatory visit. Subjects 02, 20, 24, 32, and 35 took concomitant medications over the course of the study.

DATA ANALYSIS

Pharmacokinetic Data Analysis

The analytical data were used to calculate the pharmacokinetic parameters: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, k_e, and t_{1/2}. Pharmacokinetic variables were calculated from the plasma concentration data using the WinNonLin software for a non-compartmental model.

Statistical Analysis

Summary statistics were provided for the pharmacokinetic parameters and plasma concentrations at each time point. The derived pharmacokinetic parameters were statistically analyzed using a crossover analysis of variance model. The effects due to sequence, subject within sequence, period and treatment were extracted.

Following In-transformation, AUC_{0-t}, AUC_{0-inf}, and C_{max} results was compared between treatment groups using the two one-sided test procedure. The analysis procedure utilized the following analysis of variance model:

Response = treatment + period + sequence + subject (sequence).

The error term 'subject within sequence' was utilized for the test of sequence effect. One loratadine 10 mg soft gelatin capsule under fed conditions was considered bioequivalent to one 10 mg loratadine tablet under fed conditions if the 90% confidence intervals around the ratio of the geometric means for loratadine and desloratadine In-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} values fall within 80-125%. Preliminary analysis included examining the pharmacokinetic parameters for extreme values. The impact of any outliers on the results of the analyses was evaluated.

RESULTS

Analytical Method

In-Study Validation for Loratadine

Matrix	Human Plasma	
Sample Volume Required Storage Conditions Extraction Procedure	0.200 mL -20°C Solid phase extraction	
Concentration Range	20.00 pg/mL to 4000.00 pg/mL	
HPLC Procedure	reversed-phase liquid chromatography	
Detection	Tandem mass spectrometry	
Regression Type	linear	
Coefficient of Determination	$r^2 \geq 0.9942$	
Between-Batch Accuracy	standards QCs	95.1% - 102.5% 103.5% - 110.4%
Between-Batch CV	standards QCs	3.32% - 8.66% 3.13% - 5.37%

Within-Batch	Accuracy CV	104.0% -- 109.6% 2.13% - 5.98%
Recovery	Loratadine Loratadine-ds	71.9% 39.0%
Stability in human plasma	Room temp Freeze/thaw Long term	17:38 hours-minutes 5 cycles 90 days (ongoing)
Loratadine Solution Stability	at room temp at 4°C	73:38 hours-minutes 402:53 hours- minutes
Loratadine-d5 Solution Stability	at room temp at 4°C	74:31 hours-minutes 401:08 hours- minutes
LLOQ (Accuracy / CV)	90.2% / 3.95%	
Processed Stability	at 4°C	47:56 hours-minutes
Dilution Integrity (v:v sample-blank)	1:9/3:1	99.9% / 100.0%
Ion Suppression	LLOQ (CV) ULOQ (CV)	3.29% 2.04%

In-Study Validation for Desloratadine

Matrix	Human Plasma	
Sample Volume Required Storage Conditions Extraction Procedure	0.200 mL -20°C Solid phase extraction	
Concentration Range	20.00 pg/mL to 4000.00 pg/mL	
HPLC Procedure	reversed-phase liquid chromatography	
Detection	Tandem mass spectrometry	
Regression Type	linear	
Coefficient of Determination	$r^2 \geq 0.9992$	
Between-Batch Accuracy	standards QCs	93.7% - 103.0% 99.3% - 105.2%
Between-Batch CV	standards QCs	0.93%-3.51% 2.03% - 3.69%
Within-Batch	Accuracy CV	97.0% - 100.6% 1.00% - 4.54%
Recovery	Descarboethoxy Loratadine Desloratadine-d4	58.9% 63.5%

Stability in human plasma	Room temp Freeze/thaw Long term	17:22 hours-minutes 5 cycles 90 days (ongoing)
Loratadine Solution Stability	at room temp at 4°C	74:20 hours-minutes 401:53 hours-minutes
Loratadine-d5 Solution Stability	at room temp at 4°C	74:27 hours-minutes 400:08 hours-minutes
LLOQ (Accuracy / CV)	90.2% / 3.95%	
Processed Stability	at 4°C	66:15 hours-minutes
Dilution Integrity (v:v sample-blank)	1:9/3:1	103.8%/103.2%
Ion Suppression	LLOQ (CV) ULOQ (CV)	2.66% 1.21%

Pharmacokinetic Results

A total of 33 subjects completed the study. Three (3) subject withdrew due to personal reasons (2) or adverse event (vomiting=1). Subjects 14 and 29 withdraw prior to period II dosing. Subject 16 withdraw prior to study hour 11.5/period I. The mean plasma concentration-time profiles for loratadine and desloratadine following administration of the treatments are shown in Figures 1 and 2, respectively. The mean pharmacokinetic parameters for loratadine and desloratadine are summarized in Table 2. Individual loratadine C_{max} and AUC_t values following the administration of the treatments are shown in Figures 3 and 4, respectively. Likewise, individual desloratadine C_{max} and AUC_t following administration of the treatments are represented in Figures 5 and 6, respectively.

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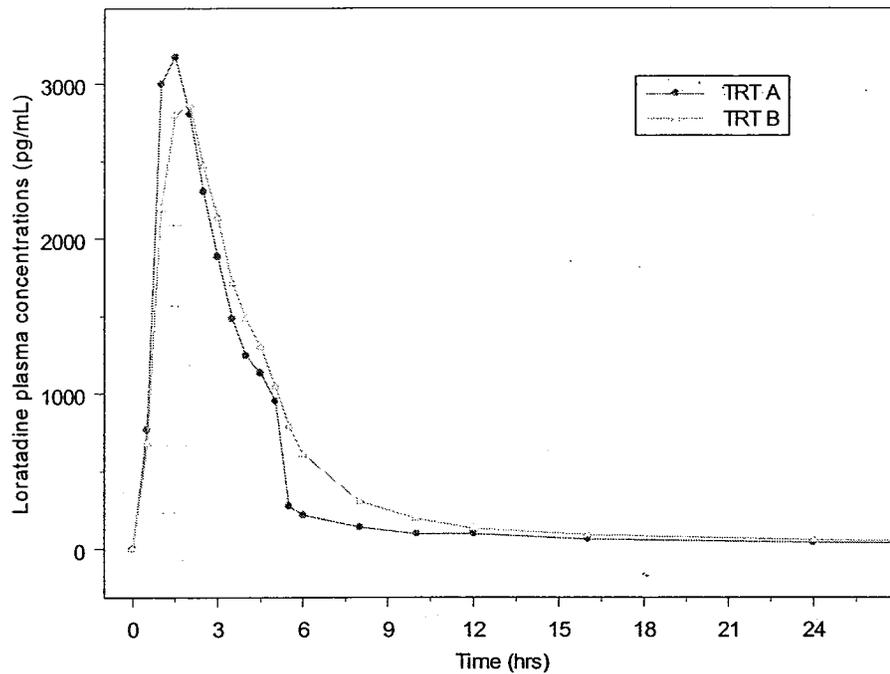


Figure 1. Mean loratadine plasma concentration-time profiles following single administration of **TRT A:** Claritin Liqui-Gels capsules 10 mg and **TRT B:** Claritin 10 mg tablets to 33 male/female healthy volunteers.

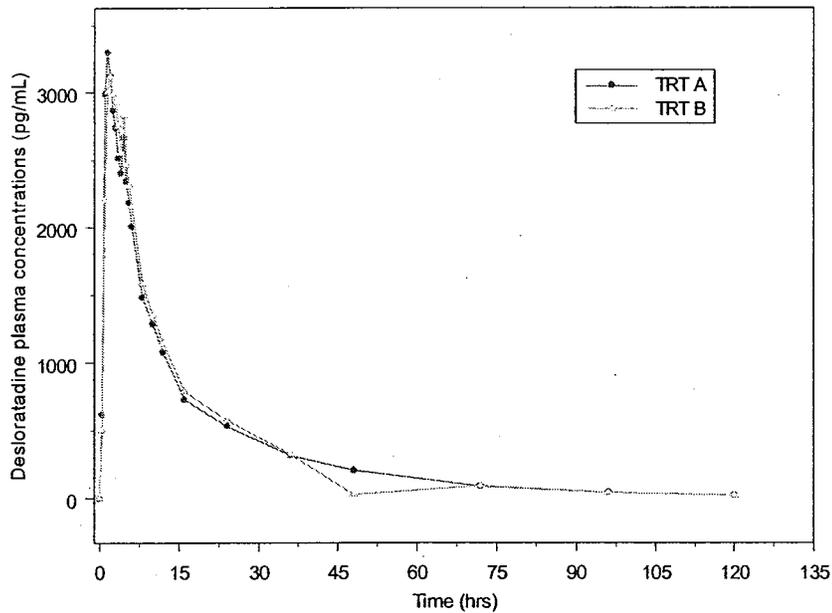


Figure 2. Mean desloratadine plasma concentration-time profiles following single administration of **TRT A:** Claritin Liqui-Gels capsules 10 mg and **TRT B:** Claritin 10 mg tablets to 33 male/female healthy volunteers.

Table 2. Mean (%CV) pharmacokinetic parameters of loratadine and desloratadine following single administration of the treatments

Treatment	Mean (SD) PK Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCinf (ng*hr/mL)	T1/2 (hr)
Loratadine (n=33)					
TRT T	4323 (75)	1.76 (54.2)	14015 (108)	14820 (104.9)	20.6 (77)
TRT R	3742 (97)	1.98 (50.2)	14123 (116.3)	15040 (113)	23.5 (82)
Desloratadine (n=32)					
TRT T	4273 (37)	2.14 (64)	45570 (28)	46619 (29)	23.4 (21)
TRT R	3933 (38)	2.5 (54)	47412 (43)	48505 (43)	22.19 (24)

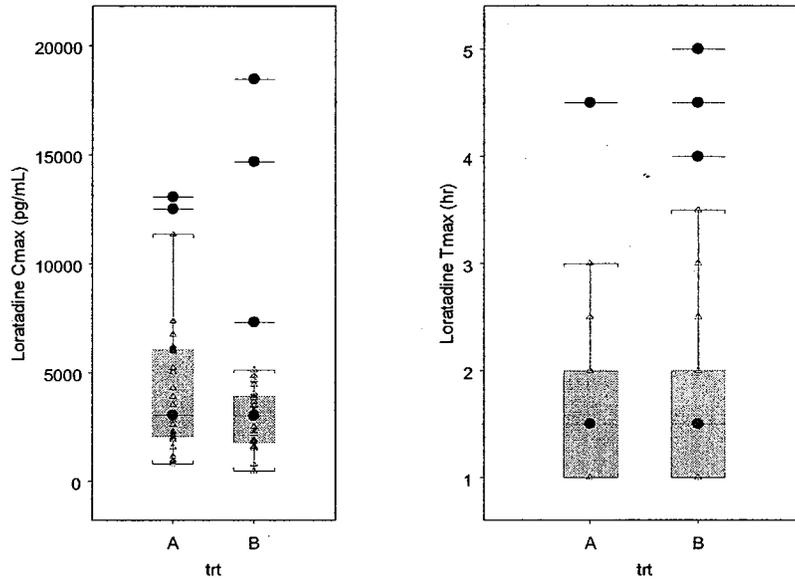


Figure 3. Individual loratadine Cmax and Tmax values following single administration of the treatments: **TRT A:** Claritin Liqui-Gels capsules 10 mg and **TRT B:** Claritin 10 mg tablets to 33 male/female healthy volunteers.

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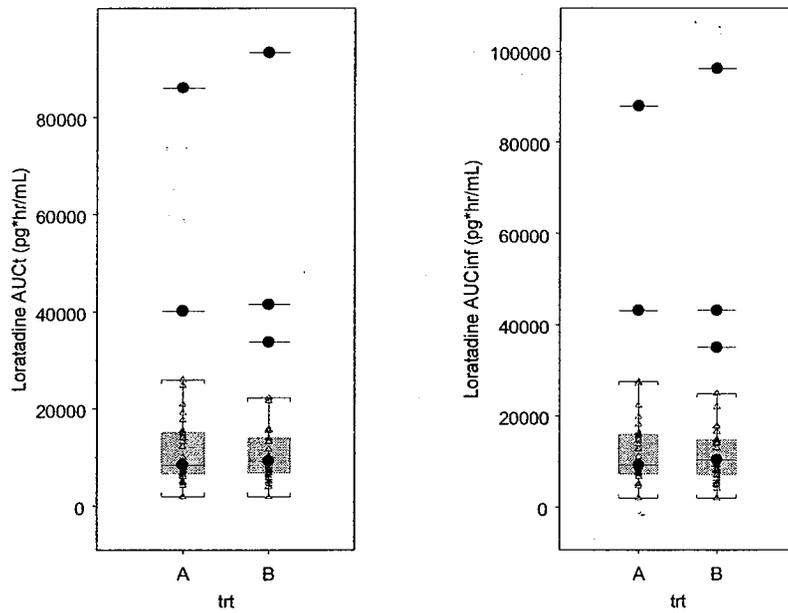


Figure 4. Individual loratadine AUCt and AUCinf values following single administration of the treatments: **TRT A:** Claritin Liqui-Gels capsules 10 mg and **TRT B:** Claritin 10 mg tablets to 33 male/female healthy volunteers.

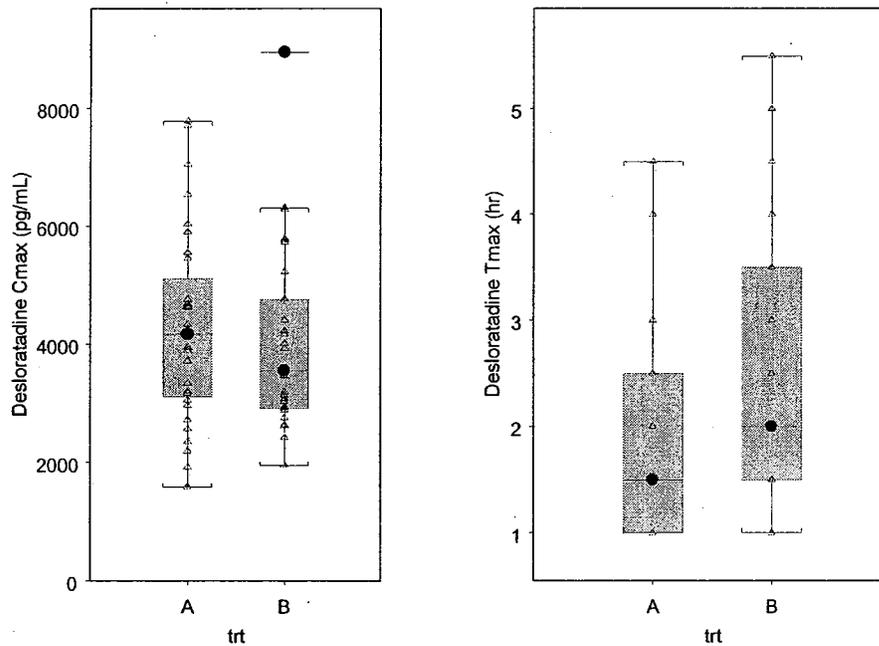


Figure 5. Individual desloratadine Cmax and Tmax values following single administration of the treatments: **TRT A:** Claritin Liqui-Gels capsules 10 mg and **TRT B:** Claritin 10 mg tablets to 32 male/female healthy volunteers.

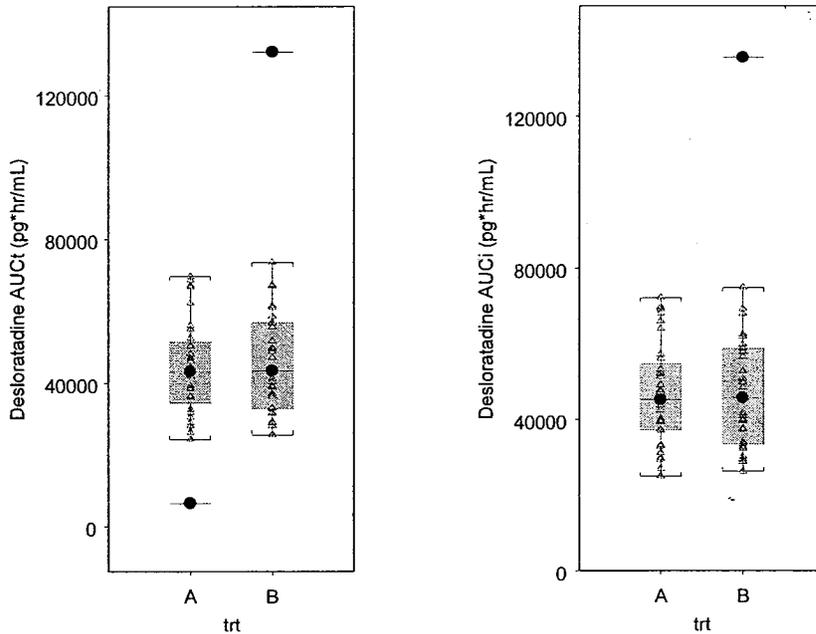


Figure 6. Individual desloratadine AUCt and AUCinf values following single administration of the treatments: **TRT A:** Claritin Liqui-Gels capsules 10 mg and **TRT B:** Claritin 10 mg tablets to 32 male/female healthy volunteers.

Plasma concentrations from 33/36 subjects were used in the statistical analysis of loratadine. Plasma concentrations from 32/36 subjects were used in the statistical analysis of desloratadine. Subject 27 was excluded from the statistical analysis of desloratadine due to a predose plasma concentration greater than 5% of Cmax. The point estimates and the 90% CIs for the log-transformed Cmax, AUCt and AUCinf for LNG and EE are presented in Table 3. The AUC(t), AUCinf, and Cmax CI for loratadine and desloratadine of R vs. T met the 80-125% bioequivalence guideline.

Table 3. Geometric means, point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of loratadine and desloratadine following single administration of the treatments

Parameter	Test	Reference	% ratio	90% CI
Loratadine				
AUCt	10421	10318.84	100.99	90.11, 113.19
AUCinf	11102.52	11097.47	100.05	89.3, 112.08
Cmax	3338.16	2864.8	116.52	94.42, 143.8
Desloratadine				
AUCt	43569.34	44347.17	98.25	(93.35, 103.4)
AUCinf	44593.38	45408.58	98.20	(93.37, 103.29)
Cmax	3946.90	3697.23	106.75	(95.89, 118.85)

Summary of Findings

- The Claritin Liqui-Gel capsule was not bioequivalent in the presence of food to the Claritin 10 mg tablet since the loratadine C_{max} 90% CI were out of BE acceptance criteria (94.4-143.8).
- Food increased the mean C_{max} (geometric mean) of loratadine by about 16% from the Liqui-Gel formulation compared to the tablet formulation.

Conclusion

Based to the package insert for the prescribed Claritin Tablets, drowsiness is observed after doses of Claritin tablets of 20 mg and higher. Although the tablet and liquiGel formulations for Claritin were not bioequivalent, the 16% higher C_{max} observed in the presence of food for the liquiGel formulation compared to the tablet may not be clinically relevant for the following reasons:

- There were two subjects taking Claritin Tablet whose C_{max} was higher than the higher value of C_{max} observed for the liquiGel formulation.
- Loratadine is classified as highly variable drug. For this kind of drugs, bioequivalence is usually assessed using a replicated design. This suggests that if the replicate design would have been used for this drug, the tablet and the liquiGel formulation may have been bioequivalent in the presence of food.

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this page is the manifestation of the electronic signature.**

/s/

Sandra Suarez
4/24/2008 02:38:27 PM
BIOPHARMACEUTICS

Wei Qiu
4/25/2008 02:38:44 PM
BIOPHARMACEUTICS

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION**

**Clinical Pharmacology & Biopharmaceutics
(HFD 860/870/880)
Tracking/Action Sheet for Formal/Informal Consults**

From: Shinja Kim

To: **DOCUMENT ROOM (LOG-IN and LOG-OUT)**
Please log-in this consult and review action for the specified IND/NDA submission

DATE: 01/24/07

IND No.:
Serial No.:

NDA No.
21-952 (s014)

DATE OF DOCUMENT
12/20/06

NAME OF DRUG
Claritin Liqui-gels capsule

PRIORITY CONSIDERATION

Date of informal/Formal Consult:
01/24/07

NAME OF THE SPONSOR: Schering-Plough, Inc.

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

- | | | |
|--|--|--|
| <input type="checkbox"/> PRE-IND | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING | <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> IN-VITRO METABOLISM | <input type="checkbox"/> IN-VIVO WAIVER REQUEST | <input type="checkbox"/> CORRESPONDENCE |
| <input checked="" type="checkbox"/> PROTOCOL | <input type="checkbox"/> SUPAC RELATED | <input type="checkbox"/> DRUG ADVERTISING |
| <input type="checkbox"/> PHASE II PROTOCOL | <input type="checkbox"/> CMC RELATED | <input type="checkbox"/> ADVERSE REACTION REPORT |
| <input type="checkbox"/> PHASE III PROTOCOL | <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> ANNUAL REPORTS |
| <input type="checkbox"/> DOSING REGIMEN CONSULT | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS | <input type="checkbox"/> FAX SUBMISSION |
| <input type="checkbox"/> PK/PD- POPPK ISSUES | <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others) | <input type="checkbox"/> OTHER (SPECIFY BELOW):
[] |
| <input type="checkbox"/> PHASE IV RELATED | | |

REVIEW ACTION

- | | | |
|---|--|--|
| <input checked="" type="checkbox"/> NAI (No action indicated) | <input type="checkbox"/> Oral communication with
Name: [] | <input type="checkbox"/> Formal Review/Memo (attached) |
| <input type="checkbox"/> E-mail comments to: | | <input type="checkbox"/> See comments below |
| <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> | <input type="checkbox"/> Comments communicated in
meeting/Telecon. see meeting minutes dated: | <input type="checkbox"/> See submission cover letter |
| <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as
appropriate and attach e-mail) | | <input type="checkbox"/> OTHER (SPECIFY BELOW):
[Comment] |

REVIEW COMMENT(S)

- NEED TO BE COMMUNICATED TO THE SPONSOR HAVE BEEN COMMUNICATED TO THE SPONSOR

COMMENTS/SPECIAL INSTRUCTIONS: In the approvable letter for NDA21-592, Agency recommended to revise the label as follows: "take on an empty stomach. Taking with food may cause drowsiness". However, the sponsor did not want this statement on the labeling, and currently a protocol for food effect study is submitted (CL2006-09). Study CL2006-09 (randomized, single-dose, 2-way crossover) will compare the PK of 10 mg Claritin Liqui-gels capsule (test) to Claritin Tablet 10 mg (reference) under fed conditions in 24 healthy volunteers. There will be at least 14 days washout period between the doses. Blood samples will be taken at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hrs post dose. Testing for BE will be conducted in accordance with the FDA guidance ("Statistical procedures for BE studies using a standard 2-treatment crossover design"); log- transformation (natural log), AUC_∞, AUC_t, and Cmax will be compared between treatment groups using the two one-sided ANOVA analysis test procedure. The test product will be considered bioequivalent to the reference product if the 90% confidence intervals around the ratio of the geometric least square mean values of AUC and Cmax for both loratadine and desloratadine fall within 80 to 125%. Preliminary analysis will include examining the PK parameters for extreme values. The impact of any outliers on the results of analyses will be evaluated.

Overall, the protocol is acceptable. No further comment is needed at this time.

SIGNATURE OF REVIEWER: Shinja Kim

Date 01/26/07 _____

SIGNATURE OF TEAM LEADER: Tayo Fadiran

Date 01/26/07 _____

CC.:

Project Manager: Elaine Abraham Date _____

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

/s/

Shinja Kim
1/26/2007 03:15:22 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
1/26/2007 03:25:47 PM
BIOPHARMACEUTICS
i concur.

CLINICAL PHARMACOLOGY REVIEW

NDA 21-952:	Submission Date: 15-March 2006
Brand Name:	Claritin® LiquiGels™ Capsule
Generic Name:	Loratadine
Reviewer:	Shinja Kim, Ph.D.
Team Leader:	Emmanuel Fadiran, Ph. D.
OCPB Division:	DCP 2
ORM Division:	DNCE
Sponsor:	Schering-Plough HealthCare Products, Inc.
Submission Type:	Original (S000)
Formulation; Strength(s):	Loratadine 10 mg
Indication:	Temporally relief of symptoms due to hay fever or other respiratory allergies for adults and children 6 years and over.

TABLE OF CONTENTS

ITEM	PAGE NUMBER
1. Executive Summary	2
1.1 Recommendation	2
1.2 Phase 4 Commitment (none)	2
1.3 Summary of Clinical Pharmacology and Biopharmaceuticals Findings	3
2. Question-Based Review	4
2.1 General attribute of Loratadine	4
2.2 General Clinical Pharmacology	5
2.5 General Biopharmaceutics	6
2.6 Analytical Section	15
3. Labeling Recommendation	15
4. Appendix	
4.1 Proposed labeling	16
4.2 OCP filing/Review Form	17

1. EXECUTIVE SUMMARY

1. **Recommendation:** The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology studies submitted to NDA 21-952, and found that the data from Study CL2004-02 showed that Claritin® Liqui-Gels™ capsules did not meet bioequivalence (BE) criteria for loratadine C_{max} (90% CI = 0.7875-0.9996) but met the BE criteria for loratadine AUC as well for the C_{max} and AUC of its active metabolite, desloratadine. However, OCP recommends approval the NDA subject to favorable DSI report. The scientific rationale of this recommendation is as follows (see details on pages 9-11):

- Desloratadine is two to four times more potent than parent loratadine as shown by in vitro and preclinical animal antihistamine activity studies. Additionally, the systemic exposure to the active metabolite (AUC) is about four times that of the parent drug although both have similar C_{max}.
- Desloratadine concentrations from 5 mg Clarinex are similar to 10 mg Claritin tablet (NDA 21-165 for Clarinex Tablets – Review by Young Moon Choi, Ph.D dated 11/21/00). The test formulation is equivalent to the reference formulation in terms of the active metabolite but marginally failed equivalence criteria with respect of the C_{max} of the parent drug.
- There has been a few occasions when Claritin or Clarinex (desloratadine) formulations have failed BE and the sponsor had conducted clinical trials; those trials have been successful in beating the placebo and the NDAs were approved (for example NDA 20-704 for Claritin RediTabs and NDA 21-605 for Clarinex D-24). These examples demonstrate that even on previous occasions failed BE formulations have proven to be effective in clinical trials.
- In one case of failed BE submitted as a 505(b) application (NDA 21-734 for Loratadine Suspension, clin pharm review by Shinja Kim, Ph. D dated 10/22/04), when sponsor repeated the BE study with more number of subjects (N increased from 43 to 70) it passed BE (NDA 21-734, clin pharm review dated 8/15/05). This may be due to high variability in the PK of loratadine.
- Phase 2 study submitted to NDA 19-670 (Claritin-D 12 Hour) showed that 5 mg Claritin was as efficacious/superior compared to placebo and comparable to 10 mg Claritin tablet (per Sponsor).
- The General BA/BE Guidance is currently being considered a revision with a proposal that BE should be based on relevant active moiety, which in this case will be desloratadine.

Recommendation on food effect: The study submitted by the sponsor (Study CL2005-17) showed a marked food effect on Claritin Liqui-Gel capsules (doubling of AUC of loratadine with food) compared to known food effect on other Claritin products (typically 30 to 40% increase in loratadine exposure). It is therefore recommended that Claritin Liqui-Gel capsule should be taken on an empty stomach.

1.2 **Phase 4 Commitment:** None

APPEARS THIS WAY ON ORIGINAL

1.3 Summary of clinical Pharmacology and Biopharmaceutics Findings

Schering-Plough HealthCare Products, Inc. submitted this original NDA for over-the-counter (OTC) marketing of new formulation, Claritin® LiquiGel™ capsule, an immediate release oral dosage form containing 10 mg loratadine on March 15, 2006.

In support of this application the sponsor submitted the results of the bioequivalence pharmacokinetic study (CL2004-02) conducted in healthy volunteers. The objective of this study was to determine the relative bioavailability/bioequivalence (BA/BE) of the proposed formulation compared to approved reference product after a single dose under fasted condition.

BA/BE Assessment (Study CL2004-02): Pharmacokinetics of loratadine and its active metabolite, desloratadine from the test product Claritin® LiquiGel™ capsule (1 x 10 mg) were compared to those from the reference product Claritin® Tablet (1 x 10 mg) in a two-way crossover study. The results in Table 1 demonstrate the equivalence of desloratadine between the two treatments, with 90% confidence intervals around the ratio of the geometric least squares means for AUC and C_{max} all falling within the range of 0.8 to 1.25. In contrast to the equivalence demonstrated for desloratadine, the loratadine results did not meet the equivalence criteria, with the lower 90% CI for C_{max} falling below the BE limit of 0.8. Therefore, the test product is not bioequivalent to Claritin® tablet.

Table 1. Analysis of Loratadine and Desloratadine bioequivalence (n = 48)

Analyte Parameter	1 x 10 mg Capsule Test	1 x 10 mg Tablet Reference	Ratio (Test/Reference)	90% CI Lower	90% CI Upper
Loratadine					
AUC	6.9581	7.6683	0.9074	0.8135	1.0121
AUC _T	6.5545	7.1760	0.9134	0.8214	1.0156
C _{max}	2.4688	2.7825	0.8873	0.7875	0.9996
Desloratadine					
AUC	38.9407	42.0624	0.9258	0.8668	0.9888
AUC _T	37.6661	40.7446	0.9244	0.8647	0.9883
C _{max}	2.9756	3.2874	0.9051	0.8375	0.9783

CI=Confidence interval

Data Source: Appendix 15 Supportive Table 5.1

Following DSI audit, Sponsor re-analyzed PK BE data shown on Page 15.

Food effect study: In FDA's filing letter (dated May 25, 2006), the lack of a food effect study for this formulation was noted as a potential review issue, and requested the Sponsor to submit additional data to support that the food effect for Claritin Liqui-Gels capsules 10 mg is expected to be the same as that seen for Claritin tablets. The sponsor submitted a meeting document on July 13, 2006 which contained a food effect study (CL2005-17) and they requested a teleconference to discuss this submission. The objective of a single-dose, two-way crossover food effect study was to evaluate the relative bioavailability of 10 mg loratadine administered as one soft gelatin capsule under fed and fasted conditions. A summary of the results is provided in Table 2.

Table 2. Analysis of Loratadine and Desloratadine bioavailability

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data (N = 11)				
Parameter	Fed	Fasting	% Ratio	90% CI
Loratadine				
AUC _{0-t} (ng-hr/mL)	13.45	6.08	221.13	(191.02, 255.99)
AUC _{0-∞} (ng-hr/mL)	14.13	6.48	218.03	(187.84, 253.07)
Cmax (ng/mL)	3.91	2.55	153.06	(113.45, 206.5)
Desloratadine				
AUC _{0-t} (ng-hr/mL)	38.10	35.99	105.87	(95.98, 116.79)
AUC _{0-∞} (ng-hr/mL)	39.66	37.33	106.24	(96.3, 117.2)
Cmax (ng/mL)	3.03	3.19	94.81	(78.69, 114.24)

The administration of Claritin® Liqui-Gels™ Capsules (loratadine 10 mg) with food increased the loratadine Cmax by 53%, AUC_{0-t} by 121%, and AUC_{0-∞} by 118%, but no significant change in desloratadine PK.

The magnitude of food effect with this new formulation compared to other marketed formulation (e.g., Claritin® Tablet 10 mg) is difficult to assess because the reference product was not included in the study. Instead, the sponsor included the results from three food effect studies, which were submitted in their respective original NDAs in this briefing meeting document (see results described on pages 12-14).

2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Schering Plough developed a Claritin® Liqui-Gels™, new formulation of loratadine containing 10 mg loratadine.

Schering Plough has other Claritin® (loratadine) products on the market as OTC: Claritin® Non-Drowsy 24 Hour Tablets 10mg (NDA 19-658), Claritin® Children's 24 Hour Non-Drowsy Allergy Syrup, 5mg/5mL (NDA 20-641) and Claritin® Reditabs® 24 Hour Non-Drowsy Orally Disintegrating Tablets 10 mg (NDA 20-704) for the treatment of seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU), and 2 extended release combination formulations with pseudoephedrine [Claritin D®-12 (NDA 19-670) and Claritin D®-24 (NDA 20-470)] for the treatment of SAR and nasal congestion.

Claritin became available as OTC drug in the above formulations in December 2002. Since coming into the OTC market, many generic formulations of loratadine are now available.

The sponsor's proposed indication for Claritin® Liqui-Gels™ capsules is to treat temporarily relief symptoms due to hay fever or other upper respiratory allergies, such as runny nose, itchy and watery eyes, sneezing, and itching of the nose or throat for adults and children 6 years and over, 1 capsule daily.

2.1.2. What are the highlights of the chemistry and physical-chemical properties of the drug substance and formulation of the drug product?

Drug Substance: The active pharmaceutical ingredient in Claritin® Liqui-Gels™ capsules is Loratadine USP. Loratadine is a white to off-white powder not soluble in water, but very soluble in acetone, alcohol, and chloroform. It has a molecular weight of 382.89, and empirical formula of C₂₂H₂₃ClN₂O₂; its chemical name is ethyl 4-(8-chloro-5, 6-dihydro- 11 H-benzo[5,6]cyclohepta [1,2- b]pyridin-11-ylidene)-1-piperidinecarboxylate.

Drug Product: Claritin® Liqui-Gels™ is an oval, clear blue liquid filled (softgel) capsules. Each capsule contains 10 mg loratadine. The components and composition of the formulation are provided in Table 3.

Table 3. Target composition: Claritin® Liqui-Gels™ Capsules

Description	Reference to Quality Standard	Function	Amount per softgel (mg)
Loratadine USP	USP and in-house	Drug Substance	10
Caprylic/Capric Acids	Vendor		
Povidone USP	USP		
Polysorbate 80 NF/FCC	NF		
	NF		
Gelatin NF	NF		Proprietary ¹
Sorbitol	Vendor		Proprietary ¹
Glycerin	Vendor		Proprietary ¹
Dye, Blue #1, FD&C	Vendor		Proprietary ¹
Water, Purified USP	USP		Proprietary ¹

b(4)

2.2. General Clinical Pharmacology

2.2.1 What are the characteristics of Clinical Pharmacology of loratadine and its (major) active metabolite, desloratadine?

Loratadine is an antihistamine, and is available in several approved products as OTC medications. As such, no other PK properties of loratadine, but one BE study and one food effect study submitted to this NDA were reviewed.

2.5. General Biopharmaceutics

2.5.1. What is the relative bioavailability of the proposed to-be-marketed formulation following single dose administration compared to that after the administration of the reference product?

Study CL2004-02 was an open-label, single dose, randomized, 2-way crossover study in 48 healthy male and female volunteers conducted to determine the bioequivalence of the proposed product compared to that of the reference product.

Eligible subjects reported to the study clinic at least 12 hours prior to the first dose of study medication. Subjects were randomized and placed into one of the two treatment groups listed below. Loratadine was administered following 10-hr overnight fast. There was a washout of at least 14 days between doses. Subjects were confined to the study site on the day prior to study drug administration and for 120 hours following study drug administration for collection of PK blood samples and safety monitoring.

- **TRT A:** 1 x 10 mg loratadine Liqui-Gel capsule (test). Lot # 04JM219
- **TRT B:** 1 x 10 mg loratadine Tablet (Claritin®) (reference), Lot # 4-RXF-16

Blood samples for determination of plasma concentrations of loratadine and desloratadine were obtained immediately prior to drug administration (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours post-dose in both study periods.

PK parameters were summarized by treatment group using descriptive statistics, as applicable. Following log- transformation (natural log), AUC_{∞} , AUC_t , and C_{max} results were compared between treatment groups using the two one-sided ANOVA analysis test procedure. The test product was considered bioequivalent to the reference product if the 90% confidence intervals (CIs) around the ratio of the geometric least square mean values of AUC and C_{max} for both loratadine and desloratadine fell within 80 to 125%. T_{max} was compared between treatments using the Wilcoxon signed rank test.

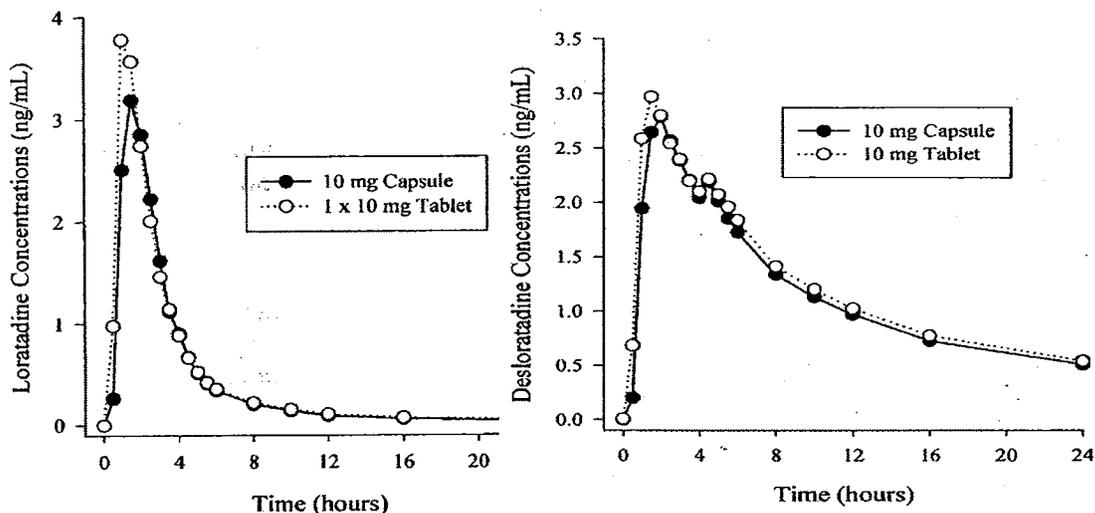
Results

Disposition of subjects: A total of 48 subjects were planned; 50 subjects were enrolled. Study medication was administered to all 50 enrolled subjects, 26 subjects in Sequence 1 and 24 subjects in Sequence 2. Subjects 012 and 013 (both in Sequence 1) discontinued from the study and received only one 10 mg dose of study drug (soft gelatin capsules). 48 subjects were included in the analysis of bioequivalence.

Demographics: The overall mean \pm SD (range) age of subjects in the study was 31.8 ± 8.16 (18 – 45) years. The majority subjects were Hispanic (42/508, 84%) and the number of females and males participating in the study were similar (26 and 24, respectively).

Pharmacokinetics: Mean plasma concentration-time profiles of loratadine and desloratadine are shown in Figure 1. Mean PK parameters for loratadine and desloratadine are presented in Tables 4-5. Bioequivalence analysis is presented in Table 6.

Figure 1. Mean Loratadine (left) and desloratadine (right) Plasma Concentration versus Time Curves by Treatment



N= 50 for the 1 × 10 mg capsule; N= 48 for the 1 × 10 mg tablet

Data Source: Appendix 15, Supportive Table 3

Subjects 030 and 034 had detectable pre-dose plasma desloratadine concentrations of 0.173 and 0.194 ng/mL, respectively. Subject 002 also had a pre-dose desloratadine concentration of 0.032 ng/mL. Subject 034 also had a pre-dose loratadine concentration of 0.036 ng/mL during Period 2 (per sponsor, the reasons for the detectable pre-dose concentrations could not be determined).

As the concentrations for Subjects 002 and 034 were <5% of the C_{max} value, their data were included in all PK measurements and calculations. Conversely, the pre-dose concentration for Subject 030 exceeded 5% of C_{max} during Period 2 (9.1%). For this reason, 2 analyses of bioequivalence were conducted: the primary analysis excluded Subject 030 for pre-dose concentrations that exceeded 5% (and Subjects 012 and 013, early termination), while the secondary analysis included all 48 subjects (i.e., exclude Subjects 012 and 013, early termination) who completed both treatment periods.

Table 4. Summary of mean (SD) Loratadine PK parameters

Parameter	1 × 10 mg Capsule (n=50)	1 × 10 mg Tablet (n=48)
	Arithmetic Mean (SD)	
C _{max} (ng/mL)	3.65 (3.80)	4.26 (4.52)
t _{max} (hr) ^a	1.50 (1.00-3.00)	1.00 (1.00-3.50)
AUC _T (ng·hr/mL)	11.03 (12.83)	12.29 (14.94)
AUC (ng·hr/mL)	11.63 (13.42)	12.93 (15.45)
λ _Z (Ke) (hr ⁻¹)	0.1363 (0.1112)	0.1234 (0.1350)
t _{1/2} (hr) ^b	5.09 (4.23)	5.62 (6.51)

^a Median (range)

^b Half-life was summarized by harmonic mean and pseudo-standard deviation of the jackknife variance.

Data Source: Appendix 15, Supportive Table 4

Table 5. Summary of mean (SD) Desloratadine PK parameters

Parameter	1 × 10 mg Capsule (n=50)	1 × 10 mg Tablet (n=48)
	Arithmetic Mean (SD)	
C _{max} (ng/mL)	3.17 (1.30)	3.41 (1.04)
t _{max} (hr) ^a	2.00 (1.00-16.00)	1.50 (1.00-10.00)
AUC _T (ng•hr/mL)	42.10 (19.90)	45.54 (21.81)
AUC (ng•hr/mL)	44.84 (26.80)	49.52 (36.41)
λ _Z (K _e) (hr ⁻¹)	0.0350 (0.0098)	0.0338 (0.0082)
t _{1/2} (hr) ^b	19.78 (5.55)	20.53 (5.00)

^a Median (range)

^b Half-life was summarized by harmonic mean and pseudo-standard deviation of the jackknife variance.

Data Source: Appendix 15, Supportive Table 4

Table 6. Analysis of Loratadine and Desloratadine bioequivalence

Analyte Parameter	1 × 10 mg Capsule Test	1 × 10 mg Tablet Reference	Ratio (Test/Reference)	90% CI Lower	90% CI Upper
Loratadine					
AUC	6.9581	7.6683	0.9074	0.8135	1.0121
AUC _T	6.5545	7.1760	0.9134	0.8214	1.0156
C _{max}	2.4688	2.7825	0.8873	0.7875	0.9996
Desloratadine					
AUC	38.9407	42.0624	0.9258	0.8668	0.9888
AUC _T	37.6661	40.7446	0.9244	0.8647	0.9883
C _{max}	2.9756	3.2874	0.9051	0.8375	0.9783

CI=Confidence interval

Data Source: Appendix 15, Supportive Table 5 1

The results in Table 6 demonstrate the equivalence of desloratadine between the two treatments, with 90% confidence intervals around the ratio of the geometric least squares means for AUC and C_{max} all falling completely within the range of 0.8 to 1.25. In contrast to the equivalence demonstrated for desloratadine, the loratadine results did not meet the equivalence criteria, with the lower 90% CI for C_{max} falling below the bioequivalence limit of 0.8 (ratio = 0.8873, 90% = 0.7875, 0.9996). Secondary analysis with 48 subjects provided similar results as shown in Table 6. The Wilcoxon Signed Rank test for t_{max} did not detect any differences between products at the 5% significance level.

Summary from this study is as follows:

- Mean exposure following administration of the soft gelatin capsule was approximately 7 to 15% lower than that observed following administration of the 10 mg tablet formulation.
- Although the results for desloratadine demonstrated the equivalence of the two treatments, the 10 mg soft gelatin capsule was not bioequivalent to the 10 mg tablet, with the lower 90% confidence interval around the ratio of the least squares means for loratadine C_{max} falling below the bioequivalence limit of 0.8.

2.5.2. Is this NDA approvable in spite of Study CL 2004-02 results?

Yes. Although the test formulation marginally failed BE with respect to the Cmax of parent drug, a recommendation for approval is made based on the following scientific rationale:

1. Relative oral potency of desloratadine (active metabolite of loratadine) is two to four times greater than loratadine in animal models, *in vitro* and *in vivo* studies (NDA 21-165, Clarinex 5 mg tablet, Pharm/Tox review by Dr. Timothy McGovern dated 9/29/00).
2. A comparative study of systemic exposure after multiple doses was conducted as a 3-way cross over design (Study P00117, NDA 21-165, clin pharm review by Dr. Choi dated 11/21/00). The results (Table 7) showed that the systemic exposure of desloratadine after 5 mg doses of Clarinex (desloratadine) tablet was comparable to that after 10 mg dose of Claritin.

Table 7. Arithmetic (%CV) and Geometric Mean Desloratadine PK Parameters on Day 10 (steady state) following Multiple-Dose Administration of Desloratadine 5 mg and 7.5 mg and Loratadine 10 mg Once Daily for 10 days. (Protocol P00117)

Parameter ^a	5 mg DL	()	7.5 mg DL	()	10 mg Loratadine	()
Cmax (ng/mL)	4.89	(72)	7.30	(75)	6.03	(63)
Cmax (Geometric Mean) (ng/mL)	4.03	()	5.97	()	5.10	()
Tmax (hr)	3.08	(72)	3.23	(86)	2.17	(121)
Tmax (Median with Range) (hr)	2	(1-8)	2	(1-10)	1.25	(1-12)
AUC(0-24hr) (ng-hr/mL)	71.9	(107)	104	(105)	74.9	(103)
AUC(0-24hr) (Geometric Mean) (ng-hr/mL)	50.6	()	75.0	()	53.1	()
t1/2 (hr)	34.9	(93)	33.5	(79)	32.7	(72)
t1/2 (Harmonic Mean) (hr)	25.2	()	25.7	()	26.0	()

a: n=24

3. There has been a few occasions when Claritin or Clarinex (desloratadine) formulations have failed BE and the Sponsor had conducted clinical trials; those trials have been successful in beating the placebo and the NDAs were approved. The following examples demonstrate that even on previous occasions failed BE formulations have proven to be effective in clinical trials:

- **CLARITIN PRODUCTS:**

- Syrup (NDA 20-641): Failed BE Studies C92-025-50 and C91-339-01
- RediTabs (NDA 20-704): Failed BE Studies C92-025-50 and C91-339-01
- Claritin-D 12 (NDA 19-670): Failed BE Study C86-019-01
- Claritin-D 24 HOUR (NDA 20-470): Failed BE Study C87-030-01

- **CLARINEX PRODUCTS:**

- Clarinex-D 24 HOUR (NDA 21-605): Failed BE Study P00439 (CPB review by Dr. Habet dated 2/3/05).

4. In one case of failed BE submitted as a 505(b) application (NDA 21-734 for Loratadine Suspension, clin pharm reviews by Dr. Shinja Kim dated 10/24/04 and 8/15/05), when sponsor repeated the BE study with more number of subjects (N increased from 43 to 70) it passed BE (NDA 21-734 clin pharm review dated 8/15/05) as shown in Tables 8-9. This may be due to high variability in the PK of loratadine.

Table 8 (NDA 21-734, review dated 10/22/04)

Parameter ¹	Trt	Pair	Loratadine		Desloratadine	
			Ratio	90% CI	Ratio	90% CI
AUC _t (ng•h/mL)	A C	A/C	0.95	84.2-104.1	1.07	101.8-112.5
AUC _{inf} (ng•h/mL)	A C	A/C	0.95	85.3-105.7	1.06	100.2-111.4
C _{max} (ng/mL)	A C	A/C	0.81	69.3-94.9	1.09	102.4-116.7

A = Taro-loratadine - Test
C = Claritin® tablet - reference

The sponsor repeated another BE study after receiving the 'approvable' letter from the Agency. The result from this study is shown in the table below (n=70).

Table 9 (NDA 21-734, review dated 8/15/05)

Parameter ¹	Trt	Pair	Loratadine		Desloratadine	
			Ratio	90% CI ²	Ratio	90% CI ²
AUC _t (ng•h/mL)	A B	A/B	108.9	99.9-118.7	105.2	101.4-109.1
AUC _{inf} (ng•h/mL)	A B	A/B	108.2	99.5-117.6	104.1	99.7-108.7
C _{max} (ng/mL)	A B	A/B	98.9	88.8-110.2	102.8	97.8-108.1

A = Taro's loratadine suspension (test) B = Claritin® tablet (reference)

5. Schering-Plough conducted a dose-ranging study (Study C93-145, NDA 19-670 for Claritin D-12) comparing once-a day dosing of loratadine 2.5 mg, 5 mg and 10 mg and placebo for the relief of allergy symptoms. Sponsor provided the results of patient diary data for the 24 hour reflective total symptoms scores over time are presented in the table below.

Study Period	Loratadine 2.5 mg (A)		Loratadine 5 mg (B)		Loratadine 10 mg (C)		Placebo (D)		Statistical Comparison ¹							
	n	Mean (% change)	n	Mean (% change)	n	Mean (% change)	n	Mean (% change)	Overall Treatment P value	A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D	
Baseline	114	14.9	108	15.0	112	15.0	110	15.1	0.99	0.82	0.88	0.71	0.94	0.89	0.83	
Change from Baseline																
Day 2	113	-2.9 (18%)	108	-3.9 (25%)	111	-4.7 (29%)	107	-2.5 (16%)	<0.01	0.11	<0.01	0.56	0.30	0.03	<0.01	
Day 3	112	-3.4 (21%)	106	-5.2 (34%)	110	-5.4 (34%)	108	-3.2 (20%)	<0.01	0.01	<0.01	0.83	0.83	<0.01	<0.01	
Day 4	111	-3.8 (24%)	105	-4.9 (32%)	108	-5.4 (32%)	105	-4.2 (27%)	0.11	0.11	0.02	0.49	0.49	0.38	0.12	
Week 1	114	-4.0 (25%)	108	-4.9 (31%)	111	-5.6 (34%)	110	-3.5 (22%)	<0.01	0.16	0.01	0.43	0.26	0.03	<0.01	
Week 2	111	-5.3 (29%)	102	-5.8 (37%)	107	-6.2 (36%)	102	-4.3 (28%)	0.05	0.47	0.19	0.17	0.57	0.04	<0.01	
Weeks 1-2	114	-4.3 (28%)	108	-4.8 (31%)	112	-5.4 (32%)	110	-3.6 (23%)	0.03	0.41	0.08	0.22	0.38	0.04	<0.01	

¹ Total nasal symptoms: nasal discharge, stuffiness, itching, and sneezing; and non-nasal symptoms: eye itching, tearing, and redness, and itching of ear and/or palate combined. Individual scores: 0=none (symptom not present), 1=mild, 2=moderate, 3=severe.

² The study summary was submitted as part of an NDA phase IV commitment to the 10 mg CLARITIN Tablets original NDA application (submission date 19 MAR 1996).

³ Based on mean scores at Baseline and mean change from Baseline. ANOVA model was used for overall comparisons; SAS Proc GLM Least Square Means procedure was used for pairwise comparisons.

The sponsor concluded that the 5 mg QD dose was significantly better for allergy symptom relief as compared to placebo ($p < 0.05$) for all studied timepoints other than Day 4 and not significantly different from the 10 mg dose. The differences from placebo were observed in the short term for the 5 mg dose for both Day 2 (end of first dose, $p < 0.03$) and Day 3 (end of second dose, $p < 0.01$). The 10 mg dose was also statistically different from placebo ($p < 0.01$) on all days except Day 4. The 2.5 mg dose was not different from placebo.

6. The General BA/BE Guidance is currently being considered a revision with a proposal that BE should be based on relevant active moiety, which in this case will be desloratadine.

2.5.3. What is the effect of food on the BA of loratadine and desloratadine from the Claritin® Liqui-Gels™ capsule formulation?

The sponsor conducted an open-label, single dose, randomized, 2-way crossover study in 11 healthy male and female volunteers conducted to evaluate the food effect of the proposed product (CL2005-17).

For the fed treatment, all subjects received a standardized high fat breakfast after fasting for at least 10 hours and then fasted for 4 hours post drug treatment. All subjects in the fasting group, fasted for at least 10 hours prior to dosing and then fasted for 4 hours post drug treatment.

Each treatment was administered with 240 mL of room temperature water. A washout period of 21 days separated each dosing period. An equal number of subjects were randomly assigned to each of the two possible dosing sequences to receive the test (fed) and reference (fasted) treatments.

- **TRT A:** 1 x 10 mg loratadine Liqui-Gel capsule under fed condition. Lot # 250747
- **TRT B:** 1 x 10 mg loratadine Liqui-Gel capsule under fasted condition. Lot # 250747

Results: Table 10 and 11 summarize the PK results for loratadine and desloratadine, respectively.

Table 10. Summary of Ln-transformed PK parameters for Loratadine

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Loratadine N=11				
Parameter	Fed	Fasting	% Ratio	90% CI
AUC ₀₋₄ (ng-hr/mL)	13.45	6.08	221.13	(191.02, 255.99)
AUC _{0-∞} (ng-hr/mL)	14.13	6.48	218.03	(187.84, 253.07)
C _{max} (ng/mL)	3.91	2.55	153.06	(113.45, 206.5)

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Table 11. Summary of Ln-transformed PK parameters for Desloratadine

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Desloratadine N=11				
Parameter	Fed	Fasting	% Ratio	90% CI
AUC _{0-t} (ng-hr/mL)	38.10	35.99	105.87	(95.98, 116.79)
AUC _{0-∞} (ng-hr/mL)	39.66	37.33	106.24	(96.3, 117.2)
C _{max} (ng/mL)	3.03	3.19	94.81	(78.69, 114.24)

The administration of Claritin® Liqui-Gels™ Capsules with food increased the loratadine C_{max} by 53%, AUC_{0-t} by 121%, and AUC_{0-∞} by 118%, but no significant change in desloratadine PK. The magnitude of food effect with this new formulation compared to other marketed formulation (e.g., Claritin® Tablet 10 mg) is difficult to assess because the reference product was not included in the study (optimal study design would be 3-way crossover, test product under fed and fast conditions and the reference product under fed condition). Instead, the sponsor included three food effect studies, shown below, which were submitted in their respective original NDAs in this briefing document.

Food Effect studies from previous NDAs

Study C85-054-01: Submitted in the original NDA 19-658, 30OCT1986.

This was a single-dose, two-way crossover study conducted in healthy male volunteers to compare the bioavailability of 4 x 10 mg CLARITIN® Tablet under fast and fed (standardized breakfast) conditions. The results from this study are summarized as follows:

- For loratadine, the mean C_{max} values were 14.3 and 13.6 ng/mL and the mean T_{max} values were 2.0 and 1.0 hr for fed and fasted subjects, respectively. The mean AUC (36 hr) value for fasted subjects was 48.0 hr•ng/mL; which is 23% lower than for fed subjects (62.2 hr•ng/mL). Statistical analysis showed the C_{max} values not statistically different from each other (p=0.75) but the AUC differences were significant (p=0.001).
- For desloratadine, the mean C_{max} values were 25.5 and 23.2 ng/mL and the mean T_{max} values were 2.5 and 1.4 hr for fed and fasted subjects, respectively. The mean AUC (60 hr) for fasted subjects was 215.5 hr•ng/mL which was 15% lower than that for fed subjects (252.8 hr•ng/mL). The C_{max} values were not significantly different from each other (p=0.21) and the difference in the AUC values were small (less than 20%) although the statistically significant (0.02).

Food alters BA of loratadine but considered clinically insignificant.

Study C94-037-01: CLARITIN® RediTabs Tablets (submitted in the original NDA 20-704, 29FEB1996)

This was a single-dose, two-way crossover study conducted in healthy volunteers to evaluate the relative bioavailability of loratadine and desloratadine following administration of a 10 mg loratadine orally disintegrating tablet (Zydys®) and consumed a standardized breakfast after a 10-15 minutes later.

A conventional 10 mg loratadine tablet (reference) was administered under fasting conditions (*Comment: this was not an optimally designed FE study*).

Results: The statistical analysis comparing the Zydis® and conventional tablets using log transformed data is presented in Table 12.

Table 12. Statistical Analysis Using Log Transformed Data

Parameter (unit)	Treatment	Geometric Mean	p-value	Power (%) ^a	Ratio (%) ^b	
					Point Estimate	Confidence Interval ^c
Loratadine						
C _{max} (ng/mL)	Zydis®	3.25	0.010	46	130	111-153
	Conventional	2.49				
AUC (t) (ng·hr/mL)	Zydis®	11.6	0.001	55	184	159-212
	Conventional	6.32				
Desloratadine						
C _{max} (ng/mL)	Zydis®	1.92	0.136	91	92.1	84-101
	Conventional	2.08				
AUC (t) (ng·hr/mL)	Zydis®	34.9	0.001	100	111	106-116
	Conventional	31.6				

^a Power to detect a 20% difference between treatment means

^b Expressed as percent of conventional tablet

^c Based on two one sided t-tests at $\alpha=0.05$

Summary: The bioavailability of loratadine from the Zydis® tablet administration with food was significantly greater than that from the conventional tablet administered under fasting conditions. The original reviewer noted that the evaluation of a food effect is confounded by the study design, thus not formally reviewed (*Comment: Therefore this study is not accepted as supportive data*).

Study C92-270-01: Submitted in the original NDA 20-704 application.

This single-dose, two-way crossover study was to characterize the effect of food on the relative bioavailability of loratadine and desloratadine when loratadine was administered as a 10 mg Zydis® tablet after a standardized high fat breakfast and under fasting conditions. The results are shown in Table 13.

Table 13. Statistical Analysis Using Log Transformed Data

Parameter (unit)	Treatment	Geometric Mean ^a	p-value ^b	Power ^c (%) ^a	Ratio (%) ^d	
					Point Estimate	Confidence Interval ^e
Loratadine						
C _{max} (ng/mL)	Fasted	1.73	0.281	50	90.7	78-106
	Fed	1.57				
AUC (t) (ng hr/mL)	Fasted	4.58	0.001	40	190	159-227
	Fed	8.72				
Desloratadine						
C _{max} (ng/mL)	Fasted	2.62	0.008	86	84.6	77-93
	Fed	2.21				
AUC (t) (ng hr/mL)	Fasted	33.7	0.039	100	106	101-110
	Fed	35.6				

^a Geometric mean is the anti-log of the log-scale mean.

^b p-Value from ANOVA

^c Power to detect a 20% difference

^d Expressed as percent of Treatment A

^e Based on two one sided t-tests at $\alpha=0.05$

Summary:

- Food reduced the loratadine C_{max} by 9.3% (90% CI = 78-106); this difference was not statistically significant (p>0.05).
- Food significantly increased the AUC_t of loratadine by 90% with a confidence interval of 159-227 (p<0.05). Sponsor stated the resultant AUC value is below that previously obtained following the administration of 40 mg of loratadine [AUC_{0-24 hr} = 69.8 ng•hr/mL].
- Food decreased the desloratadine C_{max} by 15.4% and increased the AUC_t by 6%. Sponsor stated these changes are considered clinically insignificant.

The original reviewer (Brad Gillespie, Pharm. D.) concluded that increase in total parent AUC is acceptable since this increase is well with the levels determined to be safe in a 40 mg single-dose study.

Reviewer's comment: The food effect with this new formulation, Claritin Liqui-Gels capsules, is greater than those with other approved formulations (shown above).

Amendment to Pending application

Background: For the Clartin Chewable Tablets (NDA 21-891) application, the DSI conducted an audit of the analytical portion of the study (CL2003-02) and issued a Form 483 to the Sponsor due to some objectionable observations. For example, analytical runs were accepted although more than 50% of the low QCs failed (DSI report dated May 23, 2006). Based on this observation, DSI recommended exclusion of the data from a number of subjects from the bioequivalence determination for Study CL2003-02.

Amendment: On August 2, 2006, the sponsor submitted the amendment to pending NDA to include a re-analysis of the bioequivalence data from Study CL2004-02 submitted in the original application. Sponsor stated that the re-analysis of the bioequivalence data as a result of the observations reported in Form FDA 483 for the approval of the Clartin Chewable Tablets (NDA 21-891) application. The sponsor stated the same re-analysis criteria that were recommended by DSI were applied for the current amended application.

List of Runs from Study CL2004-02, which met FDA's criteria for dropping from analysis as follows:

Loratadine

- Run 5ZMO-1-A: Subjects 13, 14, 15
- Run 9ZMO-1-A: Subjects 25, 26, 27

Desloratadine

- Run 15ZMO-2-A: Subjects 43, 44, 45
- Repeat Run 20ZMO-2-A

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Re-analyses Results:

Study CL2004-02:

Analyte	Claritin® Liqui-Gel (Test: 1x10 mg)	Claritin® Tablet (Ref: 1x10 mg)	Ratio	90% CI Lower	90% CI Upper
Loratadine					
AUC _{0-∞}	7.7357	8.6231	0.8971	0.8011	1.0046
AUC _{0-t}	7.2871	8.0533	0.9049	0.811	1.0096
Cmax	2.7255	3.0696	0.8879	0.7847	1.0047
Desloratadine					
AUC _{0-∞}	39.649	42.9958	0.9222	0.8608	0.9879
AUC _{0-t}	38.3494	41.6231	0.9214	0.859	0.9882
Cmax	3.0338	3.2913	0.9218	0.8523	0.9970

Conclusion: The results of the re-analysis of Study CL2004-02 still demonstrate bioequivalence for desloratadine for both Cmax and AUC, and no equivalence for loratadine for Cmax loratadine. Thus, re-analyses did not change the overall findings.

Reviewer's comment: The Sponsor's run acceptance for the study was _____ QCs at each level to be accurate (i.e., within ±15% of the nominal concentration), whereas, the acceptable criterion for a run by DSI is at least 50% of the QCs at each level should be accurate. The sponsor excluded subjects for re-analyses based on the acceptance criterion by DSI.

b(4)

2.6. Analytical Section

2.6.1. What bio-analytical methods are used to assess concentrations?

Plasma samples collected from this study (2252 and 552 samples from Studies CL2004-02 and CL2005-17, respectively) were analyzed for loratadine (SCH 29851) and desloratadine (SCH 34117) using a validated method using liquid chromatography tandem mass spectrometric method (LC/MS/MS) by _____ Calibration range, 0.025 ng/mL (LLOQ) - 10.0 ng/mL, was linear for loratadine and desloratadine. Calibration standards were acceptable. The QC samples demonstrated acceptable performance based on a run acceptance criterion by the Sponsor. The lowest level (0.0750 ng/mL) QC sample runs were not acceptable per DSI acceptance criterion (re-analyses were performed by the sponsor applying the acceptance criterion by DSI for a run) for Study CL2004-02. For Study CL2005-17, the QC samples demonstrated acceptable performance based on a run acceptance criterion by DSI (i.e., >50% of runs were accurate). Overall, the analytical assay is acceptable.

b(4)

3. Labeling Recommendation: Medical and clinical pharmacology review teams recommend this new formulation should be taken on an empty stomach.

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4. APPENDIX

4.1 PROPOSED PACKAGE INSERT

Drug Facts

Active ingredient (in each tablet)

Loratadine 10 mg

Purpose

Anitihistanine

Uses

Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:

- runny nose
- itchy, watery eyes
- sneezing
- itching of the nose or throat

Warnings

Do not use if you are allergic to this product or any of its ingredients.

Ask a doctor before use if you have liver or kidney disease. Your doctor should determine if you need a different dose.

When using this product do not take more than directed. Taking more than directed may cause drowsiness.

Stop use and ask a doctor if an allergic reactions to this product occurs. Seek medical help right away.

If pregnant or breastfeeding, ask a healthcare professional before use

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- Adults and children 6 years and over: 1 capsule daily; not more than 1 capsule in 24 hrs.
- Children 2 to under 6 years of age: Ask a doctor.
- Consumers with liver or kidney disease: Ask a doctor.

Other information

- safety sealed: do not use if the individual blister unit imprinted with Claritin® Liqui-Gels is open or torn
- store between 20°C to 25°C (68° to 77° F)
- protect from freezing

Inactive ingredients caprylic/capric glycerides, FD&C blue no. 1, gelatin, glycerin, pharmaceutical ink, polysorbate 80, povidone, purified water, sorbitol.

Questions or comments? 1-800-CLARITIN (1-800-7484) or www.claritin.com

[Lot number and Expiration Date]

4.2. OCP filing

Office of Clinical Pharmacology and Biopharmaceutics				
New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21-952	Brand Name	Claritin Liqui-Gels capsule	
OCPB Division (I, II, III)	DCP-II	Generic Name	Loratadine	
Medical Division	DNCE	Drug Class	Anti-Histamine	
OCPB Reviewer	Shinja Kim	Indication(s)	Allergic rhinitis	
OCPB Team Leader	Emmanuel Fadiran	Dosage Form	10 mg Liqui-Gels capsule	
		Dosing Regimen	1 capsule QD for ≥6 years of age	
Date of Submission	3/15/06	Route of Administration	Oral	
Estimated Due Date of OCPB Review	11/15/06	Sponsor	Schering-Plough	
PDUFA Due Date	1/15/07	Priority Classification	3 S	
Division Due Date	11/15/06			
3 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:				
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:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				

Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	1		SD in healthy adults
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	x			
Comments sent to firm?		You did not conduct a food effect study. This is a review issue. Please provide additional data to support that the food effect for this formulation is expected to be the same as that seen for Claritin tablet, such as a comparative <i>in vitro</i> dissolution profile of the proposed formulation to the approved tablet formulation.		
QBR questions (key issues to be considered)		<ul style="list-style-type: none"> • Is formulation used in the bio-study identical to the to-be-marketed formulation? • Is the tested formulation bioequivalent to the reference (innovator) product? • Were any subject(s) identified as "Poor Metabolizer", and how different their PK profiles of DCL compared to the mean values? • What bioanalytical methods are used to assess concentrations of active moieties? 		

Comment:

- The sponsor stated that food effect on loratadine drug products is well established and is considered not clinically significant; therefore, no new food effect study was conducted for this NDA. In previous NDA21-891, CLARITIN 5mg Chewable Tablets, the sponsor also did not conduct food effect study. The sponsor was asked to provide additional data to support that the food effect for this formulation is expected to be the same as that seen for Claritin tablet, such as a comparative *in vitro* dissolution profile of the proposed formulation to the approved tablet formulation. Therefore, we will ask the same request to the sponsor for this NDA as stated above ('Comments sent to firm').
- Request DSI consultation: Bioanalytical testing facility is _____

b(4)

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this page is the manifestation of the electronic signature.**

/s/

Shinja Kim
11/30/2006 11:35:51 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
11/30/2006 04:56:51 PM
BIOPHARMACEUTICS
I concur.