CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-512

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS TEAM LEADER'S MEMO TO THE REVIEW

NDA	21-512
Drug Substance	Loratadine
Drug Product	—
Strengths	10 mg
Route of Administration	Oral Tablets
Sponsor	Perrigo company
Type of submission	Resubmission to Original NDA
Date of submission	12/22/03
OCPB Division	DPE-II
Clinical Division	Pulmonary and Allergy Drug Products (HFD-570)
Team Leader	Emmanuel Fadiran, Ph.D.
Division Director	Henry Malinowski, Ph.D.

Background: The original NDA was submitted June 28, 2002 for the approval of a loratadine 10-mg tablet for over-the-counter (OTC) marketing, however, the Division granted an 'approvable' status due to some deficiencies. The CPB related deficiency in the approvable letter dated July 11, 2003 which was based on DSI report stated "The results of Study 003214 can not be considered valid in establishing the bioequivalence of the test loratadine tablets to the listed drug product because of the cross-contamination of the subject samples during solid phase extraction as described in the Form 483 issued to — on July 9, 2003. You will need to reassay all the subject samples to demonstrate accuracy of the loratadine and descarboethoxyloratadine plasma concentrations in this study".

After some interaction with the Agency by teleconference, Perrigo amended this application by providing the results of the reanalysis of all subject samples, in accordance with the Division's request stated in the approvable letter. The modified assay method was satisfactorily validated and found acceptable by OCPB and the results demonstrated that loratadine 10 mg Tablet manufactured by Perrigo is bioequivalent to the reference product, Claritin® Tablet (see Dr. Shinja Kim's OCPB review dated April 24, 2004).

DSI audited the — site again in February 2004 and in a memorandum dated April 20, 2004, DSI recommended that the data from reanalysis not be accepted for Agency review because of the following reasons:

1. — did not systematically investigate the source of contamination in the original automated assay.
2. There was lack of agreement between the original assay and repeat Cmax concentrations for loratadine.

After a careful consideration of each of the issues raised in the DSI report and the assay validation report submitted by the sponsor, the following conclusions were made:

1. OCPB agrees with the DSI's observation that the source of contamination in the original assay has not been systematically investigated although efforts have been made to address this issue in the modified assay used for the reanalysis of the samples. It is noted that the reanalysis was done with a validated method with appropriate controls and there was no cross-contamination of the blank cells. OCPB has therefore recommended that for future submissions where contaminations are observed during analysis, the source(s) of the contamination should identified before they are addressed by a new or modified assay method.
2. OCPB disagrees with DSI that there should be an agreement between the Cmax concentrations for loratadine from the original and repeat assays. In fact, if this was the case, it would have given some doubt to the integrity of the new data set. It could be reasonably assumed that the contamination in the original assay was random but the effect was more pronounsed with the low concentrations when compared with the high concentrations around the Cmax.

Based on these reasons OCPB accepts the results and recommends the approval of Perrigo Loratadine, 10 mg, based on the results of the BE study and the *in vitro* dissolution data submitted by the sponsor.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the resubmission, and recommends approval of Perrigo Loratadine 10 mg.

Emmanuel Fadiran, Ph.D., Team Leader

Henry Malinowski, Ph.D., Division Director, HFD-870

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

/s/

Emmanuel Fadiran
5/25/04 12:16:16 PM
BIOPHARMACEUTICS

Henry Malinowski
5/26/04 06:19:50 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-512
Drug Substance	Loratadine
Drug Product	—
Strengths	10 mg
Route of Administration	Oral Tablets
Sponsor	Perrigo company
Type of submission	Resubmission to Original NDA
Date of submission	12/22/03
OCPB Division	DPE-II
Clinical Division	Pulmonary and Allergy Drug Products (HFD-570)
Reviewer	Shinja R. Kim, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D.

Background: The original NDA was submitted June 28, 2002 for the approval of a loratadine 10-mg tablet for over-the-counter (OTC) marketing, however, the Division granted an 'approvable' status due to some deficiencies. The OCPB review of the original submission was dated February 10, 2003.

The CPB related deficiency in the approvable letter (07/11/03) stated "The results of Study 003214 can not be considered valid in establishing the bioequivalence of the test loratadine tablets to the listed drug product because of the cross-contamination of the subject samples during solid phase extraction as described in the Form 483 issued to — on July 9, 2003. You will need to reassay all the subject samples to demonstrate accuracy of the loratadine and descarboethoxyloratadine (DCL) plasma concentrations in this study".

Presently, Perrigo amends this application by providing the results of the reanalysis of all subject samples, in accordance with the Division's request stated in the approvable letter as shown above. The results of reanalysis of Study 003214 demonstrated that loratadine 10 mg Tablet manufactured by Perrigo is bioequivalent to the reference product, Claritin® Tablet as 90% confidence intervals for the ratios of both the AUC and C_{max} for loratadine and DCL were within the FDA bioequivalence acceptance range of 80-125%. Summary of the method of reanalysis and the study results is attached.

Comments to the sponsor: While the re-assay of samples has been deemed to be adequate in establishing the quality and reliability of the submitted data, the source of contamination in the original assay has not been identified although efforts have been made to address this issue in the modified assay used for the reanalysis of the samples. It is recommended that for future submissions where contaminations are observed during analysis, the source(s) of the contamination should be identified before they are addressed by a new or modified assay method. Failure to do so may result in rejection of the data and study.

Recommendation: The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the resubmission, and found it acceptable from a CPB standpoint. Please forward the above comments to the sponsor.

Shinja R. Kim, Ph.D., DPE II

Emmanuel Fadiran, Ph.D., Team Leader

ATTACHMENT

Summary of Sample Analysis

The reanalysis was performed (Study 003214-UJK) using the same analytical method as initial (study 003214-PMF). However, due to the condition of matrix of the frozen (29 month) plasma samples, the modifications were implemented, validated and employed as described below;

1. The plasma volume was decreased to ensure proper extraction, internal standard working solution (ISWS) volume and concentration were changed and additional solid phase extraction (SPE) wash steps were added.

2. To further improve the precision and accuracy of the analytical method, stable-labeled internal standards for both analytes were used.

3. To further ensure the accuracy of the reported loratadine and DCL plasma concentrations, the analytical range was truncated. The original analytical ranges, 20.0 - 50000 pg/mL for loratadine and 20.0 - 30000 pg/mL for DCL, were of a 2500 and 1500 order of magnitude respectively, a wide dynamic range. The analytical range was truncated to 40 - 10000 pg/mL for both analytes, an order of magnitude of 250 that is well within analytical limits.

With the use of the truncated analytical range, results from numerous study samples were expected to be above the upper limit of quantitation (10000 pg/mL) thus requiring pre-dilution of these samples. The pre-dilution scheme was determined by using data obtained from the original analysis (003214-PMF) as a guide. Quality control samples (QC) prepared at higher concentration than the ULOQ for loratatine and DCL were also diluted on the day of analysis.

Study 003214-UJK

Stock solution: loratadine, DCL, loratadine-D_5 (IS) and DCL-D_5 (IS) were stored at a norminal temperature of -20^{0}C.

Number of samples: Received 5156 samples, but 5025 were analyzed (the sponsor stated that 131 samples were excluded due to insufficient sample volume for re-analysis).

Analytes and Method: Concentration levels of loratadine and DCL in human plasma was analyzed by [redacted] using LS-MS-MS.

Standard curve range: 40-10,000 pg/mL for loratadine and DCL ($r^2 = 0.99$)

Precision (%CV) and Accuracy (%theoretical): Between-batch precision and accuracy of QC samples of loratadine and DCL in human plasma prepared at low (120 pg/mL), medium (2000 pg/mL), and high (8000 pg/mL) ranged 5.0-7.2% and 4.3-6.8%, and 94.2-106.3% and 91.7-103.8%, respectively.

Study 003214 (Pharmacokinetic Results)

Results obtained by re-analyzing the samples for loratadine and DCL are shown in Table 1 and 2, respectably.

Table 1. Loratadine PK parameters and Statistical analysis

Parameters	Treatment A Mean (% CV) n	Treatment B Mean (% CV) n	Ratio of least-squares means (A/B)	90% CI (A/B)[a]
AUC_t (ng.h/mL)	32.3 (120) 99	32.9 (120) 100	99.8	94.2-105.7
AUC_∞ (ng.h/mL)	34.2 (118) 97	34.3 (118) 100	100.5	94.9-106.5
C_{max} (ng/mL)	11.6 (115) 99	11.8 (117) 100	101.1	93.0-110.0
T_{max} (h)	1.27 (36) 99	1.31 (38) 100	-	-
$t_{1/2}$ (h)	19.5 (66) 97	18.4 (67) 100	-	-

Treatment A = Perrigo loratadine B = Claritin® [a]Based on geometric mean ratio

Table 2. DCL PK parameters and Statistical analysis

Parameters	Treatment A Mean (% CV) n = 99	Treatment B Mean (% CV) n = 100	Ratio of least-squares means (A/B)	90% CI (A/B)[a]
AUC_t (ng.h/mL)	183.7 (45)	186.8 (48)	98.5	94.9-102.3
AUC_∞ (ng.h/mL)	189.7 (47)	192.7 (48)	98.6	95.5-101.9
C_{max} (ng/mL)	13 (39)	13 (40)	100.6	96.0-105.4
T_{max} (h)	2.08 (56)	2.08 (53)	-	-
$t_{1/2}$ (h)	27.4 (26)	26.7 (26)	-	-

Notations are the same as Table 1

The ratios of least-squares means and 90% confidence intervals derived from the re-analyses of the ln-transformed parameters AUC_t, AUC_∞ and C_{max} for both loratadine and DCL in plasma were within the 80-125% FDA bioequivalence acceptance range (Tables 1 and 2). These results demonstrated that loratadine 10 mg Tablet manufactured by Perrigo is bioequivalent to the reference product, Claritin® Tablet.

2 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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
4/27/04 02:53:53 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
4/27/04 05:21:51 PM
BIOPHARMACEUTICS
I concur

Clinical Pharmacology & Biopharmaceutics Team Leader Review Memorandum

Memorandum to: NDA 21-512 file
Product: Loratadine ——
Memo Date: June 30, 2003
Memo From: Emmanuel O. Fadiran, Ph.D., Team Leader, DPE II, OCPB
Concurrence by: Henry Malinowski, Ph.D., Director, DPE II, OCPB

This memorandum is to document the need for DSI audit of the clinical study sites for studies submitted to this NDA. The application was submitted as a new NDA under section 505 (b)(2) of the DF&C Act which permits approvals to be based on the Agency's previous findings of efficacy and safety of an approved drug product. The sponsor (Perrigo) used Claritin® (loratadine) Tablets 10 mg as the reference product. Two clinical pharmacology studies (one pivotal bioequivalence study and one food effect study) were submitted by the sponsor to support the request for approval loratadine 10 mg for an OTC indication for temporary relief of symptoms due to hay fever —— allergies for adults and children 6 years of age and older. The two studies were reviewed in Dr. Shinja Kim's CPB review dated February 10, 2003. In summary, the Perrigo loratadine tablet is bioequivalent to Claritin tablet under fasted condition but not under fed condition, although the effects of food on both formulations were similar.

The division requested a DSI audit of the clinical sites for the pivotal bioequivalence study (Protocol 003214) because the approval of this new formulation of loratadine 10 mg tablet was going to be based on this study. It is therefore very important for the Agency to be assured of the quality and the integrity of the data that form the basis for the bioquivalence determination between Claritin Tablet 10 mg and Perrigo's Loratadine 10 mg. Additionally in an e-mail dated May 24, 2003, Dr. C T Viswanathan, Associate Director, DSI, stated that although the clinical facility has been inspected before, no loratadine bioequivalency study has been ever been audited there. Dr. Viswanathan further stated that this facility has been recently acquired by —— that performed the study and is under new management and personnel.

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

/s/

Emmanuel Fadiran
7/1/03 11:39:07 AM
BIOPHARMACEUTICS

Henry Malinowski
7/1/03 12:32:17 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-512/N-000-BZ
Drug Substance	Loratadine
Drug Product	—
Strengths	10 mg
Route of Administration	Oral Tablets
Sponsor	Perrigo company
Type of submission	Amendment to Original NDA
Date of submission	5/9/03
OCPB Division	DPE-II
Clinical Division	Pulmonary and Allergy Drug Products (HFD-570)
Reviewer	Shinja R. Kim, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D.

The original NDA was submitted June 28, 2002 for the approval of a loratadine 10-mg tablet for over-the-counter (OTC) marketing for the "temporary relief of symptoms due to hay fever or other upper respiratory allergies" for adults and children over six years of age. The sponsor submitted two PK studies (Bioequivalence and Food effect) and dissolution data in support of the NDA. Upon the review, it was found that dissolution method was adequate, but the sponsor was recommended to modify the dissolution specification to "NLT — in 30 minutes", as opposed to the sponsor's proposal of "Q of — at 45 min".

The present application amends the original NDA 21-512 in accordance with 21 CFR 314.110 to address the Agency's comments in the May 1, 2003, Approvable Letter.

CPB related comment in the Approvable Letter (*Italics*), followed by the sponsor's response (normal font) is as follows:

5.c. Modify the dissolution specification to NLT — in 30 minutes.

In accordance with the Agency's request, the dissolution specification has been revised to NLT — in 30 minutes.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed this submission and found to be acceptable. No further action is necessary.

Shinja R. Kim, Ph.D., DPE II

Emmanuel Fadiran, Ph.D., Team Leader

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
6/5/03 11:56:02 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
6/5/03 12:14:59 PM
BIOPHARMACEUTICS
I concur

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-512
Drug Substance	Loratadine
Drug Product	—
Strengths	10 mg
Route of Administration	Oral Tablets
Sponsor	Perrigo company
Type of submission	Original NDA as an OTC
Date of submission	6/28/02
OCPB Division	DPE-II
Clinical Division	Pulmonary and Allergy Drug Products (HFD-570)
Reviewer	Shinja R. Kim, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D.

1. EXECUTIVE SUMMARY

This NDA requests approval of a loratadine 10-mg tablet for over-the-counter (OTC) marketing for the "temporary relief of symptoms due to hay fever or other upper respiratory allergies" for adults and children over six years of age.

This NDA contains two studies (Bioequivalence and Food effect), and a comprehensive review of clinical data related to the efficacy and safety of loratadine. Therefore, in the absence of clinical efficacy and safety trial (however, FDA informed the sponsor that clinical trial to demonstrate the safety and effectiveness of the product is not required), this NDA relies mainly on an assessment of PK data from these two studies.

These two studies demonstrated that loratadine 10 mg Tablet manufactured by Perrigo is bioequivalent to the reference product, Claritin® Tablet. The bioavailability of loratadine was similar for the Perrigo loratadine and Claritin® tablet when the products were administered following a (standard) high-fat breakfast. Two subjects were identified as 'poor metabolizer' of loratadine (by active metabolite, descarboethoxyloratadine, plasma concentrations). The subjects had AUC_t, AUC_{inf}, and $t_{1/2}$ approximately 5-, 8- and 4-fold, respectively, higher than the observed mean values.

Plasma samples, to determine loratadine and the metabolite concentrations, were analyzed adequately using a LC/MS/MS method. Dissolution method was adequate, but the recommended specification is not less than — in 30 minutes.

1.1. Recommendation: The recommended dissolution specification is not less than — in 30 minutes (as opposed to the sponsor's proposal of Q of — at 45 min).

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Section 6, and found that NDA 21-512 is acceptable from a CPB standpoint provided that the sponsor agrees with the Agency's recommendation on the dissolution specifications as well as contingent upon the outcome of the inspection by DSI.

Shinja R. Kim, Ph.D., DPE II

Emmanuel Fadiran, Ph.D., Team Leader

2. Table of Contents

3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Two studies (Bioequivalence and Food effect) conducted in healthy men are submitted to support the NDA.

The objective of BE study (Protocol 003214) was to compare the relative bioavailability of Perrigo and Schering (Claritin®) 10 mg loratadine tablets under fasting conditions in a fully-replicated design in healthy adult volunteers, following a 40 mg dose. The 90% confidence intervals (CI) for geometric means ratios for AUC_t, AUC_{inf}, and C_{max} were within 80 to 125% for loratadine and its active metabolite, descarboethoxyloratadine (DCL), indicating that the two tablet formulations are bioequivalent.

The objective of food effect study (Protocol 010177) was to compare the bioavailability (BA) Perrigo and Schering (Claritin®) 10 mg loratadine tablets under fed conditions, following a 40 mg dose. The 90% CI geometric means ratios for AUC_t and AUC_{inf} for loratadine were within the 80-125%, FDA bioequivalence acceptance range, but it was 79.6-105.9% for C_{max}. For DCL, all parameters were within the 80-125%. Based on these results, it can be concluded that the food effect profiles were comparable between the proposed (Perrigo's loratadine) and referenced product (Claritin® Tablet).

Overall, the results of the two studies demonstrate that loratadine 10-mg tablets by Perrigo are bioequivalent to the reference drug, Schering Claritin® tablets.

The use of four 10 mg (dose of 40 mg) in these studies is in agreement with the decision between the sponsor and OGD (rational was that the high dose administration improves the assay sensitivity for blood samples).

Dissolution method was adequate, but the recommended specification is not less than — in 30 minutes (as opposed to the sponsor's proposal of Q of —, at 45 min).

4. Question Based Review

4.1 General Attributes

4.1.1 What is known about the loratadine (Background)?

Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonist activity. Loratadine is marketed for OTC use by Schering Corporation in a variety of formulae (Claritin® Tablets, Syrup and Reditabs), and it is currently indicated for the relief of symptoms of seasonal allergic rhinitis and the treatment of chronic idiopathic urticaria for patients 2 years of age or older.

Loratadine is rapidly absorbed following oral administration, is highly metabolized, and undergoes extensive first-pass metabolism. Descarboethoxyloratadine (DCL) is the major active metabolite. The current labeling for Claritin® Tablets indicates that food increased the systemic exposure (AUC) of loratadine and DCL by approximately 40% and 15%, respectively. The time to peak plasma concentration (T_{max}) of loratadine and DCL was delayed by 1 hour, but peak plasma concentrations (C_{max}) were not affected by food. Loratadine is metabolized to DCL, predominantly by cytochrome P450 3A4 (CYP3A4) and, to a lesser extent, by cytochrome P450 2D6 (CYP2D6). The initial NDAs for loratadine noted a group of 'outliers' with markedly elevated exposure to DCL (~5 fold) and significantly prolonged DCL half-life ($t_{1/2}$ >50 hr), and is now known to be due to slow formation of 3-OH-DCL from DCL. This phenotypic polymorphism was observed in about 9.2% of studied subjects. The occurrence rate of these DCL poor metabolizers is more frequent in subjects of black African descent than in Caucasians. The mean $t_{1/2}$ in normal adult subjects was 8.4 hrs for loratadine (range 3-20 hr) and 28 hrs for DCL (range 8.8-92 hr).

4.2 Biopharmaceutics

4.2.1 Is the formulation used in the BE and Food effect studies identical to the to-be-marketed formulation?

Yes. The proposed product was developed by Perrigo Pharmaceuticals to be a generic version of the currently marketed Claritin® tablet. The composition on a mg per unit dose basis follows;

Ingredient	mg per unit dose
Loratadine	
Lactose Monohydrate, NF	
Povidone USP	
Pregelatinized Starch, NF	
Magnesium Stearate, NF	

Note: The attention of the reviewing chemist has been drawn to the many significant figures in the composition formula.

4.2.2 Is the tested formulation bioequivalent to the reference (innovator) product?

Yes. Perrigo BE study, #003214, determined the BE of the pivotal batch of loratadine tablets with Claritin® tablets in replicated crossover design with single dose (4x10 mg) in healthy male volunteers. Mean plasma concentration profiles of loratadine and DCL is shown the figure 1. PK results are summarized in Tables 1-2. The 90% confidence intervals for geometric means ratios for AUC_t, AUC_{inf}, and C_{max} met the criteria of BE by falling within the 80-125% range for loratadine and DCL. It can be concluded that the proposed formulation of the loratadine tablet is bioequivalent to the Claritin® Tablet.

Figure 1. Mean plasma conc. profiles: Loratadine (left) and DCL (right)

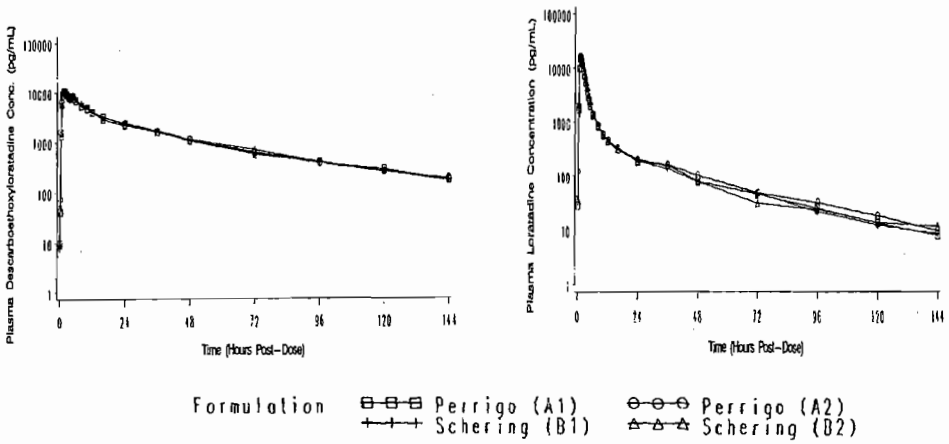


Table 1. Mean loratadine PK parameters and Statistical analysis (Excluding subject No. 50)

Parameters	Treatment A Mean (% CV) n	Treatment B Mean (% CV)	Ratio of least-squares means (A/B)	90% CI (A/B)[a]
AUC_∞ (ng.h/mL)	34.8 (112) 98	34.1 (115) 100	101.6	95.9-107.7
AUC_t (ng.h/mL)	32.7 (116) 101	32.8 (117) 102	101.3	95.5-107.5
C_{max} (ng/mL)	11.5 (117) 101	11.4 (123) 102	103.1	94.2-112.8
T_{max} (h)	1.25 (35) 101	1.27 (34) 102	-	-
Kel (h^{-1})	0.039 (81) 98	0.037 (59) 100	-	-
$t_{1/2}$ (h)	24.4 (50) 98	24.4 (47) 100	-	-

Treatment A = loratadine by Perrigo B = Claritin® [a]Based on geometric mean ratio

Table 2. Mean DCL PK parameters and Statistical analysis (Excluding subject No. 50)

Parameters	Treatment A Mean (% CV) n = 99	Treatment B Mean (% CV) n = 100	Ratio of least-squares means (A/B)	90% CI (A/B)[a]
AUC_∞ (ng.h/mL)	172.3 (56)	173.5 (57)	99.9	97-102.9
AUC_t (ng.h/mL)	167.6 (52)	168.7 (54)	99.8	96.9-102.9
C_{max} (ng/mL)	11.0 (42)	11.2 (43)	98.8	94.1-103.8
T_{max} (h)	2.4 (87)	2.2 (73)	-	-
Kel (h^{-1})	0.025 (23)	0.026 (26)	-	-
$t_{1/2}$ (h)	29.4 (33)	29.2 (32)	-	-

Treatment A = loratadine by Perrigo B = Claritin® [a]Based on geometric mean ratio

4.2.3 Are food effect profiles comparable between the proposed and referenced product?

Yes, they are comparable. BA was compared in Study 010177 between Perrigo 4x10-mg loratadine and Claritin® 4x10 mg tablet after a high-fat breakfast (2-way crossover design). The results are summarized in Tables 3-4, and the mean plasma concentration profiles are shown in Figure 2.

Table 3. Mean loratadine PK parameters and Statistical analysis (n = 30)

	Treatment A Mean (% CV)	Treatment B Mean (% CV)	Ratio (A/B)	90% CI (A/B)[a]
AUC_∞ (ng.h/mL)	73.8 (124)	81.1 (119)	92.2	83.8-101.4
AUC_t (ng.h/mL)	69.0 (122)	73.5 (117)	93.9	85.2-103.5
C_{max} (ng/mL)	17.6 (116)	19.2 (117)	91.8	79.6-105.9
T_{max} (h)	2.2 (33)	2.0 (41)		
Kel (h^{-1})	0.03 (52)	0.025 (40)		
$t_{1/2}$ (h)	29.0 (45)	31.3 (36)		

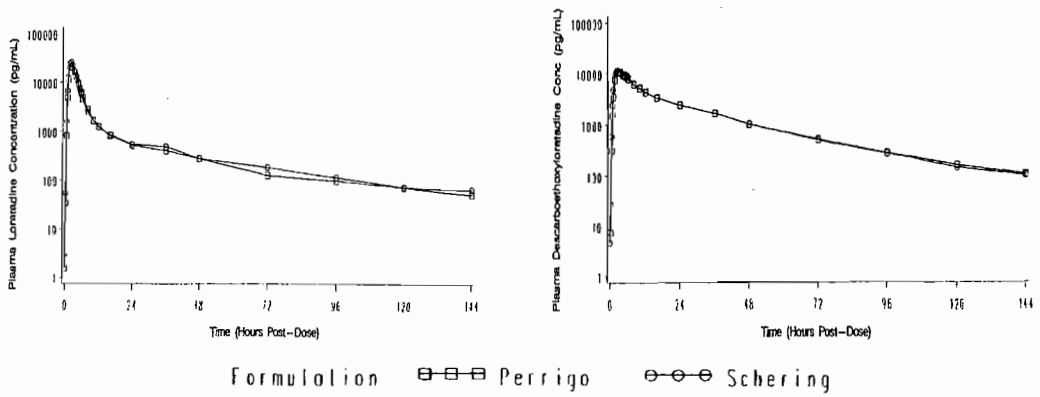
Treatment A = Perrigo (fed) B = Claritin® (fed) [a]Based on geometric mean ratio

Table 4. Mean DCL PK parameters and Statistical analysis (n = 30)

	Treatment A Mean (% CV)	Treatment B Mean (% CV)	Ratio (A/B)	90% CI (A/B)[a]
AUC_∞ (ng.h/mL)[a]	187.8 (34)	185.6 (36)	101.2	96.8-105.8
AUC_t (ng.h/mL)[a]	183.9 (34)	182.2 (35)	100.9	96.6-105.4
C_{max} (ng/mL)[a]	12.2 (35)	12.2 (41)	100.6	94.7-106.7
T_{max} (h)	2.8 (33)	2.7 (43)		
Kel (h^{-1})	0.028 (21)	0.029 (20)		
$t_{1/2}$ (h)	25.5 (20)	24.7 (19)		

Treatment A = Perrigo (fed) B = Claritin® (fed) [a]Based on geometric mean ratio

Figure 2. Mean plasma concentration profiles: Loratadine (left), DCL (right)



It can be concluded that the food effect profiles are comparable between the proposed (Perrigo's loratadine) and referenced products (Claritin® Tablet).

4.2.4 Were any subject(s) identified as "Poor Metabolizer(s)", and how different their PK profiles of DCL compared to the mean values?

Two subjects (ID#25, Black and #50, Caucasian) were identified as poor metabolizers by exposure data out of 48 subjects (2 Blacks and 46 Caucasians) who completed the BE study. The subjects had approximately 5-, 8- and 4-fold, respectively, higher AUC_t, AUC_{inf}, and $t_{1/2}$ compared to the mean values of those PK parameters (no difference in C_{max} between normal and poor metabolizers); higher exposure but longer half-life. Therefore, safety of poor metabolizer(s) following loratadine administration needs to be evaluated by the medical reviewer. None were identified as "poor metabolizer" (based on exposure data) from the food effect study.

4.2.5 Has the applicant developed adequate dissolution method and specification to assure in vivo performance and quality of the product?

The dissolution method and specification for the proposed loratadine tablets are shown in the table below:

Apparatus Type:	USP Apparatus II (paddle)
Medium:	0.1 N HCl
Volume:	900 mL
Speed:	50 rpm
Temperature:	37.0° ± 0.5° C
Limit Q:	— at 45 minutes

The results of dissolution testing on the Perrigo loratadine and Claritin® are listed in Table 5 and 6 respectively, and their dissolution profiles are shown in Figure 3.

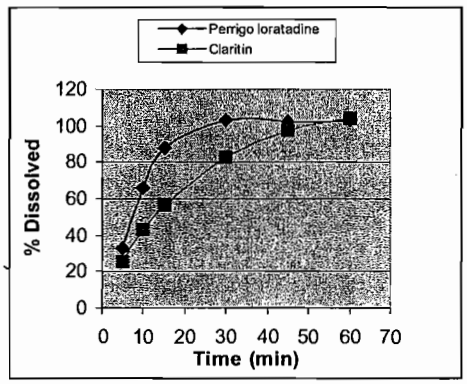
Table 5. Perrigo loratadine 10 mg Dissolution test (Lot#OC1868)

	5 min	10 min	15 min	30 min	45 min	60 min
Mean	33	66	88	103	102	103
n	12	12	12	12	12	12
min		/	/		/	/
max						

Table 6. Claritin® 10 mg Dissolution test (Lot#9RXF559)

	5 min	10 min	15 min	30 min	45 min	60 min
Mean	25	43	57	83	97	104
n	12	12	12	12	12	12
min		/	/		/	/
max						

Figure 3. Perrigo and Claritin® Tablet in 0.1N HCl at 50 rpm.



Comment to the sponsor: Dissolution method is acceptable, however, it is recommended to set specification at NLT — in 30 min as opposed to Q of —, at 45 min proposed by the sponsor (specification for the current Claritin® Tablet 10 mg is NLT — in 30 min with the same dissolution method).

4.2.6 What bioanalytical methods are used to assess concentrations of active moieties?

Plasma samples from BE and food effect studies were quantified for loratadine and DCL using a liquid chromatographic and tandem mass spectrometric (LC/MS/MS) method developed by —. The specificity, sensitivity, linearity, accuracy, precision, recovery, and stability of loratadine and DCL were determined over plasma concentration ranges of 0.02 to 50.0 ng/mL and 0.02 to 29.0 ng/mL, respectively. Overall, the methods were satisfactory.

APPEARS THIS WAY
ON ORIGINAL

Protocol #003214

Study Type: BA/BE/single dose.

Title: Comparative, Randomized, Single-Dose, 2-way Crossover Relative Bioavailability Study of Perrigo and Schering (Claritin®) 10mg Loratadine Tablets in Healthy Adult Males Under Fasting Conditions Following a 40mg Dose.

Clinical Investigators:

Objectives: Compare the single-dose, relative bioavailability of Perrigo and Schering (Claritin) 10mg loratadine tablets under fasting conditions, following a 40mg dose.

Study Design and Method: This study was a single dose, open-label, randomized, 4-way crossover, replicate design (21 days wash out period). The two sequences used in the randomization were ABAB and BABA. 60 healthy adult men ages 18-45 years were enrolled in the study. Each subject received a single dose of the test formulation and of the reference formulation on two separate occasions. Doses were administered with 240 mL of water, and were followed by a 4-hour fast.

- A: Loratadine 4x10 mg, Batch No. OC1868
- B: Claritin® 4x10 mg, Schering, Lot #9RXF559

Criteria for Evaluation: PK parameters (AUC, C_{max}, T_{max}, K_{el}, $t_{1/2}$) of loratadine and DCL.

Blood sampling times: t = 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours post dose.

Analytical Methodology
Assay Method: LC/MS/MS
Assay Sensitivity: The calibration ranges for loratiadine and DCL were 0.02-50 and 0.02-20 ng/mL. respectively.
Accuracy and Precision: Inter-day precision and accuracy for loratadine QC ranged 7.2-10.6% and 94.7-99.9%, respectively. Inter-assay precision and accuracy for DCL ranged 8.7-9.5% and 94.6-100.8%, respectively.

RESULTS:
Study Population: 48 subjects completed the clinical phase of study, and 54 subjects completed at least 2 periods of the study. There were 2 Blacks and rest of subjects was Caucasians.

Data Anaysis: DCL plasma concentration at pre-dose were non-zero in 3 subjects; Subject No. 49-in Period, 1 (formulation B), subjects Nos. 25 and 50 in Periods 2, 3 and 4. The sponsor performed PK and statistical analysis including all, except subject No. 50, since their pre-dose values were < 5% of the corresponding C_{max} values (Table 1 and 2). The sponsor used SAS (PROC) Mixed Model Procedure to perform ANOVA analyses with log transformed data of loratadine and DCL: The model included sequence, formulation and period as fixed effects.

Pharmacokinetics: Data from the replicate dosing of the test and reference products were pooled (n = 124 per parameter) and included in the PK statistical analyses. Mean PK profiles for loratadine and its metabolite, descarboethoxyloratadine, are shown in Figure 1. The PK results are summarized in Table 1 and 2 for loratadine and DCL, respectively.

Analysis was also performed including subject No. 50's loratadine (whose pre-dose DCL values were > 5% of the corresponding C_{max} values in periods 2, 3 and 4). Data was also re-analysis for DCL including subjects Nos. 25 and 50 (however, pre-dose DCL values of subjects Nos. 25 and 50 were set to zero). These analysis results for loratadine and DCL are presented in Table 3.

Figure 1. Mean plasma conc. profiles: Loratadine (left) and DCL (right)

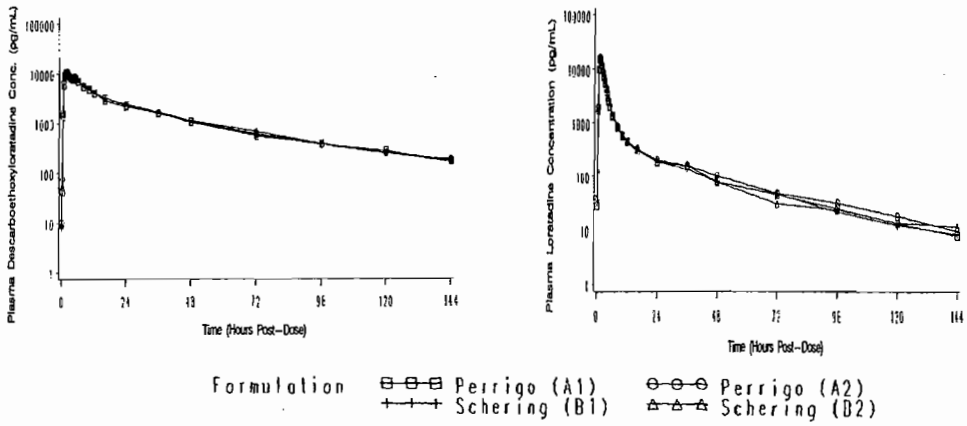


Table 1. Mean loratadine PK parameters and Statistical analysis (Excluding subject No. 50)

Parameters	Treatment A Mean (% CV) n	Treatment B Mean (% CV)	Ratio of least-squares means (A/B)	90% CI (A/B)[a]
AUC_∞ (ng.h/mL)	34.8 (112) 98	34.1 (115) 100	101.6	95.9-107.7
AUC_t (ng.h/mL)	32.7 (116) 101	32.8 (117) 102	101.3	95.5-107.5
C_{max} (ng/mL)	11.5 (117) 101	11.4 (123) 102	103.1	94.2-112.8
T_{max} (h)	1.25 (35) 101	1.27 (34) 102	-	-
Kel (h^{-1})	0.039 (81) 98	0.037 (59) 100	-	-
$t_{1/2}$ (h)	24.4 (50) 98	24.4 (47) 100	-	-

Treatment A = loratadine by Perrigo B = Claritin® [a]Geometric mean ratio

Table 2. Mean DCL PK parameters and Statistical analysis (Excluding subject No. 50)

Parameters	Treatment A Mean (% CV) n = 99	Treatment B Mean (% CV) n = 100	Ratio of least-squares means (A/B)	90% CI (A/B)[a]
AUC_∞ (ng.h/mL)	172.3 (56)	173.5 (57)	99.9	97-102.9
AUC_t (ng.h/mL)	167.6 (52)	168.7 (54)	99.8	96.9-102.9
C_{max} (ng/mL)	11.0 (42)	11.2 (43)	98.8	94.1-103.8
T_{max} (h)	2.4 (87)	2.2 (73)	-	-
Kel (h^{-1})	0.025 (23)	0.026 (26)	-	-
$t_{1/2}$ (h)	29.4 (33)	29.2 (32)	-	-

Treatment A = loratadine 10 mg, Perrigo B = Claritin® 10 mg [a]Geometric mean ratio

Table 3. Ratio of least-squares means and the 90% CI

	Loratadine		DCL	
Parameters	Ratio of least-squares means (A/B)	90% CI (A/B)	Ratio of least-squares means (A/B)	90% CI (A/B)[a]
AUC_∞ (ng.h/mL)	101.2	95.5-107.2	99.8	96.9-102.8
AUC_t (ng.h/mL)	100.9	95.1-106.9	98.7	95.4-102.1
C_{max} (ng/mL)	102.2	93.4-111.9	98.5	93.8-103.4
T_{max} (h)	1.25	1.26	2.4	2.3

A = loratadine 10 mg, Perrigo B = Claritin® 10 mg [a]Geometric mean ratio

As shown in Tables 1-3, PK parameters of loratadine and DCL following each of the treatments were comparable (BE) to each other.

Conclusion: This reviewer is in agreement with the sponsor's conclusion of the loratadine 10 mg tablets by Perrigo are bioequivalent to the reference Claritin® 10 mg tablets.

Poor Metabolizers: Two subject (ID#25, Black and #50, Caucasian) were identified as Poor Metabolizer. The subjects had approximately 5-, 8- and 4-fold, respectively, higher AUC_t, AUC_{inf}, and $t_{1/2}$ compared to the mean values of those PK parameters (C_{max} were the same compared to the mean normal subjects); higher exposure with longer half-life. Therefore, safety of poor metabolizer(s) following loratadine administration needs to be evaluated by the medical reviewer.

Protocol #010177

Study Type: Food effect/BA/Single dose

Protocol Title: Comparative, Randomized, Single-Dose, 2-way Crossover Relative Bioavailability Study of Perrigo and Schering (Claritin) 10mg Loratadine Tablets in Healthy Adult Males Under Fed Conditions Following a 40mg Dose.

Clinical Investigators:
Sample Analysis:

Objectives: Compare the single-dose, relative bioavailability of Perrigo and Schering (Claritin) 10mg loratadine tablets under fed conditions, following a 40mg dose.

Study Design: An open-label, randomized, single-dose, 2-way crossover relative bioavailability study performed in 32 healthy adult male volunteers. In each period, subjects were housed from the evening before drug administration until after their 36-hr blood draw and returned for subsequent blood draws. Both periods were separated by a washout period of 21 days. 30 minutes before dosing, subjects received a breakfast consisted of one buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, 1 serving hash brown potatoes, 240 mL of whole milk, and 180 mL orange juice.

Test Drug: Loratadine 10 mg, Batch #OC1868
Reference: Claritin® 10 mg, Schering, Lot #9RXF559

Blood sampling times: t = 0, 0.25, 0.5, 0.75, 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, 120, and 144 hours post dose.

Criteria for Evaluation: PK parameters (AUC, C_{max}, T_{max}, K_{el}, $t_{1/2}$) of loratadine and DCL.

Analytical Methodology
Assay Method: LCMS/MS
Assay Sensitivity: The calibration ranges for loratiadine and descarboethoxyloratadine were 0.02-50 and 0.02-30 ng/mL, respectively.
Accuracy and Precision: Inter-assay precision and accuracy for loratadine sample analysis ranged from 7.8 to 10.8% and 0.8 to 6.9%, respectively. Inter-assay precision and accuracy for DCL ranged 7.3-11.0% and –1.2-2.3%, respectively.

RESULTS:

Study Population: The mean subjects' age was 33.4 (±7) ranging 20-45 years old. All subjects were Caucasians.

The results for the pharmacokinetic parameters are presented in Table 1 for loratadine and Table 2 for descarboethoxyloratadine, and the mean loratadine and DCL plasma concentration profiles are presented in Figure 1.

Figure 1. Mean plasma concentration profiles: Loratadine (left), DCL (right panel)

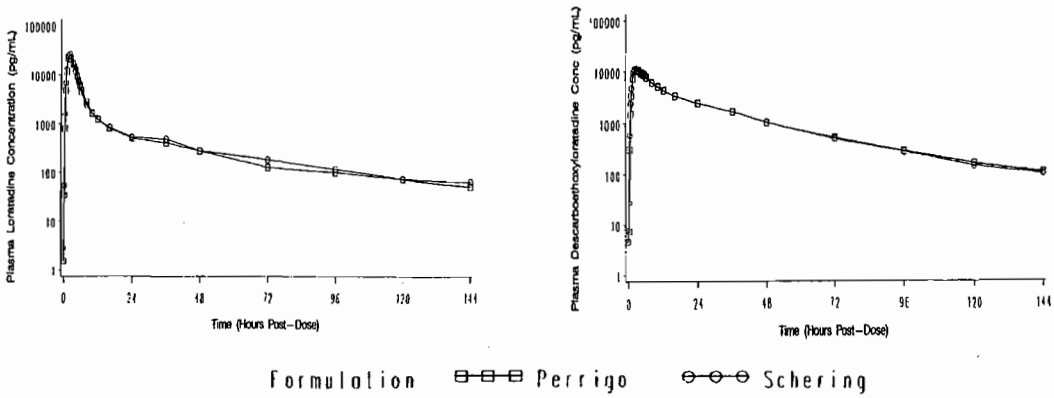


Table 1. Mean loratadine PK parameters and Statistical analysis (n = 30)

	Treatment A Mean (% CV)	Treatment B Mean (% CV)	Ratio (A/B)	90% CI (A/B)[a]
AUC_∞ (ng.h/mL)	73.8 (124)	81.1 (119)	92.2	83.8-101.4
AUC_t (ng.h/mL)	69.0 (122)	73.5 (117)	93.9	85.2-103.5
C_{max} (ng/mL)	17.6 (116)	19.2 (117)	91.8	79.6-105.9
T_{max} (h)	2.2 (33)	2.0 (41)		
Kel (h^{-1})	0.03 (52)	0.025 (40)		
$t_{1/2}$ (h)	29.0 (45)	31.3 (36)		

Treatment A = Perrigo (fed) B = Claritin® (fed) [a]Geometric mean ratio

Table 2. Mean DCL PK parameters and Statistical analysis (n = 30)

	Treatment A Mean (% CV)	Treatment B Mean (% CV)	Ratio (A/B)	90% CI (AB)[a]
AUC_∞ (ng.h/mL)	187.8 (34)	185.6 (36)	101.2	96.8-105.8
AUC_t (ng.h/mL)	183.9 (34)	182.2 (35)	100.9	96.6-105.4
C_{max} (ng/mL)	12.2 (35)	12.2 (41)	100.6	94.7-106.7
T_{max} (h)	2.8 (33)	2.7 (43)		
Kel (h^{-1})	0.028 (21)	0.029 (20)		
$t_{1/2}$ (h)	25.5 (20)	24.7 (19)		

Treatment A = Perrigo (fed) B = Claritin® (fed) [a]Geometric mean ratio

Conclusion: The sponsor concluded the food effect profiles were comparable between the proposed (Perrigo's loratadine) and referenced products (Claritin® Tablet), and this reviewer concurs with the sponsor's conclusion.

Slow Metabolizers: None was identified as slow metabolizer.

Dissolution Method and Specification

Dissolution method and specification for the proposed loratadine tablets are shown in Table 1. The results of dissolution testing on the 10-mg loratadine and Claritin® tablets are listed in Table 2. The mean dissolution profiles of these two formulation tablets are plotted in Figure 1.

Table 1. Dissolution Release Method and Proposed Specification

Apparatus Type:	USP Apparatus II (paddle)
Medium:	0.1 N HCl
Volume:	900 mL
Speed:	50 rpm
Temperature:	37 ± 0.5^0 C
Specification:	NLT — in 45 min

Figure 1. Comparative mean dissolution profile on the Perrigo brand (Lot 0C1868) and Claritin (Lot 9RXF559)

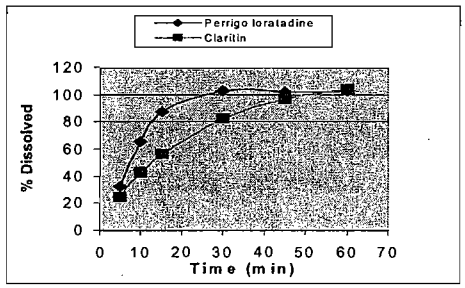


Table 2. Comparative dissolution profile on the Perrigo brand (upper) and Claritin (lower panel)

Lot # 0C1868_Perrigo Brand :Reference AD291P109-115

Tablet Wt.(mg)													
Dissolution Time (min.)	% Release												Average % Release
	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10	Tab 11	Tab 12	
5													33
10													66
15													88
30													103
45													102
60													103

Lot # 9RXF559_National Brand :Reference AD291P109-115

Tablet Wt.(mg)													
Time (min.)	% Release												Average % Release
	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10	Tab 11	Tab 12	
5													25
10													43
15													57
30													83
45													97
60													104

Comment: Dissolution method is acceptable, however, it is recommended to set specification at NLT — in 30 min as opposed to Q — at 45 min. (specification for the current Claritin® Tablet 10 mg is NLT — in 30 min with the same dissolution method)

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-512**	**Brand Name**	
OCPB Division (I, II, III)	**DPE-II**	**Generic Name**	**Loratadine**
Medical Division	**HFD-570**	**Drug Class**	**Anti-Histamine**
OCPB Reviewer	**Shinja Kim**	**Indication(s)**	**Allergic rhinitis**
OCPB Team Leader	**Emmanuel Fadiran**	**Dosage Form**	**Tablets**
		Dosing Regimen	**1 tab QD or consult a MD.**
Date of Submission	**6/28/02**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**2/28/03**	**Sponsor**	**Perrigo**
PDUFA Due Date	**4/28/03**	**Priority Classification**	**S**
Division Due Date	**3/28/03**		

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:	x	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1	1	
Dissolution:	x	1	1	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2	2	

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
2/10/03 09:08:07 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
2/10/03 09:28:19 AM
BIOPHARMACEUTICS
I concur