

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-891

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

CLINICAL PHARMACOLOGY REVIEW

NDA 21-891:	Submission Date: June 23, 2006
Brand Name:	Claritin® Chewable Tablet
Generic Name:	Loratadine
Reviewer:	Partha Roy, Ph.D.
Team Leader:	Emmanuel O. Fadiran, Ph. D.
OCP Division:	DCP 2
OND Division:	DPADP
Applicant:	Schering-Plough Health Care Products. Inc.
Submission Type:	Resubmission (Class 1)
Formulation; Strength(s):	5 mg
Dosage and administration:	2 tablets daily for ≥ 6 yrs; 1 tablet daily for <6 to ≥ 2 yrs
Indication:	Temporally relief of symptoms due to hay fever or other respiratory allergies.

1. BACKGROUND

Schering-Plough HealthCare Products, Inc. has submitted NDA 21-891 for over-the-counter (OTC) marketing of Claritin® Chewable Tablets, an immediate release chewable solid oral dosage form containing 5 mg loratadine.

In support of this application, the Sponsor submitted results of a two-way crossover bioequivalence study (CL2003-02) conducted in healthy subjects. The objective of this study was to determine the relative bioavailability/bioequivalence (BA/BE) of 2x5 mg of the proposed formulation compared to approved reference product (Claritin® 10 mg Tablet) following single dose administration under fasted condition. This study was reviewed by Dr. Shinja Kim (Clinical Pharmacology Review dated April 4, 2006) with a recommendation that it was acceptable pending favorable Division of Scientific Investigation (DSI) report.

The DSI conducted an audit of the analytical portion of the study and issued a Form 483 to the Sponsor due to the following questionable observation (DSI report dated May 23, 2006): Analytical runs were accepted although more than 50% of the low QCs failed.

Based on this observation, DSI recommended excluding the analytical data from a number of subjects for the bioequivalence determination of the study CL2003-02. The following subject data needed to be excluded as they were obtained from runs with failing QC results: Loratadine: subjects 4-6 and Desloratadine: subjects 1-3, 13-15, and 22-24.

The Office of Clinical Pharmacology (OCP) agreed with the DSI observations and recommended the following to the Sponsor (Clinical Pharmacology Team Leader's Memo by Dr. Fadiran dated May 25, 2006):

1. Reanalyze the BE data excluding the subjects as recommended by the DSI above and resubmit the BE data as an amendment to the NDA.
2. If the BE criterion is not met in 1 and the sponsor has sufficient samples from the above-mentioned subjects, reassay the samples from these subjects and submit the report of the re-analysis of the BE data as an amendment to the NDA. Also, send the analytical report to the DSI to address the analytical issues in the Form 483.

The sponsor has now provided the resubmission in response to the above-mentioned DSI and OCP recommendations.

2. REANALYSIS OF THE BIOEQUIVALENCE DATA

The resubmission includes reanalysis of the BE data excluding subjects 4-6 (3 subjects) from the loratadine data and subjects 1-3, 13-15, and 22-24 (9 subjects) from the desloratadine data as recommended above.

Pharmacokinetics of loratadine and its active metabolite, desloratadine from the test product Claritin® Chewable Tablets (2 x 5 mg) were compared to those from the reference product Claritin® Tablet (1 x 10 mg) in a two-way crossover study. The reanalysis showed that the test product is bioequivalent to the reference product as the 90% confidence intervals around the ratio of mean values of AUC and C_{max} for both loratadine and desloratadine fell within 80 to 125% range (Table 1).

Table 1. Point estimates (ratio) along with 90% confidence intervals for the log-transformed C_{max}, AUC_t, and AUC_{inf} values of loratadine and desloratadine: excludes subjects 4-6 for loratadine and subjects 1-3, 13-15, and 22-24 for desloratadine and subject 37 (pre-dose concentration >5% of C_{max}) and subject 43 (early termination) for both analytes.

Parameter ¹	Pair	Loratadine (n = 43)		Desloratadine (n = 37)	
		Ratio	90% CI	Ratio	90% CI
AUC _t (ng•h/mL)	Test/Ref	1.07	0.97-1.18	1.00	0.94-1.06
AUC _{inf} (ng•h/mL)	Test/Ref	1.06	0.96-1.18	1.00	0.94-1.06
C _{max} (ng/mL)	Test/Ref	1.07	0.94-1.22	0.92	0.85-0.99

Test = Claritin® Chewable Tablet

Ref = Claritin® Tablet

¹Geometric mean, ln-transformed data, and 90% CI ratio of parameter geometric means

3. RECOMMENDATION: The Office of Clinical Pharmacology has reviewed the sponsor's resubmission, and finds it acceptable to OCP.

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/s/

Partha Roy
7/26/2006 04:48:21 PM
PHARMACOLOGIST

Emmanuel Fadiran
7/27/2006 10:20:56 AM
BIOPHARMACEUTICS
I concur.

Addendum to Clinical Pharmacology TL's Memo

Memorandum to: NDA 21-891
Submission Date: August 2, 2005
Product: Claritin® Chewable Tablet (loratadine), 5 mg
Sponsor: Schering-Plough HealthCare Products, Inc.
Memo Date: May 25, 2006.
Memo From: Emmanuel O. Fadiran, Ph.D., OCP Team Leader

This is an addendum to the memo dated May 25, 2005 to correct the NDA number. The NDA number should be 21-891 (not 20-891 as noted in the memo).

Current Submission:

Schering-Plough HealthCare Products, Inc. submitted NDA 21-891 for OTC marketing of Claritin® Chewable tablet on August 2, 2005. In support of the NDA the Sponsor submitted a two-way crossover BE study (CL2003-02) that compared 2x5 mg of the test formulation to 10 mg Claritin® tablet. This study was reviewed by Dr. Shinja Kim (Clinical Pharmacology review dated April 4, 2006) with a recommendation that it was acceptable subject to favorable DSI report.

The DSI conducted an audit of the analytical portion of the study and issued a Form 483 to the Sponsor based on the following objectionable observation (DSI report dated May 23, 2006):

Analytical runs were accepted although more than 50% of the low QCs failed. For example, runs 1ZCO-2-A, 5ZCO-2-A, and 8ZCO-2-A for desloratadine (SCH34117) and run 2ZCO-1-A for loratadine (SCH29851) were accepted when 2 of 3 low QCs failed.

Based on this observation, DSI concludes that the following data be excluded from the bioequivalence determination for Study CL2003-02:

- Data from runs with failing QC results
 - Loratadine: subjects 4-6
 - Desloratadine: subjects 1-3, 13-15, 22-24

The OCP agrees with the DSI conclusions and makes the following recommendations to the Sponsor:

1. Re-analysis of BE data: Exclude subjects 4-6 (3 subjects) from the loratadine data and subjects 1-3, 13-15 and 22-24 (9 subjects) from the desloratadine data from the bioequivalence analysis and then repeat the analysis before submitting an amendment to the NDA.
2. Repeat assay of samples: If the BE analysis in 1 does not show that your product is bioequivalent to Claritin tab®let and you have sufficient samples for the above-mentioned subjects, you should do a repeat assay of the samples for these subjects and send the report of the re-analysis of the BE data as an amendment to the NDA

for Agency's review. You should also send the analytical report to DSI to show that the issues in the Form 483 have been adequately addressed.

Conclusion: The OCP has reviewed the DSI report and makes the above recommendations to be sent to the sponsor.

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Emmanuel Fadiran

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BIOPHARMACEUTICS

This is an addendum to the memo to correct
the NDA number in the memo.

Clinical Pharmacology TL's Memo

Memorandum to: NDA 20-891
Submission Date: August 2, 2005
Product: Claritin® Chewable Tablet (loratadine), 5 mg
Sponsor: Schering-Plough HealthCare Products, Inc.
Memo Date: May 25, 2006.
Memo From: Emmanuel O. Fadiran, Ph.D., OCP Team Leader

Current Submission:

Schering-Plough HealthCare Products, Inc. submitted NDA 20-891 for OTC marketing of Claritin® Chewable tablet on August 2, 2005. In support of the NDA the Sponsor submitted a two-way crossover BE study (CL2003-02) that compared 2x5 mg of the test formulation to 10 mg Claritin® tablet. This study was reviewed by Dr. Shinja Kim (Clinical Pharmacology review dated April 4, 2006) with a recommendation that it was acceptable subject to favorable DSI report.

The DSI conducted an audit of the analytical portion of the study and issued a Form 483 to the Sponsor based on the following objectionable observation (DSI report dated May 23, 2006):

Analytical runs were accepted although more than 50% of the low QCs failed. For example, runs 1ZCO-2-A, 5ZCO-2-A, and 8ZCO-2-A for desloratadine (SCH34117) and run 2ZCO-1-A for loratadine (SCH29851) were accepted when 2 of 3 low QCs failed.

Based on this observation, DSI concludes that the following data be excluded from the bioequivalence determination for Study CL2003-02:

- Data from runs with failing QC results
 - Loratadine: subjects 4-6
 - Desloratadine: subjects 1-3, 13-15, 22-24

The OCP agrees with the DSI conclusions and makes the following recommendations to the Sponsor:

1. Re-analysis of BE data: Exclude subjects 4-6 (3 subjects) from the loratadine data and subjects 1-3, 13-15 and 22-24 (9 subjects) from the desloratadine data from the bioequivalence analysis and then repeat the analysis before submitting an amendment to the NDA.
2. Repeat assay of samples: If the BE analysis in 1 does not show that your product is bioequivalent to Claritin tab®let and you have sufficient samples for the above-mentioned subjects, you should do a repeat assay of the samples for these subjects and send the report of the re-analysis of the BE data as an amendment to the NDA for Agency's review. You should also send the analytical report to DSI to show that the issues in the Form 483 have been adequately addressed.

Conclusion: The OCP has reviewed the DSI report and makes the above recommendations to be sent to the sponsor.

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/s/

Emmanuel Fadiran
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BIOPHARMACEUTICS

Henry Malinowski
5/25/2006 01:24:14 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-891:	Submission Date: August 2, 2005
Brand Name:	Claritin® Chewable Tablet
Generic Name:	Loratadine
Reviewer:	Shinja Kim, Ph.D.
Team Leader:	Emmanuel O. Fadiran, Ph. D.
OCP Division:	DCP 2
OND Division:	DNCE
Applicant:	Schering-Plough Health Care Products. Inc.
Submission Type:	Original (S-000)
Formulation; Strength(s):	5 mg
Dosage and administration:	2 tablets daily for ≥ 6 yrs; 1 tablet daily for <6 to ≥ 2 yrs
Indication:	Temporally relief of symptoms due to hay fever or other respiratory allergies.

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1. EXECUTIVE SUMMARY

1.1 Recommendation: The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the sponsor's submission, and found it acceptable from an OCP standpoint subject to favorable DSI findings.

1.2 Phase 4 Commitment: None

1.3 Summary of clinical Pharmacology and Biopharmaceutics Findings

Schering-Plough HealthCare Products, Inc. submits this original NDA for over-the-counter (OTC) marketing of Claritin® chewable Tablet, an immediate release chewable solid oral dosage form containing 5 mg loratadine. This new formulation will be supplied in blister packages of various tablet counts per blister card.

In support of this application the sponsor submitted the results of the bioequivalence pharmacokinetic study (CL2003-02) 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 (Claritin® 10 mg Tablet) after a single dose under fasted condition.

BE/BA Assessment (Study CL2003-02): Pharmacokinetics of loratadine and its active metabolite, desloratadine from the test product Claritin® chewable Tablets (2 x 5 mg) were compared to those from the reference product Claritin® Tablet (1 x 10 mg) in a two-way crossover study. The study shows that the test product is bioequivalent to the reference product as the 90% confidence intervals around the ratio of the mean values of AUC and C_{max} for both loratadine and desloratadine fell within 80 to 125% range (Table 1)

Table 1. Point estimates (ratio) and 90% confidence intervals for the log-transformed C_{max}, AUC_t, and AUC_{inf} values of loratadine and desloratadine following single administration of the treatments

Parameter ¹	Trt	Pair	Loratadine		DESLORATADINE	
			Ratio	90% CI	Ratio	90% CI
AUC _t (ng•h/mL)	A					
	B	A/B	1.09	0.989-1.20	0.991	0.943-1.043
AUC _{inf} (ng•h/mL)	A					
	B	A/B	1.09	0.986-1.20	0.996	0.949-1.045
C _{max} (ng/mL)	A					
	B	A/B	1.07	0.943-1.21	0.927	0.87-0.988

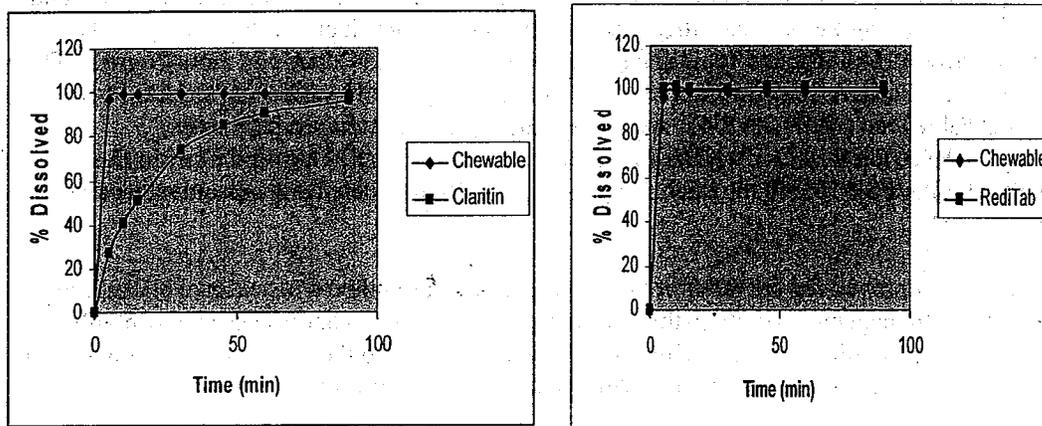
A = Claritin® chewable Tablet (Test), B = Claritin® Tablet (reference)

¹Geometric mean, ln-transformed data, and 90% CI ratio of parameter geometric means

Food effect study: The lack of study determining food effect on the new formulation of loratadine was noted as a review issue. As the food effect on other Claritin formulations is well defined based on previous NDA approvals (i.e., food alters the BA of loratadine), an option was given for the sponsor to provide comparative *in vitro* dissolution data on the proposed formulation and the approved tablet formulation(s) to show that the food effect would be similar from this proposed formulation to that from approved formulation(s). The sponsor submitted the results from the comparative *in vitro* dissolution studies (as an amendment to the pending application) on March 3, 2006, and is summarized below.

Comparative *in vitro* dissolution profiles: Dissolution profiles were obtained using 2 x 5 mg Claritin Chewable Tablet vs. 1 x 10 mg Claritin Tablet and 2 x 5 mg Claritin Chewable Tablet vs. 1 x 10 mg Claritin RediTab Tablet (Figure 1) using the USP specified dissolution conditions (paddle 2, 50 rpm, 900 ml 0.1 N HCl).

Figure 1. Mean dissolution profiles of Claritin chewable tablets vs. Claritin tablets (left panel) and RediTab tablets (right panel).



Sponsor also included three food effect studies which were submitted in the original NDA in this amended submission (detailed results on pages 12-13). Food altered the BA of loratadine after conventional Claritin tablets or Claritin RediTab tablets: Food caused about 35% increase in AUCt for Claritin tablet but substantial increase (90%) from Claritin RediTab tablet. It is difficult to conclude whether the difference in BA change is due to difference in formulation or the study that was conducted in different subjects.

Reviewer's comment: Although exact mechanism by which food changes the BA of drug product would not be known without of performing specific mechanistic studies, food effect on loratadine appears to be largely due to drug substance because food effect BE studies from previously submitted (generic) loratadine, such as NDAs ~~_____~~ and 21512 showed that similar food effect when the test products were compared to the reference products. Therefore, it is expected that food effect will be seen after Claritin Chewable tablet administration - may be, similar to that seen after Claritin RediTab tablet administration.

*In conclusion, *in vitro* dissolution data can substitute for absence of food effect study since food effect on Claritin drug products is well known. The request for the waiver of the food effect study could therefore be granted based on the similarity in the *in vitro* dissolution profiles for Claritin RediTab and Claritin Chewable tablets.*

Dissolution: Sponsor proposed the dissolution method same as specified by the current USP monograph (Paddle 2, 50 rpm, 0.1 N HCl 900 ml) for loratadine tablets, except the volume of media (500 mL 0.1 N HCl). In addition, an HPLC method is proposed in contrast to current UV method to determine the loratadine content of the dissolution media because Claritin Chewable tablet contains dye and flavor (grape) components. The proposed specification is Q of NLT ~~—~~, ii min rather than 60 min as specified by the current USP monograph for loratadine tablets and NDA19-658 (Claritin 10 mg tablet). The dissolution method and specification will be reviewed by the chemist (Tarun Metha, Ph. D.). This reviewer discussed tightening of the proposed specification (if needed) with Dr. Metha.

Table 2. Target composition: Claritin® Chewable Tablets

Ingredient	Reference To Quality Standard	Function	Amount Per Tablet (mg)
Loratadine, USP	USP	Drug Substance	5.00
Mannitol, USP	USP		
Microcrystalline Cellulose, NF	NF		
Aspartame, NF	NF		
Flavor, _____	In-house		
Citric Acid, USP	USP		
Dye, Blue #2 FD&C, Aluminum Lake	In-house		
Dye, Red #27 D&C, Aluminum Lake	In-house		
Colloidal Silicon Dioxide, NF	NF		
Sodium Starch Glycolate, NF	NF		
Stearic acid, NF/FG Veg. Powder	NF		
Magnesium Stearate, NF	NF		
Total mg/tab			250.00

1: Additional information on this flavor is incorporated by reference to DMF No. _____ See the letter of authorization from _____ in Module 1, Section 1.4.1

2: Refer to Figure 1 for a letter from the vendor _____ which explains the rationale for not requiring establishment of a Drug Master File for FD&C or D&C Dyes and Lakes.

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 submitted to this NDA is reviewed (and related issues).

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?

Study CL2003-02 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:** 2 x 5 mg loratadine chewable Tablets (test), Lot # 4 Demo 1-6
- **TRT B:** 1 x 10 mg loratadine Tablet (Claritin®) (reference), Lot # 4RXP-19

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, S, 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: All 48 subjects were included in PK population, but 2 of these subjects were excluded from the analysis of bioequivalence (Subject #43 was withdrawn for a positive urine drug screen at check-in to Period 2 and subject 37 was excluded for pre-dose desloratadine concentrations in Period 2 that represented >5% of the C_{max}).

Demographics: The overall mean ± SD (range) age of subjects in the study was 33.2 ± 8.3 (19 – 45) years. The majority subjects were Hispanic (40/48, 83.3%) and the number of females and males participating in the study was similar (25/48, 52.1% and 23/48, 47.9%, respectively).

Pharmacokinetics: Mean plasma concentration-time profiles of loratadine and desloratadine are shown in Figure 2. Mean PK parameters for loratadine and desloratadine are presented in Tables 3-4. Bioequivalence analysis is presented in Table 5.

Figure 2. Mean Loratadine (left) and desloratadine (right) Plasma Concentration vs. Time Curves by Treatment

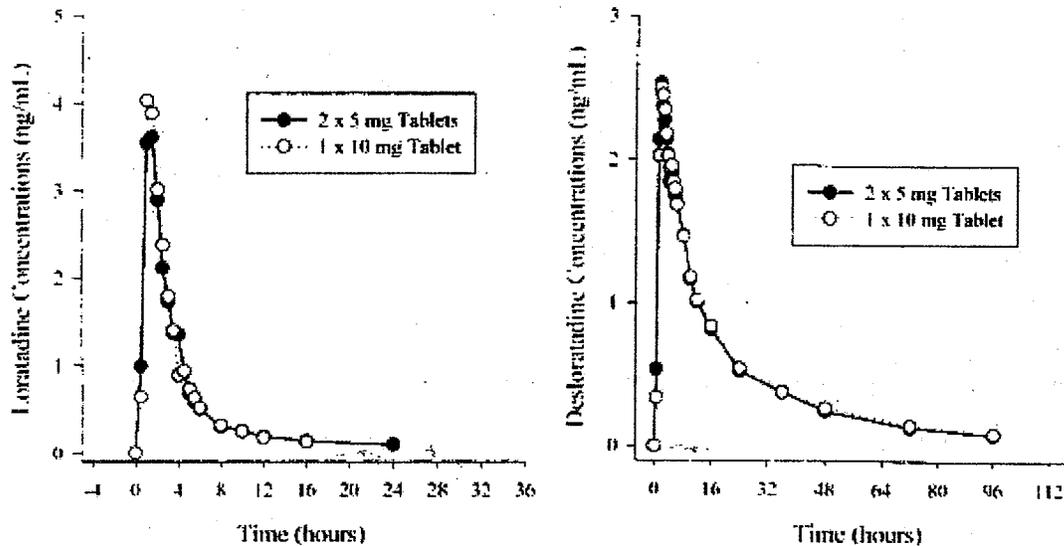


Table 3. Summary of Mean (SD) Loratadine Pharmacokinetic Parameters

Parameter	2 x 5 mg Tablets (n=48)	1 x 10 mg Tablet (n=47)
	Arithmetic Mean (SD)	
C _{max} (ng/mL)	4.31 (6.38)	4.55 (6.88)
T _{max} (hr) ^a	1.00 (1.00-4.00)	1.00 (1.00-5.00)
AUC _T (ng·hr/mL)	17.54 (43.75)	16.87 (38.01)
AUC (ng·hr/mL)	20.46 (56.27)	19.45 (47.76)
λ _z (K _e) (hr ⁻¹)	0.0986 (0.0692)	0.1201 (0.1173)
T _{1/2} (hr) ^b	7.03 (4.96)	5.77 (5.87)

^a Median (range)

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

Despite the 14-day interval between treatments, 4 subjects had detectable desloratadine predose drug concentrations during Period 2 that were confirmed during re-assay of duplicate plasma samples perhaps. However, data from only one subject (#37, appears to be 'poor metabolizer') whose plasma concentration was >5% of the C_{max} was dropped from all bioequivalence evaluation while data from the other 3 subjects were included since their concentrations were <5% of the C_{max}.

Table 4. Summary of Mean (SD) desloratadine Pharmacokinetic Parameters

Parameter	2 x 5 mg Tablets (n=48)	1 x 10 mg Tablet (n=47)
	Arithmetic Mean (SD)	
C _{max} (ng/mL)	2.78 (1.32)	2.91 (1.29)
T _{max} (hr) ^a	1.50 (1.00-10.00)	2.00 (1.00-5.50)
AUC _T (ng•hr/mL)	45.84 (34.34)	47.31 (44.56)
AUC (ng•hr/mL)	50.47 (48.45)	53.64 (72.44)
k _{el} (Kc) (hr ⁻¹)	0.0329 (0.0110)	0.0325 (0.0108)
T _{1/2} (hr) ^b	21.09 (7.10)	21.33 (7.12)

^a Median (range)

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

Table 5. 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	8.1305	7.4828	1.0866	0.9859	1.1975
AUC _T	7.5800	6.9576	1.0895	0.9886	1.2006
C _{max}	2.5926	2.4255	1.0689	0.9432	1.2114
Desloratadine					
AUC	38.1611	38.3228	0.9958	0.9489	1.0450
AUC _T	36.3022	36.6214	0.9913	0.9425	1.0425
C _{max}	2.4235	2.6152	0.9267	0.8695	0.9877

CI=Confidence interval

Analysis excludes Subjects 037 and 043

PK parameter values are Geometric mean

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 chewable tablets were bioequivalent to the 1 x 10 mg tablet.

2.5.2. What is the effect of food on the BA of loratadine and desloratadine from the Claritin chewable 5 mg tablet formulation?

No food effect study was conducted for this NDA. Sponsor submitted only one BA/BE study for this new formulation, Claritin Chewable Tablets 5 mg. In FDA's 74 days' filing letter (sent October 14, 2005), the lack of a study determining food effect was noted as a potential review issue, and the sponsor requested to provide the data such as a comparative *in vitro* dissolution profile to support that the food effect for this new formulation is expected to be the same as that seen for Claritin tablet. The Sponsor requested to have a Tcon with the Agency regarding this issue.

Summary of discussion from the Tcon: FDA stated that the development of new formulations requires bioequivalence and food effect studies. However, since the food effect on other Claritin products is well defined based on previous NDA approvals, *in vitro* comparative data against Claritin tablet may be acceptable to show that the food effect would be expected to be similar for this formulation. FDA would waive the food effect study if comparability is shown in two or three different dissolution media (e.g., 0.1 N HCL, different pH). Sponsor asked that since the chewable formulation is released quickly, would it be helpful to do a comparison with other quick release Claritin products? FDA responded that this would be acceptable.

2.5.3. Can the food effect study be waived based on *in vitro* comparative dissolution profiles as well as information from known data?

Sponsor submitted an amendment to the Claritin Chewable Tablets NDA 21-891 to provide the additional data to support the issue raised in the October 14, 2005 Filing Communication Letter and the Tcon. They are summarized below.

A. Comparative *in vitro* dissolution studies

Dissolution release profile of loratadine in Claritin® 5 mg chewable tablets vs. Claritin® 10 mg tablets:

The study involved comparison of the dissolution profiles generated using two Claritin Chewable tablets per vessel as compared to one Claritin Tablet per vessel with a total of twelve sets of samples generated for each dosage form. Testing was performed using the USP specified dissolution conditions for dosage forms (i.e., USP Apparatus 2 (Paddles) with 900 mL of dissolution medium of 0.1 N HCL and paddle speed of 50 rpm). The assays of the dissolution samples were performed using an HPLC method validated for the Claritin Chewable Tablet dosage form.

The materials used for this study are:

- Claritin Chewable Tablets (RB0 S39-174), Lot 0 5-GENI-231 (Sample ID: 27691501)
- Claritin Tablets (RBI S38-007), Lot # 5-RXF-54 (Sample ID: 13893403)

Results: Dissolution profiles of Claritin chewable tablets and Claritin tablets are presented in Table 6 and Table 7, respectively. Graphic presentation of these is shown in Figure 3.

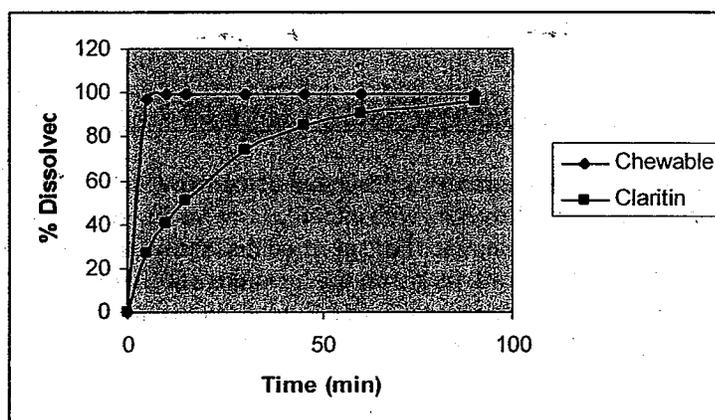
Table 6. Claritin Chewable Tablet: Dissolution Results Summary

Vessel	TIME (minutes)							
	0	5	10	15	30	45	60	90
1	0.00%	95.13%	99.94%	99.76%	99.76%	100.11%	100.11%	99.93%
2	0.00%	98.73%	98.29%	98.29%	98.72%	98.72%	98.81%	98.98%
3	0.00%	94.86%	98.42%	98.83%	98.59%	98.83%	98.43%	98.59%
4	0.00%	99.09%	99.71%	99.63%	99.54%	99.63%	99.47%	100.23%
5	0.00%	97.74%	98.63%	98.55%	98.73%	98.82%	99.08%	98.74%
6	0.00%	97.92%	98.63%	99.34%	98.82%	98.99%	98.74%	98.82%
7	0.00%	97.92%	99.17%	99.17%	99.25%	99.33%	99.50%	99.67%
8	0.00%	97.74%	99.08%	99.17%	98.90%	99.16%	99.33%	99.16%
9	0.00%	99.36%	100.16%	99.45%	99.37%	99.45%	99.71%	99.54%
10	0.00%	90.90%	97.83%	98.99%	99.42%	100.11%	99.35%	99.77%
11	0.00%	97.56%	99.25%	99.24%	99.07%	99.41%	99.59%	99.67%
12	0.00%	95.76%	99.83%	99.59%	99.59%	99.42%	99.94%	100.02%
Mean	N/A	96.9%	99.1%	99.2%	99.1%	99.3%	99.3%	99.4%
%RSD	N/A	2.5%	0.7%	0.4%	0.4%	0.5%	0.5%	0.6%

Table 7. Claritin Tablet: Dissolution Results Summary

Vessel	TIME (minutes)							
	0	5	10	15	30	45	60	90
1	0.00%	24.03%	37.74%	48.47%	83.71%	95.75%	98.98%	101.50%
2	0.00%	27.54%	39.83%	48.53%	65.93%	76.33%	85.17%	91.81%
3	0.00%	27.72%	41.87%	50.68%	68.95%	80.99%	86.35%	92.48%
4	0.00%	25.47%	41.22%	53.89%	87.91%	97.37%	100.44%	102.45%
5	0.00%	27.99%	41.16%	48.82%	65.79%	77.74%	85.31%	92.28%
6	0.00%	27.54%	42.85%	59.93%	89.85%	94.67%	97.22%	100.16%
7	0.00%	30.33%	41.99%	50.79%	68.89%	83.00%	88.70%	94.33%
8	0.00%	24.88%	37.83%	47.51%	72.91%	82.71%	88.07%	94.20%
9	0.00%	27.63%	39.56%	48.27%	66.63%	79.44%	86.33%	93.13%
10	0.00%	27.00%	40.17%	49.06%	65.51%	75.91%	82.89%	93.89%
11	0.00%	26.28%	39.54%	48.95%	67.66%	80.30%	86.93%	93.82%
12	0.00%	29.34%	42.52%	51.58%	84.81%	95.65%	99.57%	102.42%
Mean	N/A	27.1%	40.5%	50.5%	74.0%	85.0%	90.5%	96.0%
%RSD	N/A	6.8%	4.2%	6.8%	12.9%	9.8%	7.2%	4.4%

Figure 3. Mean dissolution profiles of Claritin chewable and Claritin tablets



Dissolution release profile of loratadine in Claritin® 5 mg chewable tablets vs. Claritin® 10 mg RediTabs tablets (orally disintegrating tablet):

The Procedures/method used to generate dissolution profiles for Claritin Chewable tablets and Claritin RediTabs Tablet were the same as above.

The materials used for this study are:

- Claritin Chewable Tablets (RB0 S39-174), Lot 0 5-GENI-231 (Sample ID: 27691501)
- Claritin Reditabs Tablets (RBI S38-011), Lot # S-EBT-20 (Exp. Date: JUN 2007)

Results: Dissolution profiles of Claritin chewable tablets and Claritin tablets are presented in Table 8 and Table 9, respectively. Graphic presentation of these is shown in Figure 4.

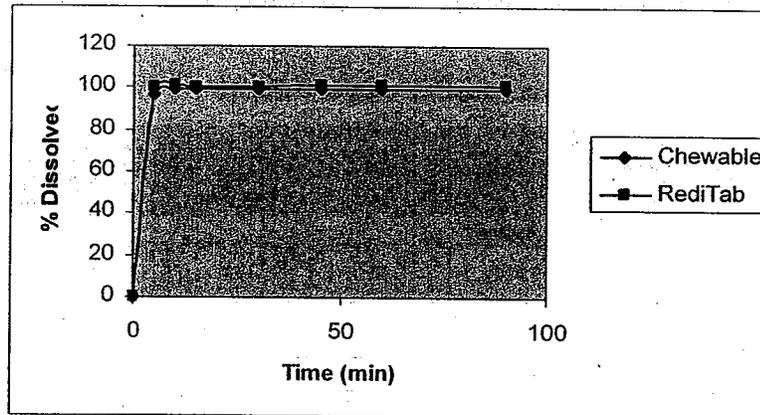
Table 8. Claritin Chewable Tablet: Dissolution Results Summary

Vessel	TIME (minutes)								
	0	5	10	15	30	45	60	90	
1	0.00%	98.37%	98.55%	98.64%	98.64%	98.65%	98.82%	98.91%	
2	0.00%	95.04%	98.60%	98.61%	98.44%	98.76%	98.78%	98.95%	
3	0.00%	98.01%	99.17%	99.17%	98.99%	99.25%	99.16%	99.07%	
4	0.00%	99.45%	99.90%	99.81%	100.16%	100.07%	100.16%	100.49%	
5	0.00%	95.85%	100.22%	100.12%	100.47%	100.39%	100.31%	100.56%	
6	0.00%	98.46%	99.26%	99.52%	99.00%	99.26%	99.26%	99.25%	
7	0.00%	97.65%	99.08%	99.25%	99.16%	99.08%	99.84%	99.59%	
8	0.00%	98.01%	99.35%	99.52%	99.78%	99.78%	99.62%	99.70%	
9	0.00%	97.65%	99.97%	99.70%	99.18%	99.44%	99.79%	99.62%	
10	0.00%	99.18%	99.45%	99.27%	99.36%	99.35%	99.61%	99.52%	
11	0.00%	90.54%	98.11%	98.99%	99.51%	99.34%	99.35%	99.52%	
12	0.00%	96.03%	99.06%	99.59%	99.50%	99.85%	99.43%	99.43%	
Mean	N/A	97.0%	99.2%	99.3%	99.3%	99.4%	99.5%	99.6%	
%RSD	N/A	2.5%	0.6%	0.5%	0.6%	0.5%	0.5%	0.5%	

Table 9. Claritin RediTab Tablet: Dissolution Results Summary

Vessel	TIME (minutes)								
	0	5	10	15	30	45	60	90	
1	0.00%	100.35%	101.69%	101.60%	101.60%	101.52%	101.61%	101.61%	
2	0.00%	94.86%	99.04%	99.13%	99.47%	99.22%	99.13%	99.38%	
3	0.00%	100.89%	101.07%	101.06%	101.06%	100.89%	101.23%	101.06%	
4	0.00%	101.61%	101.70%	101.44%	101.61%	101.87%	101.79%	101.95%	
5	0.00%	99.90%	101.32%	101.42%	101.16%	101.41%	101.42%	101.50%	
6	0.00%	99.27%	100.69%	101.22%	100.53%	100.53%	100.79%	100.96%	
7	0.00%	99.18%	99.62%	99.45%	99.63%	99.37%	100.05%	99.96%	
8	0.00%	100.71%	100.71%	100.18%	100.70%	100.79%	100.71%	100.96%	
9	0.00%	100.62%	100.71%	100.62%	100.63%	100.54%	100.63%	100.63%	
10	0.00%	100.80%	101.42%	101.69%	101.52%	102.12%	102.13%	102.13%	
11	0.00%	101.34%	101.61%	101.70%	101.61%	101.70%	101.87%	101.62%	
12	0.00%	99.36%	99.82%	99.27%	99.27%	99.35%	99.69%	99.52%	
Mean	N/A	99.9%	100.8%	100.7%	100.7%	100.8%	100.9%	100.9%	
%RSD	N/A	1.8%	0.9%	1.0%	0.9%	1.0%	0.9%	0.9%	

Figure 4. Mean dissolution profiles of Claritin Chewable and RediTab tablets



Comment: Dissolution profiles of Claritin Chewable tablets are similar to those of RediTab (Figure 4) but significantly different from those from Claritin tablets (Figure 3). However, it is difficult to determine food effect of Claritin Chewable Tablet solely by dissolution profiles. It is noted that the sponsor had not obtained comparative dissolution testing in 2 or 3 different dissolution media as Agency requested at the Teleconference (November 4, 2005).

B. Food Effect studies (from previous NDAs)

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

This 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 Cmax values were 14.3 and 13.6 ng/mL and the mean Tmax 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 Cmax values not statistically different from each other (p=0.75) but the AUC differences were significant (p=0.001).
- For desloratadine, the mean Cmax values were 25.5 and 23.2 ng/mL and the mean Tmax 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 Cmax 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).

In conclusion, 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 single-dose, two-way crossover study conducted in healthy volunteers to evaluated the relative bioavailability of loratadine and desloratadine following administration of a 10 mg loratadine orally disintegrating tablet (Zydis®) and consumed a standardized breakfast after a 10-15 minutes later (test) vs. administration of the conventional 10 mg loratadine tablet (reference) under fasting conditions.

Results: The statistical analysis comparing the Zydis® and conventional tablets using log transformed data is presented in Table 10.

Table 10. Statistical Analysis Using Log Transformed Data

Parameter (unit)	Treatment	Geometric Mean	p-value	Power (%)	Rate (%) ^a	
					Point Estimate	Confidence Interval
Loratadine						
Cmax (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						
Cmax (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 $\alpha=0.05$

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.

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 is administered as a 10 mg Zydis® tablet after a standardized high fat breakfast and under fasting conditions. The results are shown in Table 11.

Table 11. Statistical Analysis Using Log Transformed Data

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

^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: Although exact mechanism by which food changes the BA of drug product would not be known without of performing specific mechanistic studies, food effect on loratadine appears to be largely due to drug substance because food effect BE studies from previously submitted (generic) loratadine, such as NDAs 21511 and 21512 showed that similar food effect when the test products compared to the reference products. Therefore, it is expected that food effect will be seen after Claritin Chewable tablet administration - may be, similar to that seen after Claritin RediTab tablet administration.

In conclusion, in vitro dissolution data can substitute for absence of food effect study since food effect on Claritin drug products is well known. The request for the waiver of the food effect study could therefore be granted based on the similarity in the in vitro dissolution profiles for Claritin RediTab and Claritin Chewable tablets.

2.6. Analytical Section

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

Plasma samples collected from this study (2182 samples) were analyzed for loraldine and desloratadine using a validated method via _____

Calibration curve was linear over a range of _____ ng/mL (LLOQ) _____ ng/mL for both loraldine and desloratadine. Calibration standards and QC samples demonstrated acceptable performance. Overall, the analytical assay is acceptable.

3. Labeling Recommendation: None.

**APPEARS THIS WAY
ON ORIGINAL**

4. APPENDIX

4.1 PROPOSED PACKAGE INSERT

Drug Facts

Active ingredient (in each tablet)

Loratadine 5 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: Chew 2 tablets daily; not more than 2 tablets in 24 hrs.
- Children 2 to under 6 years of age: Chew 1 tablet daily; not more than 1 tablet in 24 hrs.
- Consumers with liver or kidney disease: Ask a doctor.

Other information

- phenylketonurics: contains phenylalanine 1.4 mg per tablet
- safety sealed: do not use if the individual blister unit imprinted with Children's Claritin® is open or torn
- store between 20°C to 25°C (68° to 77° F)

Inactive ingredients aspartame, citric acid anhydrous, colloidal silicon dioxide, _____, D&C Red #27 aluminum lake, FD&C blue #2 aluminum lake, flavor, magnesium stearate, mannitol, microcrystalline cellulose, sodium starch glycolate, stearic acid.

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

[Lot number and Expiration Date]

Office of Clinical Pharmacology and Biopharmaceutics				
New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21-891	Brand Name	Claritin Chewable tablet	
OCPB Division (I, II, III)	DPE-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	Chewable Tablets	
		Dosing Regimen	1 tab QD (2 - <6 years of age); 2 tabs QD for adults and ≥6 years of age	
Date of Submission	8/02/05	Route of Administration	Oral	
Estimated Due Date of OCPB Review	4/02/06	Sponsor	Schering-Plough	
PDUFA Due Date	6/02/06	Priority Classification	3 S	
Division Due Date	4/02/06			
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	I		SD in healthy adults
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	x	I		
(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		I		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	x			
Comments sent to firm?		Food effect study is not conducted; this is a review issue		
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? • 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? 			

Note: Request DSI consultation

**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
4/4/2006 01:50:46 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
4/4/2006 02:38:35 PM
BIOPHARMACEUTICS
I concur