

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-993

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

CLINICAL PHARMACOLOGY REVIEW

NDA 21-993:	Submission Date: February 10, 2006
Brand Name:	Claritin® Reditab® 12 Hour Tablets
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):	Orally Disintegrating Tablet (ODT) 5 mg
Indication:	Temporally relief of symptoms due to hay fever or other upper 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	2
2. Question-Based Review	4
2.1 General attribute of Loratadine	4
2.2 General Clinical Pharmacology	5
2.5 General Biopharmaceutics	5
2.6 Analytical Section	14
3. Labeling Recommendation (none)	14
4. Appendix	
4.1 Proposed labeling	15
4.2 OCP filing/Review Form	16

1. EXECUTIVE SUMMARY

1.1 Recommendation: The Office of Clinical Pharmacology has reviewed the NDA, and found it two bioequivalence pharmacokinetics studies were acceptable in terms of the design and the data analyses from an OCP standpoint. The data from Study CL2004-01 show that 2x5 mg Claritin® RediTabs® are bioequivalent to 1x10 mg Claritin® RediTabs®, while the data from Study CL2005-02 show that 1x5 mg Claritin® RediTabs® is not bioequivalent to the loratadine component of Claritin-D® 12. Study CL2004-01 therefore supports the approval of Claritin® RediTabs® subjects to favorable DSI findings.

1.2 Phase 4 Commitment: None

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 Claritin® RediTabs® tablet, an immediate release oral dosage form containing 5 mg loratadine orally disintegrating tablets (ODT). This new formulation will be supplied in _____ blister packages of 5 and 10 tablet counts per blister card.

In support of this application the sponsor submitted the results of two bioequivalence pharmacokinetic studies conducted in healthy volunteers. The objective of these studies was to determine the relative bioavailability/bioequivalence (BA/BE) of the proposed formulation compared to approved reference products Claritin-D® 12 hour extended release tablet (CL2005-02) or Claritin® RediTabs® 10 mg tablet (CL2004-01) after a single dose under fasted condition.

BA/BE Assessment (Study CL2005-02): Pharmacokinetics of loratadine and its active metabolite, desloratadine from the test product Claritin® RediTabs® tablet (5 mg loratadine) were compared to those from the reference product Claritin-D® 12 hour extended release tablet (5 mg loratadine) in a two-way crossover study. The results in Table 1 demonstrate the equivalence (BE) of desloratadine between the two treatments, with 90% confidence intervals around the ratio of the geometric least squares means for AUC and C_{max} falling within the range of 0.8 to 1.25. In contrast to this, equivalence was not demonstrated for loratadine because the 90% CI for AUC was above the BE limit of 1.25.

Table 1. Analysis of Loratadine and Desloratadine bioequivalence

Analyte Parameter	Claritin® RediTabs® Tablet Test	Claritin-D® 12 Hour Extended Release Tablet Reference	Ratio (Test/Reference)	90% CI Lower	90% CI Upper
Loratadine					
AUC	4.7162	3.1305	1.5066	1.3692	1.6577
AUC _T	4.5551	3.0346	1.5010	1.3630	1.6531
C _{max}	1.4372	1.2704	1.1313	1.0382	1.2328
Desloratadine					
AUC	20.6080	21.4070	0.9627	0.9093	1.0192
AUC _T	19.3942	19.9944	0.9700	0.9125	1.0311
C _{max}	1.3755	1.4845	0.9266	0.8764	0.9796

CI=Confidence interval

Data Source: Appendix 15, Supportive Table 5.1

BA/BE Assessment (Study CL2004-01): PK of loratadine and desloratadine from the test product Claritin® RediTabs® tablet (2 x 5 mg) were compared to those from the reference product Claritin® RediTabs® tablet (1 x 10 mg) in a two-way crossover study. The results in Table 2 demonstrate the BE of the two treatments, with 90% confidence intervals around the ratio of the geometric least squares means for loratadine and desloratadine AUC and C_{max} all falling within the range of 0.8 to 1.25.

Table 2. Analysis of Loratadine and Desloratadine bioequivalence

Analyte Parameter	2 x 5 mg Tablets Test	1 x 10 mg Tablet Reference	Ratio (Test/Reference)	90% CI Lower	90% CI Upper
Loratadine					
AUC	7.4486	7.7359	0.9629	0.8868	1.0454
AUC _T	6.9344	7.3049	0.9493	0.8746	1.0304
C _{max}	2.4717	2.5790	0.9584	0.8608	1.0670
Desloratadine					
AUC	41.9253	42.3708	0.9895	0.9401	1.0414
AUC _T	40.5484	41.0117	0.9887	0.9377	1.0424
C _{max}	3.0322	3.0416	0.9969	0.9466	1.0499

CI=Confidence interval

Analysis excludes Subjects 007, 021, 030, 33, 39, and 042

Data Source: Appendix 15, Supportive Table 5.1

Food effect study: No food effect study was conducted. This new Claritin® RediTabs® tablet 5 mg is the same formulation as the marketed Claritin® RediTabs® tablet 10 mg except that the amount of loratadine has been reduced by 50% (Table 3); therefore the sponsor stated no food effect study was conducted. The sponsor's rationale is acceptable. In addition, food effect with loratadine has been well defined.

Table 3. Comparative formula for Loratadine 5 mg and 10 mg Claritin® Orally Disintegrating Tablets

Description	Quality Standard	Quantity per 5 mg Tablet (mg)	Quantity per 10 mg Tablet (mg)
Loratadine USP Micronized	USP and In-house	5.000	10.000
Gelatin, NF	NF and In-house	—	—
Mannitol, USP	USP	—	—
Flavor Mint	In-house	—	—
Anhydrous Citric Acid USP	USP	—	—
Total		—	—

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® RediTabs® Tablet (loratadine orally disintegrating tablet).

Loratadine is marketed as an OTC drug product in US in 3 monotherapy formulations [Claritin® Tablets 10 mg (NDA 19-658), Syrup, 5 mg/5 mL (NDA 20-641) and Claritin® Reditabs ODT 10 mg (NDA 20-704)] for the treatment of seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU), and in 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.

Pre-IND meeting was held (meeting minute dated 2/3/05) to reach an agreement between the FDA and the sponsor's new formulation on the requirements for the proposed marketing application of a 12 hour ODT containing 5 mg loratadine for the OTC treatment of the symptoms of allergic rhinitis. Briefly, Agency's recommendation to the sponsor was as follows:

- A PK study comparing loratadine 5 mg ODT q12 vs. loratadine 10 mg q day would need to achieve bioequivalence, or
- A PK study comparing loratadine 5 mg ODT to the Claritin-D 12 Hour Tablet. SPHCP will need to establish the bioequivalence of the loratadine moiety.
- If bioequivalence (21 CFR 320) cannot be established and an acceptable rationale cannot be developed as to why this lack of equivalence would not impact clinical efficacy then new clinical trials would be necessary.

Note: The reviewing medical officer (Linda Hu, M.D.) noted that it appeared that the existing Clinical data supports the efficacy of 5 mg loratadine every 12 hours for the treatment of symptoms of SAR based on a preliminary review of the Claritin-D 12 hour trial submitted in the pre-IND meeting briefing documentation.

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® ODT 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-benzof[5,6]cyclohepta [1,2- b]pyridin-11-ylidene)-1-piperidinecarboxylate.

Drug Product: Claritin 5mg ODT contains 5 mg of loratadine for oral 12 hours of allergy relief. Per the sponsor, the drug product disintegrates in the mouth within seconds of placement on the tongue, allowing its contents to be subsequently swallowed with or water. Quantitative Formula for Claritin 5mg ODT in blister is provided in Table 4.

Table 4. Quantitative Formula for CLARITIN 5mg Orally Disintegrating Tablets

Ingredient	Reference to Quality Standard	Function	Amount Per Tablet (Solids) (mg)
Loratadine USP Micronized	USP and In-house	Drug Substance	5
Gelatin NF	NF and In-house	_____	_____
Mannitol USP	USP	_____	_____
Flavor Mint	In-house	_____	_____
Anhydrous Citric Acid USP	USP	_____	_____
Theoretical Dry Tablet Weight			_____

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 two bioequivalence studies submitted to this NDA are reviewed.

2.5. General Biopharmaceutics

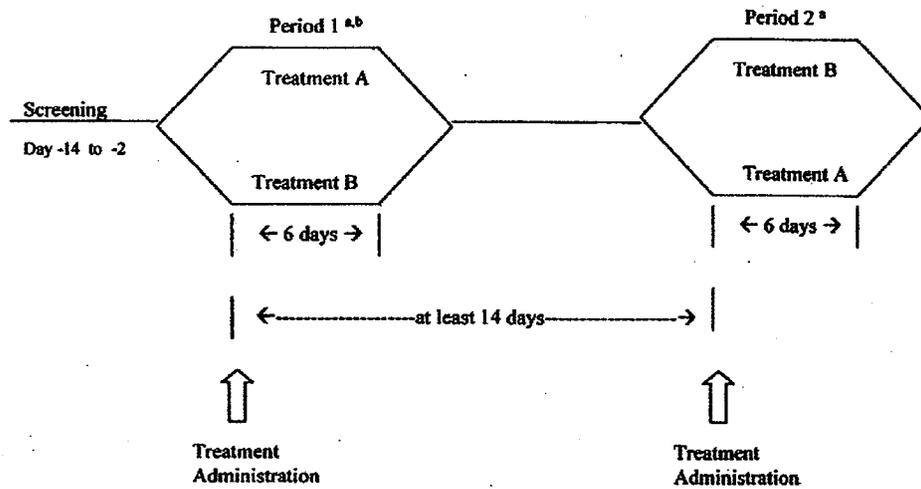
2.5.1. What is the relative bioavailability of the proposed to-be-marketed formulation following single dose administration compared to that after the administration of the reference products?

Two BE studies were conducted.

Study CL2005-02: This was an open-label, single dose, randomized, 2-way crossover study in 90 healthy male and female volunteers 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 14-day washout period separated the two doses of study medication. 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.

- Treatment A: One Claritin® RediTabs® Tablets (test) administer without water. Lot # 179466
- Treatment B: One Claritin-D® 12 Hour ER Tablet (reference) with water, Lot # 4050971

A schematic of the overall study design is shown below:



- a* Pharmacokinetic analysis for 120 hours following treatment administration.
- b* A period of at least 14 days will separate dosing.

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.

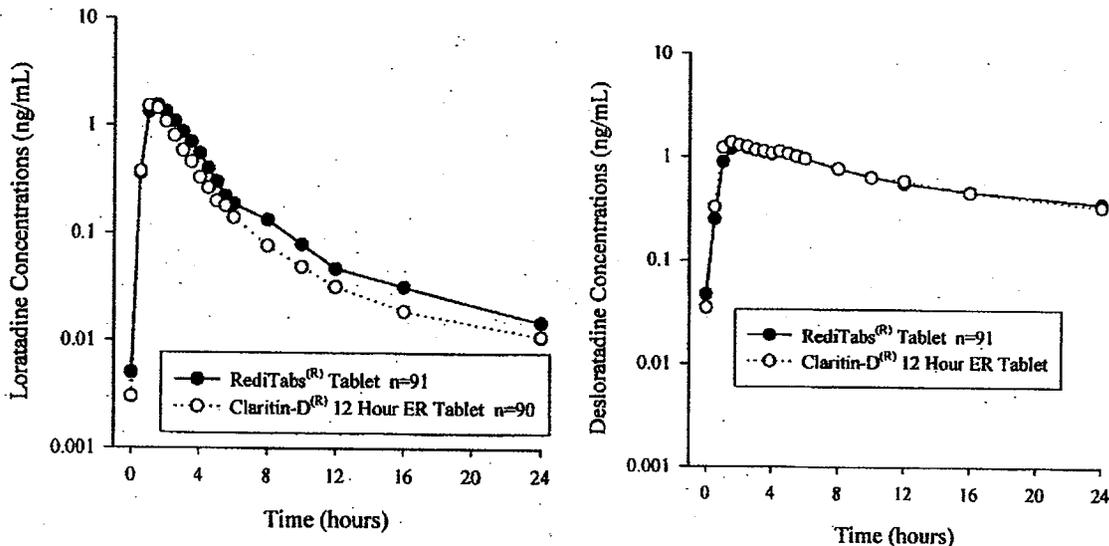
Results

Disposition of subjects: A total of 91 subjects were enrolled in this crossover study: 46 subjects were randomly assigned to receive study medication according to Sequence 1 (Claritin® RediTabs® Tablet, 5 mg and Claritin-D® 12 Hour Extended Release Tablet, 5 mg), and 45 subjects were randomly assigned to receive study medication according to Sequence 2 (Claritin-D® 12 Hour Extended Release Tablet, 5 mg and Claritin® RediTabs® Tablet, 5 mg). Of 91 subjects, 90 subjects completed the study. Subject 006 (Sequence 1) was lost to follow-up after receiving Claritin® RediTabs® Tablet during Period 1. Eighty-six subjects were included in the analysis if bioequivalence.

Demographics: The overall mean \pm SD (range) age of subjects in the study was 32 ± 7.55 (18 – 45) years. The majority subjects were Hispanic (60, 65.9%) followed by Caucasians (20, 22%) and African American (11, 12.1%). There were 55 of females (60.4%) and 36 males (39.6%) in the study.

Pharmacokinetics: Mean plasma concentration-time profiles of loratadine and desloratadine are shown in Figure 1.

Figure 1. Mean loratadine (left) and desloratadine (right) plasma concentration-time profiles



Despite the 14-day interval between treatments, 4 subjects had detectable pre-dose drug concentrations that exceeded 5% of the C_{max}. Data from these 4 subjects (Subjects 003, 037, 049, and 082) were not included in the analysis of bioavailability.

- Subject 003 had detectable pre-dose plasma loratadine concentrations of 0.279 and 0.419 ng/mL and desloratadine concentrations of 2.86 and 4.11 ng/mL, respectively, during Periods 1 and 2.
- Subject 037 had a pre-dose desloratadine concentration of 0.147 ng/mL during Period 2.
- Subject 049 had a pre-dose desloratadine concentration of 0.111 ng/mL during Period 2,
- Subject 082 had a pre-dose desloratadine concentration of 0.133 ng/mL during Period 2.

Eighty-six subjects were included in the bioequivalence determination (i.e., excluding the 4 subjects and Subject 006 who was lost to follow-up after Period 1).

Mean (SD) PK parameters for loratadine and desloratadine are presented in Tables 5-6. Bioequivalence analysis is presented in Table 7.

Table 5. Summary of Mean (SD) Loratadine Pharmacokinetic Parameters

Parameter	Claritin® RediTabs® Tablet (n=91)	Claritin-D® 12 Hour Extended Release Tablet (n=90)
	Arithmetic Mean (SD)	
C _{max} (ng/mL)	1.78 (1.15)	1.75 (1.31)
t _{max} (hr) ^a	1.50 (0.50-3.00)	1.00 (0.98-120.0)
AUC _T (ng·hr/mL)	5.97 (5.08)	5.09 (8.01)
AUC (ng·hr/mL)	5.63 (4.17)	4.50 (3.74)
λ _z (K _e) (hr ⁻¹)	0.2127 (0.1343)	0.2681 (0.1899)
t _{1/2} (hr) ^b	3.26 (2.06)	2.59 (1.84)

^a Median (range)

^b Half-life was summarized by harmonic mean and pseudo-standard deviation of the jackknife variance. N=83 for Claritin® RediTabs® Tablet AUC, λ_z, and t_{1/2}; N=85 for Claritin-D® 12 Hour Extended Release Tablet AUC, λ_z, and t_{1/2}

Data Source: Appendix 15, Supportive Table 4

Table 6. Summary of Mean (SD) desloratadine Pharmacokinetic Parameters

Parameter	Claritin® RediTabs® Tablet (n=91)	Claritin-D® 12 Hour Extended Release Tablet (n=90)
	Arithmetic Mean (SD)	
C _{max} (ng/mL)	1.57 (0.84)	1.65 (0.84)
t _{max} (hr) ^a	2.00 (0.50-72.00)	1.50 (0.98-16.00)
AUC _T (ng·hr/mL)	29.08 (37.17)	29.21 (38.68)
AUC (ng·hr/mL)	30.13 (34.45)	30.26 (32.30)
λ _z (K _e) (hr ⁻¹)	0.0402 (0.0220)	0.0392 (0.0127)
t _{1/2} (hr) ^b	17.24 (9.77)	17.69 (5.72)

^a Median (range)

^b Half-life was summarized by harmonic mean and pseudo-standard deviation of the jackknife variance. N=89 for Claritin® RediTabs® Tablet and Claritin-D® 12 Hour Extended Release Tablet AUC, λ_z, and t_{1/2}

Data Source: Appendix 15, Supportive Table 4

In general, mean loratadine C_{max} results were comparable for the Claritin® RediTabs® Tablet and Claritin-D® 12 Hour Extended Release Tablet formulations (1.78 and 1.75 ng/mL, respectively). AUC for the Claritin® RediTabs® Tablet treatment was approximately 25% greater than that of the Claritin-D® ER Tablet treatment, with respective mean values of 5.63 and 4.50 ng·hr/mL. Considerable variability in t_{max} values was observed, with respective median loratadine t_{max} occurring at 1.5 and 1.0 hours after dosing of the Claritin® RediTabs® Tablet and Claritin-D® 12 Hour ER Tablet formulations, and values that ranged from 0.5 to 120 hours.

While loratadine AUC was 25% higher for the Claritin® RediTabs® Tablet treatment, both AUC and C_{max} of desloratadine were comparable between treatments.

Table 7. Analysis of Loratadine and desloratadine Bioequivalence (n=86)

Analyte Parameter	Claritin® RediTabs® Tablet Test	Claritin-D® 12 Hour Extended Release Tablet Reference	Ratio (Test/Reference)	90% CI Lower	90% CI Upper
Loratadine					
AUC	4.7162	3.1305	1.5066	1.3692	1.6577
AUC _T	4.5551	3.0346	1.5010	1.3630	1.6531
C _{max}	1.4372	1.2704	1.1313	1.0382	1.2328
Desloratadine					
AUC	20.6080	21.4070	0.9627	0.9093	1.0192
AUC _T	19.3942	19.9944	0.9700	0.9125	1.0311
C _{max}	1.3755	1.4845	0.9266	0.8764	0.9796

CI=Confidence interval

Data Source: Appendix 15, Supportive Table 5.1

The results in Table 7 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 0.80 to 1.25. In contrast to the bioequivalence demonstrated for desloratadine, the loratadine results did not meet the bioequivalence criteria for AUC, with the 90% CI for AUC falling above the bioequivalence limit of 1.25.

According to the sponsor, dosing all subjects on the same day was not feasible due to the large number of subjects in this study, thus subjects were dosed in 2 groups, consisting of 63 and 28 subjects each. To evaluate whether there was a significant group*treatment interaction, additional terms were added to the ANOVA model to test for a group effect. This analysis demonstrated that dosing in the 2 groups did result in a significant treatment by group interaction (p > 0.10) in the analysis of loratadine bioavailability. For this reason, separate bioavailability analyses were conducted on the 2 groups, both of which produced results that were consistent with the conclusions of the overall analysis.

It was noted that since the systemic exposure (AUC) of loratadine was higher from the test product compared to that from the reference product, the Sponsor provided the rationale that the higher systemic exposure is not a safety concern.

Conclusion: The data from Study CL2005-02 show that 1x5 mg Claritin® RediTabs® is not bioequivalent to the loratadine component of Claritin-D® 12.

Reviewer's comment: The sponsor's conclusion of higher loratadine systemic exposure from the test product compared to that from the reference product is not a safety concern will be evaluated (deferred) to the reviewing medical team.

Study CL2004-01: This 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. 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 14-day washout period separated the two doses of study medication. 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:** 2 x 5 mg Claritin® RediTabs® Tablets (test). Lot # 179466
- **TRT B:** 1 x 10 mg Claritin® RediTabs® Tablets (reference), Lot # 4-EB7-6

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.

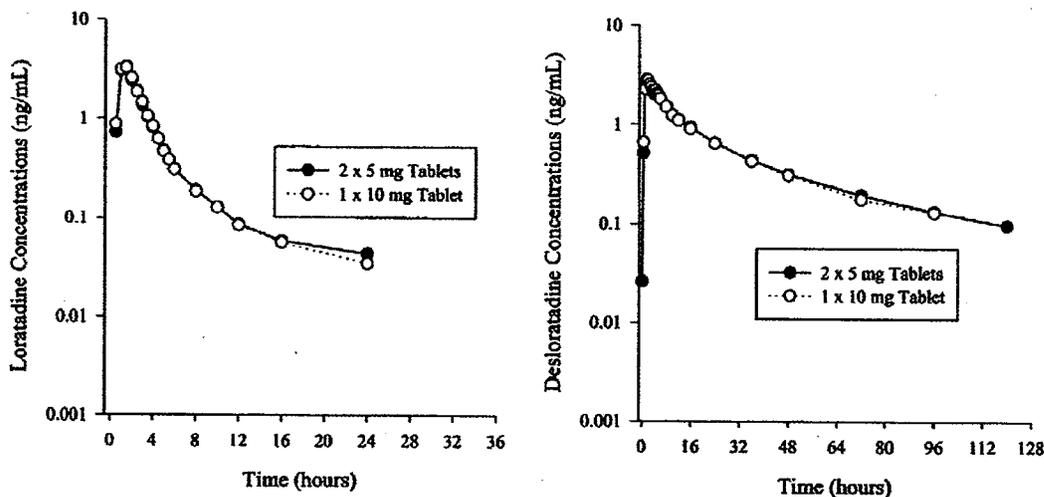
Results

Disposition of subjects: A total of 48 subjects were enrolled in this crossover study: 24 subjects were randomly assigned to receive study medication according to Sequence 1 (2 x 5 mg Claritin® RediTabs® Tablet during Period 1 followed by 1 x 10 mg and Claritin® RediTabs® Tablet during Period 2), and 24 subjects were randomly assigned to receive study medication according to Sequence 2 (1 x 10 mg and Claritin® RediTabs® Tablet during Period 1 followed by 2 x 5 mg Claritin® RediTabs® Tablet during Period 2). Of 48 subjects, 46 subjects (95.8%) completed the study. Subjects 033 and 039 did not complete the study.

Demographics: The overall mean \pm SD (range) age of subjects in the study was 33.6 ± 7.78 (18 – 45) years. Ethnic group consisted of Hispanic (36, 75.0%), African American (10, 20.8%) and Caucasians (2, 4.2%). There were 30 females (62.5%) and 18 males (37.5%) participated in the study.

Pharmacokinetics: Mean plasma concentration-time profiles of loratadine and desloratadine are shown in Figure 2.

Figure 2. Mean loratadine (left) and desloratadine (right) plasma concentration-time profiles



4 subjects (Subjects 007, 021, 030 and 042) had detectable pre-dose desloratadine concentrations during Period 2 that exceeded 5% of the C_{max}, therefore, the data from these subjects were not included in the analysis of bioequivalence. 42 subjects were included in the analysis of bioequivalence (i.e., exclude these 4 subjects and Subjects 033 and 039).

Mean (SD) PK parameters for loratadine and desloratadine are presented in Tables 8-9. Bioequivalence analysis is presented in Table 10.

Table 8. Summary of Mean (SD) Loratadine Pharmacokinetic Parameters

Parameter	2 x 5 mg Tablets (n=46)	1 x 10 mg Tablet (n=48)
	Arithmetic Mean (SD)	
C _{max} (ng/mL)	3.64 (2.94)	3.65 (2.82)
T _{max} (hr) ^a	1.25 (1.00-4.50)	1.50 (0.5-2.5)
AUC _T (ng•hr/mL)	10.86 (9.64)	10.79 (9.14)
AUC (ng•hr/mL) ^b	11.60 (10.29)	11.42 (9.58)
λ _z (Ke) (hr ⁻¹)	0.1153 (0.1226)	0.1149 (0.1218)
T _{1/2} (hr) ^c	6.02 (6.67)	6.04 (6.78)

^a Median (range)

^b N=45 for 2 x 5 mg treatment

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

Data Source: Appendix 15, Supportive Table 4

Table 9. Summary of Mean (SD) desloratadine Pharmacokinetic Parameters

Parameter	2 x 5 mg Tablets (n=46)	1 x 10 mg Tablet (n=48)
	Arithmetic Mean (SD)	
C _{max} (ng/mL)	3.12 (0.85)	3.17 (1.18)
T _{max} (hr) ^a	1.50 (1.00-16.00)	1.77 (1.00-16.00)
AUC _T (ng•hr/mL)	54.75 (46.96)	53.94 (46.96)
AUC (ng•hr/mL)	66.65 (85.95)	66.48 (91.98)
λ _z (K _e) (hr ⁻¹)	0.0316 (0.0106)	0.0317 (0.0098)
T _{1/2} (hr) ^b	21.94 (7.33)	21.90 (6.73)

^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 10. Analysis of Loratadine and desloratadine Bioequivalence (n=42)

Analyte Parameter	2 x 5 mg Tablets Test	1 x 10 mg Tablet Reference	Ratio (Test/Reference)	90% CI Lower	90% CI Upper
Loratadine					
AUC	7.4486	7.7359	0.9629	0.8868	1.0454
AUC _T	6.9344	7.3049	0.9493	0.8746	1.0304
C _{max}	2.4717	2.5790	0.9584	0.8608	1.0670
Desloratadine					
AUC	41.9253	42.3708	0.9895	0.9401	1.0414
AUC _T	40.5484	41.0117	0.9887	0.9377	1.0424
C _{max}	3.0322	3.0416	0.9969	0.9466	1.0499

CI=Confidence interval

Analysis excludes Subjects 007, 021, 030, 33, 39, and 042

Data Source: Appendix 15, Supportive Table 5.1

The results in Table 10 demonstrate the bioequivalence of loratadine and 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 0.80 to 1.25.

Conclusion: In the analysis of bioequivalence, the 90% confidence intervals around the ratio of the least squares means for loratadine and desloratadine C_{max} and AUC all fell within the bioequivalence interval of 0.8 to 1.25, demonstrating that the 2 x 5 mg Claritin RediTabs[®] tablets were bioequivalent to the 1 x 10 mg tablet.

Amendment to Pending application

Background: For the Claritin 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 data from a number of subjects from the bioequivalence determination for Study CL2003-02.

Amendment: On August 25, 2006, the sponsor submitted an amendment to the current pending NDA to include a re-analysis of the bioequivalence data from two studies (Study CL2005-02 and Study CL2004-01) submitted to the original application. Sponsor stated that the re-analysis of the bioequivalence data was done as a result of the observations reported in Form 483 (FDA DSI audit) for the approval of the Claritin Chewable Tablets (NDA 21-891) application. The sponsor stated the same re-analysis criteria were applied to the current application and the following subjects' samples were excluded from the re-analysis:

- Study CL2005-02: Loratadine subjects – None. Desloratadine subjects 79, 80, and 81 (Run 27EYO-A-2)
- Study CL2004-01:
 - Loratadine (Run 12JGO-1-A): subjects 31, 32, 33 and single sample from subject 7, 10 hr, Period 2
 - Desloratadine (Run 17JGO-2-B): subjects 46, 47 and 48

Re-analyses Results:

Study CL2005-02:

Analyte	RediTabs® (Test)	Claritin-D® (reference)	Ratio	90% CI Lower	90% CI Upper
Loratadine					
AUC _{0-∞}	4.7162	3.1305	1.5066	1.3692	1.6577
AUC _{0-t}	4.5551	3.0346	1.5010	1.3630	1.6531
Cmax	1.4372	1.2704	1.1313	1.0382	1.2328
Desloratadine					
AUC _{0-∞}	20.5670	21.3968	0.9612	0.9060	1.0198
AUC _{0-t}	19.3482	19.9659	0.9691	0.9096	1.034
Cmax	1.3824	1.4932	0.9258	0.8740	0.9806

Study CL2004-01:

Analyte	RediTabs® (Test: 2x5 mg)	RediTabs® (Ref: 1x10 mg)	Ratio	90% CI Lower	90% CI Upper
Loratadine					
AUC _{0-∞}	8.1973	8.2081	0.9987	0.9278	1.0750
AUC _{0-t}	7.6250	7.7577	0.9829	0.9123	1.0589
Cmax	2.7019	2.7214	0.9928	0.8948	1.1016
Desloratadine					
AUC _{0-∞}	41.7214	42.4980	0.9817	0.9296	1.0367
AUC _{0-t}	40.4391	41.1042	0.9838	0.9299	1.0408
Cmax	2.9906	3.0019	0.9963	0.9423	1.0533

Conclusion: The results of the re-analyses of Study CL2005-02 still demonstrated equivalence for desloratadine for both C_{max} and AUC, and no equivalence for loratadine (no subjects were excluded). The re-analyses for Study CL2004-01 demonstrated bioequivalence for C_{max} and AUC for both loratadine and desloratadine. Thus, re-analyses did not change the overall findings.

Reviewer's comment: The Sponsor's run acceptance for the study was 33% (1 out of 3) 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.

2.6. Analytical Section

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

Plasma samples collected from this study (2161 and 4163 original samples from Study CL2004-01 and Study CL2005-02, 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. Three low level (0.075 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). Overall, the analytical assay is acceptable.

3. Labeling Recommendation: None.

**APPEARS THIS WAY
ON ORIGINAL**

4. APPENDIX

4.1 PROPOSED PACKAGE INSERT



4.2. OCP filling

Office of Clinical Pharmacology and Biopharmaceutics				
New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21-993	Brand Name	Claritin RediTab 5 mg tablet	
OCP Division (I, II, III, IV,V)	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	Orally disintegrating Tablets (ODT)	
		Dosing Regimen	1 tab Q12h for ≥6 years; ask a doctor for < 6 years old	
Date of Submission	2/10/06	Route of Administration	Oral	
Estimated Due Date of OCPB Review	10/10/06	Sponsor	Schering-Plough	
PDUFA Due Date	12/10/06	Priority Classification	3 S	
Division Due Date	10/10/06			
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	2		SD in healthy adults
replicate design, single / multi dose:				
Food-drug interaction studies:				
Dissolution:	x			
(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		2		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	x			
Comments sent to firm?				
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? • Has the applicant developed adequate dissolution method and specification to assure in vivo performance and quality of the product? • What bioanalytical methods are used to assess concentrations of active moieties? 			

Background: The sponsor conducted two BE studies to support the NDA for new formulation orally disintegrating tablet (ODT), Claritin 5 mg RediTab Tablet. The results of a cursory review of these two studies are summarized below.

Study #CL2005-02: This was a randomized, open-label, single-dose, two-way crossover, BE study of two formulations of loratadine 5 mg (Claritin 5 mg RediTab Tablet vs. Claritin-D 12-Hour extended release Tablet) in 91 healthy adult subjects. A 14-day washout period separated the two doses of study medication. The result of bioequivalence analysis (n=86) is shown in Table 1.

Table 1. Analysis of loratadine and desloratadine Bioequivalence

Analyte Parameter	Claritin® RediTabs® Tablet Test	Claritin-D® 12 Hour Extended Release Tablet Reference	Ratio (Test/Reference)	90% CI Lower	90% CI Upper
Loratadine					
AUC	4.7162	3.1305	1.5066	1.3692	1.6577
AUC _T	4.5551	3.0346	1.5010	1.3630	1.6531
C _{max}	1.4372	1.2704	1.1313	1.0382	1.2328
Desloratadine					
AUC	20.6080	21.4070	0.9627	0.9093	1.0192
AUC _T	19.3942	19.9944	0.9700	0.9125	1.0311
C _{max}	1.3755	1.4845	0.9266	0.8764	0.9796

CI=Confidence interval
Data Source: Appendix 15, Supportive Table 5.1

As shown in Table 1, only the 90% CI for geometric mean ratios for AUC of loratadine did not meet the criteria of BE by falling outside 0.8-1.25 range, while others were within the BE range.

Comment: Outside of the bioequivalence range of 0.8 - 1.25 for the geometric mean test-to-reference ratio (90% CI) for AUC of loratadine is a review issue.

Study #CL2004-01: This was a randomized, open-label, single-dose, two-way crossover, BE study of two formulations of loratadine (Claritin 2 x 5 mg RediTab Tablet vs. 1 x 10 mg Claritin RediTab Tablet) in 48 healthy adult subjects. A 14-day washout period separated the two doses of study medication. The result of bioequivalence analysis (n=42) is shown in Table 2.

Table 2. Analysis of loratadine and desloratadine Bioequivalence

Table 7 Analysis of Loratadine and Desloratadine Bioequivalence					
Analyte Parameter	2 x 5 mg Tablets Test	1 x 10 mg Tablet Reference	Ratio (Test/Reference)	90% CI Lower	90% CI Upper
Loratadine					
AUC	7.4486	7.7359	0.9629	0.8868	1.0454
AUC _T	6.9344	7.3049	0.9493	0.8746	1.0304
C _{max}	2.4717	2.5790	0.9584	0.8608	1.0670
Desloratadine					
AUC	41.9253	42.3708	0.9895	0.9401	1.0414
AUC _T	40.5484	41.0117	0.9887	0.9377	1.0424
C _{max}	3.0322	3.0416	0.9969	0.9466	1.0499

CI=Confidence interval
Analysis excludes Subjects 007, 021, 030, 33, 39, and 042
Data Source: Appendix 15, Supportive Table 5.1

The results in Table 2 demonstrate the bioequivalence of the two formulations, with 90% confidence intervals around the ratio of the geometric least squares means for loratadine and desloratadine falling within the range of 0.8 to 1.25.

Note: (a) According to the sponsor, the data from subjects 007, 021, 030 and 042 are not included for BE analysis because their pre-dose concentrations exceeded 5% of C_{max} during Period 2. The sponsor also stated no appreciable difference was observed when these 4 subjects were included in the analysis, and the two treatments remained bioequivalent. (b) Subject 033 discontinued after one treatment due to adverse events and Subject 039 withdrew consent due to family emergency after one treatment.

**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
10/17/2006 09:39:05 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
10/18/2006 03:49:44 PM
BIOPHARMACEUTICS
I concur

CLINICAL PHARMACOLOGY REVIEW

Subject: Addendum to submission dated August 25, 2006, NDA 21-993
Sponsor: Schering-Plough HealthCare Products Inc.
OCP Division: DCP-II
OND Division: DNCE
Reviewer: Shinja R. Kim, Ph.D.
Team Leader: Emmanuel Fadiran, Ph.D.

The NDA was submitted to the Agency on February 10, 2006 and the original clinical pharmacology review by this reviewer (dated October 17, 2006) recommended approval subject to a favorable DSI report.

DSI Report

The DSI report by Dr. John Kadavil dated November 17, 2006 identified the following two objectionable items:

1. *Analytical runs were accepted even though more than 50% (2 out of 3) of the low QCs failed. Examples include the following:*
 - a. Study CL2005-02: Run 27EYO-A-2 for desloratadine (SCH 34117)
 - b. Study CL2004-01: Run 12JGO-1-A for loratadine (SCH 29851) and runs 10JGO-2-A and 17JGO-2-B for desloratadine (SCH 34117).

Since > 50% of the low QCs were inaccurate (i.e., > ±15% of the intended concentration) in the aforementioned analytical runs, the accuracy of the runs cannot be assured. The firm's run acceptance criterion, requiring only 33% (1 of 3) QCs to pass at each level, is not acceptable. Due to inaccuracy of the analytical runs, DSI recommends the data for the following subjects from analytical runs with failing QC results be excluded from bioequivalence determination:

Analyte	Run	Subjects	Samples
Loratadine	12JGO-1-A	7, 31, 32, 33	314,1381-1398,1400-1438,1440-1494
Desloratadine	27EYO-A-2	79, 80, 81	3589-3726
	10JGO-2-A	25, 26, 27	1105-1139, 1141-1242
	17JGO-2-B	46, 47, 48	2071-2208

2. *The sponsor did not provide objective criteria for selecting samples for pharmacokinetic (PK) repeat. Also, the reported results for sponsor-requested PK repeats ignored the original result and only compared the repeat results (re-assayed in triplicate). — followed the reporting procedures provided by the sponsor.*

While the sponsor's procedures are not acceptable, less than 2% of the samples were re-assayed as PK repeats. The repeat and original results were included in both final reports in Tables 7 and 8 (CL2005-02) and Tables 12-15 (CL2004-01). It should be noted that >50% of the repeat results were within 20% of the original value for Project EYO, and 64% of the repeat results were within 20% of the original value for Project JGO.

DSI then recommended that the data for the following subjects from analytical runs with failing QC results be excluded from bioequivalence determination:

- Study CL2005-02
 - Desloratadine: Subjects 7 (Period II, 10 hr sample), 79, 80 and 81
- Study CL2004-01
 - Loratadine: Subjects 31, 32 and 33
 - Desloratadine: Subjects 25, 26, 27, 46, 47 and 48

Note: Subject 7 from Study CL2004-01 is for loratadine, not desloratadine (see table on page 1).

Amendment submitted to pending NDA in response to DSI audit

On August 25, 2006, the sponsor submitted an amendment to the pending NDA to include a re-analysis of the bioequivalence data from two studies (Study CL2005-02 and Study CL2004-01) submitted to the original application. Sponsor stated that the re-analysis of the bioequivalence data was done as a result of the observations reported in Form 483 (FDA DSI audit) for the approval of the Clartin Chewable Tablets (NDA 21-891) application. The sponsor stated the same re-analysis criteria were applied to the current application (i.e., at least 50% of the QCs at each level are accurate) and the following subjects' samples were excluded from the re-analysis:

- Study CL2005-02:
 - Loratadine subjects – None.
 - Desloratadine subjects 79, 80, and 81 (Run 27EYO-A-2)
- Study CL2004-01:
 - Loratadine (Run 12JGO-1-A): subjects 31, 32, 33 and single sample from subject 7, 10 hr, Period 2
 - Desloratadine (Run 17JGO-2-B): subjects 46, 47 and 48

Re-analyses Results:

Table 1: Statistical analysis (Study CL2005-02)

Analyte	RediTabs [®] (Test)	Claritin-D [®] (reference)	Ratio	90% CI Lower	90% CI Upper
Loratadine					
AUC _{0-∞}	4.7162	3.1305	1.5066	1.3692	1.6577
AUC _{0-t}	4.5551	3.0346	1.5010	1.3630	1.6531
Cmax	1.4372	1.2704	1.1313	1.0382	1.2328
Desloratadine					
AUC _{0-∞}	20.5670	21.3968	0.9612	0.9060	1.0198
AUC _{0-t}	19.3482	19.9659	0.9691	0.9096	1.034
Cmax	1.3824	1.4932	0.9258	0.8740	0.9806

Table 2: Statistical analysis (Study CL2004-01)

Analyte	RediTabs [®] (Test: 2x5 mg)	RediTabs [®] (Ref: 1x10 mg)	Ratio	90% CI Lower	90% CI Upper
Loratadine					
AUC _{0-∞}	8.1973	8.2081	0.9987	0.9278	1.0750
AUC _{0-t}	7.6250	7.7577	0.9829	0.9123	1.0589
Cmax	2.7019	2.7214	0.9928	0.8948	1.1016
Desloratadine					
AUC _{0-∞}	41.7214	42.4980	0.9817	0.9296	1.0367
AUC _{0-t}	40.4391	41.1042	0.9838	0.9299	1.0408
Cmax	2.9906	3.0019	0.9963	0.9423	1.0533

As stated under #1, DSI recommended run 10JGO-2-A for desloratadine (affected subjects are 25, 26 and 27) from Study CL2004-01 to be deleted because >50% of the low QCs were inaccurate (all other affected subjects, i.e., 7, 31, 32, 33, 46, 47, 48, 79, 80, and 81 had been deleted from 'Re-PK analysis'). Run 10JGO-2-A for QC 1 (i.e., lowest QC, 0.0750 ng/ml) had 2 runs, resulting 0.0879 ng/ml (17.2%Diff) and 0.0652 ng/ml (-13.1% Diff). Therefore, the sponsor included this run for PK re-analysis.

Reviewer's comment: Including the run 10JGO-2-A (affected subjects 25, 26 and 27) for PK re-analysis is acceptable. This conclusion was discussed with Dr. Kadavil of DSI and he concurred with the recommendation to accept the sponsor's response to the 483 issues. In conclusion, the sponsor's results of 'Re-analysis' submitted as Amendment to NDA is acceptable. This NDA is therefore recommended for approval.

**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
11/29/2006 01:52:41 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
11/29/2006 02:18:39 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	21-993	Brand Name	Claritin RediTab 5 mg tablet	
OCB Division (I, II, III, IV, V)	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	Orally disintegrating Tablets (ODT)	
		Dosing Regimen	1 tab Q12h for ≥6 years; ask a doctor for < 6 years old	
Date of Submission	2/10/06	Route of Administration	Oral	
Estimated Due Date of OCPB Review	10/10/06	Sponsor	Schering-Plough	
PDUFA Due Date	12/10/06	Priority Classification	3 S	
Division Due Date	10/10/06			
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) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
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	2		SD in healthy adults
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	x			
(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		2		
Filability and OBR comments				
	"X" if yes	Comments		
Application filable?	x			
Comments sent to firm?				
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? • Has the applicant developed adequate dissolution method and specification to assure in vivo performance and quality of the product? • What bioanalytical methods are used to assess concentrations of active moieties? 			

Background: The sponsor conducted two BE studies to support the NDA for new formulation orally disintegrating tablet (ODT), Claritin 5 mg RediTab Tablet. The results of a cursory review of these two studies are summarized below.

Study #CL2005-02: This was a randomized, open-label, single-dose, two-way crossover, BE study of two formulations of loratadine 5 mg (Claritin 5 mg RediTab Tablet vs. Claritin-D 12-Hour extended release Tablet) in 91 healthy adult subjects. A 14-day washout period separated the two doses of study medication. The result of bioequivalence analysis (n=86) is shown in Table 1.

Table 1. Analysis of loratadine and desloratadine Bioequivalence

Analyte Parameter	Claritin® RediTabs® Tablet Test	Claritin-D® 12 Hour Extended Release Tablet Reference	Ratio (Test/Reference)	90% CI Lower	90% CI Upper
Loratadine					
AUC	4.7162	3.1305	1.5066	1.3692	1.6577
AUC _T	4.5551	3.0346	1.5010	1.3630	1.6531
C _{max}	1.4372	1.2704	1.1313	1.0382	1.2328
Desloratadine					
AUC	20.6080	21.4070	0.9627	0.9093	1.0192
AUC _T	19.3942	19.9944	0.9700	0.9125	1.0311
C _{max}	1.3755	1.4845	0.9266	0.8764	0.9796

CI=Confidence interval
Data Source: Appendix 15, Supportive Table 5.1

As shown in Table 1, only the 90% CI for geometric mean ratios for AUC of loratadine did not meet the criteria of BE by falling outside 0.8-1.25 range, while others were within the BE range.

Comment: Outside of the bioequivalence range of 0.8 - 1.25 for the geometric mean test-to-reference ratio (90% CI) for AUC of loratadine is a review issue.

Study #CL2004-01: This was a randomized, open-label, single-dose, two-way crossover, BE study of two formulations of loratadine (Claritin 2 x 5 mg RediTab Tablet vs. 1 x 10 mg Claritin RediTab Tablet) in 48 healthy adult subjects. A 14-day washout period separated the two doses of study medication. The result of bioequivalence analysis (n=42) is shown in Table 2.

Table 2. Analysis of loratadine and desloratadine Bioequivalence

Table 7 Analysis of Loratadine and Desloratadine Bioequivalence					
Analyte Parameter	2 x 5 mg Tablets Test	1 x 10 mg Tablet Reference	Ratio (Test/Reference)	90% CI Lower	90% CI Upper
Loratadine					
AUC	7.4486	7.7359	0.9629	0.8868	1.0454
AUC _T	6.9344	7.3049	0.9493	0.8746	1.0304
C _{max}	2.4717	2.5790	0.9584	0.8608	1.0670
Desloratadine					
AUC	41.9253	42.3708	0.9895	0.9401	1.0414
AUC _T	40.5484	41.0117	0.9887	0.9377	1.0424
C _{max}	3.0322	3.0416	0.9969	0.9466	1.0499

CI=Confidence interval
Analysis excludes Subjects 007, 021, 030, 33, 39, and 042
Data Source: Appendix 15, Supportive Table 5.1

The results in Table 2 demonstrate the bioequivalence of the two formulations, with 90% confidence intervals around the ratio of the geometric least squares means for loratadine and desloratadine falling within the range of 0.8 to 1.25.

Note: (a) According to the sponsor, the data from subjects 007, 021, 030 and 042 are not included for BE analysis because their pre-dose concentrations exceeded 5% of C_{max} during Period 2. The sponsor also stated no appreciable difference was observed when these 4 subjects were included in the analysis, and the two treatments remained bioequivalent. (b) Subject 033 discontinued after one treatment due to adverse events and Subject 039 withdrew consent due to family emergency after one treatment.

Food effect study: No food effect study was conducted. Sponsor stated that this new Claritin 5 mg ODT is the same formulation as the marketed 10 mg ODT except that the amount of loratadine has been reduced by 50% (Table 3); therefore no food effect study was conducted. The sponsor's rationale is acceptable.

Table 3. Composition

Component	Claritin RediTab 10 mg	Claritin RediTab 5 mg
	mg/tablet (— mg)*	mg/tablet (— mg)*
Loratadine micronized	10.0	5.0
Gelatin NF and Ph. Eur.	—	—
Mannitol USP and Ph. Eur.	—	—
Citric Acid USP and Ph. Eur.	—	—
Mint Flavor	—	—

*target weight

Conclusion: This NDA is filable.

**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
4/17/2006 03:37:35 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
4/17/2006 04:12:22 PM
BIOPHARMACEUTICS
I concur