CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-734

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-734:	Submission Date: 01-April 2005
Brand Name:	Children's ElixSure™-24 hr Antihistamine
Generic Name:	Loratadine
Reviewer:	Shinja Kim, Ph.D.
Team Leader:	Emmanuel O. Fadiran, Ph. D.
OCPB Division:	DPE II
ORM Division:	DPADP (HFD-570)
Applicant:	Taro Pharmaceuticals U.S.A. Inc.
Submission Type:	Amendment (N000 B2)
Formulation; Strength(s):	5 mg/5 mL Suspension
Dosage and administration:	Adults and children 6 years and older: 2 teaspoonfuls daily Children 2 to under 6 years of age: 1 teaspoonful daily
Indication:	OTC use for temporarily relief of the symptoms due to hay fever or other upper respiratory allergies

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1. EXECUTIVE SUMMARY

1.1 Recommendation: The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the bioequivalence study (protocol # R04-1776), which was submitted as an amendment to original NDA. This study supports the NDA approval from a CPB standpoint provided the sponsor agrees with the Agency's recommendation on the dissolution specification.

DSI report indicated that the data from the analytical portion of study R04-1776 is acceptable for Agency review.

1.2 Phase 4 Commitment: None

1.3 Summary of clinical Pharmacology and Biopharmaceutics Findings

The bioequivalence study (#30218), submitted to original NDA, showed that the sponsor's proposed formulation was not bioequivalent to the reference formulation (Claritin tablet) based on the C_{max} of the parent drug (loratadine). This study was conducted employing 45 healthy male subjects using 40 mg of loratadine (instead of 10 mg recommended dose). The sponsor repeated a BE study (protocol # R04-1776), and currently submitted as the amendment to the original NDA. The sponsor did not repeat food effect study; however it is acceptable since there is no formulation change.

BE Assessment (Study R04-1776): Pharmacokenetics of loratadine and its active metabolite, descarboethoxyloratadine (DCL), from Children's ElixSure™ 24 hr Antihistamine Suspension (will be referred to as the suspension) was compared to those of Claritin® Tablet in a two-way crossover study in 70 healthy subjects. The results showed that Taro's suspension is bioequivalent to Claritin® Tablet as the 90% CI for the ratios of AUC and C_{max} are within the BE range of 80-125% (Table 1).

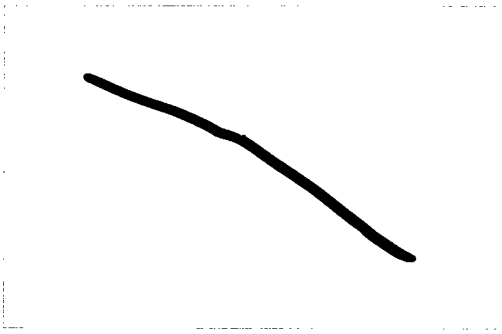
Table 1. Point estimates (ratio) and 90% confidence intervals for the log-transformed C_{max}, AUC_t, and AUC_{inf} values of loratadine and DCL following single administration of the treatments (Study R04-1776)

Parameter[1]	Trt	Pair	Loratadine		DCL	
			Ratio	90% CI[2]	Ratio	90% CI[2]
AUCt (ng•h/mL)	A B	A/B	108.9	99.9-118.7	105.2	101.4-109.1
AUC_{inf} (ng•h/mL)	A B	A/B	108.2	99.5-117.6	104.1	99.7-108.7
C_{max} (ng/mL)	A B	A/B	98.9	88.8-110.2	102.8	97.8-108.1

A = Taro's loratadine suspension (test)
B = Claritin® tablet (reference)
[1]Geometric mean, ln-transformed data
[2]90% CI for ratio of parameter geometric means

Dissolution: Since there is no formulation change, the recommendation (to the sponsor) would be the same as the original NDA submission: i.e., dissolution specification should be set at Q [redacted] in 5 minutes (instead of the sponsor's proposed NLT [redacted] in 60 min) using the proposed dissolution method (i.e., USP Apparatus II (paddle), 0.1 N HCl 900 ml, and 50 rpm at 37.0° ± 0.5° C). The dissolution profiles for the suspension and the reference (Claritin® Tablet) are shown in Figure 1.

Figure 1. Taro's (faster dissolution rate; upper curves) and Claritin® Tablet (slower dissolution rate; lower curves) using the proposed method



Recommendation (to the sponsor): The sponsor's dissolution method is acceptable but the specification should be set at Q [redacted] in 5 minutes.

2. QUESTION BASED REVIEW

2.1. General Biopharmaceutics

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

Study **R04-1776** was an open-label, single dose, randomized, 2-way crossover study in 72 (70 completed) healthy volunteers (29 males and 43 females) conducted to determine the relative BA (or BE) of the proposed product compared to the reference product. The subjects were randomized and placed into one of the two treatment groups listed below. Loratadine 10 mg was administered after an overnight fast. There was a washout of at least 14 days between doses.

- **TRT A:** Taro's loratadine 10 mg, [redacted] suspension (test)
- **TRT B:** Loratadine 10 mg Tablet (Claritin®) (reference).

Statistical analysis of the PK parameters for loratadine and DCL are shown in Table 2 and plasma concentration-time profiles of loratadine and DCL are shown in Figure 2.

The results (Table 2) indicated that Taro's suspension is bioequivalent to Claritin® tablet.

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

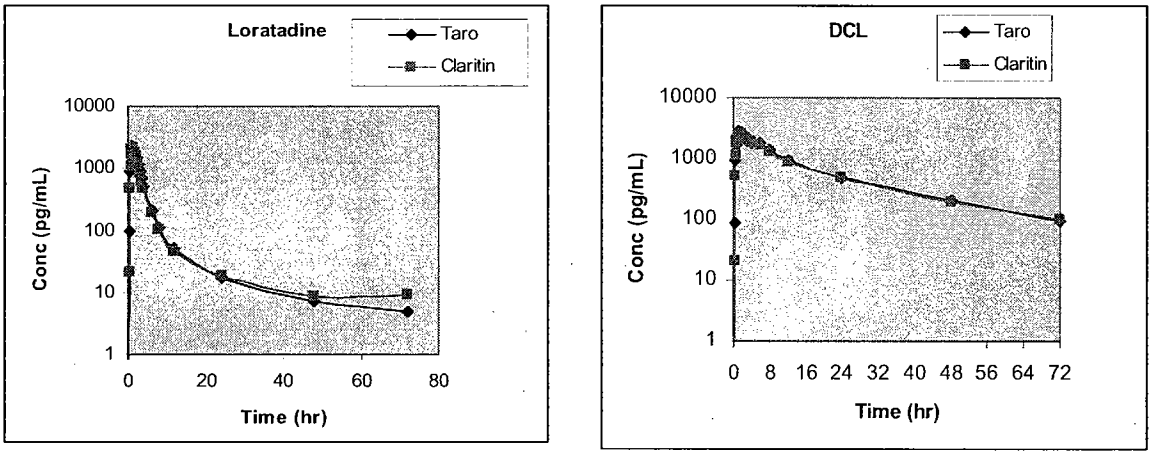


Table 2. PK parameters and statistical analysis of loratadine (N = 70) and DCL (N = 70) following single dose of the treatments

Parameter	Trt	Pair	Loratadine			DCL		
			Mean (%CV)	Treatment Comparisons		Mean (%CV)	Treatment Comparisons	
				Ratio	90% CI[2]		Ratio	90% CI[2]
AUCt[1] (ng•h/mL)	A		3.76 (135)			37.7 (32)		
	B	A/B	3.45 (132)	108.9	99.9-118.7	35.9 (36)	105.2	101.4-109.1
AUC_{inf}[1] (ng•h/mL)	A		3.93 (136)			40.1 (38)		
	B	A/B	3.63 (138)	108.2	99.5-117.6	38.6 (50)	104.1	99.7-108.7
C_{max}[1] (ng/mL)	A		1.41 (130)			2.83 (44)		
	B	A/B	1.43 (120)	98.9	88.8-110.2	2.75 (36)	102.8	97.8-108.1
T_{max} (hr)[3]	A		1.10 (30)			1.65 (48)		
	B		1.31 (36)		$p = 0.001$	1.77 (56)		$p = 0.24$
Kel (h^{-1})[3]	A		0.281 (63)			0.039 (19)		
	B		0.302 (66)		$p = 0.182$	0.038 (18)		$p = 0.32$
$t_{1/2}$ (hr)[3]	A		7.14 (156)			18.43 (22)		
	B		6.87 (154)		$p = 0.67$	19.03 (32)		$p = 0.21$

A = Taro-loratadine - Test
B = Claritin® tablet – reference
[1]Geometric mean, ln-transformed data
[2]90% confidence intervals for ratio of parameter geometric means
[3]Arithmathic mean, Un-transformed data

3. Labeling Recommendation (none)

4. APPENDIX

4.1. INDIVIDUAL STUDY REVIEW

Protocol #R04-1776

Protocol Title: A Relative Bioavailability Study of Loratadine [redacted] Oral Suspension (1 mg/mL) versus Tablets (10 mg) following the Administration of 10 mg Oral Dose Under Fasting Conditions.

Objective: To compare the rate and extent of absorption of loratadine oral suspension vs. Clantin® syrup vs Claritin® tablets under fasting conditions.

Clinical Investigators: [redacted]
Sample Analysis: [redacted]

Study Design and Method: Single center, bioequivalence, open-label, randomized, 2-way crossover study in 72 healthy adult (≥18 years) volunteers (29 males and 43 females). Subjects were dosed with single oral dose of loratadine 10 mL (1 mg/mL) [redacted] suspension or Claritin® 10 mg tablet after an overnight fast. Following a 14 day washout period, subjects were returned and were dosed with alternative treatment oer randomization.

- A (Test): Loratadine (1 mg/mL) gel [redacted] for oral suspension 10 mL, Lot No.: S189-54098, manufacture date May 22, 2003
- B (Reference): Loratadine 10 mg tablet (Claritin®), Lot No.: 3-RXF-17, Exp. Date: 8/05

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, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48 and 72 hours post dose.

Analytical Methodology
Assay Method: LCMS/MS
Caliburation standards Conc: The calibration ranges for loratiadine and DCL were [redacted] respectively.
Accuracy and Precision: Between run precision and accuracy of QC samples for loratadine ranged [redacted] respectively. Between run precision and accuracy of QC samples for DCL ranged [redacted], respectively.

Data analysis: SAS General Linear Model Procedure was utilized to perform ANOVA analyses with log transformed data of loratadine and DCL: The model used; y = sequence + subject (sequence) + treatment (= formulation) + treatment* subject (sequence) + period + carryover.

RESULTS:
Study Population: Data from 70 subjects were used in the statistical analysis. The sponsor stated that subject 11 was dropped by the investigators prior to Period II dosing due to an influenza-like illness, and subject 22 chose to withdraw prior to Period II check-in.

PK: Statistical analysis of the PK parameters and mean concentration-time profiles of loratadine and DCL following the treatments are shown Table 1 and Figure 1, respectively.

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

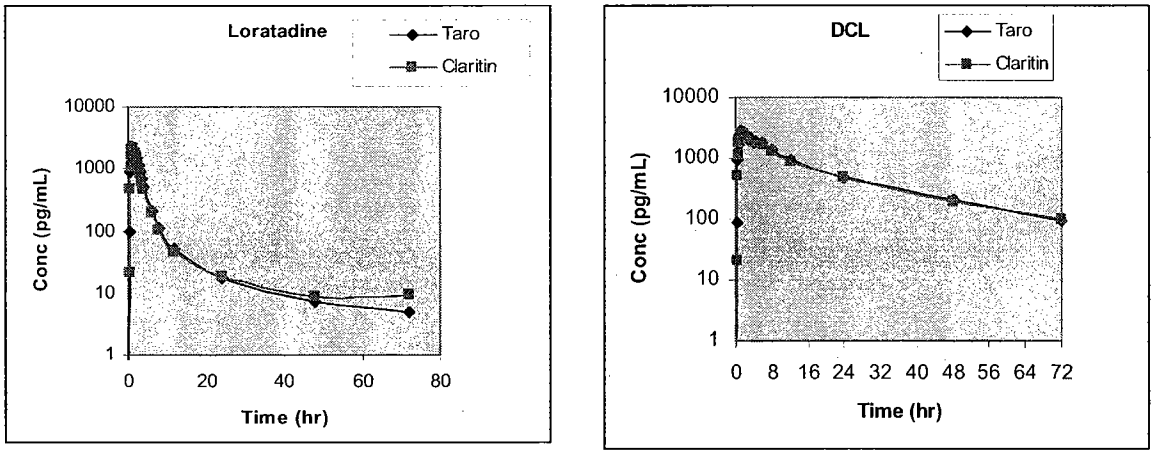


Table 1. Loratadine (N=70) and DCL (N= 70) PK parameters and Statistical analysis

			Loratadine			DCL		
				Treatment Comparisons			Treatment Comparisons	
Parameter	Trt	Pair	Mean (%CV)	Ratio	90% CI	Mean (%CV)	Ratio	90% CI
AUCt[1] (ng•h/mL)	A		3.76 (135)			37.7 (32)		
	B	A/B	3.45 (132)	108.9	99.9-118.7	35.9 (36)	105.2	101.4-109.1
AUC_{inf}[1] (ng•h/mL)	A		3.93 (136)			40.1 (38)		
	B	A/B	3.63 (138)	108.2	99.5-117.6	38.6 (50)	104.1	99.7-108.7
C_{max}[1] (ng/mL)	A		1.41 (130)			2.83 (44)		
	B	A/B	1.43 (120)	98.9	88.8-110.2	2.75 (36)	102.8	97.8-108.1
T_{max} (hr)[3]	A		1.10 (30)			1.65 (48)		
	B	A/B	1.31 (36)		$p = 0.001$	1.77 (56)		$p = 0.24$
Kel (h^{-1})[3]	A		0.281 (63)			0.039 (19)		
	B		0.302 (66)		$p = 0.182$	0.038 (18)		$p = 0.32$
$t_{1/2}$ (hr)[3]	A		7.14 (156)			18.43 (22)		
	B		6.87 (154)		$p = 0.67$	19.03 (32)		$p = 0.21$

A = Taro-loratadine - Test B = Claritin® tablet – reference [1]Geometric mean, ln-transformed data
[2]90% confidence intervals for ratio of parameter geometric means [3]Arithmathic mean, Un-transformed data

Summary: The 90% CI about the ratio of test geometric mean to the reference geometric mean for loratadine and DCL were within the BE limit of 80-125% for AUC and C_{max} of the log transformed data.

Conclusion: Taro's loratadine [redacted] suspension is bioequivalent to Claritin® Tablet.

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/s/

Shinja Kim
8/15/2005 05:01:30 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
8/15/2005 05:05:32 PM
BIOPHARMACEUTICS
I concur

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-734
Proprietary Drug Name:	Children's ElixSure™-24 hr Antihistamine
Generic Name:	Loratadine
Indication:	OTC use for temporarily relief of the symptoms due to hay fever or other upper respiratory allergies
Dosage Form:	Suspension
Strength:	5 mg/5 mL
Route of Administration:	Oral
Dosage and administration:	Adults and children 6 years and older: 2 teaspoonfuls daily Children 2 to under 6 years of age: 1 teaspoonful daily
Applicant:	Taro Pharmaceuticals U.S.A. Inc.
Clinical Division:	DPADP (HFD-570)
Submission Date:	January 19, 2004
Reviewer:	Shinja Kim, Ph.D.
Team Leader:	Emmanuel O. Fadiran, Ph. D.

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1. EXECUTIVE SUMMARY

1.1 Recommendation: The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the human pharmacokinetic and bioavailability section, and found that approval of NDA 21-734 is not supported by Study 30218 from a CPB standpoint because the proposed formulation is not equivalent to the reference formulation (Claritin tablet) based on the C_{max} of the parent drug (loratadine). The sponsor may choose to reformulate the suspension and repeat the BA/BE studies or conduct an efficacy trial to establish that the lower C_{max} for loratadine from the suspension does not have any clinically significant impact on the efficacy of the proposed formulation.

1.2 Phase 4 Commitment: None

1.3 Summary of clinical Pharmacology and Biopharmaceutics Findings

The innovator's product, Claritin (loratadine) is available in various formulations, such as syrup, tablet and RediTab as well as combination products with psedoephedrine. In support of this application the sponsor submitted the results of two pharmacokinetic studies conducted in healthy male volunteers. The objective of the PK studies was to determine the relative bioavailability/bioequivalence (BA/BE) of the proposed formulation compared to approved reference products after a single dose under fasted (Study 30218) and fed (Study 30219) conditions. Dissolution data was also provided to support the NDA.

BE/BA Assessment (Study 30218): Pharmacokenetics of loratadine and its active metabolite, descarboethoxyloratadine (DCL), from Children's ElixSure™ 24 hr Antihistamine Suspension (will be referred to as the suspension) were compared to those from Claritin® Tablet and Claritin® Syrup in a three-way crossover study. The study showed that the Suspension was (1) not equivalent to Claritin® Syrup based on loratadine, (2) equivalent to Claritin® Tablet based on AUC but not based on C_{max} of loratadine, (3) equivalent to Claritin® Syrup based on AUC but not based on C_{max} of DCL, (4) equivalent to Claritin® Tablet based on AUC and C_{max} of DCL (Table 1). It was noted that Claritin® Syrup and Claritin® Tablet were not equivalent based on AUC and C_{max} of loratadine and C_{max} of DCL but were equivalent only based on AUC of DCL (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 DCL following single administration of the treatments (Study 30218)

Parameter[1]	Trt	Pair	Loratadine		DCL	
			Ratio	90% CI[2]	Ratio	90% CI[2]
AUCt (ng•h/mL)	A	A/B	0.65	**58.3-72.1**	1.01	95.8-105.8
	B	A/C	0.95	84.2-104.1	1.07	101.8-112.5
	C	B/C	1.44	129.8-160.6	1.06	101-111.7
AUC_{inf} (ng•h/mL)	A	A/B	0.66	**59.3-73.5**	1.01	95.4-106
	B	A/C	0.95	85.3-105.7	1.06	100.2-111.4
	C	B/C	1.44	129.1-160	1.05	99.7-110.8
C_{max} (ng/mL)	A	A/B	0.53	**45.0-61.6**	0.84	**79-90.0**
	B	A/C	0.81	**69.3-94.9**	1.09	102.4-116.7
	C	B/C	1.54	131.6-180.2	1.30	121.4-138.4

A = Taro-loratadine - Test B = Children's Claritin® syrup – reference
C = Claritin® tablet – reference
[1]Geometric mean, ln-transformed data, and 90% CI ratio of parameter geometric means

BE/BA Assessment in fed condition (Study 30219):

BA of loratadine and DCL from the Suspension were compared to those from Claritin® Tablet under fed condition in a 2-way crossover design. The study showed that the BA of the suspension was

comparable to that of Claritin® Tablet based on DCL and AUC of loratadine; C_{max} of loratadine from the suspension was 22% lower compared to that from Claritin Tablet (Table 2).

Table 2. Point estimates and 90% confidence intervals for the log-transformed C_{max} and AUCs of loratadine and DCL following single administration of the treatments

Parameter[1]	Trt	Pair	Loratadine		DCL	
			Ratio	90% CI[2]	Ratio	90% CI[2]
AUCt (ng•h/mL)	A B	A/B	91.4	85.5-97.6	98.8	95.3-102.5
AUC_{inf} (ng•h/mL)	A B	A/B	91.0	85.1-97.3	98.0	94.8-101.3
C_{max} (ng/mL)	A B	A/B	78.0	**67.3-90.1**	89.9	83.3-97.1

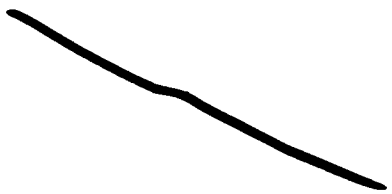
A = Taro's loratadine suspension (test) B = Claritin® tablet (reference)
[1]Geometric mean, ln-transformed data [2]90% CI for ratio of parameter geometric means

Dissolution: The dissolution method and specification for the Suspension formulation proposed by the sponsor and the dissolution profiles of the suspension and Claritin Tablet, obtained by applying the proposed method are shown below.

Method: USP Apparatus II (paddle), 0.1 N HCl 900 ml, 50 rpm at 37.0° ± 0.5° C
Specification: NLT [redacted] in 60 min
Profiles:

Time (min)	Taro's loratainde (Lot # S189-54098)						Claritin® 10 mg Tablets (Lot #2-RXF-1035)					
	Vessel #1	Vessel #2	Vessel #3	Vessel #4	Vessel #5	Vessel #6	Vessel #1	Vessel #2	Vessel #3	Vessel #4	Vessel #5	Vessel #6
4												
15												
30												
45												
60												

Figure 1. Taro's (faster dissolution rate; upper curves) and Claritin® Tablet (slower dissolution rate; lower curves) using the proposed method



Recommendation (to the sponsor): Set specification at Q [redacted] in 5 minutes (this may be changed if there is a reformulation).

2. QUESTION BASED REVIEW

2.1 General Attributes

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

This NDA is a 505(b)(2) application for a Loratadine oral suspension for children and adults, and the sponsor, Taro Pharmaceuticals Inc., has requested the approval of a 5mg/5 mL suspension as an over-the-counter (OTC) antihistamine (to be marketed in a [redacted] 8 oz bottles, [redacted]

The innovator's product, Claritin® (loratadine) by Schering Plough is available in the following formulations for the respective age groups:

- Claritin® Children's 24 Hour Non-Drowsy Allergy Syrup (5mg/5mL) for adults and children > 6 years of age 2 teaspoons daily in adults, and 1 teaspoon daily for children 2-6 years of age.
- Claritin® Non-Drowsy 24 Hour Tablets 10mg QD for adults and children > 6 years of age
- Claritin® Reditabs 24 Hour Non-Drowsy Orally Disintegrating Tablets 10 mg QD for adults and children > 6 years of age.

Also available as combination products with psedoephedrine (PSE) are Claritin D-12 (loratadine/PSE 10/120 mg) and Claritin D-24 (loratadine/PSE 10/240 mg).

Claritin® products are approved for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR) and management of idiopathic chronic urticaria (CIU). Claritin became available as OTC drug in the above formulations in December 2002. Since coming into the OTC market, many generic formulations of loratadine are now available.

2.1.1. 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 ingredient in Taro's product, Children's ElixSure™-24 hr Antihistamine Suspension is loratadine. Loratadine is a [redacted]

Drug Product:

Taro incorporated loratadine into new delivery system called [redacted] The sponsor stated that this delivery system was designed to resist spill from a spoon, intending to ease the delivery of liquid medication to children. The sponsor also stated that the physical properties of Taro's delivery system maintain drug substance uniformity throughout the expected 24 months shelf life eliminating the need for shaking. The formulation is a colorless, opaque, viscous, jelly like material with a characteristic peach odor. The components and composition of the formulation are provided in Table 3.

Table 3. Formulation of Loratadine 5mg/5ml Non-Spil™ Oral Suspension

Component and Quality Standard	Function	Quantity per unit (mg/5 ml)	Concentration % (w/w)
Purified water, USP	Suspending Medium		
Sodium Hydroxide, NF	Neutralizing Agent		
Carbomer 934P, NF	Viscosity Agent		
Sorbitol Crystalline, NF	Spreading Agent		
Poloxamer 188, NF	Wetting Agent		
Butylparaben, NF	Preservative		
Propylene glycol, USP	Solvent		
Glycerin, USP	Suspending Medium		
Loratadine	Active ingredient		
Sucralose Liquid Concentrate	Sweetener		
Masking agent	Masking agent		
Peach flavor	Flavor		
Total weight/ volume			

The batches used in the PK studies were [redacted] which represents less than [redacted] of the commercial batch size, [redacted] (the sponsor responded that commercial batch size will be [redacted]

2.1.2 What are the mechanism(s) of action, pharmacokinetic, and therapeutic indications?

Loratadine is a long-acting tricyclic antihistamine. Loratadine is extensively metabolized by hydroxylation. Loratadine is 97-99% plasma protein bound, while DCL is 73-76% bound in man. Loratadine has a large (apparent) volume of distribution (119 L/kg) in man. In both single- and multiple dose studies, biphasic disappearance of loratadine from plasma has been observed. Loratadine is metabolized to DCL by CYP3A4 and, to a lesser extent, by CYP2D6. Loratadine and/or its metabolites undergo some enterohepatic circulation.

The potency of loratadine was compared to DCL in several animal models. Loratadine and DCL were equipotent in their activity against histamine-induced contractions in guinea pig ilea. In other models, DCL was 2.5-10 times more potent than loratadine. In the histamine-induced mouse paw edema model, the ED_{50} of DCL was 4 times lower than that of loratadine. In the histamine-induced guinea pig lethality model, the ED_{50} of DCL was 2.5 times lower than that of loratadine.

The sponsor's proposed indication for loratadine suspension is to treat temporarily relief symptoms due to hay fever or other upper respiratory allergies, such as runny nose, itchy and watery eyes, sneezing, and itching of the nose or throat [redacted]

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Adults and children ≥6 years of age: 2 teaspoons daily; do not take more than 2 teaspoons daily.
Children 2 to under 6 years of age: 1 teaspoon daily; do not take more than 1 teaspoon daily
Consumers with liver or kidney disease: Ask a doctor

2.2. General Clinical Pharmacology

2.2.1 What are the characteristics of Clinical Pharmacology of loratadine and its metabolite, DCL?

Loratadine is available in several approved products as OTC medications. As such, no other PK properties of loratadine, but two BA/BE studies submitted to this NDA are 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 **30218** was an open-label, single dose, randomized, 3-period, 6-sequence crossover study in 51 (45 completed) healthy male volunteers conducted to determine the relative BA (or BE) of the proposed product compared to that of two reference products. The subjects were randomized and placed into one of the three treatment groups listed below. Loratadine 40 mg was administered after an overnight fast. There was a washout of at least 14 days between doses.

- **TRT A:** Taro's loratadine, [redacted] suspension (test)
- **TRT B:** Loratadine 5 mg/5 ml syrup (Children's Claritin®) (reference).
- **TRT C:** Loratadine 10 mg Tablet (Claritin®) (reference).

Statistical analysis of the PK parameters for loratadine and DCL are shown in Table 4 and graphical representation of the individual PK parameters of loratadine and DCL are shown in Figures 2-3.

Table 4. PK parameters of loratadine (N = 45) and DCL (N = 43) following single dose of the treatments

		Loratadine				DCL		
		Mean		Treatment comparisons		Mean	Treatment comparisons	
Parameter	Trt	(%CV)	Pair	Ratio	90% CI	(%CV)	Ratio	90% CI
AUCt[1] (ng•h/mL)	A	44.3 (109)	A/B	0.65	**58.3-72.1**	222.8 (42)	1.01	95.8-105.8
	B	68.3 (91)	A/C	0.95	84.2-104.1	221.3 (41)	1.07	101.8-112.5
	C	47.3 (108)	B/C	1.44	129.8-160.6	208.2 (42)	1.06	101-111.7
AUC_{inf}[1] (ng•h/mL)	A	47.4 (109)	A/B	0.66	**59.3-73.5**	238.3 (46)	1.01	95.4-106
	B	71.8 (92)	A/C	0.95	85.3-105.7	237 (46)	1.06	100.2-111.4
	C	49.9 (109)	B/C	1.44	129.1-160	225.5 (46)	1.05	99.7-110.8
C_{max}[1] (ng/mL)	A	13.5 (109)	A/B	0.53	**45.0-61.6**	16.5 (37)	0.84	**79-90.0**
	B	25.6 (98)	A/C	0.81	**69.3-94.9**	19.6 (38)	1.09	102.4-116.7
	C	16.6 (113)	B/C	1.54	131.6-180.2	15.1 (41)	1.30	121.4-138.4
T_{max} (hr)[3]	A	1.16 (37)	A/B		p <0.0001	2.12 (80)		p = 0.0129
	B	0.917 (41)	A/C		p <0.0001	1.41 (47)		p = 0.0129
	C	1.41 (52)	B/C		p <0.0001	2.0 (47)		p = 0.0129
$t_{1/2}$ (hr)[3]	A	13.58 (64)				18.4 (27)		
	B	13.93 (58)				18.8 (33)		
	C	12.89 (62)				19.2 (35)		

A = Taro-loratadine - Test
B = Children's Claritin® syrup – reference
C = Claritin® tablet – reference
[1]Geometric mean, ln-transformed data
[2]90% confidence intervals for ratio of parameter geometric means
[3]Arithmatic mean
p-value by Duncans's Multiple Range test

Figure 2. Individual AUC_{inf} and C_{max} of loratadine following single administration of the treatments:

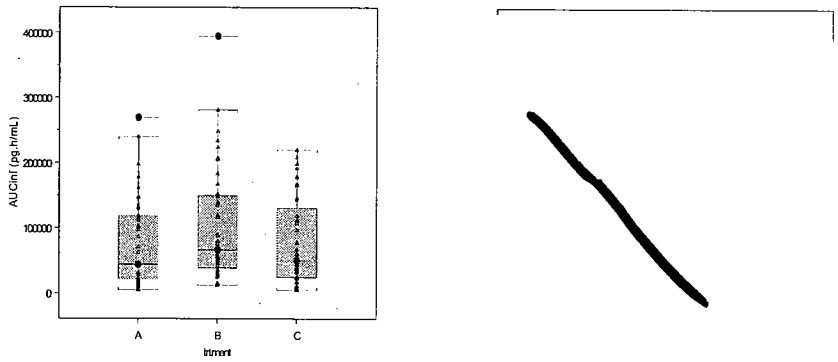
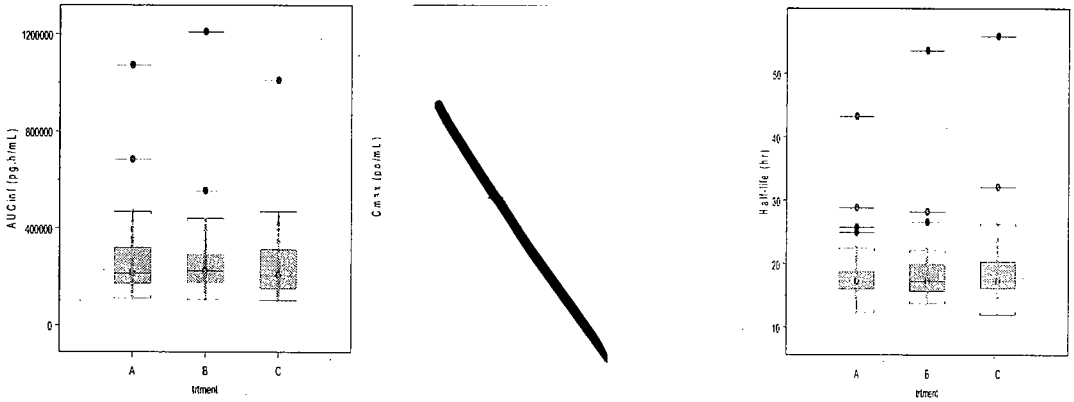


Figure 3. Individual AUC_{inf}, C_{max} and $t_{1/2}$ of DCL following single administration of the treatments:



Taro's suspension was equivalent to Claritin Tablet based on AUC but not equivalent based on Cmax. The subject's plasma loratadine concentration-time plots are shown in Figure 4 as well as the individual's loratadine concentration-time plots is shown in Figure 5.

Figure 4. Subject's plasma loratadine concentration-$time_{0\text{-}72h}$ plots and loratadine concentration-$time_{0\text{-}24h}$ plots

1 Page(s) Withheld

✓ Trade Secret / Confidential

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*Withheld Track Number: Clin Pharm/Bio-*1

As shown in the figures above, there was a high inter-subject variability. Bioequivalence test for the suspension *versus* Claritin tablet was performed excluding 4 subjects (ID nos. of 6, 28, 30 and 50), and it was still not equivalent (90% CI = 75.8-103). T_{max} occurred earlier from the suspension (1.16 hr) compared to that with Claritin tablet (1.41 hr). Usually, early T_{max} results in higher C_{max}, however this was not the case with the suspension. In Study 30219 (BA in fed conditions), C_{max} of suspension was lower than that of Claritin tablet (point estimate = 0.78; 90% CI = 67.3-90.1). Overall, it appears that the inequivalence of suspension to Claritin tablet is due to the high inter-subject variability as well as difference in formulation (or unknown reasons). Efficacy of loratadine (using Claritin 10 mg Tablet) has not been robust, thus lower C_{max} may result in inefficacy of loratadine. In the absence of a robust PK-PD relationship the efficacy of the loratadine suspension can not be established.

From this study the following conclusions were reached:

<u>*For loratadine*</u>;

- Taro's loratadine [redacted] suspension is not equivalent to Claritin® syrup as 90% CI for the ratios of AUC and C_{max} are outside the BE limit of 80-125%.
- Taro's loratadine [redacted] suspension is equivalent to Claritin® Tablet based on AUC but not based on C_{max}, however, inter-subject variability was high.
- Claritin® syrup is not equivalent to Claritin® tablet as 90% CI for the ratios of AUC and C_{max} are outside the BE limit of 80-125%.

<u>*For DCL*</u>;

- Taro's loratadine [redacted] suspension is equivalent to Claritin® tablet as 90% CI for the ratios of AUC and C_{max} are within the BE range of 80-125%.
- Taro's loratadine [redacted] suspension is equivalent to Claritin® syrup based on AUC_t and AUC_{inf}, but not based on C_{max} (90% CI = 79-90%). However, the point estimate of the ratio for C_{max} was 0.84 indicates similar BA between the Taro's loratadine suspension and Claritin® syrup.
- Claritin® syrup is equivalent to Claritin® tablet based on AUC_t and AUC_{inf}, but not based on C_{max} (90% CI = 121-138%), with the point estimate of 1.3.
- There was one subject (ID #26) identified as a potential slow metabolizer (AUC_{inf} of DCL was 4-fold higher than the mean).

Overall conclusion: The results from this study showed that Taro's loratadine [redacted] suspension is not bioequivalent to Claritin syrup and Claritin tablet.

2.5.2. What is the effect of food on the BA of loratadine and DCL from the proposed to-be-marketed formulation compared to the reference products?

A study was conducted to obtain relative BA between the suspension and the referenced drug under the fed conditions.

Study 30219 was an open-label, single-dose, randomized, 2-period crossover study in 50 healthy male non smokers. A high-fat, high-caloric breakfast was served after at least 10 hours of fasting. Drugs were administered with approximately 240 mL of water. Total dose per period was 40 mg of loratadine. There was a washout of at least 14 days between doses.

- **TRT A (test):** Taro's loratadine, [redacted] suspension.
- **TRT B (reference):** Loratadine 10 mg Tablet (Claritin®).

Statistical analysis of the PK parameters for loratadine and DCL are shown in Table 5. Graphical representation of the individual PK parameters of loratadine and are shown in Figures 7-8.

Table 5. PK parameters of loratadine (N = 48) and DCL (N = 47) following single dose of the treatments

Parameter	Trt	Loratadine				DCL		
		Mean (%CV)	Pair	Treatment comparisons		Mean (%CV)	Treatment comparisons	
				Ratio	90% CI		Ratio	90% CI
AUCt[1] (ng•h/mL)	A	90.1 (89)				218.2 (39)		
	B	98.6 (90)	A/B	91.4	85.5-97.6	220.8 (39)	98.8	95.3-102.5
AUC_{inf}[1] (ng•h/mL)	A	94.7 (90)				234.8 (41)		
	B	104.1 (91)	A/B	91.0	85.1-97.3	239.6 (41)	98.0	94.8-101.3
C_{max}[1] (ng/mL)	A	20.3 (85)				14.9 (41)		
	B	26.0 (89)	A/B	78.0	**67.3-90.1**	16.5 (40)	89.9	83.3-97.1
T_{max} (hr)[3]	A	1.64 (45)				2.34 (35)		
	B	1.77 (52)	A/B		$p = 0.441$	2.48 (37)		$p = 0.463$
$t_{1/2}$ (hr)[3]	A	16.95 (38)				19.02 (20)		
	B	18.23 (36)				19.74 (28)		

A = Taro-loratadine - Test B = Claritin® tablet – reference [1]Geometric mean, ln-transformed data
[2]90% confidence intervals for ratio of parameter geometric means [3]Arithmathic mean, Un-transformed data

Figure 7. Individual C_{max} and AUC_{inf} of loratadine single administration of the treatments

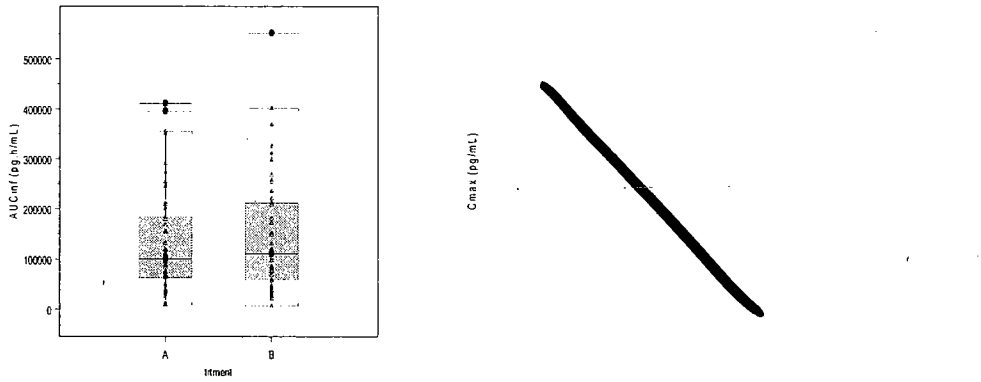


Figure 8. Individual C_{max} and AUC_{inf} of DCL single administration of the treatments

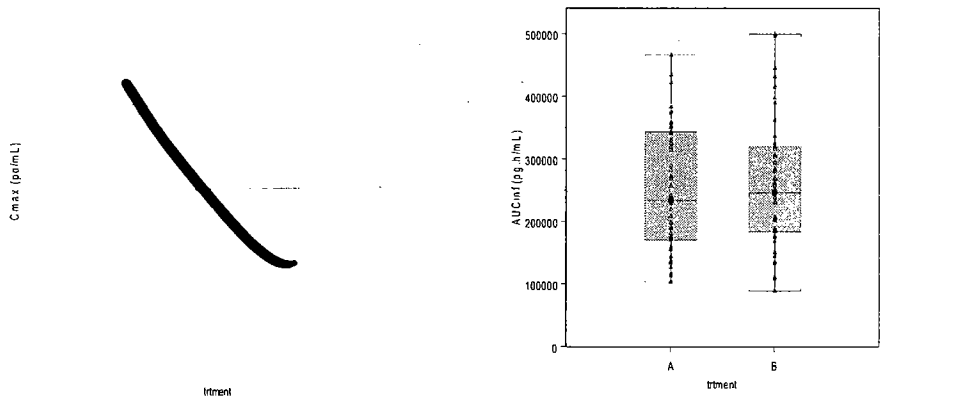
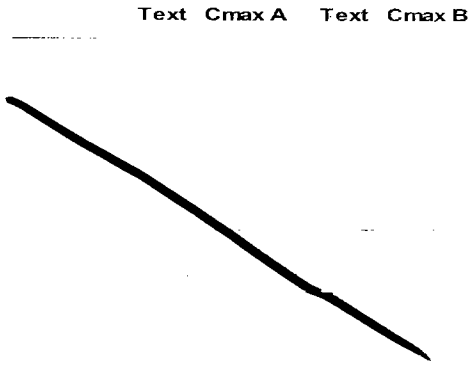


Figure 9. Individual Cmax for treatment A (blue color) and B (red color) (n = 48)



The following summarizes the findings from this study:

- C_{max} of loratadine from Taro's loratadine [redacted] suspension was 22% lower compared to that from Claritin tablet under fed condition and 90% CI falling out side of BE range (67.3-90.1%; point estimate of 0.78).
- For DCL, bioavailability from the treatments was similar as the 90% CI for the ratios of AUCs and Cmax were within BE range.
- Compared to fasted condition (Study 30218), AUC and C_{max} of loratadine from the treatments were increased by approximately 100% and 50%, respectively in fed conditions. On the other hand, AUC and C_{max} of DCL were similar with or without food conditions.

2.5.3 What is the relative bioavailability of DCL/loratadine from the proposed to-be-marketed formulation following single dose administration compared to that from other (historical) studies?

DCL is approved by FDA in various formulations such as Clarinex® Syrup (NDA 21-300), Tablet (NDA 21-165) and RediTab (NDA 21-312).

In Study P00213 from NDA 21-300, healthy adult volunteers (24 males and 6 females) received a single dose of 5 mg DCL as tablet (Clarinex® Tablet) and syrup (Clarinex® Syrup) in crossover design. In Study P01216 from NDA 21-312, healthy adult volunteers (18 male and 12 female) received 5 mg DCL as tablet (Clarinex® Tablet), RediTab (Clarinex®RediTab) and syrup (Clarinex® Syrup) in crossover design.

The results from these studies, along with the results from Study 30218 (see Table 4), are presented in Table 6.

Table 6. Comparison of **arithmetic** mean (%CV) PK parameter values of DCL after single dose of the treatments from the studies.

Study	Subject No.	Dose	Formulation	AUCt (ng.hr/mL)	AUCinf (ng.hr/mL)	C_{max} (ng/mL)
P00213[a]	30	5 mg	Clarinex® Tablet	45.8 (44)	47.4 (45)	2.44 (41)
			Clarinex® Syrup	46.2 (71)	48.4 (54)	2.3 (51)
P01216[a]	28	5 mg	Clarinex® Tablet	38.9 (45)	40.3 (45)	2.2 (35)
			Clarinex® Syrup	37.5 (47)	38.9 (47)	2.1 (33)
			Clarinex® RediTab	38 (44)	39.4 (43)	2 0 (30)
30218[b]	43	40 mg	[redacted] Suspension	242.4 (51) [60.6[c]]	266.2 (63) [66.6[c]]	17.4 (36) [4.4[c]]
			Claritin® Tablet	225.6 (46) [56.4[c]]	251.7 (61) [62.9[c]]	16.5 (52) [4.1[c]]
			Claritin® Syrup	239.3 (48) [59.8[c]]	265.6 (67) [66.4[c]]	20.9 (43) [5.2[c]]

[a]Dose = DCL 5 mg [b]Dose = Loratadine 40mg [c]Normalized to a dose of 10 mg loratadine

The results from studies that were submitted for NDA 20-641 (Claritin Syrup) and NDA 20-704 (Claritin RediTab) showed that the parent loratadine plasma concentrations from the syrup and tablet formulations were not comparable (i.e., not equivalent), while that of DCL were comparable between Claritin Tablet (reference drug) and Claritin Syrup (test drug). Similarly, loratadine from Claritin RediTab (test) was not equivalent to Claritin Tablet (reference drug), while that of DCL was equivalent between these two formulations.

Although the clinical implication of the lower Cmax for loratadine from the suspension compared to Claritin tablet is unknown, inefficacy can't be ruled out. The sponsor may choose to reformulate the suspension and repeat the BA/BE studies or conduct an efficacy trial to establish that the lower Cmax for loratadine from the suspension does not have any clinically significant impact on the efficacy of the proposed formulation.

2.3.4. How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Dissolution: The dissolution method and specification for the Suspension formulation proposed by the sponsor as well as the results of dissolution testing using this method are shown below.

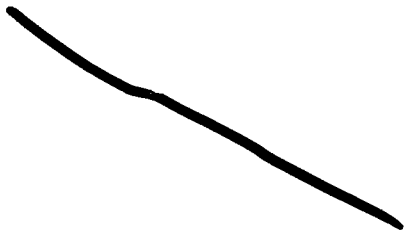
- Method and specification for the proposed loratadine suspension:

Apparatus Type:	USP Apparatus II (paddle)
Medium:	0.1 N HCl
Volume:	900 mL
Speed:	50 rpm
Temperature:	37.0° ± 0.5° C
Sampling Time:	60 min
Percent Dissolved:	NLT [redacted] in 60 min

- Dissolution Profiles (n = 6)

Taro's loratadine suspension (Lot # S189-54098)						
Time (min)	**Vessel #1**	**Vessel #2**	**Vessel #3**	**Vessel #4**	**Vessel #5**	**Vessel #6**
4						
15						
30						
45						
60						
Claritin® 10 mg Tablets (Lot #2-RXF-1035)						
4						
15						
30						
45						
60						

Figure 10. Taro's (faster dissolution rate; upper curves) and Claritin® Tablet (slower dissolution rate; lower curves) using the proposed method



Comment: It is recommended to set specification at NLT [redacted] in 5 min as opposed to NLT [redacted] at 60 min proposed by the sponsor. This specification is for the current formulation and is subject to change if there is a reformulation.

2.6. Analytical Section

2.6.1 How the active moieties are identified and measured in the plasma in the biopharmaceutics studies?

The bioassay for loratadine and DCL were determined using validated LC/MS/MS.

2.6.2 Which metabolites have been selected for analysis and why?

DCL was selected for analysis because it is the major active metabolite of loratadine. The potency of DCL was shown in the animal models to be equal or more potent than its parent loratadine. In addition, systemic exposure (AUC) of DCL in plasma was greater (~5-fold) than that of loratadine.

2.6.3 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total drug was measured for loratadine and DCL. The proposed product is one of generic drugs of innovator drug (Claritin®), thus this NDA was 505(b)(2) application.

2.6.4 What bioanalytical methods are used to assess concentrations?

Analysis of plasma concentrations of loratadine and its active metabolite, DCL, was performed using an automated solid phase extraction procedure, then injected into a high performance liquid chromatography equipped with a tandem mass spectrometry detector. The method was validated and performed at

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The standard curves for loratadine and DCL ranged respectively. A weighted ( ) linear regression analysis ( ) was performed to determine the concentration of the analytes. Plasma samples fell within the range of the standard curves or were appropriately diluted.

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ ULOQ)?

For loratadine and its metabolite, DCL, the LOQ were respectively. The ULOQ for loratadine and DCL were respectively.

2.4.4.3 What is the accuracy and precision at these limits?

The accuracy of QC% nominal concentrations for loratadine and DCL ranged respectively. The precision of QC% nominal concentrations for loratadine and DCL ranged respectively. Recovery of QC for loratadine and DCL was respectively.

2.6.4.4 What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)

Stability was evaluated under various conditions (e.g., sample collection and handling, long-term (up to 100 days at -20°C and -80°C) and short-term (48 hrs at room temperature) stability for analytes, internal standard, freeze-thaw, sample load, etc.). The stability results demonstrated satisfactory.

2.6.4.5 What is the QC sample plan?

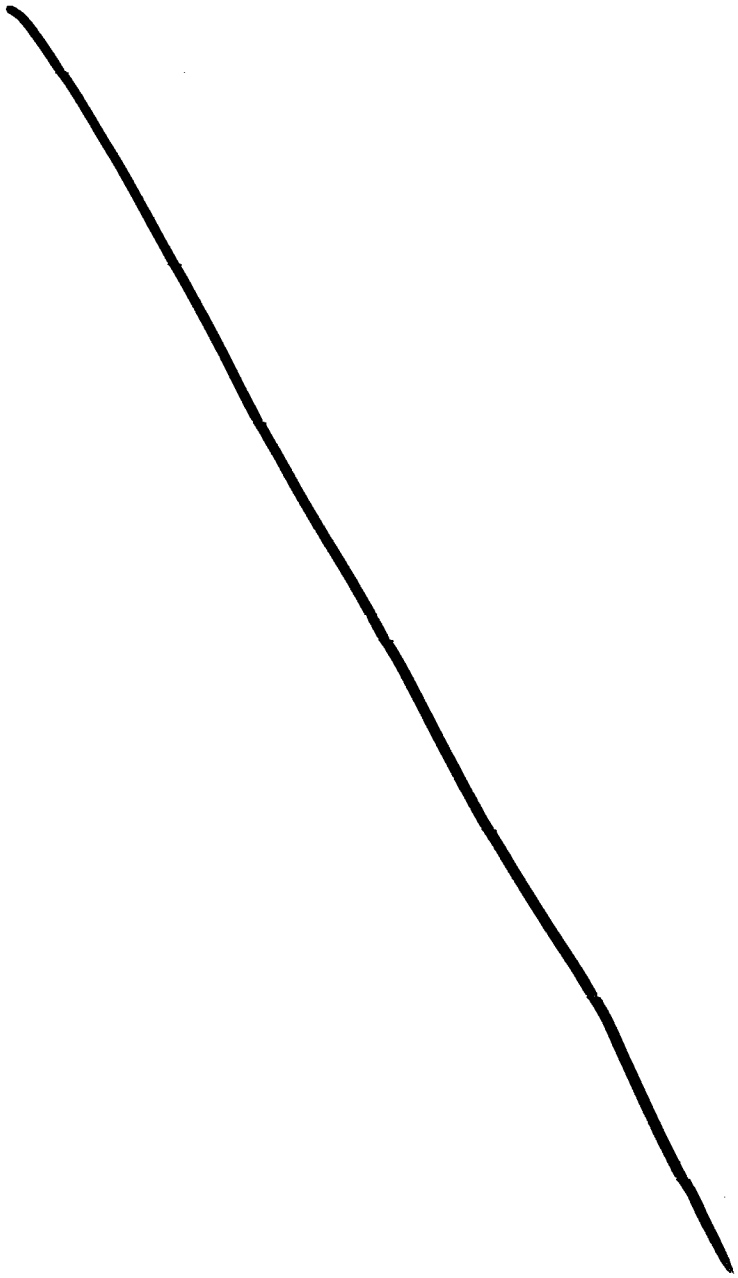
There were four QC samples for each analyte: four QC samples of loratadine were Four QC samples of DCL consisted of

3. LABELING COMMENTS

No labeling recommendations at this time.

4. APPENDICES

4.1 PROPOSED PACKAGE INSERT



4.2. INDIVIDUAL STUDY REVIEWS

Protocol #30218

Protocol Title: Randomized, 3-Way Crossover, Bioequivalence Study of Loratadine 5 mg/5 mL [redacted] Suspension and Claritin® Administered as 4 x 10 mg Tablets or 1 x 40 mL (5 mg/5 mL) Syrup in Healthy Subjects Under Fasting Conditions.

Objective: To compare the rate and extent of absorption of loratadine oral suspension vs. Clantin® syrup vs Claritin® tablets under fasting conditions.

Clinical Investigators
Sample Analysis: [redacted]

Study Design and Method: Single center, bioequivalence, open-label, randomized, 3-period, 6-sequence crossover study in 51 healthy males non-smokers. Single oral dose of loratadine 1 x 40 mL (5 mg/5 mL) [redacted] suspension or syrup or 4 x 10 mg tablets according to the randomization scheme for each of the three periods with a washout period of at least 14 days between doses. Drugs were administered with approximately 240 mL of water. Total dose per period was 40 mg of loratadine.

- A (Test): Loratadine (5 mg/5 mL) ge [redacted] for oral suspension, Lot No.: S189-54098 (EBK-L05)
- B (Reference-1): Loratadine 5 mg/5 mL syrup (Children's Claritin®), Lot No.: 3LTN2
- C (Reference-2): Loratadine 10 mg tablets (Claritin®), Lot No.: 2-RXF-1035

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, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48 and 72 hours post dose.

Analytical Methodology
Assay Method: LCMS/MS
Caliburation standards Conc: The calibration ranges for loratiadine and DCL were [redacted] respectively.
Accuracy and Precision:

Loratadine: there were 3 outliers for QC_1 (nominal concentration of [redacted] for between run analysis (total run [redacted] with precision (%CV) [redacted] for QC_1. Without these outliers (i.e., n = 61), precision and accuracy were [redacted] respectively which is similar to results obtained during the assay validation. %CV for other QCs (QC_2-QC_4) ranged [redacted] with accuracy range of [redacted]

DCL: precision (%CV) of [redacted] accuracy) for QC_1 (nominal concentration of [redacted] was noted, and without the outlier precision and accuracy wer [redacted] respectively for QC_1. Precision and accuracy for other QCs (QC_2-QC_4) range [redacted] respectively.

Data analysis: SAS General Linear Model Procedure was utilized to perform ANOVA analyses with log transformed data of loratadine and DCL: The model used; y = sequence + subject (sequence) + treatment (= formulation) + treatment* subject (sequence) + period + carryover.

RESULTS:
Study Population: A total of 51 healthy males non-smokers were enrolled in the study. However, Subjects No. 11, 18, 20, 21, 33, and 46 did not complete the study. Therefore, pharmacokinetic and statistical analyses were carried out using 45 subjects.

Statistical analysis of the PK parameters and mean concentration-time profiles of loratadine and DCL following the treatments are shown Table 1 and Figure 1, respectively. A graphical representation of the individual PK parameters of loratadine and DCL are shown in Figures 2-3.

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

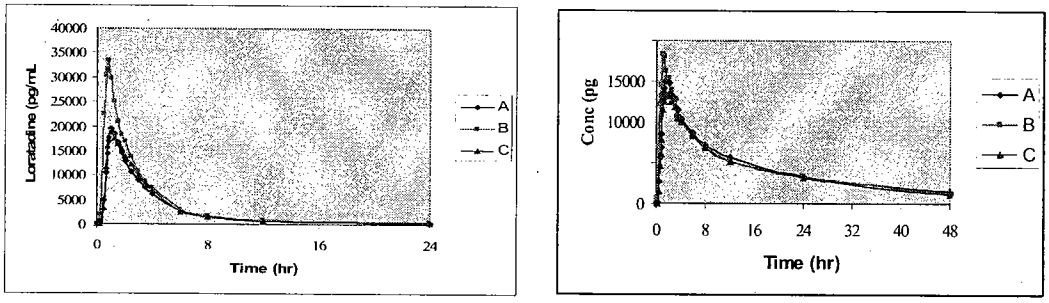


Table 1. Loratadine (N=45) and DCL (N=43) PK parameters and Statistical analysis

			Loratadine			DCL		
				Treatment Comparisons			Treatment	
Parameter	**Trt**	**Pai**	**(%CV)**	**Ratio**	**90% CI**	**(%CV)**	**Ratio**	**90% CI**
AUCt[1] (ng•h/mL)	A	A/B	44.3 (109)	0.65	**58.3-72.1**	222.8 (42)	1.01	95.8-105.8
	B	A/C	68.3 (91)	0.95	84.2-104.1	221.3 (41)	1.07	101.8-112.5
	C	B/C	47.3 (108)	1.44	129.8-160.6	208.2 (42)	1.06	101-111.7
AUC_{inf}[1] (ng•h/mL)	A	A/B	47.4 (109)	0.66	**59.3-73.5**	238.3 (46)	1.01	95.4-106
	B	A/C	71.8 (92)	0.95	85.3-105.7	237 (46)	1.06	100.2-111.4
	C	B/C	49.9 (109)	1.44	129.1-160	225.5 (46)	1.05	99.7-110.8
C_{max}[1] (ng/mL)	A	A/B	13.5 (109)	0.53	**45.0-61.6**	16.5 (37)	0.84	**79-90.0**
	B	A/C	25.6 (98)	0.81	**69.3-94.9**	19.6 (38)	1.09	102.4-116.7
	C	B/C	16.6 (113)	1.54	131.6-180.2	15.1 (41)	1.30	121.4-138.4
T_{max} (hr)[3]	A	A/B	1.16 (37)		p <0.0001	2.12 (80)		p = 0.0129
	B	A/C	0.917 (41)		p <0.0001	1.41 (47)		p = 0.0129
	C	B/C	1.41 (52)		p <0.0001	2.0 (47)		p = 0.0129
Kel (h^{-1})[3]	A		0.093 (97)			0.039 (18)		
	B		0.082 (90)			0.039 (18)		
	C		0.11(106)			0.039 (21)		
$t_{1/2}$ (hr)[3]	A		13.58 (64)			18.4 (27)		
	B		13.93 (58)			18.8 (33)		
	C		12.89 (62)			19.2 (35)		

A = Taro-loratadine - Test
B = Children's Claritin® syrup – reference
C = Claritin® tablet – reference
[1]Geometric mean, ln-transformed data
[2]90% confidence intervals for ratio of parameter geometric means
[3]Arithmatic mean
p-value by Duncans's Multiple Range test

Note: Subjects no 15 and 51, for DCL, the pre-dose concentration at periods 2 and 3 were >5% of the C_{max}, therefore, these subjects were excluded from the analyses.

Figure 2. Individual AUC_{inf} and Cmax of loratadine following single administration of the treatments:

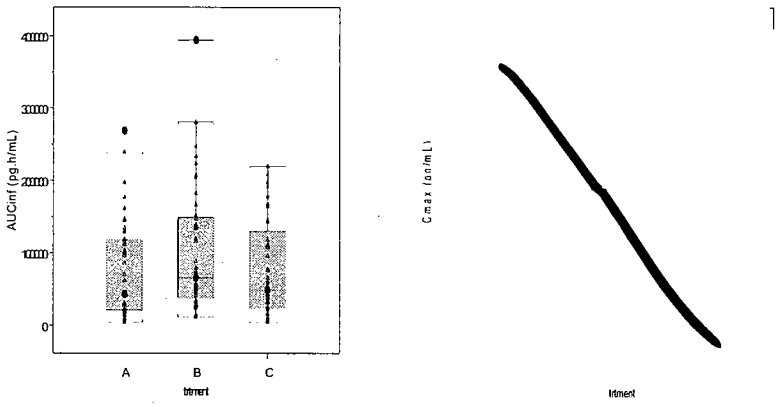
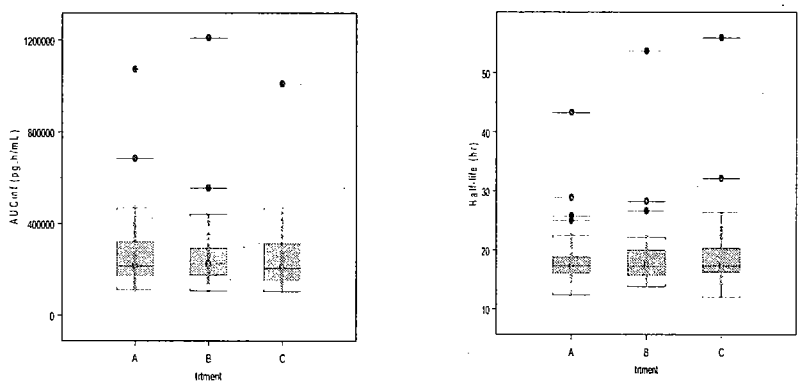


Figure 3. Individual AUC_{inf} and $t_{1/2}$ of DCL following single administration of the treatments:



Potentially Poor DCL Metabolizers: DCL is metabolized to 3-OH-DCL, predominantly by CYP3A4 and, to a lesser extent, by CYP2D6 (other enzymes may be involved). There was (at least) one subject (ID #26) identified as a potential poor metabolizer by PK DCL profile. Subject 26 (Black, 26 years of age) had approximately 3-, 4- and 3-fold, respectively, higher AUC_t, AUC_{inf}, and $t_{1/2}$ compared to the mean values of those PK parameters. The other outlier (Subject 13, Caucasian, 40-years of age) had approximately 2-fold higher AUC_t, AUC_{inf}, and $t_{1/2}$ compared to the mean values of those PK parameters. However, PK data of 3-OH-DCL (metabolite of DCL) is not available, thus, the ratio of AUC of 3-OH-DCL/DCL is not known.

Thus, safety of poor metabolizers following loratadine administration needs to be evaluated by the medical reviewer.

DCL concentrations from other studies:

DCL is known to be at least as active as loratadine in antihistaminic activity in human. In fact, DCL is approved by FDA in various formulations such as Clarinex® Syrup (NDA 21-300), Tablet (NDA 21-165) and RediTab (NDA 21-312).

In Study P00213 from NDA 21-300, healthy adult volunteers (24 males and 6 females) received single dose of 5 mg DCL as tablet (Clarinex® Tablet) and syrup (Clarinex® Syrup) in crossover design.

In Study P01216 from NDA 21-312, healthy adult volunteers (18 male and 12 female) received 5 mg DCL as tablet (Clarinex® Tablet), rediTab (Clarinex®RediTab) and syrup (Clarinex® Syrup) in crossover design. The results from these studies, along with the results from the present study, are presented in Table 3.

Table 3. Comparison of **arithmetic** mean (%CV) PK parameter values of DCL after single dose of the treatments from the studies.

Study	Subjects	Dose	Formulation	AUCt (ng.hr/mL)	AUCinf (ng.hr/mL)	C_{max} (ng/mL)
P00213[a]	30	5 mg	Clarinex® Tablet	45.8 (44)	47.4 (45)	2.44 (41)
			Clarinex® Syrup	46.2 (71)	48.4 (54)	2.3 (51)
P01216[a]	28	5 mg	Clarinex® Tablet	38.9 (45)	40.3 (45)	2.2 (35)
			Clarinex® Syrup	37.5 (47)	38.9 (47)	2.1 (33)
			Clarinex® RediTab	38 (44)	39.4 (43)	2 (30)
30218[b]	43	40 mg	Nonspil Suspension	242.4 (42) [60.6[c]]	266.2 (46) [66.6[c]]	17.4 (37) [4.4[c]]
			Claritin® Tablet	225.6 (42) [56.4[c]]	251.7 (46) [62.9[c]]	16.5 (41) [4.1[c]]
			Claritin® Syrup	239.3 (41) [59.8[c]]	265.6 (46) [66.4[c]]	20.9 (38) [5.2[c]]

[a]Dose = DCL 5 mg [b]Dose = Loratadine 40mg [c]Normalized to a dose of 10 mg loratadine

Summary:

For loratadine;

- Taro's loratadine [redacted] suspension is not equivalent to Claritin® syrup as 90% CI for the ratios of AUC and C_{max} are outside the BE limit of 80-125%.
- Taro's loratadine [redacted] suspension is equivalent to Claritin® Tablet based on AUC but not based on C_{max}
- Claritin® syrup is not equivalent to Claritin® tablet as 90% CI for the ratios of AUC and C_{max} are outside the BE limit of 80-125%.

For DCL;

- Taro's loratadine [redacted] suspension is equivalent to Claritin® tablet as 90% CI for the ratios of AUC and C_{max} are within the BE range of 80-125%.
- Taro's loratadine [redacted] suspension is equivalent to Claritin® syrup based on AUC_t and AUC_{inf}, but not based on C_{max} (90% CI = 79-90%). However, the point estimate of the ratio for C_{max} was 0.84 indicates similar BA between the Taro's loratadine [redacted] suspension and Claritin® syrup.
- Claritin® syrup is equivalent to Claritin® tablet based on AUC_t and AUC_{inf}, but not based on C_{max} (90% CI = 121-138%), with the point estimate of 1.3.
- Subject 26 and 34 were considered as Poor Metabolizer (by systemic exposure. Subject 26 had approximately 3-, 4- and 3-fold, respectively, higher AUC_t, AUC_{inf}, and $t_{1/2}$ compared to the mean values of those PK parameters. Subject 34 had about 4-fold higher AUC_t, AUC_{inf} and Cmax compared to the mean values of those PK parameters. Thus, safety of poor metabolizer(s) following loratadine administration needs to be evaluated by the medical reviewer.
- PK parameter values of DCL obtained from this study are slightly higher than those obtained from other studies, although studies were performed in different population (Table 3).

Protocol 30219

Study Type: Food effect/BA/Single dose

Protocol Title: Randomized, 2-way crossover bioequivalence study of Loratadine 5 mg/5 mL [redacted] Suspension and Claritin® Administered as 4 x 10 mg Tablets in Healthy Subjects under fed Conditions.

Clinical Investigators: [redacted]

Sample Analysis: [redacted]

Objectives: To compare the rate and extent of absorption of loratadine oral suspension vs. Claritin® tablets under fed conditions.

Study Design and Method: Single center, open-label, randomized, 2-period crossover study.

Study Population: 50 healthy adult males and non-smokers, 18 years of age or older (sponsor stated that females were excluded because of possible evidence of human fetal risk associated with loratadine use. Loratadine is FDA Pregnancy Category B). A single oral dose of the assigned drug was administered to each subject in each period. No food was allowed from at least 10 hours until 30 minutes pre-dose, at which time a high-fat, high-caloric breakfast was served. After drug administration, subjects fasted for at least 4 hours. A controlled meal was served no less than 4 hours after dosing and standard meals were served at appropriate times thereafter. Drugs were administered with approximately 240 mL of water. Total dose per period was 40 mg of loratadine. There was a washout of at least 14 days between doses.

- A (Test): Loratadine (5 mg/5 mL) gel [redacted] oral suspension, Lot No.: S189-54098 (EBK-L05)
- B (Reference): Loratadine 10 mg tablets (Claritin®), Lot No.: 2-RXF-1035

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, 0.667, 0.75, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48 and 72 hours post dose.

Analytical Methodology

Assay Method: LCMS/MS

Caliburation standards Concentration: The calibration ranges for loratiadine and DCL were [redacted] respectively.

Accuracy and Precision:

Loratadine: there were 2 outliers for QC_1 (nominal concentration of [redacted] for between run analysis (total run [redacted] with precision (%CV) and accuracy of [redacted], respectively for QC_1. Without these outliers, precision and accuracy were [redacted] respectively which is similar to results obtained during the assay validation. %CV for other QCs (QC_2-QC_4) ranged [redacted] accuracy range of [redacted].

DCL: precision (%CV) of [redacted] accuracy) for QC_1 (nominal concentration of 1 [redacted] was noted, and without the outlier precision and accuracy were [redacted] respectively for QC_1. Precision and accuracy for other QCs (QC_2-QC_4) ranged [redacted] respectively.

Statistical Analyses: Using SAS, ANOVA was performed on untransformed T_{max}, Kel, and $t_{1/2}$ and on ln-transformed AUC and C_{max} at the a. level of 0.05. For bioequivalence determination, 90% confidence intervals were determined for the ratios (T/R) of least-squares geometric mean AUCs and C_{max} for loratadine and its active metabolite DCL.

RESULTS:

Study Population: 48 subjects completed the study. Subject 02, the pre-dose DCL concentration was >5% of C_{max}, therefore, this subject was not included for PK analysis.

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

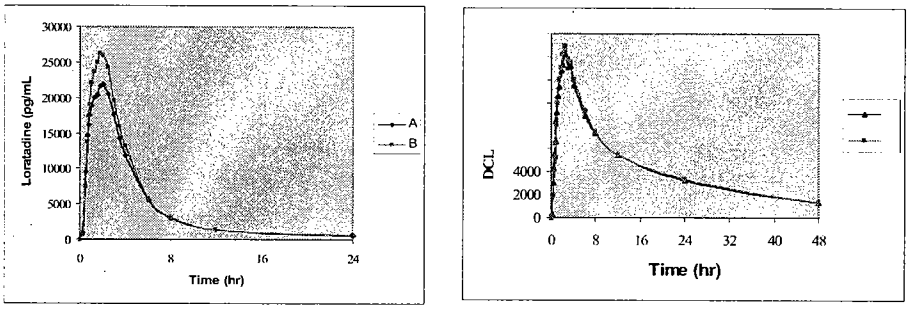
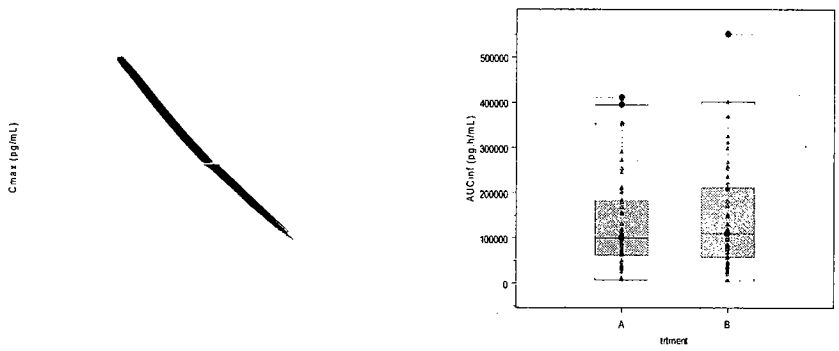


Table 1. Loratadine (N=48) and DCL (N=47) PK parameters and Statistical analysis

Parr	T	Pairr	Loratadine Mean (%CV)	Loratadine Treatment Comparisons Ratio	Loratadine Treatment Comparisons 90% CI	DCL Mean (%CV)	DCL Treatment Comparisons Ratio	DCL Treatment Comparisons 90% CI
AUCt[1] (ng•h/mL)	A		90.1 (89)			218.2 (39)		
	B	A/B	98.6 (90)	91.4	85.5-97.6	220.8 (39)	98.8	95.3-102.5
AUC_{inf}[1] (ng•h/mL)	A		94.7 (90)			234.8 (41)		
	B	A/B	104.1 (91)	91.0	85.1-97.3	239.6 (41)	98.0	94.8-101.3
C_{max}[1] (ng/mL)	A		20.3 (85)			14.9 (41)		
	B	A/B	26.0 (89)	78.0	67.3-90.1	16.5 (40)	89.9	83.3-97.1
T_{max} (hr)[3]	A		1.64 (45)			2.34 (35)		
	B	A/B	1.77 (52)		$p = 0.441$	2.48 (37)		$p = 0.463$
Kel (h^{-1})[3]	A		0.058 (97)			0.038 (18)		
	B		0.050 (89)			0.037 (20)		
$t_{1/2}$ (hr)[3]	A		16.95 (38)			19.02 (20)		
	B		18.23 (36)			19.74 (28)		

A = Taro-loratadine - Test B = Claritin® tablet – reference [1]Geometric mean, ln-transformed data
[2]90% confidence intervals for ratio of parameter geometric means [3]Arithmathic mean, Un-transformed data

Figure 2. Individual C_{max} and AUC_{inf} of loratadine following single administration of the treatments



Summary:

- C_{max} of loratadine from Taro's loratadine [redacted] suspension was lower by 22% compared to that from Claritin tablet in fed condition as 90% CI falling out side of BE range , [redacted]
- For DCL, bioavailability from the treatments was similar as the 90% CI for the ratios of AUCs and C_{max} were within BE range.
- None was identified as slow metabolizer (for DCL).

4.3. Consult Review: None

1.4 OCPB FILING/REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-734**	**Brand Name**	**Children's ElixSure™-24 hr Antihistamine**
OCPB Division (I, II, III)	**DPE-II**	**Generic Name**	**Loratadine**
Medical Division	**HFD-570**	**Drug Class**	**Anti-Histamine**
OCPB Reviewer	**Shinja Kim**	**Indication(s)**	**Symptoms of allergic rhinitis**
OCPB Team Leader	**Emmanuel Fadiran**	**Dosage Form**	**5 mg/5 mL oral suspension**
		Dosing Regimen	**≥6 years and adults: 2 tsp qd 2-6 years: 1 tsp qd**
Date of Submission	**01/19/04**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**09/19//04**	**Sponsor**	**Taro Pharmaceuticals**
PDUFA Due Date	**11/19/04**	**Priority Classification**	**S**
Division Due Date	**10/19/04**		

3 Clin. Pharm. and Biopharm. Information

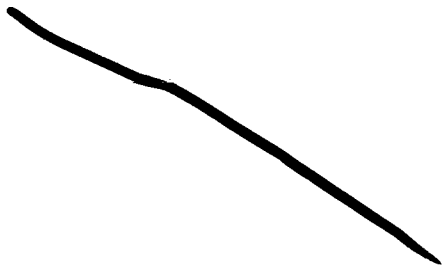
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical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

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

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	x	
Comments sent to firm?		
QBR questions (key issues to be considered)	• Is the formulation used in the bio-studies identical to the to-be-marketed formulation? • Is the tested formulation bioequivalent to the reference products? • Are food effect profiles comparable/BE between the proposed and referenced 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 moiety?	

Note: Request for DSI consultation for the BE study by the project manager.

Analysis of the plasma samples undertaken by



Background:

This NDA is a 505(b)(2) application and it is proposed to market as an OTC product. The sponsor conducted 2 Clinical Pharmacology and Biopharmceutics studies to satisfy BA/BE requirements (BE with single dose, #30218 and food effect, #30219). The sponsor provided study results as shown below.

Table 1. PK loratadine (N=45) and DCL (N=43) parameters and Statistical analysis from Study 30218

Loratadine					
Parameter	**Trt**	**Mean[1] (%CV)**	**Pair**	**Ratio**	**90% CI[2]**
AUCt (ng•h/mL)	A	44.3 (109)	A/B	0.65	***58.3-72.1***
	B	68.3 (91)	A/C	0.94	84.2-104.1
	C	47.3 (109)	B/C	1.44	129.8-160.6
AUC_{inf} (ng•h/mL)	A	47.4 (109)	A/B	0.66	***59.3-73.5***
	B	71.8 (92)	A/C	0.95	85.3-105.7
	C	49.9 (109)	B/C	1.44	129.1-160
C_{max} (ng/mL)	A	13.5 (109)	A/B	0.53	***45.0-61.6***
	B	25.6 (98)	A/C	0.81	***69.3-94.9***
	C	16.6 (113)	B/C	1.54	131.6-180.2
Descarboethoxy					
AUCt (ng•h/mL)	A	222.8 (42)	A/B	1.01	95.8-105.8
	B	221.3 (41)	A/C	1.07	101.8-112.5
	C	208.2 (42)	B/C	1.06	101-111.7
AUC_{inf} (ng•h/mL)	A	238.3 (46)	A/B	1.01	95.4-106
	B	237 (46)	A/C	1.06	100.2-111.4
	C	225.5 (46)	B/C	1.05	99.7-110.8
C_{max} (ng/mL)	A	16.8 (37)	A/B	0.84	***79-90.0***
	B	19.6 (38)	A/C	1.09	102.3-116.7
	C	15.1 (41)	B/C	1.3	121.3-138.4

A = Taro-loratadine - Test B = Children's Claritin® syrup – reference
C = Claritin® tablet – reference [1]Geometric mean, ln-transformed data
[2]90% confidence intervals for ratio of parameter geometric means

Table 2. PK loratadine (N=48) and DCL (N=47) parameters and Statistical analysis from Study 30219

Loratadine					
Parameter	**Trt**	**Mean (%CV)**	**Pair**	**Ratio**	**90% CI[2]**
AUCt (ng•h/mL)	A	90.1 (89)			
	B	98.6 (90)	A/B	0.91	85.5-97.6
AUC_{inf} (ng•h/mL)	A	94.7 (90)			
	B	104.1 (91)	A/B	0.91	85.1-97.3
C_{max} (ng/mL)	A	20.3 (85)			
	B	26.0 (89)	A/B	0.78	***67.3-90.1***
Descarboethoxy-loratadine					
AUCt (ng•h/mL)	A	218.2 (39)			
	B	220.8 (39)	A/B	0.99	95.3-102.5
AUC_{inf} (ng•h/mL)	A	234.8 (41)			
	B	239.6 (41)	A/B	0.98	94.8-101.3
C_{max} (ng/mL)	A	14.9 (41)			
	B	16.5 (40)	A/B	0.9	83.3-97.1

A = Taro-loratadine - Test B = Claritin® tablet – reference
Other notations are the same as Table 1

Comments: The following review issues were identified at filling of this NDA:

- The 90% CI for C_{max} comparisons for loratadine in two studies (30218 & 30219) are outside the BE range of 80 to 125%.
- The 90% CI for AUC of loratadine from the test product compared to Claritin Syrup (A *vs* B) in BE study (#30218) is outside the BE range of 80 to 125%, while comparison between test vs Claritin tablet (A *vs*. C) is within the range.
- Biobatch size [redacted] used in PK studies are [redacted] of commercial batch size [redacted] therefore, the additional dissolution (and stability) data may need to be submitted, when the sponsor produces the planned commercial batch of [redacted]

Conclusion: Submission is filable. DSI is requested for BE study 30218.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceuticals / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed of NDA 21-734 submitted on January 19, 2004 for filing and finds it filable. Please request for DSI for Study 30218. Blood samples from these studies were analyzed by [redacted]

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
10/22/04 10:15:46 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
10/22/04 10:22:03 AM
BIOPHARMACEUTICS
I concur