CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-375

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-375
Drug Substance	Loratadine
Drug Product	"Alavert" and "Dimetapp Allergy"
Strengths	10 mg
Route of Administration	Orally Disintergrating tablet
Sponsor	Whitehall-Robins Healthcare (div. of American Home Products Co.)
Type of submission	Original NDA as an OTC
Date of submission	8/23/01
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 Orally Disintergrating Tablet for over-the-counter (OTC) marketing under two trade names; "Alavert" and "Dimetapp Allergy". It proposes to be used for temporary relief of symptoms —— hay fever ——— for adults and children over six years of age.

This NDA contains information that is also contained in ANDA 75-822 (generic version of Caritin® RediTabs™), submitted by ESI Lederle for a prescription version of this same product. American Home Products Corporation (AHPC), ESI Lederle, Wyeth-Ayerst Pharmaceuticals and Whitehall-Robins Healthcare are all unincorporated divisions of AHPC.

This NDA contains two studies (Bioequivalence and Food effect) to support the NDA. In the absence of clinical efficacy and safety trial, this NDA relies mainly on an assessment of PK data from these two studies.

The results from the two studies demonstrated that the proposed product is bioequivalent to the reference product, Claritin® Reditabs by Schering Pharmaceuticals. The bioavailability of loratadine was similar for the ESI loratadine and Claritin® Reditab when the products were administered following a (standard) high-fat breakfast. From the studies, four subjects were identified as 'poor metabolizer' evidenced by markedly elevated exposure and prolonged half-life to descarboethoxyloratadine (~ 5-fold increase).

1.1 Recommendation: It is recommended that the sponsor should set dissolution specification at Q = — ir— minutes.

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Section 6, and found that NDA 21-375 is acceptable from a CPB standpoint provided that the sponsor agrees with the Agency's recommendation on the dissolution specification.

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 bioequivalence (BE) study was to determine the BE of the loratadine 10-mg orally dissolving tablet by ESI with the marketed Claritin® Reditabs. The 90% confidence intervals for the geometric means of 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 was to determine the bioavailability (BA) of ESI-loratadine orally dissolving tablet when it was administered under fasted and fed conditions, and to compare the BA of ESI loratadine tablet with the Claritin® Reditabs under fed conditions. For loratadine plasma levels, the least square mean ratios for the comparison loratadine 10 mg orally disintegrating tablets fed to fasted for log transformed AUC_t, AUC_{inf}, and C_{max} were 1.62, 1.64, and 0.93 respectively, demonstrating increased BA of loratadine in the fed compared to the fasted state. For DCL, AUC_t, AUC_{inf}, and C_{max} were within the boundary conditions of 0.80 – 1.20 of BE. The bioavailability of loratadine was similar for the ESI loratadine and Claritin® Reditab when the products were administered following a (standard) high-fat breakfast (the least square mean ratios for the log transformed AUC_t and AUC_{inf} were within 92-130% and 85-130% for C_{max}).

Overall, the results of the two studies demonstrate that loratadine 10 mg orally disintegrating tablets are bioequivalent to the reference drug, Schering Claritin® Reditabs.

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 prescription 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 listed 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

nd

from DCL. This

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 biostudies identical to the to-be-marketed formulation?

Yes. The formulation of the biostudy batch (#990043) that was used in BE and Food effect studies is representative of the proposed market formulation of Loratadine 10 mg Orally Disintegrating Tablets. The quantitative Formula is shown in the table below;

Ingredient	Loratadine 10 mg Orally Disintegrating Tablets (Clinical and Proposed Market Formula)				
	Role	%W/W	Quantity per Tablet (mg)	Quantity per Batch (kg)	Notes
Loratadine	Active pharmaceutical ingredient (API)	3.33	10.0		
Mannitol, USP					
Microcrystalli... Cellulose, NF					
Crospovidone, NF					
Aspartame, NF					
Sodium Bicarbonate, No. 1 USP					
Citric Acid,					
Magnesium Stearate, NF					
Colloidal Silicon Dioxide, NF					
Natural and Artificial Flavor					
TOTAL					

1. Quantity per batch is rounded to three decimal places if the amount to be weighed is less than
2. Quantity per batch is rounded to one decimal place if the amount to be weighed is more than
3. This is the range for Mannitol. The actual amount to be used in the batch will be determined based on the Loratadine assay value of the Loratadine
4. The ranges for Microcrystalline cellulose, Crospovidone, and Magnesium stearate are based on the range for the that maybe used, which will differ based on the Loratadine assay va...

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

Yes. Clinical Study 99-104-MA was crossover study with a single-dose comparing loratadine 10 mg orally disintegrating tablets and Claritin® Reditabs in healthy, male and female subjects under fasted conditions. Mean plasma concentration profiles of loratadine and DCL are shown in Figure 1. The 90% confidence intervals for the geometric means of AUCT (i.e., AUC_{0-t}), AUCI (i.e., AUC_{0-inf}), and C_{max} were within 80 to 125% for loratadine and its active metabolite, DCL (Tables 1-2), indicating that the two tablet formulations are bioequivalent.

Table 1. Mean loratadine PK parameters and 90% Confidence Intervals (N=127)

Treatment	AUCI (ngehr/mL)	AUCT (ngehr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	Kel (1/hr)
Loratadine Orally Disintegrating Tablet (A)	11.55	10.94	3.66	1.04	23.78	0.059
Schering Claritin® Reditab (B)*	11.57	10.98	3.60	1.13	23.65	0.054
A/B* ratio (%)	1.00	1.00	1.02	0.92	1.01	1.10
A/B* 90% CI	92.55-102.92†	92.35-102.87†	91.46-104.90†	83.46-99.59	93.47-107.49	93.94-127.08

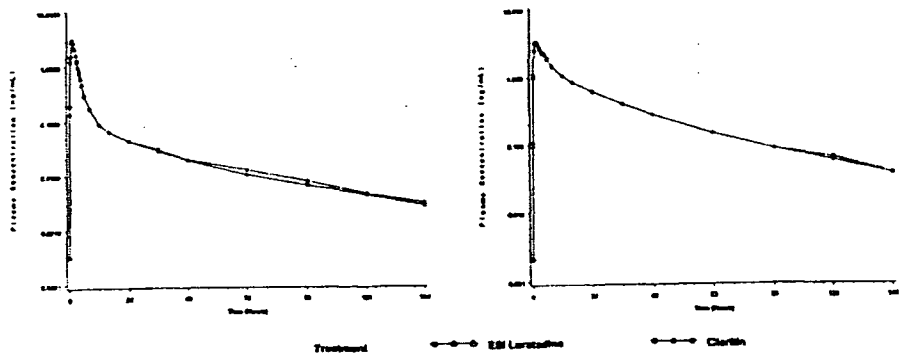
* - Reference product; † Based on log transformed data

Table 2. Mean DCL PK parameters and 90% Confidence Intervals (N=127)

Treatment	AUCI (ngehr/mL)	AUCT (ngehr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	Kel (1/hr)
Loratadine Orally Disintegrating Tablet (A)	56.42	51.14	3.75	1.94	24.9	0.031
Schering Claritin® Reditab (B)*	56.53	51.44	3.82	1.76	24.98	0.031
A/B* ratio (%)	1.00†	0.99†	0.98†	1.10	1.00	1.01
A/B* 90% CI	96.44-101.86†	96.13-101.24†	94.36-101.34†	100.76-120.02	97.58-101.75	99.04-102.44

* - Reference product; † Based on log transformed data

Figure 1. Mean plasma concentration profiles of loratadine (left) and DCL (right).



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

They are comparable. Study 99-105-MA determined the BA of ESI loratadine fast dissolving tablet when it was administered under fasted and fed conditions, and compared the BA of ESI loratadine fast dissolving tablet with that of the marketed Claritin® Reditabs under fed conditions. Mean plasma concentration profiles are shown in Figure 2. For loratadine plasma

levels, the least square mean ratios for the comparison of loratadine 10 mg — dissolving tablet fed to fasted for log transformed AUCT and AUCI were 1.62 and 1.64 (with C_{max} = 0.93) respectively, demonstrating increased BA of loratadine in the fed compared to the fasted state (Table 3). For DCL, AUCT, AUCI, and C_{max} were within the boundary conditions of 0.80 - 1.20 of BE criteria (Table 4). The bioavailability of loratadine (Table 3) was similar for the ESI loratadine and Claritin® Reditab when the products were administered following a (standard) high-fat breakfast (the least square mean ratios were within 85-130% for the key PK parameters of log transformed AUC_t, AUC_{inf} and C_{max}). It can be concluded that food effect profiles were comparable between the proposed and referenced products.

Table 3. Mean loratadine PK parameters and 90% Confidence Intervals (N=24)

Treatment	AUCI (ng•hr/mL)	AUCT (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	Kel (1/hr)
Loratadine Orally Disintegrating Tablet – Fasted (A)	11.15	10.66	3.18	1.21	22.81	0.054
Loratadine Orally Disintegrating Tablet- Fed (B)	17.66	16.78	3.17	3.73	36.00	0.030
Schering Claritin® Reditab - Fed (C)*	14.08	13.38	2.38	3.90	32.96	0.023
B/A ratio (%)	1.64†	1.62†	0.93†	3.09†	1.58	0.56
B/C ratio (%)	1.10†	1.09†	1.05†	0.96	1.09	1.30
B/A 90% CI	137.69-195.45†	135.68-192.85†	75.05-115.61†	271.62-346.72	129.98-185.67	19.31-92.62
B/C 90%CI	92.19-130.85†	91.58-130.16†	84.87-130.74†	84.20-107.48	89.97-128.52	44.72-214.51

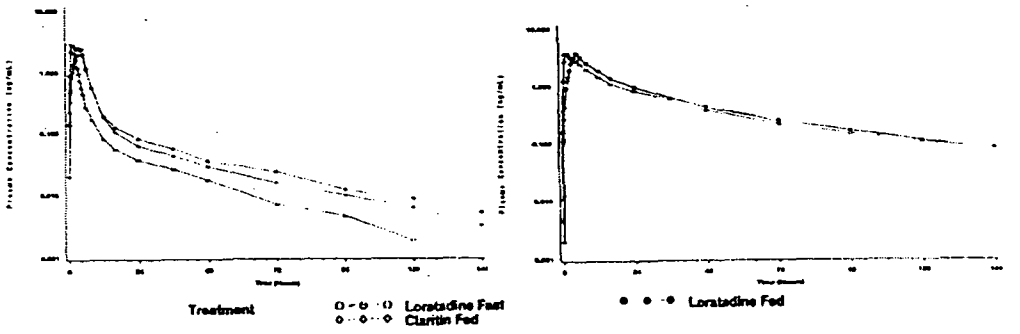
† Based on log transformed data

Table 4. Mean DCL PK parameters and 90% Confidence Intervals (N=24)

Treatment	AUCI (ng•hr/mL)	AUCT (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	Kel (1/hr)
Loratadine Orally Disintegrating Tablet – Fasted (A)	84.96	68.68	3.98	2.14	29.93	0.030
Loratadine Orally Disintegrating Tablet – Fed (B)	85.90	74.53	3.95	4.90	28.39	0.029
Schering Claritin® Reditab - Fed (C)*	85.82	73.25	3.98	4.99	28.33	0.029
B/A ratio (%)	1.11†	1.12†	0.98†	2.29	0.95	0.96
B/C* ratio (%)	1.04†	1.05†	0.98†	0.98	1.00	0.98
B/A 90% CI	103.78-117.68†	105.1-119.09†	89.19-108.25†	195.37-263.11	85.38-104.36	91.15-101.39
B/C 90%CI	98.04-111.17†	98.42-111.53†	89.39-108.49†	83.64-112.65	90.19-110.23	92.62-103.03

† Based on log transformed data

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



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

Three subjects [2 female Hispanics (2 out of 21 Hispanics) and one Black male (1 out of 4 Blacks)] from BE study and one Black female (1 out of 6 Blacks) from food effect study were identified as poor metabolizers (by exposure data). Approximately, systemic exposure (AUC_T = 254 69 ng h/mL) and $t_{1/2}$ (103 23 hr) of poor metabolizers were increased 5 fold compared to the mean values.

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 — dissolving tablets is shown in the table below;

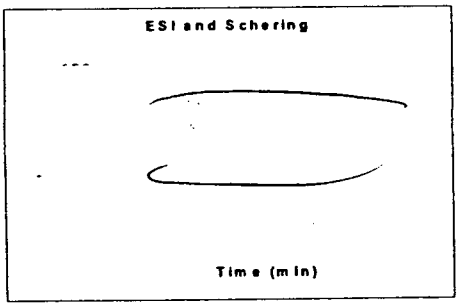
Apparatus Type:	USP Apparatus
Medium:	
Volume:	
Speed:	
Temperature:	
Sampling Time:	
Specification:	Q = — in — min. Stage dissolved in — min.

The results of dissolution testing on the ESI 10-mg loratadine and Claritin® Reditabs are listed in Table 6, and their dissolution profiles are shown in Figure 3.

Table 6. ESI and Schering loratadine 10 mg Dissolution test

		ESI			Schering	
Mean	96	99	99	100	101	101
% rsd	3.2	1.6	1.2	1.7	1.4	1.4
n	12	12	12	12	12	12
min						
max						

Figure 3. ESI and Schering (Claritin® Reditab) in —



Similarity factor (f2) for dissolution between ESI 10-mg loratadine and Claritin® Reditab was ___ suggests the dissolution profiles of these two formulations are similar.

Comment to the sponsor: Dissolution method is acceptable, however, it is recommended to set specification Q = ___ in ___min as opposed to Q ___ at ___min.

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

Plasma samples from BE and Food effect studies were analyzed for loratadine and DCL using a liquid chromatographic ___ mass spectrometric (LC/MS/MS) method developed by ___ Loratadine and the metabolite concentrations were determined from ___ plasma samples. The specificity, sensitivity, linearity, accuracy, precision, recovery, and stability of loratadine and DCL were determined over plasma concentration ranges of ___ respectively. Overall, the methods were satisfactory.

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Protocol 99-104-MA

Study Type: Bioequivalence/Relative Bioavailability/Single dose.

Title: A single-dose, randomized, crossover study comparing ESI Lederle loratadine 10mg — dissolving tablets and Schering (Claritin® Reditabs) in healthy, male and female subjects under fasted conditions.

Clinical Investigators

Objectives: Compare the bioavailability of ESI Lederle loratadine 10mg — dissolving tablets and Schering (Claritin® Reditabs) 10 mg loratadine tablets.

Study Design and Method: A single dose, open-label, randomized, two-way crossover comparative bioavailability study in 130 healthy adult volunteers (127 completed), with 28 days wash out period. At dosing, each subject placed a single Reditabs or — dissolving tablet on the tongue and allowed it to disintegrate for 30 seconds and swallowed the disintegrated tablet followed by 240 mL water. Subjects continued fasting for 4 hours after dosing; other than the water consumed at dosing, no fluids were permitted for 1 hour before or after dosing. Subjects received the following 2 treatments in a randomized sequence:

- A: Loratadine 10 mg, ESI Lederle, Lot #990043
- B: Claritin® Reditabs 10 mg, Schering, Lot #9EBT-88

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

Sampling times: blood samples were collected at 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: LCMS/MS

Assay Sensitivity: The calibration ranges for loratiadine and descarboethoxyloratadine were — , respectively.

Accuracy and Precision: Inter-assay precision and accuracy of the QC samples for loratadine ranged from , respectively. Inter-assay precision and accuracy of the QC samples for DCL ranged from respectively.

RESULTS:

Study Population: The average age, weight, and height of the subjects were 34.2 years (range: 18 to 65 years), 156.1 pounds (range: 108 to 226 pounds), and 67.9 inches (range: 60.2 to 76.0 pounds), respectively. There were 58 males and 69 females. The majority of the subjects were Caucasian (98 subjects), followed by Hispanic (21 subjects), Black (4 subjects), American Indian (2 subjects) and Asian (2 subjects).

The mean loratadine and DCL plasma concentration curves are presented in Figure 1. The 90% confidence intervals for AUC_t, AUC_{inf}, and C_{max}, using log transformed plasma concentration data, met the criteria of BE by falling within the 80-125% range for loratadine as well as DCL (Tables 1-2).

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

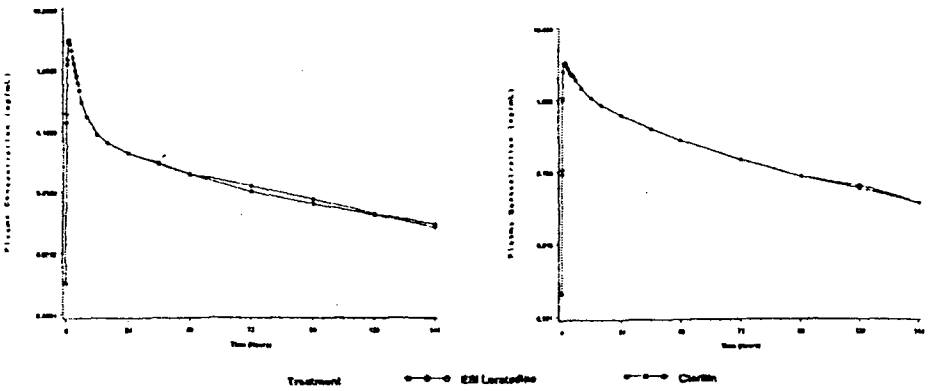


Table 1. Mean loratadine PK parameters and 90% Confidence Intervals (N=127)

Treatment	AUCI (ng•hr/mL)	AUCT (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	Kel (1/hr)
Loratadine Orally Disintegrating Tablet (A)	11.55	10.94	3.66	1.04	23.78	0.059
Schering Claritin® Reditab (B)*	11.57	10.98	3.60	1.13	23.65	0.054
A/B* ratio (%)	1.00	1.00	1.02	0.92	1.01	1.10
A/B* 90% CI	92.55-102.92†	92.35-102.87†	91.46-104.90†	83.46-99.59	93.47-107.49	93.94-127.08

* - Reference product; † Based on log transformed data

Table 2. Mean DCL PK parameters and 90% Confidence Intervals (N=127)

Treatment	AUCI (ng•hr/mL)	AUCT (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	Kel (1/hr)
Loratadine Orally Disintegrating Tablet (A)	56.42	51.14	3.75	1.94	24.9	0.031
Schering Claritin® Reditab (B)*	56.53	51.44	3.82	1.76	24.98	0.031
A/B* ratio (%)	1.00†	0.99†	0.98†	1.10	1.00	1.01
A/B* 90% CI	96.44-101.86†	96.13-101.24†	94.36-101.34†	100.76-120.02	97.58-101.75	99.04-102.44

* - Reference product; † Based on log transformed data

Note: $AUCI = AUC_{0-\infty}$, $AUC_T = AUC_{0-T}$

Comment: The data obtained from this study showed that the proposed product and Claritin® Reditabs are bioequivalent to each other.

Poor Metabolizers: Three subjects [2 female, 22 and 38 years old, Hispanic subjects (2 out of 21 hispanics) and one Black, 42 years old, male (1 out of 4 blacks)] were identified as poor metabolizers. Their mean DCL (i.e., data from treatment A and B) PK parameters for $AUC_{0-\infty}$, AUC_{0-T}, C_{max}, T_{max} and $t_{1/2}$ were 415.7 ± 87 ng•h/mL, 254.4 ± 69 ng•h/mL, 3.1 ± 1.1 ng/mL, 9.7 ± 3.7 hr and 103.1 ± 23.2 hr, respectively. Approximately, AUC_t, AUC_{inf}, T_{max} and $t_{1/2}$ of slow metabolizers were 5-, 7.4-, 5.2- and 4.1-fold, respectively increased compared to the mean values (all subjects). Note that AUC_{inf} and $t_{1/2}$ values may not be accurate since extrapolated area (i.e., from last time-point to infinity) is > 20% of AUC_{inf}.

Protocol 99-105-MA

Study Type: Food effect/Relative bioavailability/Single dose

Protocol Title: A comparative, randomized, 3-way crossover study comparing ESI Lederle loratadine 10mg — dissolving tablets and Schering (Claritin® Reditabs) in healthy, male and female subjects under fed and fasted conditions.

Clinical Investigators. [redacted]

Objectives: Food effect of ESI Lederle loratadine 10mg — dissolving tablets, also compare the bioavailability between ESI Lederle and Claritin® Reditabs 10 mg loratadine tablets under fed conditions.

Study Design and Method: Open-label, randomized, 3-way crossover study in 24 healthy adult volunteers under fed and fast conditions, with 21 days wash out period. There were 3 treatment groups. Subjects received the following treatments:

- Treatment A (loratadine 10mg orally disintegrating tablets; fasting condition) a single, fast-dissolving tablet placed on the tongue and allowed it to disintegrate for 30 seconds and then swallowed with 240 mL water.
- Treatment B (loratadine 10mg orally disintegrating tablets; fed) and C (Claritin® Reditabs; fed) subjects were given a high-fat meal 30 minutes prior to dosing. The standardized high-fat meal consisted of one buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, one serving of hash browned potatoes, 8 ounces (240 mL) of whole milk, and 6 ounces (180 mL) orange juice. Upon complete the meal, each subject placed a single, fast-dissolving tablet or Reditab on the tongue and allowed it to disintegrate for 30 seconds and swallowed the disintegrated tablet followed with 240 mL water.

Test Drug: Loratadine 10 mg, ESI Lederle, Lot #990043

Reference: Claritin® Reditabs 10 mg, Schering, Lot #9EBT-88

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

Sampling times: blood samples at 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: LCMS/MS

Assay Sensitivity: The calibration ranges for loratiadine and descarboethoxyloratadine were [redacted], respectively.

Accuracy and Precision: Inter-assay precision and accuracy of the QC samples for loratadine ranged from [redacted] respectively. Inter-assay precision and accuracy of the QC samples for DCL ranged from [redacted] respectively.

RESULTS:

Study Population: The average age, weight, and height of the subjects were 34.7 years (range: 18 to 60 years), 163.6 pounds (range: 122 to 231 pounds), and 68.5 inches (range: 64 to 78 inches), respectively. There were 15 males and 9 females. The majority of the subjects were Caucasian (17 subjects), followed by Black (6 subjects), and Asian (1 subject).

Pharmakokinetics: The mean loratadine and DCL plasma concentration curves are presented in Figure 1. For loratadine plasma levels, the least square mean ratios for the comparison loratadine 10 mg orally disintegrating tablets fed to fasted for log transformed AUC_t, AUC_I, and C_{max} were 1.62, 1.64, and 0.93 respectively, demonstrating increased BA of loratadine in the fed compared to the fasted state (Table 1). For DCL, AUC_t, AUC_I, and C_{max} were within the boundary conditions of 0.80 - 1.20 of BE (Table 2). Under fed conditions, ESI loratadine 10 mg orally disintegrating tablet was BE to the referenced Schering Claritin® Reditabs loratadine 10 mg tablet as evidenced by the least square mean ratios being within 0.80 - 1.20 for the log transformed AUC_t, AUC_{inf}, and C_{max}.

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

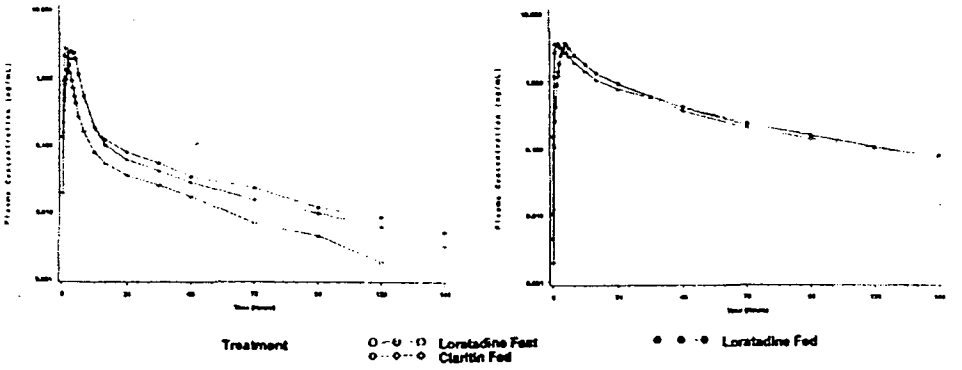


Table 1. Mean loratadine PK parameters and 90% Confidence Intervals (N=24)

Treatment	AUCI (ng•hr/mL)	AUCT (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	Kel (1/hr)
Loratadine Orally Disintegrating Tablet – Fasted (A)	11.15	10.66	3.18	1.21	22.81	0.054
Loratadine Orally Disintegrating Tablet- Fed (B)	17.66	16.78	3.17	3.73	36.00	0.030
Schering Claritin® Reditab - Fed (C)*	14.08	13.38	2.38	3.90	32.96	0.023
B/A ratio (%)	1.64†	1.62†	0.93†	3.09†	1.58	0.56
B/C ratio (%)	1.10†	1.09†	1.05†	0.96	1.09	1.30
B/A 90% CI	137.69-195.45†	135.68-192.85†	75.05-115.61†	271.62-346.72	129.98-185.67	19.31-92.62
B/C 90%CI	92.19-130.85†	91.58-130.16†	84.87-130.74†	84.20-107.48	89.97-128.52	44.72-214.51

† Based on log transformed data

Table 2. Mean DCL PK parameters and 90% Confidence Intervals (N=24)

Treatment	AUCI (ng•hr/mL)	AUCT (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	Kel (1/hr)
Loratadine Orally Disintegrating Tablet – Fasted (A)	84.98	68.68	3.98	2.14	29.93	0.030
Loratadine Orally Disintegrating Tablet – Fed (B)	85.90	74.53	3.95	4.90	28.39	0.029
Schering Claritin® Reditab - Fed (C)*	85.82	73.25	3.98	4.99	28.33	0.029
B/A ratio (%)	1.11†	1.12†	0.98†	2.29	0.95	0.96
B/C* ratio (%)	1.04†	1.05†	0.98†	0.98	1.00	0.98
B/A 90% CI	103.78-117.68†	105.1-119.09†	89.19-108.25†	195.37-263.11	85.38-104.36	91.15-101.39
B/C 90%CI	98.04-111.17†	98.42-111.53†	89.39-108.49†	83.64-112.65	90.19-110.23	92.62-103.03

† Based on log transformed data

Comment: The sponsor concluded that the proposed product and Claritin® RediTabs are BE under fed conditions, however, 'the two formulations are similar' is a more accurate statement since 90% CI ranged 85-130% for AUC and C_{max} for loratadine (Table 1).

Slow Metabolizer: One subject (female/35years of age/Black) was identified as slow metabolizer. For DCL AUC_{0-T} and $t_{1/2}$ were approximately 5-fold increased in this subject compared to mean values (AUC_{0-T} = 332 ± 7 ng•h/mL, $t_{1/2}$ = 133 ± 22 hr).

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 and 3, respectively. The dissolution profiles of these two formulations for the individual tablets are plotted in Figure 1.

Table 1. Proposed Dissolution Release Method and Specification

Apparatus Type:	USP Apparatus
Medium:	
Volume:	
Speed:	
Temperature:	
Sampling Time:	
Percent Dissolved (Q):	

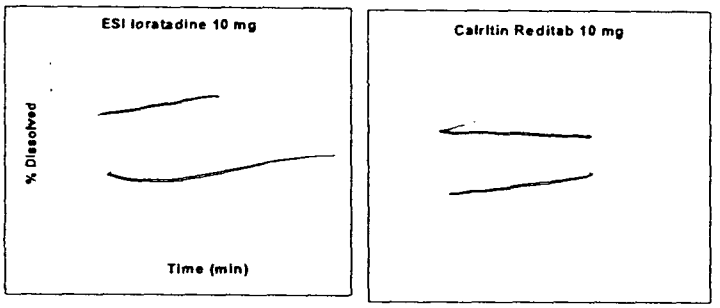
Table 2. Dissolution for ESI-Loratadine Tablets (Lot 990043) in 0.1

	minutes		
Tablet No.			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
mean	96	99	99
minimum	88	95	96
%RSD	3.2%	1.6%	1.2%

Table 3. Dissolution for Claritin® RediTabs (Lot 9-EBT-88) in

	minutes		
Tablet No.			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
mean	100	101	101
minimum	97	99	100
%RSD	1.7%	1.4%	1.4%

Figure 1. Teva loratadine (left) and Claritin® Tablet (right) in [redacted]



Similarity factor (f2) for dissolution between ESI 10-mg loratadine and Claritin® Reditab was [redacted] suggesting the dissolution profiles of these two formulations are similar.

Note: Dissolution method and specification for Claritin® Reditab, which was submitted in NDA 20-704, are as follows;

Apparatus Type:	USP Apparatus [redacted]
Speed:	[redacted]
Medium:	[redacted]
Specification:	Q = [redacted] in [redacted] minutes

Discussion: The dissolution test data from the biobatch for ESI-loratadine (Table 2) suggests that the specification should be set Q = [redacted] at [redacted] min. However, the review chemist was consulted before we set the (final) specification for this proposed product. Based on the stability data submitted to the NDA the CPB and chemist team, agreed to recommend to the sponsor that the specification should be set Q = [redacted] at [redacted] min. The chemist noted that the sponsor proposed dissolution method is acceptable (as opposed to using the same dissolution method as for the innovator drug, Claritin® Reditab) because of the formulation differences between the generic and the innovator products.

APPEARS THIS WAY
ON ORIGINAL

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-375	Brand Name	Alavert; Dimetapp Allergy
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	Orally disintegrating tablets
		Dosing Regimen	1 tab QD or consult a MD.
Date of Submission	8/23/01	Route of Administration	Oral
Estimated Due Date of OCPB Review	4/23/02	Sponsor	Whitehall-Robins
PDUFA Due Date	6/23/02	Priority Classification	S
Division Due Date	5/23/02		

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	Claritin® Reditabs
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1	1	Claritin® Reditabs-arm included
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		3	3	

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/s/

Shinja Kim
5/3/02 08:33:57 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
5/3/02 12:28:24 PM
BIOPHARMACEUTICS
I concur