CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-822

Name: Loratadine Orally Disintegrating Tablets, 10 mg (OTC)

Sponsor: Wyeth Consumer Healthcare

Approval Date: February 10, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-822

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-822

APPROVAL LETTER

FEB 10 2003

ANDA 75-822

Wyeth Consumer Healthcare
Attention: David Smith
5 Giralda Farms
Madison, NJ 07940

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated March 9, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Loratadine Orally Disintegrating Tablets, 10 mg (OTC).

Reference is also made to your amendments dated December 12, 2000; January 21, January 22, October 17, December 10, December 13, and December 18, 2002; and January 10, 2003. We also refer to your correspondence dated June 8, and August 1, 2000; and September 5, 2002 addressing patent issues related to the reference listed drug product (RLD).

The listed drug product (RLD) referenced in your application, Claritin® Reditabs™ of Schering Corporation (Schering), is subject to periods of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the Orange Book", U.S. Patent No. 4,659,716 (the '716 patent) is scheduled to expire on October 21, 2004, and U.S. Patent No. 4,863,931 (the '931 patent) is scheduled to expire on May 15, 2009. Your application contains paragraph IV certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Loratadine Orally Disintegrating Tablets, 10 mg, will not infringe the claims of the '716 and '931 patents. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Wyeth Consumer Healthcare (Wyeth) for infringement of either the '716 or '931 patents that were the subject of the paragraph IV certifications. This action must be brought against Wyeth prior to the expiration of forty-five (45) days from the date the notice provided by Wyeth to the NDA/patent holder(s) under paragraph (2)(B)(i) was received by the

patent/NDA holder(s).

You have notified the agency that Wyeth complied with the requirements of Section 505(j)(2)(B) of the Act. As a result, in June, 2000, Schering initiated a patent infringement suit involving certain claims of Schering's '716 patent against you in the United States District Court for the District of New Jersey (Schering Corporation v. American Home Products Corp., Wyeth-Ayerst Laboratories and ESI-Lederle, Civil Action No. 00-2944(JAG)). In an order dated August 8, 2002, and entered August 12, 2002, the Chief Judge of the United States District Court for the District of New Jersey granted the defendant's motion for summary judgment, ruling that the contested claims of the '716 patent were invalid. These were the only claims in this case. On August 8, 2002, Schering Corporation appealed this decision to the United States Court of Appeals for the Federal Circuit where it is currently pending.

The Agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application, has expired as to the '716 patent. We also note that no action was brought against Wyeth by either the patent holder or the NDA holder with regard to the '931 patent.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for Over-the-Counter (OTC) use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Loratadine Orally Disintegrating Tablets, 10 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Claritin® Reditabs™, 10 mg, of Schering Corporation. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

With respect to 180-day generic drug exclusivity, we note that Wyeth was the first applicant to submit a substantially complete ANDA containing paragragh IV certification to the '716 and '931 patents. Therefore, with this approval Wyeth is eligible for 180-days of market exclusivity for this drug product with respect to the '716 and '931 patents, as provided for under Section 505 (j)(5)(B)(iv) of the Act. With respect to the '716 and '931 patents, such exclusivity will begin to run on the earlier of either (1) the date Wyeth begins commercial marketing of its Loratadine Orally Disintegrating Tablets, 10mg, or (2) with respect to each patent, the date of a decision of the appellate court affirming the decision

of the district court that the contested claims of the '716 and '931 patents are invalid, unenforceable, or not infringed.

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that you will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to your application stating the date you commence commercial marketing of this product.

If you have any questions concerning the effective date of approval of an ANDA and the elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998, Federal Register (Volume 63, No. 214, at p. 59710).

Under 21 CFR 314-70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Sincerely yours,

Gary Buehler 2/10/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

ANDA 75-822
Division File
Field Copy
HFD-610/RWest
HFD-330/
HFD-205/
HFD-600/C.Parise
HFD-600/H.Hare

Endorsements:
HFD-623/R.Trimmer/ 1-22-03
HFD-623/D.Gill/ DSGill 1-22-03
HFD-617/S.Kim/ S.K. 1/22/03
HFD-613/D.Catterson/ Deborah M. Catterson 1/22/03
HFD-613/J.Grace/ 1/22/2003

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F/T by:

APPROVAL

1/28/03

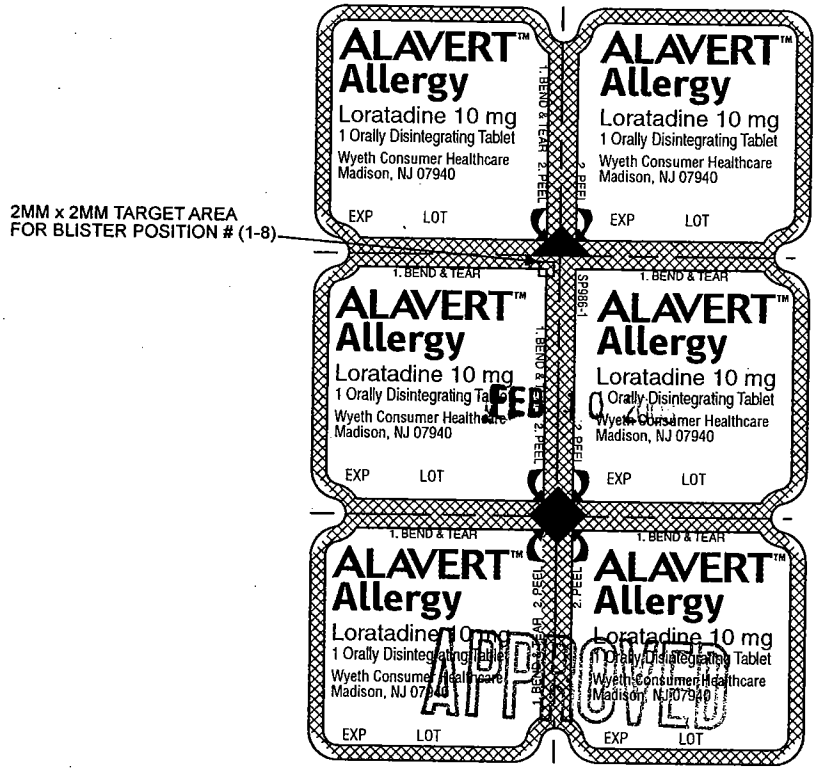
2/10/2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-822

APPROVED LABELING


2MM x 2MM TARGET AREA
FOR BLISTER POSITION # (1-8)
ALAVERT™
Allergy
Loratadine 10 mg
1 Orally Disintegrating Tablet
Wyeth Consumer Healthcare
Madison, NJ 07940
EXP
LOT
1. BEND & TEAR
2. PEEL
SP9861
FEB
APPROVED

Alavert Allergy provides **24 hours** of allergy symptom relief **without causing drowsiness when taken as directed** (See Drug Facts Panel). It contains **prescription strength** loratadine. **Just one tablet a day** relieves runny nose, sneezing and itchy, watery eyes. It is safe and effective for adults and children 6 years and over. The mint flavored tablet melts in your mouth. So convenient, it can be taken without water.

Visit our website at **www.alavert.com**

7248

LOT
EXP

UK24027-1

17045

ALAVERT™ allergy Non-Drowsy* Allergy Relief

ALAVERT™ allergy Non-Drowsy* Allergy Relief

NEW! One Tablet - 24 hrs.

ALAVERT™ allergy

(Loratadine Orally Disintegrating Tablet, 10mg, Antihistamine)

Non-Drowsy* Allergy Relief

24-Hour Relief of

- Sneezing
- Runny Nose
- Itchy, Watery Eyes
- Itching of Nose & Throat

MELTS IN YOUR MOUTH

12 Orally Disintegrating Tablets

*When taken as directed. See Drug Facts Panel.

Wyeth®
Distributed by:
Wyeth Consumer Healthcare
Madison, NJ 07940

*When taken as directed. See Drug Facts Panel.

ALAVERT™ allergy Non-Drowsy* Allergy Relief

EACH TABLET IS BLISTER SEALED.
DO NOT USE IF SEAL IS BROKEN.

Drug Facts

Active ingredient (in each tablet) — **Purpose**

Loratadine 10 mg ..... Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
- runny nose
- sneezing
- itchy, watery eyes
- itching of the nose or throat

Warnings

Do not use if you have ever had an allergic reaction to this product or any of its ingredients

Ask a doctor before use if you have liver or kidney disease.
Your doctor should determine if you need a different dose.

When using this product do not use more than directed. Taking more than recommended may cause drowsiness.

Stop use and ask a doctor if an allergic reaction to this product occurs. Seek medical help right away.

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ tablet melts in mouth. Can be taken with or without water.

Age	Dose
adults and children 6 years and over	1 tablet daily; do not use more than 1 tablet daily
children under 6	ask a doctor
consumers who have liver or kidney disease	ask a doctor

Other information
■ Phenylketonurics: Contains Phenylalanine 8.4 mg per tablet ■ store at 20-25°C (68-77°F) ■ keep in a dry place

Inactive ingredients artificial & natural flavor, aspartame, citric acid, colloidal silicon dioxide, corn syrup solids, crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, modified food starch, sodium bicarbonate

Questions or comments? call weekdays from 9 AM to 5 PM EST at **1-800-ALAVERT (1-800-252-8378)**

42-01707-900

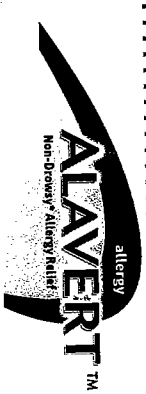
3 0573-2620-12 1

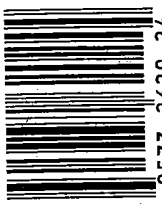
Alavert Allergy provides **24 hours** of allergy symptom relief **without causing drowsiness when taken as directed** (See Drug Facts Panel). It contains **prescription strength** loratadine.

Just one tablet a day relieves runny nose, sneezing and itchy, watery eyes. It is safe and effective for adults and children 6 years and over.

The mint flavored tablet melts in your mouth. So convenient, it can be taken without water.

Visit our website at **www.alavert.com**





Drug Facts

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- sneezing
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- itching of the nose or throat

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Questions or comments? call weekdays from 9 AM to 5 PM EST at **1-800-ALAVERT (1-800-252-8378)**

LOT
EXP

Wyeth
Distributed by:
Wyeth Consumer Healthcare, Madison, NJ 07940

42-01715-900

UK24026-1

7249

17044

allergy

ALAVERT™

Non-Drowsy* Allergy Relief

Alavert Allergy provides **24 hours** of allergy symptom relief **without causing drowsiness when taken as directed** (See Drug Facts Panel). It contains **prescription strength** loratadine.

Just one tablet a day relieves runny nose, sneezing and itchy, watery eyes. It is safe and effective for adults and children 6 years and over.

The mint flavored tablet melts in your mouth. So convenient, it can be taken without water.

Visit our website at **www.alavert.com**

Drug Facts

Active ingredient (in each tablet)	Purpose
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- sneezing
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- itching of the nose or throat

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Do not use if you have ever had an allergic reaction to this product or any of its ingredients

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Your doctor should determine if you need a different dose.

When using this product do not use more than directed. Taking more than recommended may cause drowsiness.

Stop use and ask a doctor if an allergic reaction to this product occurs. Seek medical help right away.

If pregnant or breast-feeding, ask a health professional before use.
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Questions or comments? call weekdays from 9 AM to 5 PM EST at **1-800-ALAVERT (1-800-252-8378)**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-822

LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-822

Date of Submission: March 9, 2000 (Original Submission)

Applicant's Name: ESI Lederle

Established Name: Loratadine Orally Disintegrating Tablets, 10 mg

---

Labeling Deficiencies:

1. **CONTAINER** (Unit-Dose Blister Packages of 6 tablets):
2. **CARTON** (5 x 6 Blister Packages)
   Please refer to the attached mocked-up copy of your draft blister card labels and carton labeling for the requested labeling revisions.

3. **INSERT:**

   a. GENERAL COMMENT:

      Due to changes in the approved labeling of the reference listed drug (Claritin® (loratadine) Tablets, Syrup, and Rapidly-Disintegrating Tablets; revised September 2000; approved December 4, 2000] revise your package insert labeling accordingly. (Please refer to the enclosed December 4, 2000 approval letter and labeling.)

   In addition, please make the following changes to your insert labeling:

   b. DESCRIPTION:

      i. In accordance with your Component and Composition statements, revise the following inactive ingredient to read: "[redacted] citric acid".

      ii. Since the inactive ingredients are common nouns, delete the use of capital letters.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachments: Copy of firm's mocked-up container label and carton labeling.
Reference Listed Drug's Approved Labeling.

APPEARS THIS WAY
ON ORIGINAL

_3_ pages of draft labeling have been removed from this portion of the document.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-641/S-007

Schering Corporation
US Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Joseph F. Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs

Dear Dr. Lamendola:

Please refer to your supplemental new drug application dated November 24, 1999, received November 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Claritin (loratadine) Syrup.

We acknowledge receipt of your submissions dated February 14, March 15, and October 3, 2000. Your submission of October 3, 2000, constituted a complete response to our September 26, 2000, action letter.

This supplemental new drug application provides for the use of Claritin (loratadine) Syrup for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria in patients 2 years of age and older.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

1. In the first paragraph of the Pediatric section, the number 13 is to be added as the number of pediatric volunteers for subjects ages 8 to 12 years old, and the number 13 is to be removed as the number of pediatric volunteers for subjects ages 2 to 5 years old.

2. The expression of the age groups is to be consistent throughout the labeling (e.g., "2 to 5 years old" instead of "2-5 years old").

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted October 3, 2000, immediate container and carton labels submitted October 3, 2000). These revisions are terms of the approval of this application.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled

Providing Regulatory Submissions in Electronic Format - NDAs (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-641/S-007." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have fulfilled the pediatric study requirement at this time.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Vicky Borders, Pharm.D., Regulatory Project Manager, at (301) 827-5580.

Sincerely,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

FPO

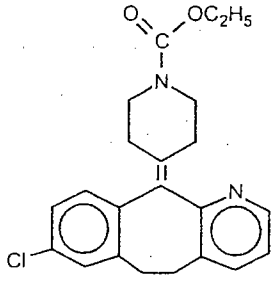
S 2 5 6 3 4

F-19649873 1711

PRODUCT INFORMATION

CLARITIN®
brand of loratadine
TABLETS, SYRUP, and RAPIDLY-DISINTEGRATING TABLETS

DESCRIPTION Loratadine is a white to off-white powder not soluble in water, but very soluble in acetone, alcohol, and chloroform. It has a molecular weight of 382.89, and empirical formula of $C_{22}H_{23}ClN_2O_2$; its chemical name is ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate and has the following structural formula:



CLARITIN Tablets contain 10 mg micronized loratadine, an antihistamine, to be administered orally. It also contains the following inactive ingredients: corn starch, lactose, and magnesium stearate.

CLARITIN Syrup contains 1 mg/mL micronized loratadine, an antihistamine, to be administered orally. It also contains the following inactive ingredients: citric acid, edetate disodium, artificial flavor, glycerin, propylene glycol, sodium benzoate, sugar, and water. The pH is between 2.5 and 3.1.

CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) contain 10 mg micronized loratadine, an antihistamine, to be administered orally. It disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be subsequently swallowed with or without water. CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) also contain the following inactive ingredients: citric acid, gelatin, mannitol, and mint flavor.

CLINICAL PHARMACOLOGY Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic activity.

Human histamine skin wheal studies following single and repeated 10 mg oral doses of CLARITIN have shown that the drug exhibits an antihistaminic effect beginning within 1 to 3 hours, reaching a maximum at 8 to 12 hours, and lasting in excess of 24 hours. There was no evidence of tolerance to this effect after 28 days of dosing with CLARITIN.

Whole body autoradiographic studies in rats and monkeys, radiolabeled tissue distribution studies in mice and rats, and *in vivo* radioligand studies in mice have shown that neither loratadine nor its metabolites readily cross the blood-brain barrier. Radioligand binding studies with guinea pig pulmonary and brain H_1-receptors indicate that there was preferential binding to peripheral versus central nervous system H_1-receptors.

Repeated application of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) to the hamster cheek pouch did not cause local irritation.

Pharmacokinetics: ***Absorption:*** Loratadine was rapidly absorbed following oral administration of 10 mg tablets, once daily for 10 days to healthy adult volunteers with times to maximum concentration (T_{max}) of 1.3 hours for loratadine and 2.5 hours for its major active metabolite, descarboethoxyloratadine. Based on a cross-study comparison of single doses of loratadine syrup and tablets given to healthy adult volunteers, the plasma concentration profile of descarboethoxyloratadine for the two formulations is comparable. The pharmacokinetics of loratadine and descarboethoxyloratadine are independent of dose over the dose range of 10 mg to 40 mg and are not altered by the duration of treatment. In a single-dose study, food increased the systemic bioavailability (AUC) of loratadine and descarboethoxyloratadine by approximately 40% and 15%, respectively. The time to peak plasma concentration (T_{max}) of loratadine and descarboethoxyloratadine was delayed by 1 hour. Peak plasma concentrations (C_{max}) were not affected by food.

Pharmacokinetic studies showed that CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) provide plasma concentrations of loratadine and descarboethoxyloratadine similar to those achieved with CLARITIN Tablets. Following administration of 10 mg loratadine once daily for 10 days with each dosage form in a randomized crossover comparison in 24 normal adult subjects, similar mean exposures (AUC) and peak plasma concentrations (C_{max}) of loratadine were observed. CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) mean AUC and C_{max} were 11% and 6% greater than that of the CLARITIN Tablet values, respectively. Descarboethoxyloratadine bioequivalence was demonstrated between the two formulations. After 10 days of dosing, mean peak plasma concentrations were attained at 1.3 hours and 2.3 hours (T_{max}) for parent and metabolite, respectively.

In a single-dose study with CLARITIN REDITABS (loratadine rapidly-disintegrating tablets), food increased the AUC of loratadine by approximately 48% and did not appreciably affect the AUC of descarboethoxyloratadine. The times to peak plasma concentration (T_{max}) of loratadine and descarboethoxyloratadine were delayed by approximately 2.4 and 3.7 hours, respectively, when food was consumed prior to CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) administration. Parent and metabolite peak concentrations (C_{max}) were not affected by food.

In a single-dose study with CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in 24 subjects, the AUC of loratadine was increased by 26% when administered without water compared to administration with water, while C_{max} was not substantially affected. The bioavailability of descarboethoxyloratadine was not different when administered without water.

Metabolism: *In vitro* studies with human liver microsomes indicate that loratadine is metabolized to descarboethoxyloratadine predominantly by cytochrome P450 3A4 (CYP3A4) and, to a lesser extent, by cytochrome P450 2D6 (CYP2D6). In the presence of a CYP3A4 inhibitor ketoconazole, loratadine is metabolized to descarboethoxyloratadine predominantly by CYP2D6. Concurrent administration of loratadine with either ketoconazole, erythromycin (both CYP3A4 inhibitors), or cimetidine (CYP2D6 and CYP3A4 inhibitor) to healthy volunteers was associated with substantially increased plasma concentrations of loratadine (see **Drug Interactions** section).

Elimination: Approximately 80% of the total loratadine dose administered can be found equally distributed between urine and feces in the form of metabolic products within 10 days. In nearly all patients, exposure (AUC) to the metabolite is greater than to the parent loratadine. The mean elimination half-lives in normal adult subjects (n = 54) were 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for descarboethoxyloratadine. Loratadine and descarboethoxyloratadine reached steady-state in most patients by approximately the fifth dosing day. There was considerable variability in the pharmacokinetic data in all studies of CLARITIN Tablets and Syrup, probably due to the extensive first-pass metabolism.

Special Populations: ***Pediatric:*** The pharmacokinetic profile of loratadine in children in the 6- to 12-year age group is similar to that of adults. In a single-dose pharmacokinetic study of 13 pediatric volunteers (aged 8 to 12 years) given 5 mL of CLARITIN Syrup containing 10 mg loratadine, the ranges of individual subject values of pharmacokinetic parameters (AUC and C_{max}) were comparable to those following administration of a 10 mg tablet or syrup to adult volunteers.

The pharmacokinetic profile of loratadine in children in the 2 to 5-year age group (n = 18) is similar to that of adults. In a single-dose pharmacokinetic study of pediatric subjects (age 2 to 5 years) given 5 mL of CLARITIN Syrup containing

5 mg loratadine, the range of individual subject values of pharmacokinetic parameters (AUC and C_{max}) were comparable to those following administration of a 10 mg tablet or syrup to adult volunteers or children eight years of age and older.

Geriatric: In a study involving 12 healthy geriatric subjects (66 to 78 years old), the AUC and peak plasma levels (C_{max}) of both loratadine and descarboethoxyloratadine were approximately 50% greater than those observed in studies younger subjects. The mean elimination half-lives for the geriatric subjects were 18.2 hours (range = 6.7 to 37 hours) for loratadine and 17.5 hours (range = 11 to 38 hours) for descarboethoxyloratadine.

Renal Impairment: In a study involving 12 subjects with chronic renal impairment (creatinine clearance ≤ 30 mL/min) both AUC and C_{max} increased by approximately 73% for loratadine and by 120% for descarboethoxyloratadine, as compared to six subjects with normal renal function (creatinine clearance ≥ 80 mL/min). The mean elimination half-lives of loratadine (7.6 hours) and descarboethoxyloratadine (23.9 hours) were not substantially different from that observed in normal subjects. Hemodialysis does not have an effect on the pharmacokinetics of loratadine or descarboethoxyloratadine in subjects with chronic renal impairment.

Hepatic Impairment: In seven patients with chronic alcoholic liver disease, the AUC and C_{max} of loratadine were double while the pharmacokinetic profile of descarboethoxyloratadine was not substantially different from that observed in other trials enrolling normal subjects. The elimination half-lives for loratadine and descarboethoxyloratadine were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

Clinical Trials: Clinical trials of CLARITIN Tablets involved over 10,700 patients, 12 years of age and older, who received either CLARITIN Tablets or another antihistamine and/or placebo in double-blind randomized controlled studies. In placebo-controlled trials, 10 mg once daily of CLARITIN Tablets was superior to placebo and similar to clemastine (1 mg BID) or terfenadine (60 mg BID) in effects on nasal and non-nasal symptoms of allergic rhinitis. In these studies, somnolence occurred less frequently with CLARITIN Tablets than with clemastine and at about the same frequency as terfenadine or placebo. In studies with CLARITIN Tablets at doses two to four times higher than the recommended dose of 10 mg, a dose-related increase in the incidence of somnolence was observed. Therefore, some patients, particularly those with hepatic or renal impairment and the elderly, or those on medications that impair clearance of loratadine and its metabolites, may experience somnolence. In addition, three placebo-controlled, double-blind, 2-week trials in 188 pediatric patients with seasonal allergic rhinitis aged 6 to 12 years, were conducted at doses of CLARITIN Syrup up to 10 mg once daily. In a double-blind, placebo-controlled study, the safety of 5 mg loratadine, administered in 5 mL of CLARITIN Syrup, was evaluated in 60 pediatric patients between 2 and 5 years of age. No unexpected adverse events were observed.

Clinical trials of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) involved over 1300 patients who received either CLARITIN REDITABS (loratadine rapidly-disintegrating tablets), CLARITIN Tablets, or placebo. In placebo-controlled trials, one CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) once daily was superior to placebo and similar to CLARITIN Tablets in effects on nasal and non-nasal symptoms of seasonal allergic rhinitis.

Among those patients involved in double-blind, randomized, controlled studies of CLARITIN Tablets, approximately 1000 patients (age 12 and older), were enrolled in studies of chronic idiopathic urticaria. In placebo-controlled clinical trials, CLARITIN Tablets 10 mg once daily were superior to placebo in the management of chronic idiopathic urticaria, as demonstrated by reduction of associated itching, erythema, and hives. In these studies, the incidence of somnolence seen with CLARITIN Tablets was similar to that seen with placebo.

In a study in which CLARITIN Tablets were administered to adults at four times the clinical dose for 90 days, no clinically significant increase in the QT_c was seen on ECGs.

In a single-rising dose study in which doses up to 160 mg (16 times the clinical dose) were studied, loratadine did not cause any clinically significant changes on the QT_c interval in the ECGs.

INDICATIONS AND USAGE CLARITIN is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria in patients 2 years of age or older.

CONTRAINDICATIONS CLARITIN is contraindicated in patients who are hypersensitive to this medication or to any of its ingredients.

PRECAUTIONS **General:** Patients with liver impairment or renal insufficiency (GFR < 30 mL/min) should be given a lower initial dose (10 mg every other day). (See **CLINICAL PHARMACOLOGY: Special Populations.**)

Drug Interactions: Loratadine (10 mg once daily) has been coadministered with therapeutic doses of erythromycin, cimetidine, and ketoconazole in controlled clinical pharmacology studies in adult volunteers. Although increased plasma concentrations (AUC 0-24 hrs) of loratadine and/or descarboethoxyloratadine were observed following coadministration of loratadine with each of these drugs in normal volunteers (n = 24 in each study), there were no clinically relevant changes in the safety profile of loratadine, as assessed by electrocardiographic parameters, clinical laboratory tests, vital signs, and adverse events. There were no significant effects on QT_c intervals, and no reports of sedation or syncope. No effects on plasma concentrations of cimetidine or ketoconazole were observed. Plasma concentrations (AUC 0-24 hrs) of erythromycin decreased 15% with coadministration of loratadine relative to that observed with erythromycin alone. The clinical relevance of this difference is unknown. These above findings are summarized in the following table:

Effects on Plasma Concentrations (AUC 0-24 hrs) of Loratadine and Descarboethoxyloratadine After 10 Days of Coadministration (Loratadine 10 mg) in Normal Volunteers

	Loratadine	Descarboethoxyloratadine
Erythromycin (500 mg Q8h)	+ 40%	+46%
Cimetidine (300 mg QID)	+103%	+ 6%
Ketoconazole (200 mg Q12h)	+307%	+73%

There does not appear to be an increase in adverse events in subjects who received oral contraceptives and loratadine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: In an 18-month carcinogenicity study in mice and a 2-year study in rats, loratadine was administered in the diet at doses up to 40 mg/kg (mice) and 25 mg/kg (rats). In the carcinogenicity studies, pharmacokinetic assessments were carried out to determine animal exposure to the drug. AUC data demonstrated that the exposure of mice given 40 mg/kg of loratadine was 3.6 (loratadine) and 18 (descarboethoxyloratadine) times the exposure in adults and 5 (loratadine) and 20 (descarboethoxyloratadine) times the exposure in children given the maximum recommended daily oral dose. Exposure of rats given 25 mg/kg of loratadine was 28 (loratadine) and 67 (descarboethoxyloratadine) times the exposure in adults and 40 (loratadine) and 80 (descarboethoxyloratadine) times the exposure in children given the maximum recommended daily oral dose. Male mice given mg/kg had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg, and males and females given 25 mg/kg. Exposure of rats given 10 mg/kg of loratadine was 10 (loratadine) and 15 (descarboethoxyloratadine) times the exposure in adults and 15 (loratadine) and 20 (descarboethoxyloratadine) times the exposure in children given the maximum recommended daily oral dose. The clinical significance of these findings during long-term use of CLARITIN is not known.

In mutagenicity studies, there was no evidence of mutagenic potential in reverse (Ames) or forward point mutation (CHO-HGPRT) assays, or in the assay for DNA damage (rat primary hepatocyte unscheduled DNA assay) or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenesis assay and the mouse bone marrow erythrocyte micronucleus assay). In the mouse lymphoma assay, a positive finding occurred in the nonactivated but not the activated phase of the study.

Decreased fertility in male rats, shown by lower female conception rates, occurred at an oral dose of 64 mg/kg (approximately 50 times the maximum recommended human daily oral dose on a mg/m^2 basis) and was reversible with cessation of dosing. Loratadine had no effect on male or female fertility or reproduction in the rat at an oral dose of approximately 24 mg/kg (approximately 20 times the maximum recommended human daily oral dose on a mg/m^2 basis).

Pregnancy Category B: There was no evidence of animal teratogenicity in studies performed in rats and rabbits at oral doses up to 96 mg/kg (approximately 75 times and 150 times, respectively, the maximum recommended human daily oral dose on a mg/m^2 basis). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CLARITIN should be used during pregnancy only if clearly needed.

Nursing Mothers: Loratadine and its metabolite, descarboethoxyloratadine, pass easily into breast milk and achieve concentrations that are equivalent to plasma levels with an AUC_{milk}/AUC_{plasma} ratio of 1.17 and 0.85 for loratadine and descarboethoxyloratadine, respectively. Following a single oral dose of 40 mg, a small amount of loratadine and descarboethoxyloratadine was excreted into the breast milk (approximately 0.03% of 40 mg over 48 hours). A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when CLARITIN is administered to a nursing woman.

Pediatric Use: The safety of CLARITIN Syrup at a daily dose of 10 mg has been demonstrated in 188 pediatric patients 6 to 12 years of age in placebo-controlled 2-week trials. The safety and tolerability of CLARITIN Syrup at a daily dose of 5 mg has been demonstrated in 60 pediatric patients 2 to 5 years of age in a double-blind, placebo-controlled, 2-week study. The effectiveness of CLARITIN for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in children aged 2 to 12 years is based on an extrapolation of the demonstrated efficacy of CLARITIN in adults in these conditions and the likelihood that the disease course, pathophysiology, and the drug's effect are substantially similar to that of the adults. The recommended dose for the pediatric population is based on cross-study comparison of the pharmacokinetics of CLARITIN in adults and pediatric subjects and on the safety profile of loratadine in both adults and pediatric patients at doses equal to or higher than the recommended doses. The safety and effectiveness of CLARITIN in children under 2 years of age have not been established.

ADVERSE REACTIONS **CLARITIN Tablets:** Approximately 90,000 patients, aged 12 and older, received CLARITIN Tablets 10 mg once daily in controlled and uncontrolled studies. Placebo-controlled clinical trials at the recommended dose of 10 mg once a day varied from 2 weeks' to 6 months' duration. The rate of premature withdrawal from these trials was approximately 2% in both the treated and placebo groups.

REPORTED ADVERSE EVENTS WITH AN INCIDENCE OF MORE THAN 2% IN PLACEBO-CONTROLLED ALLERGIC RHINITIS CLINICAL TRIALS IN PATIENTS 12 YEARS OF AGE AND OLDER

	PERCENT OF PATIENTS REPORTING			
	LORATADINE 10 mg QD n = 1926	**PLACEBO** n = 2545	**CLEMASTINE** 1 mg BID n = 536	**TERFENADINE** 60 mg BID n = 684
Headache	12	11	8	8
Somnolence	8	6	22	9
Fatigue	4	3	10	2
Dry Mouth	3	2	4	3

Adverse events reported in placebo-controlled chronic idiopathic urticaria trials were similar to those reported in allergic rhinitis studies.

Adverse event rates did not appear to differ significantly based on age, sex, or race, although the number of nonwhite subjects was relatively small.

CLARITIN REDITABS (loratadine rapidly-disintegrating tablets): Approximately 500 patients received CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in controlled clinical trials of 2 weeks' duration. In these studies, adverse events were similar in type and frequency to those seen with CLARITIN Tablets and placebo.

Administration of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) did not result in an increased reporting frequency of mouth or tongue irritation.

CLARITIN Syrup: Approximately 300 pediatric patients 6 to 12 years of age received 10 mg loratadine once daily in controlled clinical trials for a period of 8 to 15 days. Among these, 188 children were treated with 10 mg loratadine syrup once daily in placebo-controlled trials. Adverse events in these pediatric patients were observed to occur with type and frequency similar to those seen in the adult population. The rate of premature discontinuance due to adverse events among pediatric patients receiving loratadine 10 mg daily was less than 1%.

ADVERSE EVENTS OCCURRING WITH A FREQUENCY OF ≥ 2% IN LORATADINE SYRUP-TREATED PATIENTS (6 TO 12 YEARS OLD) IN PLACEBO-CONTROLLED TRIALS, AND MORE FREQUENTLY THAN IN THE PLACEBO GROUP

	PERCENT OF PATIENTS REPORTING		
	LORATADINE 10 mg QD	**PLACEBO**	**CHLORPHENIRAMINE** 2-4 mg BID/TID

	10 mg QD n = 188	n = 262	2-4 mg BID/TID n = 170
Nervousness	4	2	2
Wheezing	4	2	5
Fatigue	3	2	5
Hyperkinesia	3	1	1
Abdominal Pain	2	0	0
Conjunctivitis	2	<1	1
Dysphonia	2	<1	0
Malaise	2	0	1
Upper Respiratory Tract Infection	2	<1	0

Sixty pediatric patients 2 to 5 years of age received 5 mg loratadine once daily in a double-blind, placebo-controlled clinical trial for a period of 14 days. No unexpected adverse events were seen given the known safety profile of loratadine and likely adverse reactions for this patient population. The following adverse events occurred with a frequency of 2 to 3 percent in the loratadine syrup-treated patients (2 to 5 years old) during the placebo-controlled trial, and more frequently than in the placebo group: diarrhea, epistaxis, pharyngitis, influenza-like symptoms, fatigue, stomatitis, tooth disorder, earache, viral infection, and rash.

In addition to those adverse events reported above (≥ 2%), the following adverse events have been reported in at least one patient in CLARITIN clinical trials in adult and pediatric patients:

Autonomic Nervous System: altered lacrimation, altered salivation, flushing, hypoesthesia, impotence, increased sweating, thirst.

Body as a Whole: angioneurotic edema, asthenia, back pain, blurred vision, chest pain, earache, eye pain, fever, leg cramps, malaise, rigors, tinnitus, weight gain.

Cardiovascular System: hypertension, hypotension, palpitations, supraventricular tachyarrhythmias, syncope, tachycardia.

Central and Peripheral Nervous System: blepharospasm, dizziness, dysphonia, hypertonia, migraine, paresthesia, tremor, vertigo.

Gastrointestinal System: altered taste, anorexia, constipation, diarrhea, dyspepsia, flatulence, gastritis, hiccup, increased appetite, loose stools, nausea, vomiting.

Musculoskeletal System: arthralgia, myalgia.

Psychiatric: agitation, amnesia, anxiety, confusion, decreased libido, depression, impaired concentration, insomnia, irritability, paroniria.

Reproductive System: breast pain, dysmenorrhea, menorrhagia, vaginitis.

Respiratory System: bronchitis, bronchospasm, coughing, dyspnea, hemoptysis, laryngitis, nasal dryness, sinusitis, sneezing.

Skin and Appendages: dermatitis, dry hair, dry skin, photosensitivity reaction, pruritus, purpura, urticaria.

Urinary System: altered micturition, urinary discoloration, urinary incontinence, urinary retention.

In addition, the following spontaneous adverse events have been reported rarely during the marketing of loratadine: abnormal hepatic function, including jaundice, hepatitis, and hepatic necrosis; alopecia; anaphylaxis; breast enlargement; erythema multiforme; peripheral edema; thrombocytopenia; and seizures.

DRUG ABUSE AND DEPENDENCE There is no information to indicate that abuse or dependency occurs with CLARITIN.

OVERDOSAGE In adults, somnolence, tachycardia, and headache have been reported with overdoses greater than 10 mg with the Tablet formulation (40 mg-180 mg). Extrapyramidal signs and palpitations have been reported in children with overdoses of greater than 10 mg of CLARITIN Syrup. In the event of overdosage, general symptomatic and supportive measures should be instituted promptly and maintained for as long as necessary.

Treatment of overdosage would reasonably consist of emesis (ipecac syrup), except in patients with impaired consciousness, followed by the administration of activated charcoal to absorb any remaining drug. If vomiting is unsuccessful, or contraindicated, gastric lavage should be performed with normal saline. Saline cathartics may also be of value for rapid dilution of bowel contents. Loratadine is not eliminated by hemodialysis. It is not known if loratadine is eliminated by peritoneal dialysis.

No deaths occurred at oral doses up to 5000 mg/kg in mice (approximately 1200 and 1400 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m^2 basis). No deaths occurred at oral doses up to 5000 mg/kg in matured rats (approximately 2400 and 2900 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m^2 basis). However, lethality occurred in juvenile rats at an oral dose of 125 mg/kg (approximately 100 and 70 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m^2 basis). No deaths occurred at oral doses up to 1280 mg/kg in monkeys (approximately 2100 and 1500 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION Adults and children 6 years of age and over: The recommended dose of CLARITIN is one 10 mg tablet or reditab, or 2 teaspoonfuls (10 mg) of syrup once daily.

Children 2 to 5 years of age: The recommended dose of CLARITIN Syrup is 5 mg (1 teaspoonful) once daily.

In adults and children 6 years of age and over with liver failure or renal insufficiency (GFR < 30 mL/min), the starting dose should be 10 mg (one tablet or two teaspoonfuls) every other day. In children 2 to 5 years of age with liver failure or renal insufficiency, the starting dose should be 5 mg (one teaspoonful) every other day.

Administration of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets): Place CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) on the tongue. Tablet disintegration occurs rapidly. Administer with or without water.

HOW SUPPLIED **CLARITIN Tablets:** 10 mg, white to off-white compressed tablets; impressed with the product identification number "458" on one side and "CLARITIN 10" on the other; high-density polyethylene plastic bottles of 100 (NDC 0085-0458-03) and 500 (NDC 0085-0458-06). Also available, CLARITIN Unit-of-Use packages of 30 tablets (10 tablets per blister card) (NDC 0085-0458-05); and 10 x 10 tablet Unit Dose-Hospital Pack (NDC 0085-0458-04).

Protect Unit-of-Use packaging and Unit Dose-Hospital Pack from excessive moisture.

Store between 2° and 30°C (36° and 86°F).

CLARITIN Syrup: Clear, colorless to light-yellow liquid, containing 1 mg loratadine per mL; amber glass bottles of 16 fluid ounces (NDC 0085-1223-01).

Store between 2° and 25°C (36° and 77°F).

CLARITIN REDITABS (loratadine rapidly-disintegrating tablets): CLARITIN REDITABS (loratadine rapidly-disintegrating tablets), 10 mg, white to off-white blister-formed tablet; impressed with the letter "C" on one side; Unit-of-Use polyvinyl chloride blister packages of 30 tablets (three laminated foil pouches, each containing one blister card of 10 tablets) supplied with Patient's Instructions for Use (NDC 0085-1128-02).

Keep CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in a dry place.

Store between 2° and 25°C (36° and 77°F). Use within 6 months of opening laminated foil pouch, and immediately upon opening individual tablet blister.

Schering Corporation
Kenilworth, NJ 07033 USA

Rev. 9/00

B-19649873
19628477T

CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) are manufactured for Schering Corporation by Scherer DDS, England.

U.S. Patent Nos. 4,282,233 and 4,371,516.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)	X		

Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for CLARITIN® by Schering; NDA 20-641/SE5-007; approved December 4, 2000. The CLARITIN insert labeling is a combined one for CLARITIN Tablets, Syrup, and Rapidly Disintegrating Tablets (REDITABS). All references to the Tablets and Syrup should be carved out of the generic firm's labeling. But certain references pertaining to the Syrup provide pertinent information relating to the pharmacokinetics, pediatric use, adverse reactions, and overdosage of loratadine. The "First Generic" for loratadine tablets included these Syrup references. Therefore, I will have the firm include these particular loratadine syrup references in their labeling.

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 20-704 (Claritin Reditabs)

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4282233	June 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	IV	None
4282233*PED	December 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	IV	None
4659716	April 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4659716*PED	October 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4863931	September 15, 2008	N/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
4863931*PED	March 15, 2009	N/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 20-704

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. MANUFACTURING FACILITY

[ ]

4. SCORING

NDA - unscored

ANDA - unscored

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

NDA - Keep CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in a dry place. Store between 2° and 25°C (36°-77°F).

ANDA - Store between —and 25°C (—-77°F). Keep loratadine orally-disintegrating tablets in a dry place.

6. DISPENSING STATEMENT COMPARISON

NDA - Use within 6 months of opening laminated foil pouch, and immediately upon opening individual tablet blister.

ANDA - Use immediately upon opening individual tablet blister.

7. INACTIVE INGREDIENTS

We have asked the firm to revise one of the inactive ingredient statements for accuracy. (Volume A1.16, Section VII, Page 6470).

8. The "description and solubility" of the drug products found in the DESCRIPTION section is identical with those described in the innovator's insert labeling.

9. PACKAGING CONFIGURATIONS

NDA – Cartons of 3 x 10 tablet Unit-of-use blister cards, with each blister card enclosed in a laminated foil pouch.

ANDA - Cartons of 5 x 6 tablet unit-dose blister packages, with no pouch enclosure.

10. CONTAINER/CLOSURE SYSTEM

Blister foil: —

Child Resistant Peelable Top Lidding: —

— (See pages 6749 and 6750, Vol. A.1.16, Section XIII).

11. The tablet embossings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). The tablets are described as white to off-white, round, unscored and ← "511" on one side, and "L71" on the other.

Date of Review: 7/19/01

Date of Submission: March 9, 2000 (Original Submission)

Primary Reviewer: Lillie Golson for Debra Catterson

Date:

L N Golson

7/25/01

Team Leader: John Grace

Date:

Debra M. Catterson for/

7/25/01

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cc: ANDA: 75-822
DUP/DIVISION FILE
HFD-613/LGolson for Debra Catterson/JGrace (no cc)
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Review

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-822

Dates of Submission: January 10, 2003; December 10, 2002; and January 22, 2002 (Amendments)

Applicant's Name: ESI Lederle – Wyeth Consumer Healthcare

Established Name: Loratadine Orally Disintegrating Tablets, 10 mg (OTC)

Proprietary Name: Alavert™

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes.

CONTAINER Labels – Unit Dose Blister Card of 6 Tablets:
Satisfactory as of the January 10, 2003 submission. [Vol. 4.1]

CARTON Labels –Boxes of 12, 24, and 48:
Satisfactory as of the December 10, 2002 submission. [Vol. 4.1]

Revisions needed post-approval: **Yes**. The firm was asked to remove the word "Antihistamine" from the parentheses on the carton label. [See the Dec. 19, 2002 approval letter for NDA 21-375.]

Patent Data – NDA 20-704

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4282233	June 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4282233*PED	December 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4659716	April 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4659716*PED	October 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4863931	September 15, 2008	N/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
4863931*PED	March 15, 2009	N/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 20-704

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:

Was this approval based upon a petition? No.

What is the RLD on the 356(h) form: CLARITIN® RediTabs®

NDA Number: 20-704

NDA Drug Name: Loratadine Orally DisintegratingTablets 10 mg

NDA Firm: Schering Corporation

Date of Approval of NDA Insert and supplement: Nov. 27, 2002; NDA 20-704/SE6-008 (Rx to OTC Switch)

Has this been verified by the MIS system for the NDA? Yes.

Was this approval based upon an OGD labeling guidance? No.

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		x	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? **The proposed name "Alavert™" was found acceptable by DMETS (ODS) on July 3, 2002 (Consult #02-0132) under NDA 21-375 (Division of Pulmonary & Allergy Drug Products, HFD-570).**	X		
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x

Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	

USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for CLARITIN® Tablets by Schering; NDA 20-704/SE6-008 (Rx to OTC switch); approved November 27, 2002.
This review was also based on the Alavert labeling that was approved on December 19, 2002, under NDA 21-375 [a 505(b)(2) application submitted to the Division of Pulmonary & Allergy Drug Products].

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 20-704 (Claritin Reditabs)

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4282233	June 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4282233*PED	December 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4659716	April 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4659716*PED	October 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4863931	September 15, 2008	N/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
4863931*PED	March 15, 2009	N/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 20-704

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

NDA - Store between 2° and 25°C (36° and 77°F). Keep in a dry place. Use within 6 months of opening foil pouch. Use RediTabs® tablet immediately after opening individual blister.
ANDA - Store at 20°- 25°C (68° - 77°F). Keep in a dry place.

Note: The RLD packages its blister card in a laminated foil pouch. The pouch is then placed in the carton. However, Alavert's blister card of 6 tablets is NOT packaged in any pouch enclosure before being placed in their carton.

4. INACTIVE INGREDIENTS

The listing of inactive ingredients in the Drug Facts labeling appears to be consistent with the listing of inactive ingredients found in the statement of Components and Composition. [Note: "Modified food starch" and "corn syrup solids" are in the flavoring (per David Smith's 12-13-02 email).] (Volume A1.16, Section VII, Page 6470).

5. CONTAINER/CLOSURE SYSTEM

Blister foil: [redacted]

Child Resistant Peelable Top Lidding: [redacted]. (See pages 6749 and 6750, Vol. A.1.16, Section XIII).

6. NOMENCLATURE:

The firm proposed the proprietary name "Alavert™" for their product under NDA 21-375 (Division of Pulmonary & Allergy Drug Products). DMETS (ODS) concluded on July 3, 2002 that "Alavert" was an acceptable name for this drug product (Consult #02-0132).

7. INPUT FROM THE DIVISION OF OVER-THE-COUNTER DRUG PRODUCTS

Dr. Charles Ganley (supervisory medical officer) and Marina Chang (lead pharmacist) from the OTC Division reviewed the firm's labeling and font size legend, and did not have any objections. Attached is the email correspondence between Dr. Ganley and Ms. Chang and OGD.

Date of Review: 1/17/03 Dates of Submission: 1/10/03; 12/10/02; and 1/22/02

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 1/17/03

Team Leader: John Grace Date:

John J Grace 1/21/2003

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cc:

ANDA: 75-822
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:\firmsam\esileder\ltrs&rev\75822APL.doc
Review

Catterson, Debra M

From: Ganley, Charles J
Sent: Wednesday, January 08, 2003 6:49 PM
To: Catterson, Debra M; Chang, Marina Y
Cc: Buehler, Gary J; West, Robert L; Grace, John F; Hare, Donald B; Kim, Sarah; Parise, Cecelia M
Subject: RE: Wyeth Consumer Healthcare's Loratadine OTC Labeling (Alavert)

I have no problem if it is identical to what was approved as a B2.

-----Original Message-----
From: Catterson, Debra M
Sent: Wednesday, January 08, 2003 11:55 AM
To: Ganley, Charles J; Chang, Marina Y
Cc: Buehler, Gary J; West, Robert L; Grace, John F; Hare, Donald B; Kim, Sarah; Parise, Cecelia M
Subject: RE: Wyeth Consumer Healthcare's Loratadine OTC Labeling (Alavert)

Marina and Dr. Ganley,

I just wanted to let you know that a decision has been made here in OGD to go ahead and approve our ANDA 75-822 for Wyeth's Alavert product. This was communicated to me by our project manager, Sarah Kim.

As you mentioned in your earlier email, the ANDA labels do appear to be identical to the labels that you approved under NDA 21-375 on December 19, 2002. With my labeling approval summary, I will also include your post-approval request for Wyeth to move the word "Antihistamine" out of the parentheses of the established name.

If for some reason you disagree with my approving the Alavert labeling, please let me know. Otherwise, I will approve the labeling so we can move forward with approving the application.

Thank you again for all of your help!
Debbie

-----Original Message-----
From: Chang, Marina Y
Sent: Thursday, December 19, 2002 9:44 AM
To: Catterson, Debra M
Cc: Grace, John F; Buehler, Gary J; Ganley, Charles J
Subject: RE: Wyeth Consumer Healthcare's Loratadine OTC Labeling (Alavert)

Debbie:

In a quick look, it seems like it is identical to the NDA labels. The only thing is we have asked the sponsor to further revise the established name statement on the PDP, post-approval, to read "(Loratadine Orally Disintegrating Tablet, 10 mg) Antihistamine", at the time of next printing. (i.e., move the word "Antihistamine" out off the parenthesis)

Dr. Ganley is discussing with Gary Buehler on the issue of identical labels for both the ANDA and NDA products. We just have to wait for instruction.

Marina

-----Original Message-----
From: Catterson, Debra M
Sent: Wednesday, December 18, 2002 6:32 PM
To: Chang, Marina Y; Ganley, Charles J
Cc: Grace, John F; Buehler, Gary J
Subject: Wyeth Consumer Healthcare's Loratadine OTC Labeling (Alavert)

Hi Marina and Dr. Ganley,

Attached are scanned copies of the "Alavert" OTC loratadine labeling that was submitted to us by Wyeth Consumer Healthcare under ANDA 75-822.

I believe the attached ANDA labeling looks identical to the Alavert labeling submitted to you by Wyeth on October 14, 2002 under NDA 21-375. Since you tentatively approved the Alavert labeling under NDA 21-375 on December 12, 2002 , and the ANDA labeling appears to be identical, I believe we should go ahead and approve the attached labeling for ANDA 75-822.

Could you let me know if this is OK with you?

Many thanks!
Debbie

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-822

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Chemistry, Manufacturing and Control Review

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-822 **[Loratadine Orally Disintegating Tablets]**

3. NAME AND ADDRESS OF APPLICANT
ESI Lederle
Attention: Nicholas Tantillo (Senior Director, Regulatory Affairs)
Tel: (914) 732-4137 FAX: (914) 732-5689
401 N. Middletown Rd.
Pearl River, NY 10965

Mailing address: P.O. Box 41502, Philadelphia, PA 19101

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Claritin® RediTabs™
Innovator Company: Schering Corporation

ESI Lederle stated that there is no unexpired exclusivity for the listed drug. ESI Lederle also certified (p. 9) the following: US Patent #4,659,716 is invalid, and US Patent #4,863,931 will not be infringed (Paragraph IV). US Patent #4,371,516 expired February 1, 2000 (Paragraph II). US Patent #4,282,233 will expire June 19, 2002 (Paragraph III).

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME
Loratadine Orally Disintegrating Tablets, 10 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
ESI Lederle:

03/09/00	Submission of ANDA (received at OGD 03/10/00)
04/10/00	Submission of EVA (CMC and BA/BE)
05/16/00	Request information on First to File
06/08/00	Patent amendment (Re:Paragraph IV)
06/16/00	Correspondence from Schering's counsel
08/01/00	Correspondence from ESI (Re: Patent issue)

FDA:

04/20/00	Acknowledgment letter (acceptable for filing:03/10/00)

10. PHARMACOLOGICAL CATEGORY Tricyclic Antihistamine

11. Rx or OTC Rx

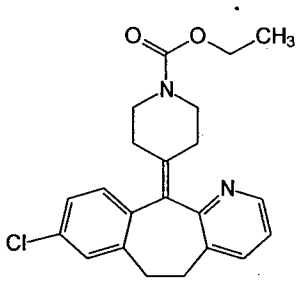
12. RELATED IND/NDA/DMF(s)
Innovator Product: Claritin® RediTabs™
NDA #20-704, approved
Innovator Company: Schering Corporation

DMF number	DMF type	DMF holder	Date LOA(s)
	II		02/23/00
	III		06/29/99
	III		02/23/00
	IV		02/25/00

13. DOSAGE FORM Tablet

14. STRENGTH 10 MG

15. CHEMICAL NAME AND STRUCTURE
Chemical name: 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-, ethyl ester
Formula: $C_{22}H_{23}ClN_2O_2$
Molecular weight: 382.89
CAS registry number(s): 79794-75-5
Chemical structure:



16. RECORDS AND REPORTS N/A

17. COMMENTS
Both Drug substance and drug product are not listed in the USP 24 as of this review. Type II DMF for drug substance is adequate. There are CMC deficiencies. Labeling and bioequivalence review are pending. Method validation request will not be issued in this review cycle pending results of bioequivalence review. Acceptable EER is pending.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Apprvable (MAJOR AMENDMENT)

19. REVIEWER: Shing H. Liu, Ph.D.
DATE COMPLETED: 07/26/00. Revised on 08/28/00 and 09/01/00

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CHEMISTRY REVIEW #1

3. Labeling portion of your application is under review. Any deficiencies will be conveyed to you in a separate letter.

4. Bioequivalence portion of your application is under review. The acceptance of your dissolution stability data is contingent upon acceptance of your dissolution method and specifications by the Division of Bioequivalence.

5. Please be advised that if the Division of Bioequivalence recommends different specifications for the dissolution from what you have used to conduct your stability studies on the executed batch lot #990043, it will be necessary for you to provide additional accelerated stability data using the revised dissolution specifications as soon as possible.

Sincerely yours,

9/20/00

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-822
Division File
Field Copy

Endorsements:

HFD-623/S.Liu, Ph.D./07-26-00/08-28-00/09-01-00 S.H.Liu 09/01/00
HFD-623/D. Gill, Ph.D./ DSGill 9-5-00
HFD-617/R. Yu, Pharm. D./ RYu 9-6-00
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F/T

NOT APPROVABLE: MAJOR AMENDMENT

APPEARS THIS WAY
ON ORIGINAL

Office of Generic Drugs

Chemistry, Manufacturing and Control Review

1. CHEMISTRY REVIEW #2

2. ANDA #75-822 **Loratadine Orally Disintegating Tablets**

3. NAME & ADDRESS of APPLICANT
   ESI Lederle
   Attention: Nicholas Tantillo
   Senior Director, Regulatory Affairs
   Tel: (914) 732-4137; FAX: (914) 732-5689
   401 N. Middletown Rd.
   Pearl River, NY 10965
   P.O. Box 41502 (mailing address)
   Philadelphia, PA 19101

4. LEGAL Basis for Submission:
   Innovator Product: Claritin® RediTabs™
   Innovator Company: *Schering Corporation*

5. SUPPLEMENT N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME
   Loratadine Orally Disintegrating Tablets, 10 mg

8. SUPPLEMENT PROVIDE FOR: n/a

9. AMENDMENTS & OTHER DATES:
   ESI Lederle:
   03/09/00 Submission of ANDA
   03/22/00 PPD Development Inc./MV report. NC
   04/10/00 Submission of EVA
   05/16/00 Request information on First to File
   06/08/00 Patent amendment (Re:Paragraph IV)
   06/16/00 Correspondence from Schering's counsel
   08/01/00 Correspondence from ESI (Re: Patent issue)
   12/12/00 Bio Amendment
   *12/26/00 Major Chemistry **Amendment**
   01/12/01 Electronic CMC Amendment
   FDA:
   09-20-00 NA letter with 11 CMC deficiencies
   10-04-00 Bio letter re dissolution data
   03-08-01 Bio review: not acceptable
   03-19-01 DBE issued **NA letter** re dissolution.

10. PHARMACOLOGICAL CATEGORY: Tricyclic Antihistamine

11. Rx or OTC: Rx

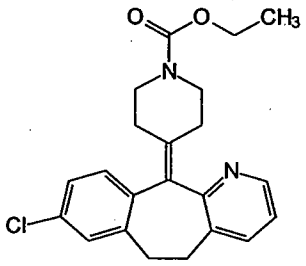
12. RELATED DMF's

DMF number		DMF type	DMF holder		Date LOA(s)
		II			02/23/00
		III			06/29/99
		III			02/23/00
		IV			02/25/00

13. DOSAGE FORM Tablet

14. STRENGTH 10 mg

15. CHEMICAL NAME & STRUCTURE
1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-, ethyl ester
Formula: $C_{22}H_{23}ClN_2O_2$, MW: 382.89



16. RECORDS & REPORTS n/a

17. COMMENTS
Both Drug substance and drug product are not listed in the USP 24 as of this review. Type II DMF for drug substance is adequate. There are CMC deficiencies. Labeling and bioequivalence review are pending. Method validation request will not be issued in this review cycle pending results of bioequivalence review. Acceptable EER is pending.

COMMENTS and Applicant's Response:
1. [redacted]

APPLICANT RESPONSE:
[redacted]

Our COMMENT: [redacted] A Revised Table was added to the review. See comments in section #23.

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CHEMISTRY REVIEW #2 (pp 3-5)

10. Stability data (per approved test protocol) of at least three production batches are needed for extension. Please revise your Post Approval Commitment accordingly.

APPLICANT RESPONSE:

The commitment has been revised by the applicant per our request. This is found in section XVI.

Our COMMENT: sat.

11. In the specifications for finished product, the description of the tablets is "White to off-white, flat-faced, 3/8 inch round, beveled tablets, ——— "511" on one side and "L71" on the other" (see p. 6798). However, in the specifications for stability, the description is "White to off-white, flat-faced, 3/8 inch round, beveled tablets, **debossed** upper with "511" and lower with L71". Please clarify.

APPLICANT RESPONSE:

The correct spec is as follows: "White to off-white, flat-faced, 3/8 inch round, beveled tablets, debossed upper with "511" and lower with L71". The applicant has made the corrections in sections XIV and XVI.

Our COMMENT: sat.

B. In addition to responding to the deficiencies presented above please note and acknowledge the following comments in your response:

1. The applicant acknowledged that referenced firms must be in compliance with CGMPS.

2. The applicant will have sample ready for the FDA District Laboratory.

3. The applicant acknowledged that labeling is under review.

4. The applicant understands that the Bio portion is under review.

5. The applicant understands that if the DBE recommends different specifications for the dissolution test it will be necessary to provide additional accelerated stability data using the revised dissolution spec as soon as possible.

18. CONCLUSIONS RECOMMENDATIONS
Not Approvable (MINOR)

19. REVIEWER: Robert W. Trimmer, Ph.D.
revised: 6-6-2001

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information from

CHEMISTRY REVIEW #2

2. Your amendment should also include your response to the Bioequivalency comments faxed to you on March 19, 2001. The acceptance of your dissolution stability data is contingent upon acceptance of your dissolution method and specifications by the Division of Bioequivalence.

Sincerely yours,

_____

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-822
Division File
Field Copy

Endorsements:

HFD-623/R.W.Trimmer, Ph.D./6/6/01 6-8-01
HFD-623/D.S. Gill, Ph.D./6/7/01 DSGill 6-8-01
HFD-617/R. Yu, Pharm. D./6/8/01 RY 6-11-01

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F/T by: DJ 6/8/01

NOT APPROVABLE: **MINOR**

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application
Chemistry, Manufacturing and Controls Review

1. **CHEMISTRY REVIEW #3**

2. **ANDA #75-822** (***Loratadine Orally Disintegating Tablets***)

3. NAME & ADDRESS of **APPLICANT**:

ESI Lederle (——— is the finished dosage manufacturer in —)
Attention: Nicholas Tantillo
Senior Director, Regulatory Affairs
Tel: (914) 732-4137; FAX: (914) 732-5689
401 N. Middletown Rd.
Pearl River, NY 10965
P.O. Box 41502 (mailing address)
Philadelphia, PA 19101

4. LEGAL Basis for Submission:
Innovator Product: ***Claritin***® RediTabs™
Innovator Company: *Schering Corporation*

5. SUPPLEMENT n/a

6. PROPRIETARY NAME n/a

7. NONPROPRIETARY NAME: **Loratadine Orally Disintegrating Tablets, 10 mg**

8. SUPPLEMENT PROVIDES For: n/a

9. AMENDMENTS & Other DATES:
ESI Lederle:
03/09/00 Submission of ANDA
12/26/00 Major Chemistry Amendment (12-22-00)
01/12/01 Electronic CMC Amendment
*12-05-01 MINOR amendment
01-21-02 Bioeq. amendment
01-22-02 labeling submission
FDA:
09-20-00 NA letter with 11 CMC deficiencies
10-04-00 Bio letter re dissolution data
03-08-01 Bio review: not acceptable
07-25-01 labeling deficient
01-04-02 Bio comment to be provided to be applicant (done)
03-19-01 DBE issued NA letter re dissolution.
03-22-02 DBE review **sat.**
05-08-02 The applicant was asked in a telecon to revise specs but they did not respond.

10. PHARMACOLOGICAL CATEGORY: Tricyclic Antihistamine

11. Rx or OTC: Rx

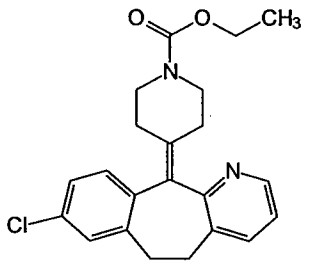
12. RELATED DMF's

DMF number	DMF type	DMF holder	Date LOA(s)
	II		02/23/00
	III		06/29/99
	III		02/23/00
	IV		02/25/00

13. DOSAGE FORM: Tablet

14. STRENGTH: 10 mg

15. CHEMICAL NAME & STRUCTURE:
1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-, ethyl ester
Formula: $C_{22}H_{23}ClN_2O_2$, MW: 382.89



16. RECORDS & REPORTS n/a

17. COMMENTS
Neither Drug substance and drug product are listed in the USP.

Pending CMC deficiencies.

Labeling review are pending.

Bioequivalence review is adequate as of March 2002.

DMF for the bulk drug substance was adequate as of 3-29-2002.

Method Validation package was forwarded to Diane O'Brian March 2002.
Acceptable EER dated April 23, 2002.

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CHEMISTRY REVIEW #3

38. CHEMISTRY COMMENTS To Be PROVIDED To The APPLICANT

ANDA: **75-822** APPLICANT: **ESI Lederle**

DRUG PRODUCT: **Loratadine Orally Disintegrating Tablets, 10 mg**

A. The deficiencies presented below represent **MINOR** deficiencies.

1. Regarding your **drug substance** specifications:

a. [redacted]

b. [redacted]

c. [redacted]

2. Regarding your specifications for the **finished product** and **stability:**

a. [redacted]

b. [redacted]

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

The labeling portion of your application is under review. Any deficiencies will be conveyed to you in a separate letter.

Sincerely yours,

Paul Schwenger 6/28/02

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-822
Division File
Field Copy

Endorsements:

HFD-623/R.W.Trimmer, Ph.D./6/13/02 6-20-2002
HFD-623/D.S. Gill, Ph.D./6/19/02 DSGill 6-20-02
HFD-617/R. Wu, Pharm. D./6/19/02 6/20/02

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F/T by: gp/6/20/02

NOT APPROVABLE: **MINOR - Firm didn't response to the 5/8/02 Telephone deficiencies**

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application
Chemistry, Manufacturing and Controls Review

1. **CHEMISTRY REVIEW #4**

2. **ANDA #75-822** (*Loratadine Orally Disintegating Tablets*)

3. NAME & ADDRESS of APPLICANT:
Wyeth Consumer Healthcare
(formerly ***ESI Lederle;*** (———— is the finished dosage manufacturer in ——)
Attention: David S. Smith, Ph.D., Director, Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

4. LEGAL Basis for Submission:
Innovator Product: ***Claritin***® RediTabs™
Innovator Company: *Schering Corporation*

5. SUPPLEMENT: n/a

6. PROPRIETARY NAME: Alavert

7. NONPROPRIETARY NAME: **Loratadine Orally Disintegrating Tablets, 10 mg**

8. SUPPLEMENT Provides For: n/a

9. AMENDMENTS & Other DATES:

ESI Lederle/Wyeth Consumer Healthcare:
03/09/00 Submission of ANDA
12/26/00 Major Chemistry Amendment (12-22-00)
01/12/01 Electronic CMC Amendment
12-05-01 MINOR amendment
01-21-02 Bioeq. amendment
01-22-02 Labeling submission
10-17-02 Minor Amendment
12-13-02 Blister card of 6 meets requirement for TAMPER packaging.
12-18-02 In NC, firm reported the Corn Syrup & Food Starch are found in Flavor
01-10-03 Labeling Amendment

FDA:
09-20-00 NA letter with 11 CMC deficiencies
10-04-00 Bio letter re dissolution data
03-08-01 Bio review: not acceptable
07-25-01 labeling deficient
01-04-02 Bio comment to be provided to be applicant (done)
03-19-01 DBE issued NA letter re dissolution.
03-22-02 DBE review **sat**.
05-08-02 The applicant was asked in a telecon to revise specs.
07-08-02 NA MINOR
12-12-02 Telecon re Tamper resistant packaging
01-21-03 Labeling review sat.

10. PHARMACOLOGICAL CATEGORY: Tricyclic Antihistamine

11. Rx or OTC: OTC

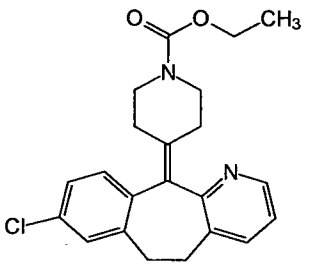
12. RELATED DMF's

DMF number	DMF type	DMF holder	Date LOA(s)
	II		02/23/00
	III		06/29/99
	III		02/23/00
	IV		02/25/00

13. DOSAGE FORM: Tablet

14. STRENGTH: 10 mg

15. CHEMICAL NAME & STRUCTURE:
1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-, ethyl ester
Formula: $C_{22}H_{23}ClN_2O_2$, MW: 382.89



16. RECORDS & REPORTS n/a

17. COMMENTS

The Drug substance and the drug product are not listed in the USP.

The CMC deficiencies were corrected as of this review.

The Labeling review is now acceptable.

The Bioequivalence review is adequate as of March 2002.

The DMF for the bulk drug substance was found adequate as of 3-29-2002.

Method Validation package: November 18, 2002
The DS met requirements for assay, residual solvents, and impurity tests, and the DP also met requirements for assay, residual solvents, and impurity tests.

Acceptable EER dated April 23, 2002.

COMMENTS and Applicant's Response: [vol. 3.1]

1. Regarding your **drug substance** specifications:

a. [redacted]
APPLICANT RESPONSE:
[redacted]

OUR COMMENT:
This is now acceptable to us.

b. [redacted]
APPLICANT RESPONSE:
[redacted]

OUR COMMENT:
This is now acceptable to us.

c. [redacted]
APPLICANT RESPONSE:
[redacted]

OUR COMMENT:
This is now acceptable to us.

2. Regarding your specifications for the **finished product** and **stability**:

a. [redacted]

APPLICANT RESPONSE:

[redacted]

OUR COMMENT:
This limit is now acceptable to us.

b. [redacted]

APPLICANT RESPONSE:

[redacted]

OUR COMMENT:
This limit is now deemed sat.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

The labeling portion of your application is under review. Any deficiencies will be conveyed to you in a separate letter.

APPLICANT RESPONSE:
This was acknowledged.

OUR COMMENT:
The labeling review was found acceptable Jan. 21th 2003.

18. CONCLUSIONS RECOMMENDATIONS
For Approval

19. REVIEWER: Robert W. Trimmer, Ph.D.
Date: revised January 23, 2003

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CHEMISTRY REVIEW #4

APPROVAL SUMMARY PACKAGE	
ANDA #75-822 Firm: **Wyeth Consumer Healthcare**	Drug: Loratadine Orally Disintegrating Tablets Dosage: tablets Strength: **10 mg**
1. CGMP Statement/EIR Update Status:	EER status: acceptable 4-23-02
2. Bio Study:	adequate 3-22-2002
3. Methods Validation - description of Dosage Form the same as the firm's:	November 18, 2002 met requirements
4. Stability - Are Containers used in the Study Identical to those in the Container Section (#26):	Identical?: yes
5. Labeling:	Acceptable 1-21-03
6. Sterilization Validation (if applicable):	n/a
7. Size of *Bio/Test Batch* (Firm's source of Bulk DS satisfactory?):	DMF # ——— 'acceptable Source: ——— Size: ———
8. Size of Stability Batches (If different from bio batch were they mfg. *via* the same process?):	Same: same process
9. Proposed Production Batch (Manufacturing process the same as Bio/Stability batch?):	Size: ——— Same: yes no change
10. List of DP and DS specifications? Composition listed?	yes
	1-24-03 *R.W. Trimmer*, Ph.D. *D.S. Gill*, Ph.D.

cc: ANDA 75-822
Division File
Field Copy

Endorsements:

HFD-623/R.W.Trimmer, Ph.D./01-23-03 1-24-03
HFD-623/D.S. Gill, Ph.D. /01-23-03 DSGill 1-28-03
HFD-617/S. Kim, Pharm. D./01-23-03 for 1/28/03

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F/T by:rt/1/23/03

For Approval.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-822

BIOEQUIVALENCE REVIEW(S)

LORATADINE ORALLY DISINTEGRATING TABLETS, 10MG
ANDA 75-822
Reviewer: Z. Z. Wahba
V:\firmsam\lederle\ltrs&rev\75822sd.300

Lederle
Philadelphia, PA
Submission Date: 03/09/00

Review of Bioequivalence Studies and Dissolution Data (Electronic Submission)

Introduction

Indication: It is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria in patients 6 years of age or older.

Type of Submission:
Original ANDA

Contents of Submission:
Single-dose fasting and non-fasting bioequivalence studies.

RLD: Claritin® Reditabs, manufactured by Schering.

Recommended Dose:
For adults and children 12 years of age and over, the recommended dose of Claritin is 10 mg once daily. For children 6-11 years of age, the recommended dose of Claritin® Reditabs is 10 mg once daily.

Background

Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic activity.

The drug is rapidly absorbed and extensively metabolized to an active metabolite, descarboethoxyloratadine. Limited information is available on loratadine pharmacokinetic studies. In a study involving twelve healthy geriatric subjects (66 to 78 years old), the AUC and peak plasma levels (Cmax) of both loratadine and descarboethoxyloratadine were significantly higher (approximately 50% increased) than in studies of younger subjects. The mean elimination half-lives for elderly subjects were 18.2 hours (with a range of 6.7 to 37 hours) for loratadine and 17.5 hours (with a mean range of 11 to 38 hours) for the active metabolite. The elimination half-lives found in studies in normal adult subjects were 8.4 hours (with a range of 3 to 20 hours) for loratadine and 28 hours (with a range of 8.8 to 92 hours) for the active metabolite, descarboethoxyloratadine. Approximately 80% of the total administered dose can be found equally

distributed between urine and feces in the form of metabolic products after 10 days. The pharmacokinetics of loratadine and descarboethoxyloratadine are independent of dose over the dose range of 10 to 40 mg and are not altered by the duration of treatment. In a single-dose study, food increased the systemic bioavailability (AUC) of loratadine and descarboethoxyloratadine by approximately 40% and 15%, respectively. The time to peak plasma concentration (T_{max}) of loratadine and descarboethoxyloratadine was delayed by 1 hour. Peak plasma concentrations (C_{max}) were not affected by food.

The Firm's Financial Disclosure:
The firm's financial disclosure statements submitted with the bioequivalence section in support of this application did not indicate any conflict of interests between the CRO's investigators and the firm.

Protocol No.: 99-104-MA, A single-dose, randomized, crossover study comparing ESI Lederle's Loratadine Orally Disintegrating Tablets, 10 mg, and Schering's Claritin® Reditabs, 10 mg, in healthy, male and female subjects under fasting conditions.

Study Information

STUDY FACILITY INFORMATION	
Clinical Facility:	[redacted]
Medical Director:	[redacted], MD
Scientific Director:	[redacted], MD
Clinical Study Dates:	12/11/99 to 01/21/00
Analytical Facility	[redacted]
Principal Investigator:	[redacted], MD
Analytical Study Dates:	01/24/00 to 02/16/00

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Lederle's Loratadine Orally Disintegrating Tablets	Schering's Claritin® Reditabs
Manufacture Date:	11/16/99	N/A
Expiration Date:	N/A	6/2001
ANDA Batch Size:	[redacted]	N/A
Full Batch Size:	[redacted]	N/A
Batch/Lot Number:	990043	9EBT88
Potency:	99.5%	Not given
Content Uniformity:	99.6%	Not given
Strength:	10 mg	10 mg
Dosage Form:	tablet	Tablet
Dose Administered:	10 mg	10 mg
Study Condition:	fasting	Fasting

RANDOMIZATION		DESIGN	
Randomized:	Y	Design Type:	Crossover
No. of Sequences:	2	Replicated Treatment Design:	N
No. of Periods:	2	Balanced:	Y
No. of Treatments:	2	Washout Period:	28 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	130
Route of Administration:	oral	No. of Subjects Completing:	127
Dosing Interval:	hr	No. of Subjects Plasma Analyzed:	127
Number of Doses:	N/A	No. of Dropouts:	3
Loading Dose:	mg	Sex(es) Included:	Both
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	0

Dietary Restrictions:	Use of alcohol, caffeine or xanthine containing products is prohibited for 48 hours before dosing for each phase or during the study.
Activity Restrictions:	Confinement to the Phase I Clinic from the evening prior to administration of the test medication until the 48 hour post-dose blood collection.
Drug Restrictions:	No prescription medication within 14 days of dosing and OTC medication within 7 days of dosing. During the study, no prescription or OTC medication will be permitted that may interfere with the evaluation of the study medication.
Blood Sampling:	Blood samples were obtained at 0 (pre-dose) and 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 after administration of the dose.

Study Results

1) Clinical

Adverse Events: No serious medical events were reported. All medical events were mild to moderate. The adverse events were similar for both treatments (pages 124-126, Section VI - Bioavailability/ Bioequivalence, volume C1.2).

Dropouts:

SUBJECT NO.:	3	5	126
REASON:	Subject did not receive the complete dose at the time of dosing. Pill fell off tongue after 30 second of dissolving	Subject dropped out due to phlebotomy difficulties	Subject dropped out due to an adverse event - did not return for Period 2
PERIOD:	1	1	1
REPLACEMENT:	N	N	N

2) **Analytical (Not to be Released Under FOI)**

[redacted]

3) Pharmacokinetic:

The plasma concentrations and pharmacokinetic parameters of Loratadine and Descarboethoxyloratadine under fasting conditions were analyzed using SAS-GLM procedure for analysis of variance.

Note: The firm conducted the study in two groups. Group-1 included subjects #1-2, 4, and 6-65; and Group-2 included subjects #66-125, and 127-130.

For statistical analysis, the following are considered:

- The clinical study for the two groups was carried out at the same clinical facility.
- Study subjects in both groups were recruited from the same enrollment pool and have similar demographics.
- All enrolled subjects were randomly assigned to the study treatments.
- Plasma samples from both groups were analyzed as composite study samples by the same analytical facility.

The following model used for statistical analysis using the SAS-GLM procedure: seq subj(seq) per(group) trt. Data have also been analyzed using the following full model considering "group" effect for the purpose of comparison, group seq group*seq sub(group*seq) per(group) trt group*trt. No significant group effect and group*trt was found for the pharmacokinetic parameters LAUCt, LAUCi and LCMAX.

The following plasma concentrations and pharmacokinetic parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 were analyzed using SAS-GLM procedure without the group effect:

FOR LORATADINE:

Table #1
Mean Loratadine Concentrations (ng/mL) in plasma in 127 Subjects Following a Single Oral Dose of 1X10mg Loratadine Tablet, Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	0.20	0.35	0.14	0.16	1.41
0.5	1.51	2.06	1.21	1.17	1.25
0.75	3.07	3.39	2.81	2.66	1.09
1	3.27	3.41	3.19	2.96	1.03
1.5	2.73	3.10	2.73	2.60	1.00
2	2.07	2.22	2.09	2.04	0.99
2.5	1.59	1.76	1.61	1.67	0.99
3	1.21	1.31	1.30	1.66	0.93
3.5	0.95	1.08	0.98	1.24	0.97
4	0.76	0.85	0.82	1.04	0.93
4.5	0.61	0.69	0.61	0.73	0.99
5	0.47	0.57	0.46	0.55	1.01
6	0.30	0.35	0.30	0.36	1.01
8	0.18	0.21	0.18	0.22	1.02
12	0.09	0.11	0.09	0.11	1.04
16	0.06	0.08	0.06	0.08	0.98
24	0.04	0.06	0.04	0.06	0.98

36	0.03	0.05	0.03	0.05	0.94
48	0.02	0.03	0.02	0.04	0.97
72	0.01	0.02	0.01	0.03	0.81
96	0.01	0.02	0.01	0.03	0.84
120	0.00	0.01	0.00	0.02	0.94
144	0.00	0.01	0.00	0.01	0.89

MEAN1=Test-Product MEAN2=Ref.-Product

Table #2
Mean Pharmacokinetic Parameters (Arithmetic) for Loratadine in 127 Subjects Following a Single Oral Dose of 1X 10 mg Loratadine, Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	11.55	13.43	11.57	13.49	1.00
AUCT	10.94	12.62	10.98	12.60	1.00
CMAX	3.66	3.86	3.60	3.20	1.02
KE	0.06	0.07	0.05	0.06	1.10
*LAUCI	7.83	0.86	8.02	0.82	0.98
*LAUCT	7.38	0.86	7.57	0.83	0.98
*LCMAX	2.51	0.85	2.57	0.84	0.98
THALF	23.78	15.76	23.65	14.82	1.01
TMAX	1.04	0.39	1.13	0.50	0.92

MEAN1=Test-product MEAN2=Ref.-product
UNIT: AUC=NG.HR/ML CMAX=NG/ML
* The values represent the geometric mean (antilog of the means of the logs).

Table #3
LSMeans and The 90% Confidence Interval (Loratadine) In 127 Subjects Following a Single Oral dose of 1X 10 mg Loratadine, Under Fasting Conditions

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	7.83	8.02	0.98	92.61	102.98
LAUCT	7.38	7.57	0.98	92.41	102.92
LCMAX	2.51	2.57	0.98	91.52	104.92

MEAN1=Test-product MEAN2=Ref.-product
UNIT: AUC=NG.HR/ML CMAX=NG/ML
LOWCI 12=Lower C.I. for T/R UPPCI12=Upper C.I. for T/R

Comment on the fasting study (Loratadine):
Under fasting conditions, the mean plasma loratadine levels for the test and reference products were comparable to each other as shown in Table #1 and Figure #1. The 90% confidence intervals for the LSMeans log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #3). The T/R mean ratios (RLSM12) for the log-

transformed AUCt, AUCi and Cmax were within the acceptable range of 0.8-1.25% (Table #3).

FOR DESCARBOETHOXYLORATADINE:

Table #4
Mean Loratadine Concentrations (ng/mL)
in plasma in 127 Subjects Following a Single Oral Dose of 1X10mg Loratadine Tablet, Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.01	0.00	0.00	.
0.25	0.10	0.14	0.09	0.18	1.14
0.5	1.08	0.85	0.98	0.80	1.10
0.75	2.45	1.35	2.46	1.47	0.99
1	3.17	1.55	3.27	1.59	0.97
1.5	3.26	1.31	3.33	1.35	0.98
2	3.04	1.24	3.15	1.25	0.97
2.5	2.78	1.12	2.84	1.05	0.98
3	2.49	0.95	2.63	1.04	0.95
3.5	2.30	0.87	2.38	0.87	0.97
4	2.16	0.92	2.22	0.89	0.97
4.5	2.21	0.82	2.24	0.76	0.99
5	2.09	0.83	2.10	0.71	0.99
6	1.82	0.68	1.85	0.68	0.98
8	1.42	0.58	1.43	0.53	0.99
12	1.05	0.51	1.05	0.46	1.00
16	0.82	0.45	0.83	0.44	0.99
24	0.60	0.37	0.59	0.34	1.01
36	0.39	0.36	0.38	0.34	1.01
48	0.27	0.34	0.27	0.31	1.00
72	0.14	0.26	0.14	0.24	1.02
96	0.08	0.21	0.08	0.20	1.00
120	0.06	0.20	0.06	0.20	1.10
144	0.04	0.17	0.03	0.17	1.01

MEAN1=Test-Product MEAN2=Ref.-Product

Table #5
Mean Pharmacokinetic Parameters (Arithmetic) for Decarboethoxyloratadine
in 127 Subjects Following a Single Oral Dose of 1X 10 mg Loratadine, Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	56.42	59.96	56.53	59.96	1.00
AUCT	51.14	38.05	51.44	36.54	0.99
CMAX	3.75	1.52	3.82	1.54	0.98
KE	0.03	0.01	0.03	0.01	1.01
*LAUCI	46.87	0.50	47.29	0.50	0.99

*LAUCT	44.77	0.46	45.38	0.46	0.99
*LCMAX	3.46	0.40	3.54	0.40	0.98
THALF	24.90	13.98	24.98	13.44	1.00
TMAX	1.94	1.79	1.76	1.37	1.10

MEAN1=Test-product MEAN2=Ref.-product
UNIT: AUC=NG.HR/ML CMAX=NG/ML
* The values represent the geometric mean (antilog of the means of the logs).

Table #6
LSMeans And The 90% Confidence Interval (Loratadine) in 127 Subjects Following a Single Oral Dose of 1X 10mg Loratidine, Under Fasting Conditions

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	46.90	47.33	0.99	96.44	101.84
LAUCT	44.80	45.41	0.99	96.15	101.24
LCMAX	3.46	3.54	0.98	94.35	101.31

MEAN1=Test-product MEAN2=Ref.-product
UNIT: AUC=NG.HR/ML CMAX=NG/ML
LOWCI 12=Lower C.I. for T/R UPPCI12=Upper C.I. for T/R

Comment on the fasting study (Descarboethoxyloratadine):
Under fasting conditions, the mean plasma descarboethoxyloratadine levels for the test and reference products were comparable to each other as shown in Table #4 and Figure #2. The 90% confidence intervals for the LSMeans log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #6). The T/R mean ratios (RLSM12) for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.8-1.25% (Table #6).

Protocol No.: 9-105-MA, A comparative, randomized, 3-way crossover study comparing ESI Lederle's Loratadine Orally Disintegrating Tablets, 10 mg, and Schering's Claritin® Reditabs, 10 mg, in healthy, male and female subjects under fed and fasted conditions.

Study Information

STUDY FACILITY INFORMATION
Clinical Facility: _____
Medical Director: _____, MD
Scientific Director: _____, MD
Clinical Study Dates: 12/11/99 to 02/14/00
Analytical Facility _____
Principal Investigator: _____, MD
Analytical Study Dates: 02/09/00 to 02/16/00

TREATMENT INFORMATION

Treatment ID:Test or Reference:	A	B	C
Product Name:	T	T	R
Manufacturer:	Loratadine Orally Disintegrating Tablets	Loratadine Orally Disintegrating Tablets	Claritin® Reditabs
Manufacture Date:	11/16/99	11/16/99	Schering
Expiration Date:	--	--	6/2001
ANDA Batch Size:	[redacted]	[redacted]	N/A
Full Batch Size:	[redacted]	[redacted]	N/A
Batch/Lot Number:	990043	990043	9EBT88
Potency:	99.5%	99.5%	Not given
Content Uniformity:	99.6%	99.6%	Not given
Strength:	10 mg	10 mg	10 mg
Dosage Form:	tablet	tablet	tablet
Dose Administered:	10 mg	10 mg	10 mg
Study Condition:	fasting	fed	fed
Standardized Breakfast:	N	Y	Y
Breakfast Specifics:	N/A	Standardized FDA high-fat breakfast	Standardized FDA high-fat breakfast
Standardized Lunch:	Y	Y	Y
Lunch Specifics:	All subjects were given standardized meals	All subjects were given standardized meals	All subjects were given standardized meals
Standardized Dinner:	Y	Y	Y
Dinner Specifics:	All subjects were given standardized meals	All subjects were given standardized meals	All subjects were given standardized meals

RANDOMIZATION		DESIGN	
Randomized:	Y	Design Type:	crossover
No. of Sequences:	6	Replicated Treatment Design:	N
No. of Periods:	3	Balanced:	Y
No. of Treatments:	3	Washout Period:	21 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	24
Route of Administration:	oral	No. of Subjects Completing:	24

Dosing Interval:	hr	No. of Subjects Plasma Analyzed:	24
Number of Doses:	N/A	No. of Dropouts:	0
Loading Dose:	mg	Sex(es) Included:	both
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	0

Dietary Restrictions:	Use of alcohol, caffeine or xanthine containing products is prohibited for 48 hours before dosing for each phase and during the study.
Activity Restrictions:	Confinement to the Phase I Clinic from the evening prior to administration of the test medication until the 48 hour post-dose blood collection.
Drug Restrictions:	No prescription medication within 14 days of dosing and OTC medication within 7 days of dosing. During the study, no prescription or OTC medication will be permitted that may interfere with the evaluation of the study medication.
Blood Sampling:	Blood samples were obtained at 0 (pre-dose) and 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 after administration of the dose.

Study Results

1) Clinical
Adverse Events: No serious medical events were reported. All medical events were mild and all subjects completed the study (page 4786, Bioequivalence Study Report, volume C1.11).

2) Analytical (Not to be released Under FOI)
Same as in study protocol #99-104-MA (under fasting conditions).

IN VIVO BE STUDY & STATISTICAL ANALYSIS:

The plasma concentrations and pharmacokinetic parameters of loratadine and descarboethoxyloratadine under non-fasting conditions were analyzed using SAS-GLM procedure for analysis of variance.

The plasma concentrations and pharmacokinetic parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the Tables below:

FOR LORATADINE

Table #7
Mean Loratadine Concentrations (ng/mL) in plasma in 24 Subjects Following a Single Oral Dose of 1X 10 mg Loratadine Tablet Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.25	0.13	0.11	0.02	0.02	0.02	0.03	6.95
0.5	0.86	0.63	0.21	0.32	0.15	0.19	4.10
0.75	2.09	1.36	0.45	0.70	0.32	0.37	4.68
1	2.79	1.68	0.79	1.33	0.50	0.46	3.54
1.5	2.69	1.68	1.31	1.90	0.94	0.72	2.05
2	2.06	1.30	1.98	3.32	1.29	0.91	1.04
2.5	1.52	0.94	2.36	3.79	1.62	1.02	0.65
3	1.17	0.76	2.47	3.27	1.90	1.15	0.47
3.5	0.91	0.59	2.45	2.76	1.88	1.02	0.37
4	0.71	0.46	2.24	2.08	1.93	1.11	0.32
4.5	0.53	0.33	2.36	1.88	1.95	1.09	0.23
5	0.42	0.27	1.95	1.26	1.74	1.08	0.22
6	0.26	0.16	1.15	0.77	1.07	0.85	0.23
8	0.16	0.09	0.53	0.34	0.56	0.68	0.30
12	0.08	0.05	0.18	0.14	0.17	0.14	0.42
16	0.05	0.03	0.12	0.11	0.10	0.06	0.44
24	0.03	0.02	0.08	0.10	0.06	0.04	0.45
36	0.02	0.02	0.05	0.07	0.04	0.03	0.46
48	0.02	0.02	0.03	0.04	0.03	0.02	0.49
72	0.01	0.01	0.02	0.04	0.01	0.02	0.30
96	0.00	0.01	0.01	0.02	0.01	0.01	0.38
120	0.00	0.01	0.01	0.02	0.01	0.01	0.21
144	0.00	0.00	0.00	0.01	0.00	0.01	0.00

(CONTINUED)

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.25	7.10	1.02
0.5	5.78	1.41
0.75	6.60	1.41
1	5.53	1.56
1.5	2.85	1.39
2	1.59	1.53
2.5	0.94	1.45
3	0.62	1.30
3.5	0.48	1.30
4	0.37	1.16
4.5	0.27	1.21
5	0.24	1.12
6	0.25	1.08
8	0.28	0.95

12	0.45	1.06
16	0.53	1.21
24	0.59	1.30
36	0.60	1.30
48	0.61	1.23
72	0.45	1.53
96	0.46	1.22
120	0.29	1.39
144	0.00	1.63

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table #8
Mean Pharmacokinetic Parameters for Loratadine in 24 Subjects Following a Single Oral Dose of 1X 10mg Loratadine Tablet, Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	9.97	6.18	18.11	18.95	14.82	8.58	0.55
AUCT	9.47	5.88	17.25	18.33	14.10	8.31	0.55
CMAX	3.05	1.77	3.17	3.76	2.51	1.24	0.96
KE	0.05	0.06	0.03	0.02	0.03	0.02	1.93
*LAUCI	8.21	0.67	13.92	0.67	12.58	0.60	0.59
*LAUCT	7.79	0.68	13.13	0.68	11.91	0.61	0.59
*LCMAX	2.50	0.70	2.32	0.71	2.22	0.52	1.08
THALF	23.30	13.93	35.40	16.97	33.07	15.67	0.66
TMAX	1.19	0.35	3.81	1.10	3.83	0.95	0.31

(CONTINUED)

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.67	1.22
AUCT	0.67	1.22
CMAX	1.21	1.26
KE	1.87	0.97
*LAUCI	0.65	1.11
*LAUCT	0.65	1.10
*LCMAX	1.13	1.04
THALF	0.70	1.07
TMAX	0.31	0.99

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: AUC=NG.HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
*The values represent the geometric means (antilog of the means of the logs).

Comment on the non-fasting study (Loratadine):
Under non-fasting conditions, the mean plasma loratadine levels for the test and reference products were comparable to each other as shown in Table #7 and Figure #3. The ratios of the test mean to the

reference mean (RMEAN2/3) for the log-transformed AUCt, AUCi, and Cmax, were all within the acceptable range of 0.8 to 1.25 (Table #8).

FOR DESCARBOETHOXYLORATADINE

Table #9
Mean Descarboethoxyloratadine Concentrations (ng/mL) in plasma in 24 Subjects Following a Single Oral Dose of 1X 10 mg Loratadine Tablet Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.01	0.05	0.00	0.00	0.00	0.02	.
0.25	0.15	0.15	0.00	0.01	0.01	0.03	77.14
0.5	1.19	0.88	0.10	0.11	0.12	0.16	11.47
0.75	2.63	1.65	0.25	0.21	0.26	0.27	10.44
1	3.47	1.91	0.42	0.30	0.42	0.35	8.26
1.5	3.71	1.77	0.91	0.54	0.86	0.59	4.10
2	3.48	1.62	1.40	0.76	1.21	0.68	2.49
2.5	3.20	1.53	1.85	0.95	1.75	0.91	1.72
3	2.93	1.32	2.38	1.22	2.36	1.34	1.23
3.5	2.70	1.13	2.73	1.39	2.69	1.53	0.99
4	2.57	1.04	3.04	1.48	3.07	1.54	0.85
4.5	2.70	1.03	3.66	1.77	3.53	1.61	0.74
5	2.64	1.00	3.51	1.48	3.50	1.59	0.75
6	2.31	0.93	3.13	1.21	3.00	1.14	0.74
8	1.86	0.75	2.46	1.01	2.35	0.96	0.76
12	1.40	0.73	1.80	0.84	1.75	0.70	0.78
16	1.05	0.67	1.33	0.65	1.30	0.69	0.79
24	0.78	0.55	0.94	0.55	0.91	0.56	0.83
36	0.56	0.71	0.60	0.51	0.60	0.57	0.94
48	0.36	0.47	0.42	0.51	0.41	0.49	0.85
72	0.20	0.41	0.24	0.45	0.23	0.41	0.85
96	0.14	0.37	0.16	0.38	0.16	0.41	0.89
120	0.10	0.33	0.11	0.34	0.10	0.32	0.96
144	0.08	0.32	0.08	0.30	0.08	0.31	0.94

(CONTINUED)

	RMEAN13	RMEAN23
TIME HR		
0	2.34	0.00
0.25	12.50	0.16
0.5	10.25	0.89
0.75	10.19	0.98
1	8.32	1.01
1.5	4.31	1.05
2	2.87	1.15
2.5	1.83	1.06
3	1.24	1.01
3.5	1.00	1.01
4	0.84	0.99

4.5	0.77	1.04
5	0.75	1.00
6	0.77	1.04
8	0.79	1.04
12	0.80	1.03
16	0.81	1.02
24	0.85	1.03
36	0.94	1.00
48	0.89	1.04
72	0.90	1.06
96	0.86	0.97
120	0.97	1.01
144	0.96	1.03

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table #10
Mean Pharmacokinetic Parameters for Descarboethoxyloratadine in 24 Subjects Following a Single Oral Dose of 1X 10mg Loratadine Tablet, Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	83.81	128.40	88.45	115.11	84.44	105.60	0.95
AUCT	68.02	60.67	75.44	61.12	73.01	58.87	0.90
CMAX	4.04	1.71	3.92	1.70	3.95	1.64	1.03
KE	0.03	0.01	0.03	0.01	0.03	0.01	1.03
*LAUCI	59.89	0.65	67.30	0.60	64.35	0.62	0.89
*LAUCT	56.62	0.54	64.21	0.51	61.48	0.55	0.88
*LCMAX	3.71	0.42	3.60	0.41	3.64	0.42	1.03
THALF	29.84	27.76	29.16	22.33	27.64	18.68	1.02
TMAX	2.11	2.33	4.92	0.87	5.00	2.58	0.43

(CONTINUED)

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.99	1.05
AUCT	0.93	1.03
CMAX	1.02	0.99
KE	1.00	0.97
*LAUCI	0.93	1.05
*LAUCT	0.92	1.04
*LCMAX	1.02	0.99
THALF	1.08	1.05
TMAX	0.42	0.98

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: AUC=NG.HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
*The values represent the geometric means (antilog of the means of the logs).

Comment on the non-fasting study (Descarboethoxyloratadine):
Under non-fasting conditions, the mean plasma descarboethoxyloratadine levels for the test and reference products were comparable to each other as shown in Table #9 and Figure #4. The ratios of the test mean to the reference mean (RMEAN2/3) for the log-transformed AUCt, AUCi, and Cmax, were all within the acceptable range of 0.8 to 1.25 (Table #10).

Formulation (Not to be released under FOI)

Ingredient	mg per tablet
LORATADINE	10
ASPARTAME	
CITRIC ACID	
COLLOIDAL SILICON DIOXIDE	
CROSPOVIDONE	
MAGNESIUM STEARATE	
MANNITOL	
MICROCRYSTALLINE CELLULOSE	
NATURAL AND ARTIFICIAL MINT FLAVOR	
SODIUM BICARBONATE	

Comments on the Formulation:

1. Lederle's formulation for its test product Loratadine Orally Disintegrating Tablets, 10 mg, is shown in Attachment #1.

2. Generally, dosage for loratadine tablet, should not exceed 10 mg once a day for adults and children (6-11 years).

3. The proposed test product contains natural and artificial mint flavor . This flavor is not included in the FDA Inactive Ingredient Guide (1996).

4. The manufacturer and supplier of the above flavor reported its inactive ingredients in DMF # . The components of the mint flavor are shown in Table #1.

5. The potential toxicity of the following botanically-derived flavors was extensively reviewed by an expert panel prior to inclusion in the GRAS 3 list (Oser and Ford, *Food Technol*, 1991; 40:84-97).

Component	CAS No.	Amt in Drug Prod. per 10 mg/day	Conclusion
			GRAS 3
			GRAS 3
			GRAS 3

Therefore, it is concluded that the above extracts do not pose a safety problem at the levels used in this drug.

6. The PAFA database, maintained by the FDA Center for Food Safety and Applied Nutrition (CFSAN), was searched for information about acceptable daily intake as well as for the outcome of preclinical toxicology studies for the mint Flavor's ingredients. The WHO/FAO Joint Expert Committee on Food Additives (JECFA) has set an acceptable daily intake (ADI) for human consumption for food additives.

7. A JECFA ADI is established for ——. The ADI for this additive exceeded the estimated daily consumption for 10 mg loratadine orally disintegrating tablet. Therefore, it is concluded that this flavoring component, at the amount in Lederle's Loratadine Orally Disintegrating Tablet, 10 mg, do not pose safety problems (Table 2).

8. ——— were evaluated by the CDER Computational Toxicology Consult Service. The predicted NOEL daily doses of these four flavoring components exceed the amounts in Lederle's Loratadine Orally Disintegrating Tablet (10 mg dose).

9. Where data from preclinical toxicology studies were available, the no observed effect level (NOEL) for the test animal species was determined. In all cases, the species used was rats. The rodent NOEL was divided by 100 to estimate a NOEL for humans. For ——— and Peppermint Oil, this value exceeds the estimated daily consumption for 10 mg Loratadine Orally Disintegrating Tablet (10 mg dose). Therefore, it is concluded that this group of flavoring components, at the amount in Lederle's Loratadine Orally Disintegrating Tablet, 10 mg, do not pose safety problems (Table 3).

10. A NOEL of ——— mg/kg for human has been estimated for ——— (DBE review of ANDA #40-364).

Table 1. Mint Flavor ———

Description	Percent of Flavor	CAS	FEMA

DISSOLUTION (Not to be released under FOI)

The firm provided the following dissolution specifications and data.

Dissolution Medium: 0.1N HCl
Volume: 900ml
Apparatus Type: Apparatus 2 (paddles)
Speed: 50 rpm

Dissolution Data

Test				REFERENCE		
Lot No.: 990043				Lot No.: 9EBT88		
Strength: 10mg				Strength: 10mg		
No. of Units: 12				No. of Units: 12		
Time (minutes)	Mean (Test product)	Range	%CV	Mean (Ref. product)	Range	%CV
5	95.5		3.04	99.92		1.68
10	98.5		1.47	101.25		1.47
15	98.92		1.25	101.58		1.22

Important notes (not to be released under FOI):

On August 18, 1999, the firm requested the Agency's advise for developing a dissolution method for a generic version of the RLD Claritin RediTabs. On December 7, 1999, the Agency responded to the

firm's letter that there is currently no official method for this product. In the letter, the Agency suggested that the firm develop its own dissolution method, using USP method I (basket) or II (Paddle), and try the following method: USP Method I (basket) at 50 rpm in 900 mL of SGF without enzyme, at ——nm. A copy of the Agency letter in attached to the review (Attachment #4).

DEFICIENCY:

The firm is requested to submit dissolution data applying the following method and specification:

For the test method: use an automated system with UV detection at —— nm. The dissolution testing should be conducted in 900 mL of stimulated gastric fluid (no pepsin) as the dissolution medium at 37°C with apparatus 1 (basket) at 50 rpm. The dissolution specifications for the test product will be established based on acceptable submitted dissolution data (Following the innovator' method, please see Attachment #5).

RECOMMENDATIONS

1. The two in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions conducted by ESI Lederele, on its Loratadine Orally Disintegrating Tablets 10 mg, lot #990043, comparing it to the RLD Schering's Claritin® Reditabs, 10 mg, have been found to be incomplete due to the deficiency cited above.

2. The dissolution testing conducted by the firm on its test product Lederle's Loratadine Orally Disintegrating Tablets 10 mg (lot #990043) has been found incomplete due to the deficiency cited above.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
for FT INITIALLED RMHATRE Mohib H. Makary

for Concur: Barbara M Conner Date: 9/29/00
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

CC: ANDA 75-822
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer (Z. Wahba)
HFD-658/ Team Leader (B. Davit)

Endorsements:
HFD-658/ Z. Wahba 9/29/00
HFD-658/ B. Davit
for Joe HFD-650/ D. Conner

v:\new\firmsam\Lederle\ltrs&rev\75822sd.300

BIOEQUIVALENCY - **INCOMPLETE** submission date: 3/09/2000

OK 1. **FASTING STUDY** (STF) Strengths: **10 mg**
Clinical: _____ **Outcome: IC**
Analytical: _____

OK 2. **NON-FASTING STUDY** (STF) ?? (STP) Strengths: **10mg**
Clinical: _____ **Outcome: IC**
Analytical: _____

OUTCOME DECISIONS: IC - Incomplete
WINBIO COMMENTS: **Incomplete** Biostudy

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-822 APPLICANT: ESI Lederle

DRUG PRODUCT: Loratadine Orally Disintegrating Tablets, 10 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

Please submit dissolution data applying the following method and specification:

For the test method: use an automated system with UV detection at — nm. The dissolution testing should be conducted in 900 mL of stimulated gastric fluid (no pepsin) as the dissolution medium at 37°C with apparatus 1 (basket) at 50 rpm. The dissolution specifications for the test product will be established based on acceptable submitted dissolution data.

Sincerely yours,

Barbara M Dale

for Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FIG P-1 . PLASMA LORATADINE LEVELS

LORATADINE TABLETS, 10 MG, ANDA #75-822
UNDER FASTING CONDITIONS
DOSE=1 X 10 MG

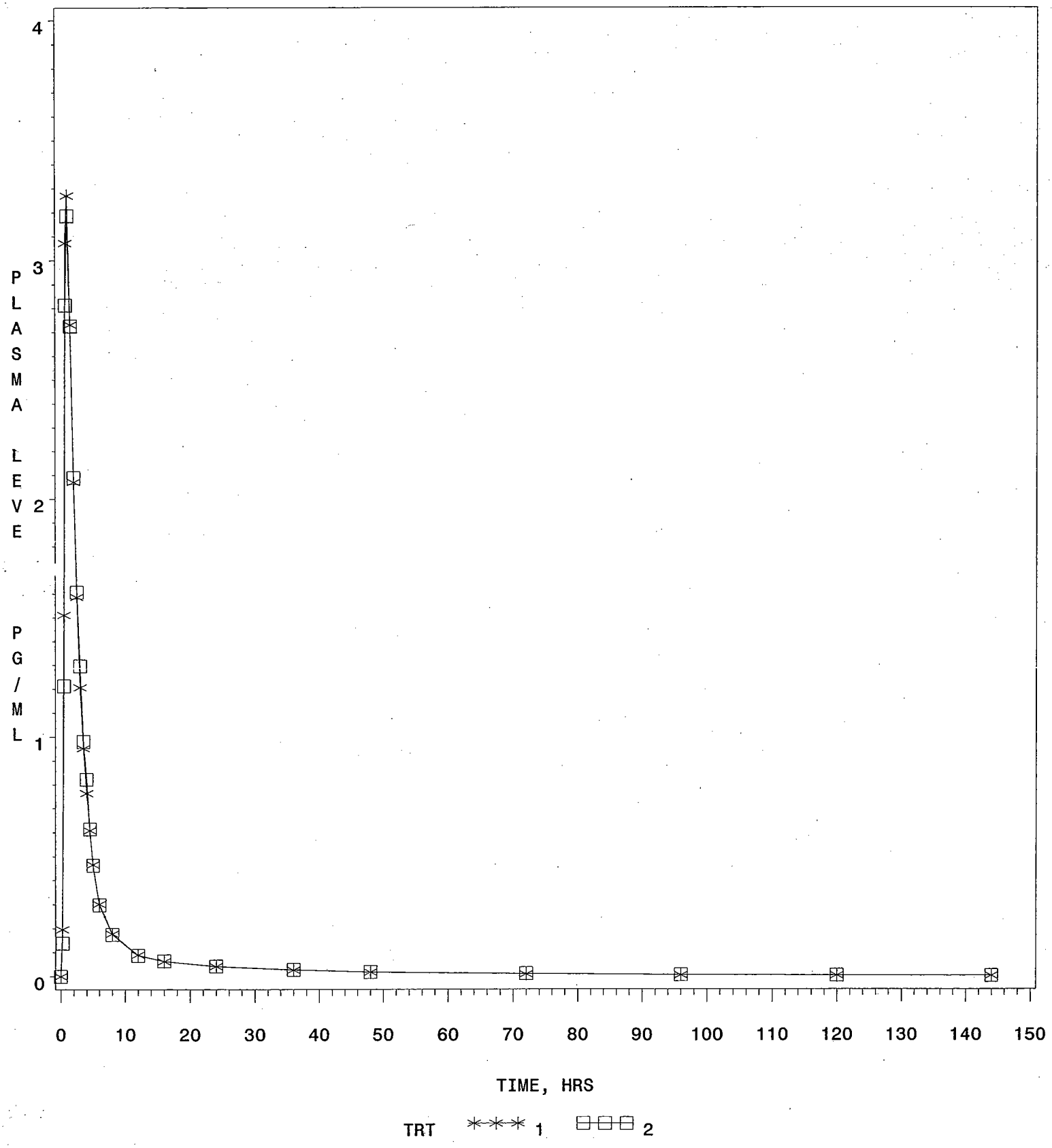


FIG. P-2 . PLASMA DESCARBOETHOXYLORATADINE LEVELS

LORATADINE TABLETS, 10 MG, ANDA #75-822
UNDER FASTING CONDITIONS
DOSE=1 X 10 MG

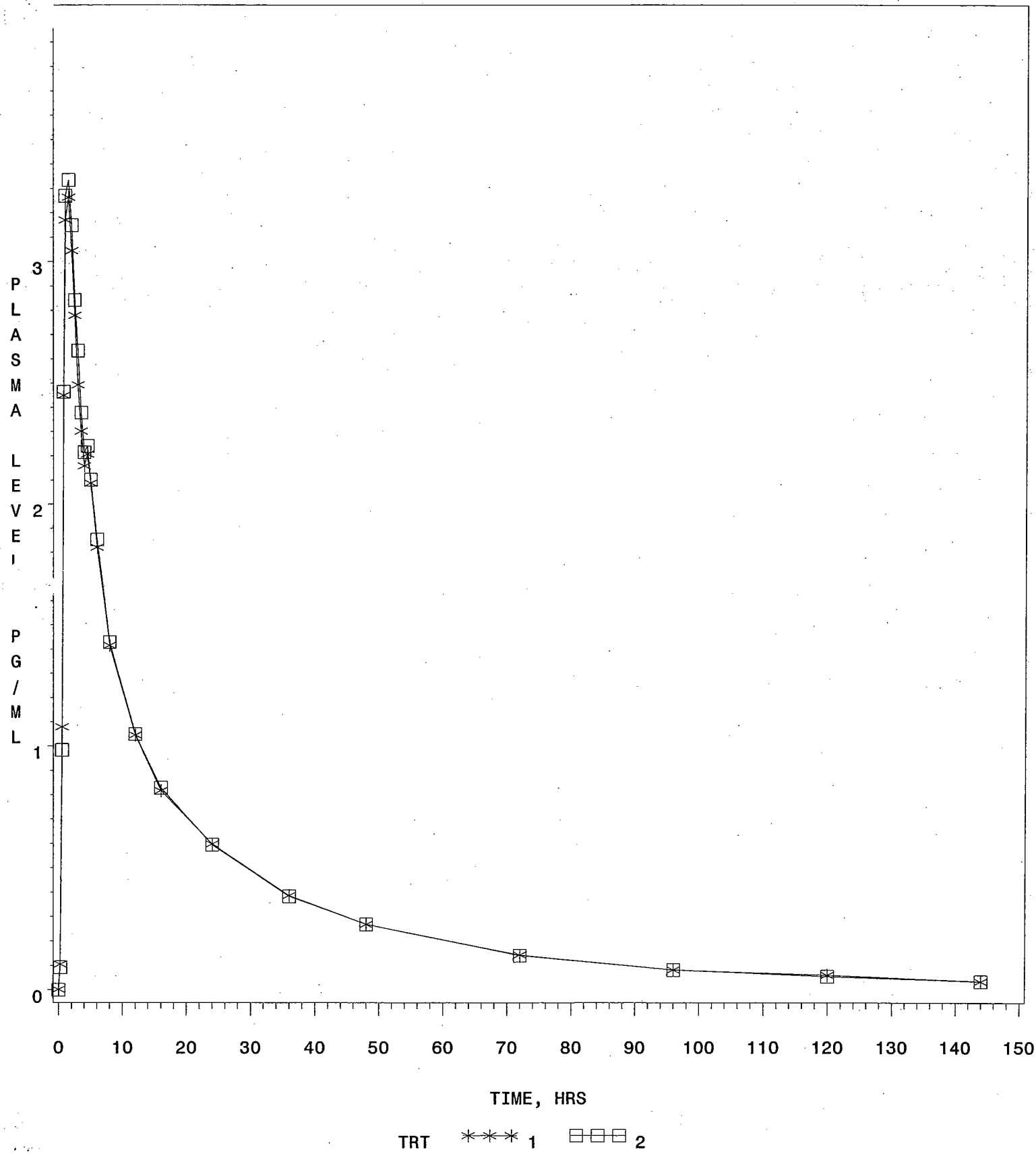


FIG P-3 . PLASMA LORATADINE LEVELS

LORATADINE TABLETS, 10 MG, ANDA #75-822
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 10 MG

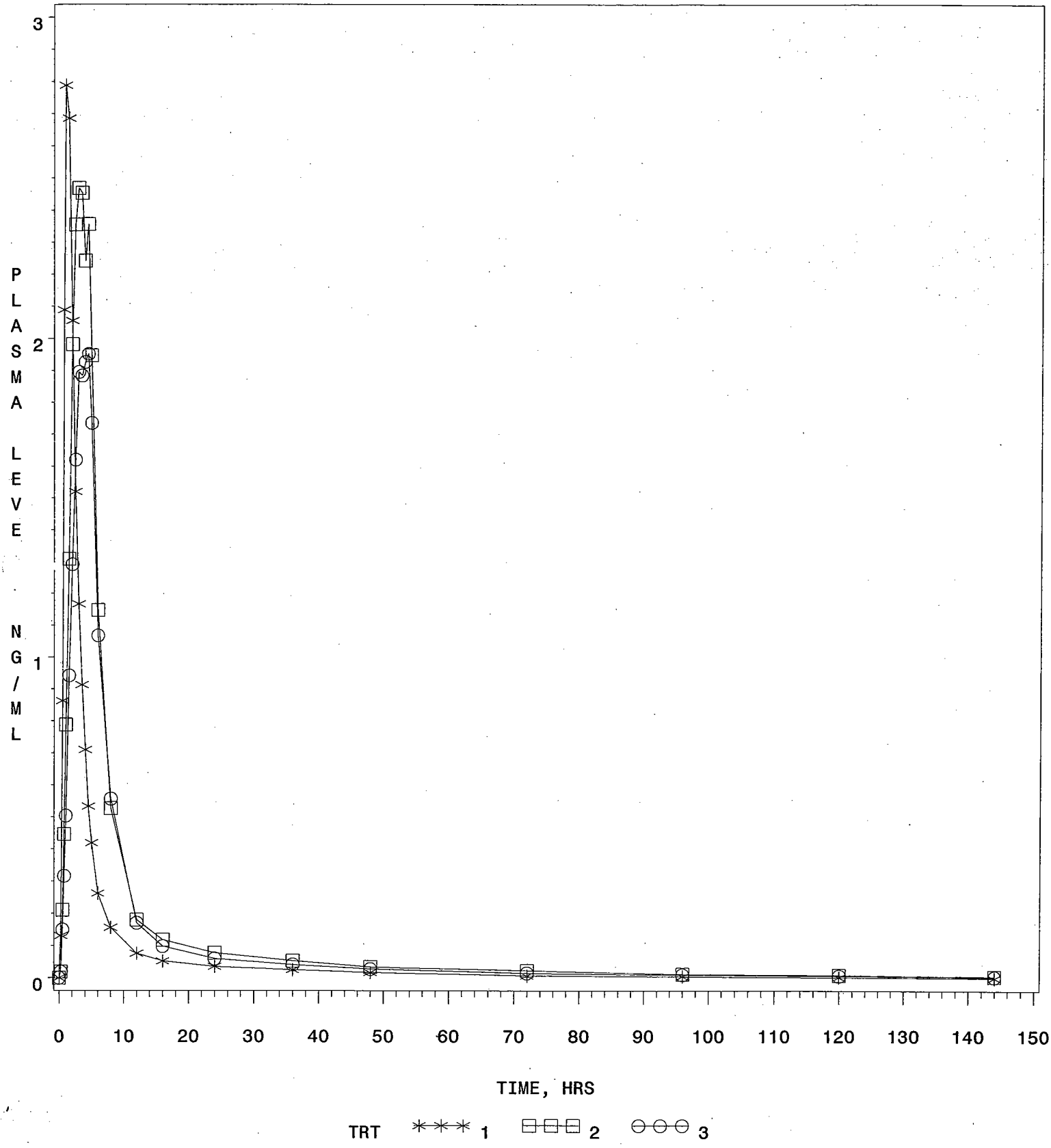
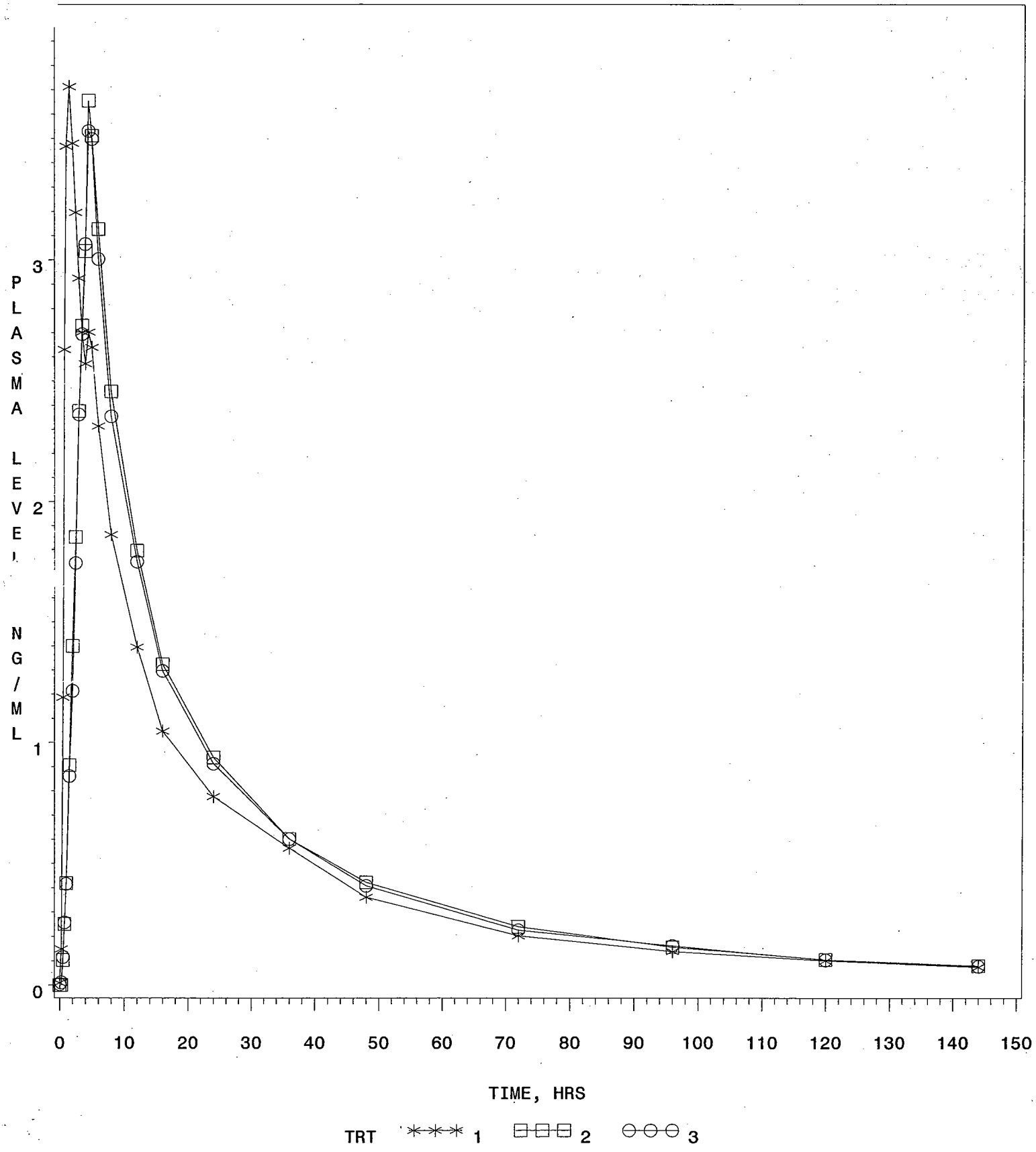


FIG P-4 . PLASMA DESCARBOETHOXYLORATADINE LEVELS

LORATADINE TABLETS, 10 MG, ANDA #75-822
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 10 MG



Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW (ATTACHMENT #1)

Attachment #2

TELEPHONE MEMO

TO: Nick Tantillo
ESI Lederle
914-732-4137

REF# ANDA 75-822

FROM: Jennifer Fan

SUBJECT: Loratadine Orally Disintegrating Tablets, 10 mg
ESI Lederle
Natural and Artificial Mint Flavor ————

DATE: June 30, 2000

REQUESTED BY: Zakaria Wahba

ATTENDANTS: Nick Tantillo, ESI Lederle
Zakaria Wahba, DBE
Jennifer Fan, DBE

The firm was called to request for the following information:

1. The quantitative composition of each component in the Natural and Artificial Mint Flavor ————. The amount (e.g. mg) per tablet, percentage of weight per tablet (%W/W), etc.
2. Provide the chemical name and chemical synonyms of each component in the Natural and Artificial Mint Flavor.
3. Provide the CAS number, including the correct hyphenation, if any, for each component included in the above flavor.

The firm had informed the Agency that information regarding the above flavor was sent to the Agency's Regulatory Division. The Agency will check to see what information was sent and will call the firm back.

The firm was recommended to submit this as a telephone amendment in 10 business days.

Attachment #2
(Continued)

DATE: July 6, 2000

REQUESTED BY: Zakaria Wahba

ATTENDANTS: Nick Tantillo, ESI Lederle
Zakaria Wahba, DBE
Jennifer Fan, DBE

DBE has checked to see what information was needed. All 3 of the above requested information are still needed by the Agency.

The firm believes that the supplier will be unwilling to comply with the submission of the quantitative component of the element. The supplier may not be able to give the exact mg of each element of the flavor per tablet since the supplier does not know how much is in the tablet. DBE can accept the percentage of each element per 100% flavor and the reviewer can calculate how many mg is in per tablet.

The firm will communicate this information to their flavor supplier ———————
———————.

The firm explained that it might take more than 10 days to get the information to the Agency. The reviewer will allow a delay.

DATE: July 14, 2000

REQUESTED BY: ———
———————————
———————

ATTENDANTS: ———————
Jennifer Fan, DBE

Dr. Fan reiterated the above information that was needed by the supplier —— The DMF disclosure to the Agency was did not have enough information. The supplier will comply with #2 and #3 of the requested information, but is not willing to supply the exact amounts of each element in the Natural and Artificial Mint Flavor. The supplier explained that they are given in percentage ranges due to confidentiality issues. They would like to know why we need this information. Dr. Fan suggested that a teleconference be held between the supplier and DBE's reviewer.

Attachment #2
(Continued)

DATE: July 19, 2000

REQUESTED BY: ———

ATTENDANTS: ———
———
———
Zakaria Wahba, DBE
Jennifer Fan, DBE

DBE informed the supplier that the Agency would need to see the requested information on the coloring and flavoring of all submitted products.

However, the supplier argued that flavor has been seen by the FDA; they are all FEMA GRAS. The components of the flavor is given in ranges so that the exact amount of each element is not revealed due to confidentiality issues. DBE stressed that the information will be kept confidential.

The problem with the elements being given in ranges is that when the percentages are added up, it does not total to 100%. The exact amount is needed to determine what is the maximum total daily dose for the product. It is a safety concern if it does exceed the recommended maximum total daily allowance.

The firm stressed that one of the elements (which is above — %), ———, is a food and is ingested daily in higher concentrations.

The firm would like DBE to fax over a written policy which explains what information DBE needs in regards to inactive ingredients and why.

DATE: July 24, 2000

REQUESTED BY: Jennifer Fan

ATTENDANTS: ———
Lizzie Sanchez, DBE
Jennifer Fan, DBE

DBE had explained that it is a new office policy that DBE will be looking at colors and flavors when reviewing application submissions. Therefore, specific information of each element of the flavor is required so that DBE can assess the safety of each element.

The firm had wanted the Agency to fax an office policy to the firm, which details what information is needed from the suppliers of colors and flavors.

DBE explained that we have the authority through 21 CFR § 314.127 to request for more information on the inactive ingredients.

Attachment #2
(Continued)

The supplier was worried about confidentiality issues even though DBE assured him that the information that we were asking for would be kept confidential.

The supplier will not give the specific percentage or mg of each element in the Natural and Artificial Mint Flavor. The supplier was told that ESI Lederle should be expecting a deficiency letter.

Attachment #3

Telecon Record

Date: 4/7/00

ANDA: 75-822

Firm: ESI Lederle

Drug: Loratadine Orally Disintegrating Tablets, 10 mg

FDA Participants: Paras Patel

Industry Participants: Nicholas Tantillo

Phone #: 914-732-4137

Agenda:

1. Paras asked Nicholas to provide components and composition for Natural and Artificial Mint Flavor ——— Nicholas said he will have the manufacturer contact the agency directly.

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW . ATTACHMENT #3

Attachment #4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

ESI Lederle
401 North Middletown Rd.
Pearl River, NY 10965-1299

DEC 7 1999

Reference Number: OGD 99-302

Dear Ms. O'Dea:

This letter is in response to your correspondence dated August 18, 1999. You request that the Office of Generic Drugs (OGD) provide comments regarding the dissolution method for Loratadine RediTabs, 10 mg. OGD provides the following comments:

At the present time, there is no official dissolution method for this product. You are encouraged to develop your own dissolution method, using USP Method I (Basket) or II (Paddle). You can also try the following suggested method: USP Method I (basket) at 50 RPM in 900 ml of SGF without enzyme, at — nm.

You should also consider developing a dispersion test.

If you have any questions, please call Jennifer Fan, Pharm.D., Project Manager, Division of Bioequivalence, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Dr. Tran, OGD

Phone Number: _____

Fax Number 301-594-0181

FROM: Ramana Uppoor

OCPB

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1050 FAX: (301) 827-1271

Total number of pages, including cover sheet: 5 Date: 10/18/99

COMMENTS: Per your request, material related to dissolution specs. for Claritin Reditabs.

Attachment #5
(continued)

E L E C T R O N I C M A I L M E S S A G E

sitivity: COMPANY CONFIDENTIAL

Date: 26-Feb-1998 10:34am EST
From: Craig Bertha
BERTHAC
Dept: HFD-570 PKLN 10B45
Tel No: 301-827-1095 FAX 301-827-1271

: Arthur Shaw (SHAWA)
Craig Bertha (BERTHAC)
: Maria Ysern (YSERNM)
: Janusz Rzeszotarski (RZESZOTARSKI)

: Arthur Shaw (SHAWA)
: Yana Mille (MILLEY)
: William Hess (HESS)
: Guiragos Pocc.ikian (POCCHIKIAN)

bject: Re: Rapidly-Disintegrating Tablets nomenclature

rt,

n terms of your questions on the disintegration/dissolution aspects of r divisions Claritin RediTabs (loratadine rapidly-disintegrating ablets) I have the following information:

. Q: Is there a disintegration specification?
If so how is it measured and is it a reasonable value?

A: There is not a regulatory specification for disintegration of he Claritin RediTab, however there is an in-process test for dispersion. For the test a tablet is dropped into 200 mL of water at oC and the time it takes to become fully wetted is noted. The test is assed if this time is less than 10 seconds. I do not recall any data eing included in the application but when I repeated this test with oom temperature water in the office with several samples supplied by he firm, the dispersion time as I interpreted it, was less than about 5 econds. I do remember that when our division met with you and others Eric Duffey, Michael Folkendt) from GI drugs and Dan Boring of LNC, we decided that an oral product with a dispersion or disintegration time of l minute could be considered as a "rapidly-disintegrating tablet."

. Q: What is the dissolution spec?

A: The dissolution specification for Claritin RediTabs is as follows:

The acceptance criteria: Meets the dissolution requirement of current USP, Q = — % in 6 minutes. The test method: The method uses an automated system with UV detection at — nm. The apparatus is the USP type I (baskets) assembled according to the USP. The solution is 900 mL of simulated gastric fluid (no pepsin) and the testing is performed at 37oC with a speed of rotation of 50 rpm.

LORATADINE ORALLY DISINTEGRATING TABLETS, 10MG
ANDA 75-822
Reviewer: Z. Z. Wahba
V:\firmsam\lederle\ltrs&rev\75822a1.d00

Lederle
Philadelphia, PA
Submission Date: 12/12/00

REVIEW OF AN AMENDMENT

History of the submission

1. The firm previously submitted two in vivo bioequivalence studies (single-dose under fasting and non-fasting conditions) comparing its test product Loratadine Orally Disintegrating Tablets 10 mg, to the reference listed drug Schering's Claritin® Reditabs, 10 mg.

2. The submission was reviewed and was found incomplete by the Division of Bioequivalence (review date 9/29/00, ANDA #75-822) due to unacceptable dissolution data. The firm's dissolution testing did not meet the Agency dissolution conditions. The test product did not pass the innovator's dissolution method specifications.

Comments (not to be released under FOI)

1. The firm was requested to submit dissolution data applying the following method and specification:

   For the test method: use an automated system with UV detection at — nm. The dissolution testing should be conducted in 900 mL of stimulated gastric fluid (no pepsin) as the dissolution medium at 37°C with apparatus 1 (basket) at 50 rpm.

2. On 12/12/00, the firm responded that the above dissolution test method is not acceptable for its product Loratadine Orally Disintegrating Tablets 10 mg due to the fact that a mass of undisintegrated tablet was physically trapped at the top of the baskets.

3. The following items should be pointed out:

   a. Lederle's formulation is considerably different from the RLD's formulation (see Attachment #1 and #2).
   b. The RLD's label states that it disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be subsequently swallowed with or without water.
   c. Lederle's bioequivalence study protocol states that the subjects placed a single tablet of test or reference product

on his/her tongue and allowed it to disintegrate for 30 seconds, and swallowed the disintegrated tablet. The subjects then consumed 240 mL of room temperature water (original submission, page #109, vol. C1.2). It is not known from the submission whether or not the test product disintegrates in the same manner as the RLD.

4. On 02/12/01, the Division of Bioequivalence (DBE) held a meeting regarding ANDA #75-822. The meeting was chaired by DBE director and included members from different disciplines of the Office of Generic Drugs (OGD), (please see the attached Meeting Minutes, Attachment #3). At this meeting a concern was raised about the different dissolution behavior of Lederle's Loratadine Orally Disintegrating Tablets 10 mg, compared to the RLD Schering's Claritin® Reditabs, 10 mg. The test product may not be pharmaceuticaly equivalent to the RLD. The conclusion of this meeting is that the DBE should send a deficiency letter to the firm requesting additional in vivo data regarding performance of the test product when it is given to subjects without water.

Deficiency

The firm is requested to submit additional information regarding the performance of the test product when it is given to subjects, allowed to disintegrate in the mouth, and swallowed without water.

Recommendations

Since your test product does not pass the tolerances of the Agency-recommended dissolution method, additional information is needed to determine whether Lederle's Loratadine Orally Disintegrating Tablets, 10 mg, are pharmaceutically equivalent to the RLD Schering's Claritin® Reditabs, 10 mg. The firm is requested to provide data showing that the test product is bioequivalent to the RLD when both are administered to subjects and swallowed without water.

Zakaria Z Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT 3/5/01
FT INITIALLED BDAVIT 3/5/01

Concur: _____ Date: 3/8/2001
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-822 APPLICANT: ESI Lederle

DRUG PRODUCT: Loratadine Orally Disintegrating Tablets, 10 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified.

Since your test product does not pass the tolerances of the Agency-recommended dissolution method, additional information is needed to determine whether your Loratadine Orally Disintegrating Tablets, 10 mg, are pharmaceutically equivalent to the RLD Schering's Claritin® Reditabs, 10 mg. Please indicate if you have any data showing that your product is bioequivalent to the RLD when both are administered to subjects and swallowed without water.

Sincerely yours,

for Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-822
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer (Z. Wahba)
HFD-658/ Team Leader (B. Davit)

Endorsements:
HFD-658/ Z. Wahba 3/5/01
HFD-658/ B. Davit 3/5/01
HFD-650/ D. Conner for 3/8/2001

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BIOEQUIVALENCY - **INCOMPLETE** submission date: 12/12/00

OIC 1. **Study Amendment** Strengths: **10 mg**
Outcome: IC

OUTCOME DECISIONS: IC - Incomplete
WINBIO COMMENTS: **Incomplete** Biostudy

APPEARS THIS WAY
ON ORIGINAL

LORATADINE ORALLY DISINTEGRATING TABLETS, 10MG
ANDA 75-822
Reviewer: Z. Z. Wahba
V:\firmsam\lederle\ltrs&rev\75822a2.d00

Lederle
Philadelphia, PA
Submission Date: 12/12/00

ADDENDUM TO THE REVIEW

BACKGROUND

1. The firm previously submitted two in vivo bioequivalence studies (single-dose under fasting and non-fasting conditions) comparing its test product Loratadine Orally Disintegrating Tablets 10 mg, to the reference listed drug Schering's Claritin® Reditabs, 10 mg (submission date: 3/09/00).

2. The submission was reviewed and was found incomplete by the Division of Bioequivalence (review date 9/29/00, ANDA #75-822) due to unacceptable dissolution data. The firm's dissolution testing did not meet the Agency dissolution conditions. The test product did not pass the innovator's dissolution method specifications.

3. On August 18, 1999, the firm requested the Agency's advice for developing a dissolution method for a generic version of the RLD Claritin Reditabs. On December 7, 1999, the Agency responded to the firm's letter and stated that there is currently no official method for this product. The Agency suggested that the firm develop its own dissolution method, using USP Apparatus I (basket) or II (Paddle), and also try using USP Apparatus I (basket) at 50 rpm in 900 mL of SGF without enzyme, at ⟵ nm.

4. In the submission dated 03/09/00, the firm submitted the following dissolution method and data.

   Dissolution Medium: 0.1N HCl
   Volume: 900ml
   Apparatus Type: Apparatus 2 (paddles)
   Speed: 50 rpm

   Dissolution Data

Test	REFERENCE
Lot No.: 990043	Lot No.: 9EBT88
Strength: 10mg	Strength: 10mg
No. of Units: 12	No. of Units: 12

Time (minutes)	Mean (Test product)	Range	%CV	Mean (Ref. product)	Range	%CV
5	95.5	\	3.04	99.92	\	1.68
10	98.5		1.47	101.25		1.47
15	98.92		1.25	101.58		1.22

5. The DBE reviewed the dissolution data (review date: 3/08/01) and sent the following comments to the firm in a letter dated 3/19/01:

   Since your test product does not pass the tolerances of the Agency-recommended dissolution method, additional information is needed to determine whether your Loratadine Orally Disintegrating Tablets, 10 mg, are pharmaceutically equivalent to the RLD Schering's Claritin® Reditabs, 10 mg. Please indicate if you have any data showing that your product is bioequivalent to the RLD when both are administered to subjects and swallowed without water.

FIRM'S RESPONSE TO DEFICIENCY COMMENTS:

1. The firm informed the DBE in a teleconference (June 7, 2001) that it did not have any data showing that their product was bioequivalent to the RLD when both are administered to subjects and swallowed without water.

2. The firm referred the DBE to their previously submitted in vitro dispersion data (pages 6466-6467, volume A1.15). The firm conducted dispersion testing on both Loratadine 10 mg Orally Disintegrating Tablets (Lot #990033) and Claritin® Reditabs (Lot #9-EBT-25). Dispersion was tested visually using 200 mL water at room temperature. Claritin Reditabs floated on the surface of the water and disintegrated with an average dispersion time of 2 seconds. Lederle'sLoratadine Orally Disintegrating Tablets sank to the bottom of the containers for 10 seconds, then floated and disintegrated. The average dispersion time for loratadine tablets was 17 seconds.

3. The firm sent some of Loratadine 10 mg Orally Disintegrating Tablets and Claritin® Reditabs to the OGD. DBE and Division of Chemistry I staff checked the dissolution of the test product in the mouth. OGD staff verified that the tablets dissolve completely within the mouth in 30 seconds.

REVIEWER'S COMMENTS: The firm's response is acceptable.

RECOMMENDATIONS:

1. The two in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions conducted by ESI Lederele, on its Loratadine Orally Disintegrating Tablets 10 mg, lot #990043, comparing it to the RLD Schering's Claritin® Reditabs, 10 mg, are acceptable. The studies demonstrate that Lederle's Loratadine Orally Disintegrating Tablets 10 mg, is bioequivalent to Schering's Claritin® Reditabs, 10 mg.

2. The dissolution testing conducted by the firm on its test product Lederle's Loratadine Orally Disintegrating Tablets 10 mg (lot #990043) is acceptable.

3. The dissolution testing should be conducted in 900 mL of 0.1N HCl using apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications.

   Not less than — % (Q) of the labeled amount of the drug in the dosage form is dissolved in 6 minutes.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

BNM 7/31/01

RD INITIALED BDAVIT
FT INITIALED BDAVIT Barbara M. Davit Date: 7/31/01

Concur: Dale P. Conner Date: 8/3/01
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-822 APPLICANT: ESI Lederle

DRUG PRODUCT: Loratadine Orally Disintegrating Tablets, 10 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet, and has no further questions at this time.

The following dissolution testing should be incorporated into your manufacturing controls and stability program:

The dissolution testing should be conducted in 900 mL of 0.1N HCl using apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications.

> Not less than —% (Q) of the labeled amount of the drug in the dosage form is dissolved in 6 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the toxicology data, chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation in not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-822
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer (Z. Wahba)
HFD-658/ Team Leader (B. Davit)

Endorsements:
HFD-658/ Z. Wahba ZW 7/31/01
HFD-658/ B. Davit BD 7/31/01
HFD-650/ D. Conner 8/3/01

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BIOEQUIVALENCY - ACCEPTABLE submission date: 12/12/00

OK 1. **Study Amendment** Strengths: 10 mg
Outcome: AC

OUTCOME DECISIONS: AC - Acceptable
WINBIO COMMENTS: Acceptable Biostudy

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-822 SPONSOR : ESI Lederle

DRUG AND DOSAGE FORM : Loratadine Orally Disintegrating Tablets

STRENGTH(S) : 10 mg

TYPES OF STUDIES : In vivo bioequivalence studies under fasting and non-fasting conditions.

CLINICAL STUDY SITE(S) : ———————

ANALYTICAL SITE(S) : ———————

STUDY SUMMARY : The two studies demonstrated that under fasting and non-fasting conditions, Lederle's Loratadine Orally Disintegrating Tablet, 10 mg, is bioequivalent to Schering's Claritin® Reditabs, 10 mg.

DISSOLUTION : The dissolution data for the 10 mg are acceptable.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _No__ New facility _ For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III

INITIAL : ZZW DATE : 7/31/01

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : BMD DATE : 7/31/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 8/3/01

LORATADINE ORALLY DISINTEGRATING TABLETS,
10 MG
ANDA **75-822**
Reviewer: Z. Z. Wahba
V:\firmsam\lederle\ltrs&rev\75822a3.d01

Lederle
Philadelphia, PA
Submission Date:
December 05, 2001

Minor Amendment

Background

- The firm previously submitted two in vivo bioequivalence studies (single-dose under fasting and non-fasting conditions) comparing its test product Loratadine Orally Disintegrating Tablets 10 mg, to the RLD Schering's Claritin® Reditabs, 10 mg (submission date: 3/09/00).

- The submission was reviewed and was found acceptable by the Division of Bioequivalence (DBE review date 8/03/01). The DBE provided the firm with the following dissolution conditions:

  The dissolution testing should be conducted in 900 mL of 0.1N HCl using apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications.

  Not less than —% (Q) of the labeled amount of the drug in the dosage form is dissolved in 6 minutes.

- In this submission, the firm is asking the Agency to change its Loratadine Orally Disintegrating Tablet dissolution specification. The proposed dissolution specification changes from "NLT —% (Q) of the labeled amount of the drug in the dosage form is dissolved in 6 minutes" to " NLT —% (Q) of the labeled amount of the drug in the dosage form is dissolved in 10 minutes." The firm indicated that its finished product dissolution data from release and stability testing (18 months) of the submission batch suggest that Stage 2 testing would be required 56% of the time at the 5 minute time point.

Comments:

In general, for Lot #990043 (the bio-batch) the dissolution rate decreased with duration of storage, compared with initial values from the fresh tablets. In particular, the dissolution data obtained from the 18-month stability samples at the 5, 10, and 15-minute sampling time points showed variation in drug release compared to the dissolution data obtained from the fresh bio-batch at the same the time points.

The obtained dissolution data are summarized below:

Table #1. Initial Dissolution Profile Lot #990043 (number of units = 12)			
Time (minutes)	Mean	Range	%CV
5	96		3.2
10	99		1.6
15	99		1.2

Table #2. Three month Dissolution Profile Lot #990043 (number of units = 6)			
Time (minutes)	Mean	Range	%CV
5	94		6.5
10	97		2.2
15	98		1.7

Table #3. Six month Dissolution Profile Lot #990043 (number of units = 6)			
Time (minutes)	Mean	Range	%CV
5	86		7.2
10	97		4.2
15	98		3.5

Table #4. Nine month Dissolution Profile Lot #990043 (number of units = 6)			
Time (minutes)	Mean	Range	%CV
5	89		5.0
10	93		2.3
15	93		2.0

Table #5. Twelve month Dissolution Profile Lot #990043 (number of units = 6)			
Time (minutes)	Mean	Range	%CV
5	90		5.9
10	96		3.1
15	97		2.8

Table #6. Eighteen month Dissolution Profile Lot #990043 (number of units = 6)			
Time (minutes)	Mean	Range	%CV
5	83		6.6
10	91		1.9
15	93		1.8

Comment on the firm's request: The firm's request to change the dissolution specification from "NLT —% (Q) in 6 minutes" to "NLT —% (Q) in 10 minutes" is denied.

RECOMMENDATIONS

The firm's request for changing the dissolution specification from "NLT —% (Q) in 6 minutes" to "NLT —% (Q) in 10 minutes" is denied.

Therefore, the current dissolution conditions should still remain the same (DBE review date: 8/03/01). The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications.

Not less than —% (Q) of loratadine in the dosage is dissolved in 6 minutes.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

BMD 12/18/01

RD INITIALED BDAVIT
FT INITIALED BDAVIT Barbara M Davit Date: 12/19/01

Concur: for Dale P. Conner Date: 12/27/2001

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-822 APPLICANT: ESI Lederle

DRUG PRODUCT: Loratadine Orally Disintegrating Tablets, 10 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following comment is provided in response to your request for changing the dissolution specifications:

You request to change the dissolution specification to "Not less than —% (Q) of loratadine in the dosage is dissolved in 10 minutes" is denied.

Therefore, the current dissolution conditions will still remain the same. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications.

Not less than —% (Q) of loratadine in the dosage is dissolved in 6 minutes.

Sincerely yours,

for Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-822
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer (Z. Wahba)
HFD-658/ Team Leader (B. Davit)

Endorsements:
HFD-658/ Z. Wahba ZW 12/19/01
HFD-658/ B. Davit BWD 12/19/01
HFD-650/ D. Conner for DMC 12/27/2001

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BIOEQUIVALENCY - INCOMPLETE submission date: 12/05/00

1. Study Amendment Strengths: 10 mg
Outcome: IC

OUTCOME DECISIONS: IC - Incomplete
WINBIO COMMENTS: Incomplete Biostudy

APPEARS THIS WAY
ON ORIGINAL

LORATADINE ORALLY DISINTEGRATING TABLETS, 10 MG
ANDA 75-822
Reviewer: Z. Z. Wahba
V:\firmsam\lederle\ltrs&rev\75822A01024.doc

Lederle
Philadelphia, PA
Submission Date:
January 21, 2002

Study Amendment

Background

1. The firm previously submitted two in vivo bioequivalence studies (single-dose under fasting and non-fasting conditions) comparing its test product Loratadine Orally Disintegrating Tablets 10 mg, to the RLD Schering's Claritin® Reditabs, 10 mg (submission date: 3/09/00).

2. The submission was reviewed and was found acceptable by the Division of Bioequivalence (DBE review date 8/03/01). The DBE provided the firm with the following dissolution conditions:

   The dissolution testing should be conducted in 900 mL of 0.1N HCl using apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications.

   Not less than —% (Q) of the labeled amount of the drug in the dosage form is dissolved in 6 minutes.

   Note: Dissolution method for Lederle's product is different from the NDA method. See attachment for details.

3. On 12/05/01, the firm requested the FDA to change its Loratadine Orally Disintegrating Tablet dissolution specification from "NLT —% (Q) of the labeled amount of the drug in the dosage form is dissolved in 6 minutes" to "NLT —% (Q) of the labeled amount of the drug in the dosage form is dissolved in 10 minutes". The firm indicated that its finished product dissolution data from release and stability testing (18 months) of the submission batch suggest that Stage 2 testing would be required 56% of the time at the 5 minute time point. The Division of Bioequivalence reviewed the submitted dissolution data and denied the firm's request.

4. In this submission, the firm accepted the FDA's current specification on its Loratadine Orally Disintegrating Tablet of "NLT —% (Q) of the labeled amount of the drug in the dosage form is dissolved in 6 minutes".

RECOMMENDATIONS:

1. The two in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions conducted by ESI Lederele, on its Loratadine Orally Disintegrating Tablets 10 mg, lot #990043, comparing it to the RLD Schering's Claritin® Reditabs, 10 mg, are acceptable. The studies demonstrate that Lederle's Loratadine Orally Disintegrating Tablets 10 mg, is bioequivalent to Schering's Claritin® Reditabs, 10 mg.

2. The dissolution testing conducted by the firm on its test product Lederle's Loratadine Orally Disintegrating Tablets 10 mg (lot #990043) is acceptable.

3. The dissolution testing should be conducted in 900 mL of 0.1N HCl using apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications.

   Not less than –% (Q) of the labeled amount of the drug in the dosage form is dissolved in 6 minutes.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

testing RD INITIALED MGOKHALE Mamata Gokhale Date: 3/19/02
FT INITIALED MGOKHALE _____

Concur: _____ Date: 3/22/2002
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-822 APPLICANT: ESI Lederle

DRUG PRODUCT: Loratadine Orally Disintegrating Tablets, 10 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet, and has no further questions at this time.

The following dissolution testing should be incorporated into your manufacturing controls and stability program:

The dissolution testing should be conducted in 900 mL of 0.1N HCl using apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications.

> Not less than — % (Q) of the labeled amount of the drug in the dosage form is dissolved in 6 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the toxicology data, chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation in not approvable.

Sincerely yours,

for Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-822
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer
HFD-658/ Team Leader

Endorsements:
HFD-658/ Z. Wahba ZW 3/18/02
HFD-658/ M. Gokhale MSK 3/19/02
HFD-650/ D. Conner for RWP 3/22/2002

v:\new\firmsam\Lederle\ltrs&rev\75822A01024.doc

BIOEQUIVALENCY - ACCEPTABLE submission date: 01/21/02

1. **Study Amendment** Strengths: **10 mg**
Outcome: AC

OUTCOME DECISIONS: AC - Acceptable
WINBIO COMMENTS: Acceptable Biostudy

APPEARS THIS WAY
ON ORIGINAL

Attachment

-----Original Message-----
From: Tran, Nhan L
Sent: Tuesday, March 12, 2002 8:07 AM
To: CDER-OGDBIO
Cc: Conner, Dale P; Patnaik, Rabindra N; Ouderkirk, Larry A; Nerurkar, Shriniwas G; Huang, Yih Chain; Tran, Nhan L
Subject: LORATIDINE ORALLY DISINTEGRATING TABLET DISSOLUTION

Dear Colleagues:

There is confusion on the dissolution requirements for this drug product. The NDA method and tolerances are: Basket 50 RPM, 900 ml SGF (no enzyme) with the tolerances of NLT (Q) —% in 6 minutes. You also will find another dissolution method for this product (ANDA 75-822, Lederle): Paddle 50 RPM, 900 ml 0.1 N HCl and the tolerances are NLT (Q) —% in 6 minutes. The reason for this is Lederle's product had a problem using the NDA method. Lederle indicated that a mass of undisintegrated tablet was physically trapped at the top of the basket giving erroneous results. Lederle therefore would like to use the paddle method instead of the basket method. The DBE accepted Lederle's method since the in-vivo study was acceptable.

Therefore, to answer the firm's request on the dissolution requirements of loratidine orally disintegration tablets, I suggest the following: Recommend the NDA method first. If the firm runs into problems similar to that of Leaderless, the second method can be used (Lederle's method).
I hope this will clear up some confusion.

Thanks,

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-822 SPONSOR : ESI Lederle

DRUG AND DOSAGE FORM : Loratadine Orally Disintegrating Tablets

STRENGTH(S) : 10 mg

TYPES OF STUDIES : In vivo bioequivalence studies under fasting and non-fasting conditions.

CLINICAL STUDY SITE(S) : ———————

ANALYTICAL SITE(S) : ———————

STUDY SUMMARY : The two studies demonstrated that under fasting and non-fasting conditions, Lederle's Loratadine Orally Disintegrating Tablet, 10 mg, is bioequivalent to Schering's Claritin® Reditabs, 10 mg.

DISSOLUTION : The dissolution data for the 10 mg are acceptable.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _No__ New facility _ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III

INITIAL : ZZW DATE : 3/18/02

TEAM LEADER : Mamata Gokhale, Ph.D. BRANCH : III

INITIAL : MSG DATE : 3/19/02

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

for

INITIAL : [signature] DATE : 3/22/2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-822

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : March 15, 2000

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 3/15/00

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Loratadine Orally Disintegrating Tablets, 10 mg, to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355 (j)(5)(B)(iv).

ESI Lederle has submitted ANDA 75-822 for Loratadine Orally Disintegrating Tablets, 10 mg.
The ANDA contains a certification pursuant to 21 USC 355 (j)(2)(A)(vii)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the study submitted by ESI Lederle on March 9, 2000 for its Loratadine product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

ANDA 75-822

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

✓ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

Director, Division of Bioequivalence — Date 3/21/00

Telecon Record

Date: 4/7/00

ANDA: 75-822

Firm: ESI Lederle

Drug: Loratadine Orally Disintegrating Tablets, 10 mg

FDA Participants: Paras Patel

Industry Participants: Nicholas Tantillo

Phone #: 914-732-4137

Agenda:

1. Paras asked Nicholas to provide components and composition for Natural and Artificial Mint Flavor ——— Nicholas said he will have the manufacturer contact the agency directly.

MEETING MINUTES

Meeting Date: 12 February 2001 **Time:** 1000

Location: MPNII, Conference Room B

Drug Name: Loratadine Orally Disintegrating Tablets, 10 mg
ANDA 75-822

Meeting Type: Internal

Meeting Chair: Dale Conner, Pharm.D.

Meeting Recorder: Steven Mazzella, R.Ph.

FDA Attendees, titles and offices:

Dale Conner, Pharm.D.	Director, DBE
Rabi Patnaik, Ph.D.	Deputy Director, DBE
Barbara Davit, Ph.D.	Team Leader, Branch III, DBE
Zakaria Wahba, Ph.D.	Reviewer, Branch III, DBE
Steven Mazzella, R.Ph.	Project Manager, DBE
Paul Schwartz, Ph.D	Acting,Deputy Director ChemistryI
Dave Gill, Ph.D	Team Leader, Chemistry Team 4
Greg Davis, R.Ph.	Branch Chief,Regulatory Support
John Grace, R.Ph.	Branch Chief,Labeling
Shing Liu, Ph.D	Reviewer, Chemistry Team 4
Ruby Yu, Pharm.D.	Project Manager, Chemistry Team 4

Meeting Objectives:

1. To decide whether Lederle's Loratadine Orally Disintegrating Tablets, 10 mg are pharmaceutically equivalent to the reference listed drug (RLD).

Discussion Points:

1. Lederle has submitted ANDA 75-822, Loratadine Orally Disintegrating Tablets, 10 mg to the Office of Generic Drugs (OGD) for review. The RLD is Schering's Claritin® Reditabs, Loratadine Rapidly Disintegrating Tablets, 10 mg. Both products have the same active ingredient and route of administration. Currently, the 2000 USP doesn't include the dosage form rapidly disintegrating tablets.

2. ANDA 75-822 was found to be bioequivalent to the RLD based on an acceptable bioequivalence study. However, the product was unable to pass the innovator's dissolution method. Lederle concluded that the RLD's dissolution test method is not acceptable for their Loratadine Orally Disintegrating Tablets due to the fact that a mass of undisintegrated tablet was physically trapped at the top of the baskets. Lederle has asked the Agency if they would consider an alternate dissolution method.

3. Lederle's formulation is considerably different than the RLD, enclosure (1).

4. The RLD's label states that it disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be subsequently swallowed with or without water enclosure (2). Lederle's bioequivalence study protocol states that the subjects placed a single reditab or a single generic tablet on his/her tongue and allowed it to disintegrate for 30 seconds and swallowed the disintegrated tablets. The subjects then consumed 240 mL of room temperature water enclosure (3). It is not known from the submission whether or not Lederle's product disintegrates in the mouth in same manner as the RLD.

Decisions (agreements) reached:

1. There is not enough information to determine that the two products are the same.

2. A better determination can be made if Lederle submits data regarding its product's performance under all conditions of use.

Unresolved issues or issues requiring further discussion:

None

Action items:

1. The Division of Bioequivalence (DBE) will send a deficiency letter to Lederle requesting additional data regarding the product's performance without water.

Distribution: ANDA # 75-822
All Attendees (##)
Office Director Reading File
Firm File

Dale Conner\
Rabi Patnaik\
Zakaria Wahba\
Barbara Davit\
Steven Mazzella\
Paul Schwartz\
Dave Gill\
Greg Davis\
John Grace\
Ruby Yu\
Shing Liu\

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Attachment

MEETING MINUTES

Meeting Date: 7 June 2001 **Time:** 1530

Location: MPNII, Room E-146

Drug Name: Loratadine Orally Disintegrating Tablets, 10 mg
ANDA 75-822

Meeting Type: External

Meeting Chair: Barbara Davit, Ph.D.

Meeting Recorder: Steven Mazzella, R.Ph.

FDA Attendees, titles and offices:

Barbara Davit, Ph.D.	Team Leader, Branch III, DBE
Zakaria Wahba, Ph.D.	Reviewer, Branch III, DBE
Steven Mazzella, R.Ph.	Project Manager, DBE
Eric Messner	ESI Lederle
———————	ESI Lederle
——————— ,MD	ESI Lederle

Meeting Objectives:

1. To discuss the March 19, 2001 deficiency letter sent to ESI Lederle from the Division of Bioequivalence (DBE) regarding ANDA 75-822, Loratadine Orally Disintegrating Tablets, 10 mg.

Discussion Points:

1. ESI Lederle has submitted ANDA 75-822, Loratadine Orally Disintegrating Tablets, 10 mg to the Office of Generic Drugs (OGD) for review. The RLD is Schering's Claritin® Reditabs, Loratadine Rapidly Disintegrating Tablets, 10 mg. Both products have the same active ingredient and route of administration. Currently, the 2000 USP doesn't include the dosage form rapidly disintegrating tablets.

2. ANDA 75-822 was found to be bioequivalent to the RLD based on an acceptable bioequivalence study. However, the product was unable

to pass the innovator's dissolution method. ESI Lederle concluded that the RLD's dissolution test method is not acceptable for their Loratadine Orally Disintegrating Tablets due to the fact that a mass of undisintegrated tablet was physically trapped at the top of the baskets. ESI Lederle has asked the Agency if they would consider an alternate dissolution method.

3. Lederle's formulation is considerably different than the RLD. In addition, RLD's label states that it disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be subsequently swallowed with or without water. ESI Lederle's bioequivalence study protocol states that the subjects placed a single reditab or a single generic tablet on his/her tongue and allowed it to disintegrate for 30 seconds and swallowed the disintegrated tablets. The subjects then consumed 240 mL of room temperature water. It is not known from the submission whether or not ESI Lederle's product disintegrates in the mouth in same manner as the RLD.

4. The Division of Bioequivalence (DBE) sent a deficiency letter to ESI Lederle on March 19, 2001, requesting additional information regarding their product's performance without water in order to determine whether their product is pharmaceutically equivalent to the RLD.

5. ESI Lederle does not have any data regarding its product's performance without water. [redacted] MD, observed that the subjects no longer felt a physical tablet 15-20 seconds after it was placed on their tongue during the bioequivalence study. However, this observation was not documented.

6. ESI Lederle has included dispersion test results for both products on pages 6465 - 6467 of their original submission.

Decisions (agreements) reached:

1. The DBE has requested that ESI Lederle send ten tablets of both the test and reference products to the Agency to aid in the determination that the two products are the same.

2. The DBE encourages ESI Lederle to use the same dissolution method as the RLD, however, the DBE can consider another dissolution method.

Unresolved issues or issues requiring further discussion:

None

Action items:

1. ESI Lederle will send approximately ten tablets of both the test and reference products to the Agency.

2. The DBE will review the dispersion test results in the original application.

Distribution: ANDA # 75-822
All Attendees (##)
Office Director Reading File
Firm File

Zakaria Wahba\
Barbara Davit\
Steven Mazzella\

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RECORD OF TELEPHONE CONVERSATION

The firm was asked to revise the following specifications:

For Drug Substance:

- [redacted]
- [redacted]
- [redacted]

For Drug Product Release and Stability

- [redacted]
- [redacted]

The response will be submitted as a telephone amendment.

DATE:
May 8, 2002

ANDA NUMBER:
75-822

PRODUCT NAME:
Loratadine Orally Disintegrating Tablets

FIRM NAME:
ESI Lederle

FIRM REPRESENTATIVE:
Nick Tantillo

PHONE NUMBER:
845-602-4137

FDA REPRESENTATIVES:
Dave Gill
Bob Trimmer
Ruby Wu

SIGNATURES:
Dave Gill DSGill
Bob Trimmer
Ruby Wu

5-8-02

5/8/02

CC: ANDA 75-822
Telecon Binder

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 27, 2002

FROM: Gary J. Buehler
Director
Office of Generic Drugs

SUBJECT: Loratadine Over-the-Counter and Patent Certifications

TO: The Records for all active Loratadine ANDA's (list attached)

Loratadine Background

Issue:

Now that the Schering NDA supplements converting the status of loratadine to OTC are approved, will an applicant that has already submitted an ANDA for approval of the Rx version of the drug be required to submit new patent certifications as part of the amendment to seek approval for a generic drug with the new OTC labeling?

Background:

The Schering NDA supplements for OTC use of loratadine products were approved on November 27, 2002. The approved product will be the OTC version of loratadine labeled for treatment of rhinitis only. Schering has indicated that it will not continue to market an Rx loratadine product to treat urticaria.

There are various products that contain loratadine that will migrate to over-the-counter status (i.e., oral tablets, orally disintegrating tablets, oral liquid, loratadine and pseudoephedrine sulfate extended release tablets with 12 hour and 24 hour dosing intervals.

The primary patent, U.S.Patent No. 4,282,223, (the '223 patent) barring ANDA/505(b)(2) approvals expires (with its pediatric exclusivity extension) on December 19, 2002. In the case of the other listed patents, the NDA holder did not sue in response to notice of certification for U.S. Patent No. 4,863,931 (the '931 patent). In addition the 30-month stay either remains in place or

in some instances has expired with respect to U.S. Patent No. 4,659,716 (the '716 patent). In the United States District Court,District of New Jersey, Schering Corporation v. Impax Laboratories, Inc. Civil Action No. 01-0520(JWB), claims 1 and 3 of the '716 patent were found invalid. Claims 1 and 3 were the only claims that Schering asserted as being infringed. This was with respect to Impax's ANDA 76-050 for Loratadine/Pseudoephedrine Sulfate Extended-release Tablets, 5mg/120mg (a generic version of Claritin D-12).

Three 505(b)(2) applications have been submitted for loratadine. These were 505(b)(2) applications because the sponsors (Wyeth, Perrigo) were seeking approval for an OTC version of loratadine products (i.e. tablets and orally disintegrating tablets) prior to Schering's submission of an application for an over-the-counter version of Claritin. These three applications would be approvable independent of Claritin going OTC, based upon the agency's stated view that the product may be used safely and effectively OTC. Because these applicants have only been seeking approval for the OTC use, their patent certifications to Schering asserted that their proposed OTC product did not infringe the patent. Only one 505(b)(2), Wyeth's NDA 21-375 for loratadine orally disintegrating tablets, is currently ready for final approval on December 19, 2002.

There are multiple ANDAs for the five different Schering loratadine drug products (syrup, immediate release tablets, rapidly disintegrating tablets, in combination with pseudoephedrine with 12 and 24 hour dosing intervals). These ANDAS are currently for the prescription form of the drug, because that was the approved reference listed drug prior to the switch to OTC. Now that the Schering OTC supplements are approved, and they have withdrawn their prescription product for urticaria, there will no longer be a prescription product to reference. Pending ANDAs, therefore must either be withdrawn or amended to reference the approved OTC form of the drug.

The issue for OGD is what new patent certifications, if any, will be required in ANDA amendments to revise the proposed generic prescription labeling to the new OTC Claritin labeling.

The regulations require that an NDA applicant submit to FDA as part of a supplement (1) any new patents that claim the drug or use of a drug for which approval of the supplement is sought and (2) information on any already submitted patent that claims the changed product. 21 CFR 314.53(d)(2).

According to the review division, Schering is making no changes to its product except to the labeling, and it has submitted no new patents or information on already submitted patents that

protect the new labeling.

FDA has consistently interpreted the FFDCA to require new patent certifications in ANDAs when new patents are submitted for an unchanged RLD before the ANDA is approved. In addition, the agency has required new patent certifications when the RLD is changed in some way (e.g., a new formulation) and a new patent is submitted to claim the change. In addition, the FDA has also required a new patent certification when the ANDA product is changed in some way (e.g., a new formulation) and there are existing patents listed with the FDA. There does not appear to be much experience with changes to the innovator drug product that are not accompanied by new patent information.

Recommendation:

Our view is that, if the ANDA applicant has already submitted adequate patent certifications for those aspects of the drug product that will not be changed by either the NDA supplement or the corresponding ANDA amendment, the inquiry is whether the innovator product has obtained or asserted new protections for the new aspect of the drug that will be duplicated by the generic company or whether existing patents also cover the new aspect of the drug. If the innovator does not assert any new protections for the changed product, the ANDA applicant will have no obligation to submit new patent certifications. If, however, the ANDA applicant changes the proposed generic drug in a way that could change its relation to the patent, then it will be required to certify to the relevant patents. This approach is in accordance with the requirements in 21 CFR 314.94(b)(12)(viii)(C) that "an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate."

In the loratidine case, this would mean that if Schering submits no new patents or patent claims for the OTC loratidine products **and** the ANDA applicants amend their applications only to conform with the labeling changes Schering made in the listed drug, the ANDA applicants would have no new patent certification obligations. If, however, an ANDA applicant decided to change its product to add the new OTC labeling AND to change the formulation, then that applicant would be required to provide new patent certifications.

Once the new labeling is submitted to an ANDA file, the application may proceed to approval after December 19, 2002, if it is otherwise ready for approval and all scientific and legal issues have been resolved.

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Drafted by: L. Dickinson, 11/7/02
Revised by: C. Parise 11/15/02
Concur: L. Dickinson 11/22/02
Edited by: R. West 11/27/02
Edited by: G. Buehler 11/27/02

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 23, 2002

FROM: Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

SUBJECT: Loratadine Orally Disintegrating Tablets

TO: ANDA 75-822 – ESI Lederle
ANDA 75-990 - Andrx
ANDA 76-011 - IMPAX

An internal FDA meeting was held on April 15, 2002, to discuss Impax's Orally Disintegrating Tablets and the issue of sameness of the dosage form. The issue is that Impax's Loratadine Orally Disintegrating Tablets take longer to disintegrate on the tongue than Schering's Claritin RediTabs. An informal test by OGD personnel indicated that the Impax product took 20-25 seconds to disintegrate vs. 5 seconds for Clairitin RediTabs.

There is no USP monograph that describes an orally disintegrating tablet and the amount of time required for disintegration. In addition, there are no specifications in Schering's NDA 20-704 for the amount of time it takes to disintegrate on the tongue.

The labeling for these products will be the same as the reference listed drug, Claritin RediTabs, with respect to the directions for use and the route of administration. Therefore, the patients will use the product in the same manner.

All of the ANDA Loratadine Orally Disintegrating Tablets are "orally disintegrating" the same as Claritin RediTabs (i.e., orally disintegrating). There is no specification in the NDA or the USP regarding the amount of time it takes for one of these tablets to disintegrate; therefore, these products will be considered to be the same as the reference listed drug, Claritin, and will be pharmaceutically equivalent. In addition, if shown to be bioequivalent, the products will be considered to be therapeutically equivalent.

All three products meet the dissolution specifications established by the FDA.

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cc: ANDA 76-011
ANDA 75-990
ANDA 75-822

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-822 Applicant Wyeth Consumer Healthcare
Drug Loratadine Orally Disintegrating Tablets Strength 10 mg

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:

	DRAFT Package	FINAL Package
1. Project Manager, Team 4 Sarah Kim Review Support Br	Date 1/21/03 Initials SKM	Date 1/22/03 Initials SKM

Application Summary:

Original Rec'd date 3/10/00
Date Acceptable for Filing 3/10/00 ✓
II 133 - exp 12/19/02 Patent Certification (type) III, IV
Date Patent/Exclus.expires _____
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
I 116 - exp 10/21/04, 131 - exp 3/15/09 First Generic Yes ☐ No ☒
(If YES, Pediatric Exclusivity Tracking System (PETS) 1st gen. admit on 75-990
RLD =
Date checked _____ NDA# _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐
Previously reviewed and tentatively approved po ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 4/23/02
Date of Office Bio Review 8/3/01, 3/8/01, 12/27/ 3/22/
Date of Labeling Approv. Sum 1/21/03
Date of Sterility Assur. App. NA
Methods Val. Samples Pending Yes ☒ No ☒
Commitment Rcd. from Firm Yes ☐ No ☐
MV samples sent 5/31/02
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐ N/A

2. Gregg Davis **PPIV ANDAs Only** Date 23-JAN-2003 Initials ☒ Date 23-JAN-2003 Initials ☒
Supv., Reg. Support Branch

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐
Has case been settled: Yes ☐ No ☒
Date settled:
Is applicant eligible for 180 day Generic Drugs Exclusivity for each strength: Yes ☒ No ☐
Comments:

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
Date Checked Previously granted
#III, #IV
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐
RLD-Claritin Reditabs 10mg Schering Corp. NDA 20-70 (cc

Firm is first w/ pIII for '716 & '931 - not sued on '931 & 30 mos expired for '716 on 11/2/02 - OK for full approval w/ 180 day exclusivity.
There is no unexpired Exclusivity listed in the Orange Book for this drug product.

3. Div. Dir./~~Deputy Dir.~~ Chemistry Div. I ~~or II~~ Date 1/22/03 Initials RK
Comments:

The CMC section is satisfactory.

REVIEWER: **FINAL ACTION**

4. Frank Holcombe
Assoc. Dir. For Chemistry
Date ___
Initials ___
Comments: (First generic drug review)
~~A~~ ANDA 75-990 (Andrx) received tentative approval on 11/15/02 for this drug product.
N/A

5. Peter Rickman
~~Acting~~ Director, DLPS
Date 1/31/03
Initials [illegible] for
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: Acceptable EES dated 4/23/02 (Verified 1/31/03), No OAI alerts noted. Bioequivalence studies (Single-dose fasting and non-fasting) found acceptable 7/31/01. Dissolution studies also found acceptable. Bio studies performed by [redacted] (dosing and analytical) This facility was an acceptable DSI inspectional history. Office-level bio endorsed 4/3/01, and 3/22/02. On 12/3/02 OGD informed ANDA applicants to submit OTC labeling. FPL found acceptable 1/21/03. CMC found acceptable 1/28/03. Methods validation was completed and found acceptable.
~~OR~~

5. Robert L. West
~~Acting~~ Deputy Director, OGD
Date 2/10/2003
Initials Robert West
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: In memo dated 11/27/02, OGD asserted that ANDA holders of bioratable drug products would not have to recertify to Schering's patents when the RLD ~~vested~~ from Rx to OTC status (provided Schering listed no new patents - it didn't). [redacted] (formerly ANDA holder's name) made paragraph IV certifications to both the '716 and '931 patents. ESI [redacted] (now Wyeth Consumer Healthcare) was sued only on the '716 patent. A district court decision was made on 8/8/02 stating that the claims of the '716 patent were not infringed. Schering has appealed this decision. This approval is based upon the expiration of the 30 month period (11/2/02). This is also a "pre-Hyken" application - 180-day exclusivity trigger is first marketing or ~~appeals~~ court decision.

6. Gary Buehler
Director, OGD
Date GB
Initials 2/10/03
Comments: for ① disintegrating tablets

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg. Issue ☐

7. Project Manager, Team Sarah Kim
Review Support Branch
Date 2/10/03
Initials SK

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
4:21 pm Time notified of approval by phone 4:26 pm Time approval letter faxed

FDA Notification:
2/10/03 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
2/10/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

eports\approval\approvrou2.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-822

CORRESPONDENCE

BA/BE and CMC ESDs to follow within 30 days

March 9, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Loratadine Orally Disintegrating Tablets, 10 mg

Dear Sir/Madam:

We are submitting a complete Abbreviated New Drug Application pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Loratadine Orally Disintegrating Tablets, 10 mg.

This application provides for the manufacture, processing, testing, labeling and packaging of the dosage form at a third party contract manufacturing facility, [redacted]

This application, containing 17 unnumbered volumes, is organized in the format suggested in the February 1999 Guidance for Industry entitled "Organization of an ANDA."

The reference listed drug product in this application is Claritin® RediTabs™, 10 mg, manufactured by Schering. The active ingredient, dosage form, strength and route of administration of the proposed product are the same as those of the reference listed drug. A side-by-side comparison of the proposed product labeling to the listed drug product labeling is included in this application. The proposed product, like the innovator product, will be marketed as a prescription drug as stated in the labeling.

The agency publication, "Approved Drug Products with Therapeutic Equivalence Evaluations", 19th Edition through supplement 12, hereafter referred to as the "Orange Book", indicates that there is no unexpired exclusivity for the listed drug.

The Orange Book lists four U.S. patents for Claritin® RediTabs™. This application contains a paragraph II certification with respect to U.S. Patent 4,371,516, which expired February 1, 2000. This application also contains a paragraph III certification with respect to U.S. patent 4,282,233, which is presently scheduled to expire on June 19, 2002. We request that approval of this application be made effective on the expiration of U.S. patent 4,282,233 on

June 19, 2002. This application additionally contains paragraph IV certifications with respect to U.S. patent 4,659,716, expiring on April 21, 2004 and U.S. patent 4,863,931 expiring on September 15, 2008. We are giving the required notice under section 505(j)(2)(B)(i) of the Federal Food, Drug, and Cosmetic Act to the owner of the patents which are the subjects of the certifications and the holder of the approved application for Claritin® RediTabs™ (Schering).

To demonstrate the bioequivalence of ESi Lederle's Loratadine Orally Disintegrating Tablets to Claritin® RediTabs™, two *in vivo* studies were conducted. One study is entitled "A Single-Dose, Randomized, Crossover Study Comparing ESi Lederle Loratadine 10 mg Fast Dissolving Tablets and Schering Claritin® RediTabs in Healthy, Male and Female Subjects Under Fasted Conditions". The other study is entitled "A Comparative, Randomized, 3-Way Crossover Study Comparing ESi Lederle Loratadine 10 mg Fast Dissolving Tablets and Schering Claritin® RediTabs in Healthy, Male and Female Subjects Under Fed and Fasted Conditions". The two completed studies, included in Section VI of this application, demonstrate the *in vivo* bioequivalence of the proposed product to the reference product. A BA/BE ESD will follow this application within 30 days.

We are using Loratadine bulk drug substance manufactured by ——————— ——————— This application contains a letter from ——————— authorizing FDA to refer to their DMF # ———on behalf of ESi Lederle.

The submission batch size for Loratadine Orally Disintegrating Tablets was ———tablets, the same as the anticipated production batch size. The submission batch was packaged in unit dose blister cards using the same packaging materials proposed for marketing.

We are providing a brief, general description of the ——————— facility, operations, and controls.

With respect to analytical methods, two copies of the methods validation are being submitted with this application since we are proposing our own methods of testing for the drug product and drug substance which are not compendial articles.

In accordance with 21 CFR 314.94 requiring the submission of an additional copy of the chemistry, manufacturing and controls section of applications, we are providing a field copy directly to the Minneapolis, Minnesota District Office. We certify that the field copy is a true copy of the chemistry, manufacturing and controls section of our application.

This application contains a certification statement with respect to convictions or persons debarred under 21 USC 335a(a) or (b).

Please contact the undersigned if you need any additional information. Our fax number is (914) 732-5689.

Sincerely,

Nicholas C. Tantillo
Senior Director, Regulatory Affairs
ESi Lederle
(914) 732-4137

ANDA 75-822

ESI Lederle
Attention: Nicholas Tantillo
P.O. Box 41502
Philadelphia, PA 19101

APR 20 2000

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated April 7, 2000 and to the correspondence dated April 13, 2000.

NAME OF DRUG: Loratadine Orally Disintegrating Tablets, 10 mg

DATE OF APPLICATION: March 9, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 10, 2000

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Nasser Mahmud, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Ruby Yu
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-822
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/NMahmud, Chief, RSB date 4/19/00
HFD-615/PPatel, CSO date 4/19/00
Word File V:\Firmsam\ESILeder\ltrs&rev\75822.PIV
FT/mjl/4/19/00
ANDA Acknowledgment Letter!

PATENT AMENDMENT

NEW CORRESP
NC.

June 8, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Loratadine Orally Disintegrating
Tablets, 10 mg
ANDA 75-822

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on March 9, 2000 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Loratadine Orally Disintegrating Tablets, 10 mg.

Reference is also made to the Paragraph IV patent certifications submitted in our original application with respect to U.S. patent numbers 4,659,716 and 4,863,931.

In accordance with 21 CFR 314.95(a) and section 505(j)(2)(B)(ii) of the Food, Drug, and Cosmetic Act, we have provided notice of certification to Schering Corporation, the holder of the approved NDA for the reference listed drug, Claritin® RediTabs™, and the owner of record of the above referenced patents. We certify that the notice met the requirements of 21 CFR 314.95(c).

The notice of certification was originally sent to Schering Corporation on May 1, 2000 via U.S. certified mail with return receipt requested. The return receipt has not been received by us and is presumed lost. The notice of certification was resent to Schering Corporation on May 17, 2000, this time via the U.S. Postal Service's Express Mail with return receipt requested. Again, we have not received the return receipt. U.S. Express Mail allows tracking of the package via the Internet and we were able to determine that the notice of certification was delivered to Schering on May 18, 2000. A copy of the U.S. Express Mail label with the tracking number, addressed to Schering Corporation's General Counsel, and the tracking confirmation for the package showing receipt by Schering on May 18, 2000, is included in Section III of this amendment. Based on this, we compute the 45-day period provided for in section 505(j)(4)(B)(iii) of the Federal Food, Drug and Cosmetic Act to begin on May 19, 2000.

401 North Middletown Rd., Pearl River, NY 10965-1299 Tel: (914) 732-5000

Please contact the undersigned if you need any additional information. Our fax number is (914) 732-5689.

Sincerely,

Eric J Messner /for

Nicholas C. Tantillo
Senior Director, Regulatory Affairs
ESI Lederle
(914) 732-4137

APPEARS THIS WAY
ON ORIGINAL

ESI LEDERLE

PATENT AMENDMENT

NEW CORRESP

August 1, 2000

Lederle sued on 7/6 only w/in 45d

Start of 45 clock was 5/3/00 : on 6/15

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Loratadine Orally Disintegrating Tablets, 10 mg
ANDA 75-822

Start of 30 mos clock 5/2/0

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on March 9, 2000 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Loratadine Orally Disintegrating Tablets, 10 mg.

Reference is also made to our June 8, 2000 Patent Amendment in which we submitted documentation of the notice of certification provided to Schering Corporation with respect to U.S. patent numbers 4,659,716 and 4,863,931. Schering, the holder of the approved NDA for the reference listed drug, Claritin® RediTabs™, and the owner of record of the referenced patents, received the notice of certification on May 2, 2000.

Schering initiated patent infringement proceedings against us within the 45-day statutory period with regard to patent no. 4,659,716. No action is being taken against us with regard to patent no. 4,863,931. Civil Action No. 00-2944 for the infringement of patent number 4,659,716 was filed in the United States District Court for the District of New Jersey on June 15, 2000. A copy of the summons and complaint is included in Section III of this amendment.

Please contact the undersigned if you need any additional information. Our fax number is (845) 732-5689.

Sincerely,

Eric J. Messner for

Nicholas C. Tantillo
Senior Director, Regulatory Affairs
ESI Lederle
(845) 732-4137

CENTER FOR EVALUATION AND RESEARCH RECD AUG 0 2 2000 OGD

401 North Middletown Rd., Pearl River, NY 10965-1299 Tel: (914) 732-5000

MAJOR AMENDMENT

SEP 20 2000

ANDA 75-822

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Esi Lederle

TEL: 845-732-4137

ATTN: Nicholas C. Tantillo

FAX: 845-732-5689 or 914-732-5689

FROM: Ruby Yu

PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 9, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine Orally Disintegrating Tablet, 10 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance

SPECIAL INSTRUCTIONS:
Chemistry comments are provided. Bioequivalency and labeling comments will be provided when the reviews are completed.

RPM
9/20/00

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

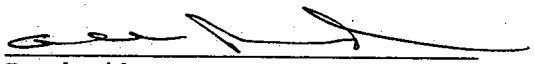
9/20/2000 FDA FAX

3. Labeling portion of your application is under review. Any deficiencies will be conveyed to you in a separate letter.

4. Bioequivalence portion of your application is under review. The acceptance of your dissolution stability data is contingent upon acceptance of your dissolution method and specifications by the Division of Bioequivalence.

5. Please be advised that if the Division of Bioequivalence recommends different specifications for the dissolution from what you have used to conduct your stability studies on the executed batch lot #990043, it will be necessary for you to provide additional accelerated stability data using the revised dissolution specifications as soon as possible.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY AMENDMENT

OCT 4 2000

ANDA 75-822

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: ESI Lederle

TEL: 845-732-4137

ATTN: Nicholas C. Tantillo

FAX: 845-732-5689

FROM: Steven Mazzella

PROJECT MANAGER: 301-827-5847

Dear Nicholas C. Tantillo:

This facsimile is in reference to the bioequivalency data submitted on March 9, 2000, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine Orally Disintegrating tablets,10 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

OCT 4 2000

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-822 APPLICANT: ESI Lederle

DRUG PRODUCT: Loratadine Orally Disintegrating Tablets, 10 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

Please submit dissolution data applying the following method and specification:

For the test method: use an automated system with UV detection at ___ nm. The dissolution testing should be conducted in 900 mL of stimulated gastric fluid (no pepsin) as the dissolution medium at 37°C with apparatus 1 (basket) at 50 rpm. The dissolution specifications for the test product will be established based on acceptable submitted dissolution data.

Sincerely yours,

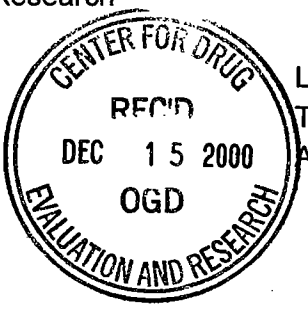
Barbara M Davis

for Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY AMENDMENT

December 12, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855



ANDA 75-822 AMENDMENT

Loratadine Orally Disintegrating Tablets, 10 mg
ANDA 75-822

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on March 9, 2000 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Loratadine Orally Disintegrating Tablets, 10 mg.

Reference is also made to your comment letter dated October 4, 2000 which identified the following deficiency in our application. Our reply is as follows:

COMMENT: **Please submit dissolution data applying the following method and specification:**

For the test method: use an automated system with UV detection at ——nm. The dissolution testing should be conducted in 900 mL of simulated gastric fluid (no pepsin) as the dissolution medium at 37°C with apparatus 1 (basket) at 50 rpm. The dissolution specifications for the test product will be established based on acceptable submitted dissolution data.

REPLY: Dissolution data using the test method described above were included in report RA 2000-27, *Dissolution of Loratadine Tablets using Baskets at 50 rpm in Simulated Gastric Fluid without Enzymes,* located on pages 6462-6464 of our original submission. For ease of your review, a copy of the report is included with this amendment. The report concludes that this test method is not acceptable for our Loratadine Orally Disintegrating Tablets due to the fact that a mass of undisintegrated tablet was physically trapped at the top of the baskets.

In accordance with 21 CFR 314.94 requiring the submission of an additional copy of the chemistry, manufacturing and controls section of applications, we are providing a field copy directly to the Minneapolis, Minnesota District Office. We certify that the field copy is a true copy of the chemistry, manufacturing and controls section of our application.

We trust that we have adequately addressed your comments. Please contact the undersigned should you need any additional information.

Sincerely,

Eric J Messner /for

Nicholas C. Tantillo
Senior Director, Regulatory Affairs
ESI Lederle
(845) 732-4137

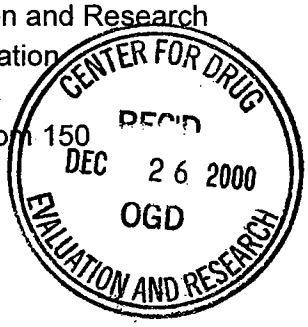
MAJOR AMENDMENT

CMC ESD to follow within 30 days

December 22, 2000

NDA ORIG AMENDMENT
N/AC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855



Loratadine Orally Disintegrating Tablets, 10 mg
ANDA 75-822

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on March 9, 2000 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Loratadine Orally Disintegrating Tablets, 10 mg.

Reference is also made to your comment letter dated September 20, 2000 which outlined deficiencies noted in our application. We understand our response will be considered a Major Amendment. Our reply is as follows:

A. DEFICIENCIES:

COMMENT 1:

REPLY:

Redacted 6 page(s)

of trade secret and/or

confidential commercial

information from

ESI/LEDERLE 12/22/2000 LETTER

COMMENT 3: **Labeling portion of your application is under review. Any deficiencies will be conveyed to you in a separate letter.**

REPLY: We understand that the labeling portion of our application is under review and that any deficiencies will be conveyed to us in a separate letter.

COMMENT 4: **Bioequivalence portion of your application is under review. The acceptance of your dissolution stability data is contingent upon acceptance of your dissolution method and specifications by the Division of Bioequivalence.**

REPLY: We understand that the bioequivalence portion of our application is under review and that the acceptance of our dissolution stability data is contingent upon acceptance of our dissolution method and specifications by the Division of Bioequivalence.

COMMENT 5: **Please be advised that if the Division of Bioequivalence recommends different specifications for the dissolution from what you have used to conduct your stability studies on the executed batch lot #990043, it will be necessary for you to provide additional accelerated stability data using the revised dissolution specifications as soon as possible.**

REPLY: We understand that if the Division of Bioequivalence recommends different specifications for the dissolution test from what we have used to conduct our stability studies on the executed batch lot #990043, it will be necessary for us to provide additional accelerated stability data using the revised dissolution specifications as soon as possible.

In accordance with 21 CFR 314.94 requiring the submission of an additional copy of the chemistry, manufacturing and controls section of applications, we are providing a field copy directly to the Minneapolis, Minnesota District Office. We certify that the field copy is a true copy of the chemistry, manufacturing and controls section of our application.

We trust that we have adequately addressed your comments. Please contact the undersigned should you need any additional information.

Sincerely,

Eric J Messner /for

Nicholas C. Tantillo
Senior Director, Regulatory Affairs
ESi Lederle
(845) 732-4137

APPEARS THIS WAY
ON ORIGINAL

ELECTRONIC CMC AMENDMENT ENCLOSED

January 11, 2001

Office of Generic Drugs
CDER FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/AC

Loratadine Orally Disintegrating
Tablets, 10mg
ANDA 75-822

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application which was submitted on March 9, 2000 pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act for Loratadine Orally Disintegrating Tablets, 10mg.

Reference is also made to our amendment dated December 22, 2000. We have prepared an electronic submission of the CMC amendment for the referenced product using FDA's Electronic Validation Application (EVA) version 4.14, and we are submitting the information for use during review of our ANDA for Loratadine Orally Disintegrating Tablets, 10mg. The information is contained on two 3½" diskettes (1 original, 1 copy).

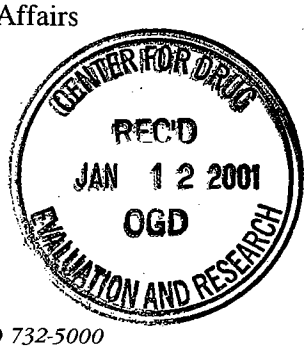
We certify that the data that is submitted electronically is identical to the data contained in the hard copy submission.

If you need any clarification of the information provided or additional data, please feel free to contact me at (845) 732 - 4340.

Sincerely,

Linda O'Dea

Linda O'Dea
Associate Director
Regulatory Affairs



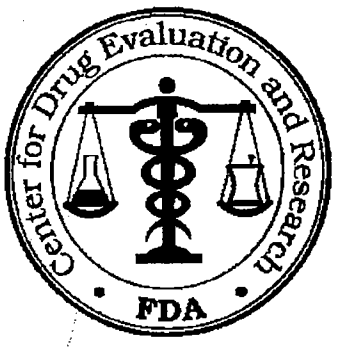
401 North Middletown Rd., Pearl River, NY 10965-1299 Tel: (845) 732-5000

BIOEQUIVALENCY AMENDMENT

ANDA 75-822

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAR 19 2002



TO: APPLICANT: ESI Lederle

TEL: 845-732-4137

ATTN: Nicholas C. Tantillo

FAX: 845-732-5689

FROM: Steven Mazzella

PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on December 12, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine Orally Disintegrating Tablets, 10 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

MAR 19 2001

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-822 APPLICANT: ESI Lederle

DRUG PRODUCT: Loratadine Orally Disintegrating Tablets, 10 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified.

Since your test product does not pass the tolerances of the Agency-recommended dissolution method, additional information is needed to determine whether your Loratadine Orally Disintegrating Tablets, 10 mg, are pharmaceutically equivalent to the RLD Schering's Claritin® Reditabs, 10 mg. Please indicate if you have any data showing that your product is bioequivalent to the RLD when both are administered to subjects and swallowed without water.

Sincerely yours,

/s/

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

ANDA 75-822

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUN 13 2001

TO: APPLICANT: ESI Lederle

TEL: 845-732-4137

ATTN: Nicholas C. Tantillo

FAX: 845-732-5689

FROM: Ruby Yu

PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 9, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine Orally Disintegrating Tablets.

Reference is also made to your amendment(s) dated: December 22, 2000, and Janauary 11, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided.

RY
6/13/01

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of trade secret and/or

confidential commercial

information from

6/13/2001 FDA FAX

2. Your amendment should also include your response to the Bioequivalency comments faxed to you on March 19, 2001. The acceptance of your dissolution stability data is contingent upon acceptance of your dissolution method and specifications by the Division of Bioequivalence.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Office of Generic Drugs

7500 STANDISH PLACE (HFD-600), ROCKVILLE, MD 20855

Phone: (301) 827-5763
Fax: (301) 594-0180

FAX TRANSMISSION COVER SHEET

Date: August 15, 2001

To: ESI Lederle, Attn: Nicholas Tantillo 845-732-4137

Fax: 845-732-5689

Re: ANDA 75-822

Sender: Ruby Yu, Project Manger

TOTAL NUMBER OF PAGES: __1__
(Excluding Cover Sheet)

SPECIAL INSTRUCTIONS:

Bioequivalency comments provided.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-822 APPLICANT: ESI Lederle

DRUG PRODUCT: Loratadine Orally Disintegrating Tablets, 10 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet, and has no further questions at this time.

The following dissolution testing should be incorporated into your manufacturing controls and stability program:

The dissolution testing should be conducted in 900 mL of 0.1N HCl using apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications.

> Not less than — % (Q) of the labeled amount of the drug in the dosage form is dissolved in 6 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the toxicology data, chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation in not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

December 5, 2001

Mr. Gary Buehler, Director
Office of Generic Drugs HFD 150
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 286
Rockville, MD 20855

DRUG AMENDMENT
N/AM

Loratadine Orally Disintegrating
Tablets, 10 mg
ANDA 75-822

Dear Mr. Buehler,

Reference is made to our abbreviated new drug application dated March 9, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Loratadine Orally Disintegrating Tablets, 10 mg.

Reference is also made to the June 13, 2001 and August 15, 2001 FDA facsimile communications to ESI Lederle providing chemistry and bioequivalency comments, respectively. The June 13, 2001 communication indicated that the response will be considered to represent a MINOR AMENDMENT.

Following is our response to each of the agency's comments:

A. Chemistry Deficiencies

1.

RESPONSE:

2

RESPONSE:

12/13/01

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EVALUATION AND RESEARCH

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information from

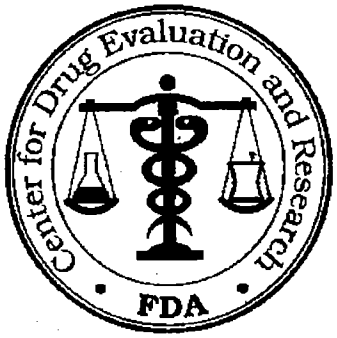
ESI/LEDERLE 12/5/2001 LETTER

BIOEQUIVALENCY AMENDMENT

ANDA 75-822

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JAN - 4 2002



TO: APPLICANT: ESI Lederle

TEL: 845-602-4137

ATTN: Nicholas C. Tantillo

FAX: 845-602-5689

FROM: Steven Mazzella

PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on December 5, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine Orally Disintegrating Tablets, 10 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

JAN -- 4 2002

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-822 APPLICANT: ESI Lederle

DRUG PRODUCT: Loratadine Orally Disintegrating Tablets, 10 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following comment is provided in response to your request for changing the dissolution specifications:

You request to change the dissolution specification to "Not less than —% (Q) of loratadine in the dosage is dissolved in 10 minutes" is denied.

Therefore, the current dissolution conditions will still remain the same. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications.

Not less than —% (Q) of loratadine in the dosage is dissolved in 6 minutes.

Sincerely yours,

for

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ESI LEDERLE

Bioequivalency Amendment

January 21, 2002

ORIG AMENDMENT
N/AB
BIOAVAILABILITY

Mr. Gary Buehler, Director
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Loratadine Orally Disintegrating
Tablets, 10 mg
ANDA 75-822

Dear Mr. Buehler,

Reference is made to our abbreviated new drug application submitted on March 9, 2000 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Loratadine Orally Disintegrating Tablets, 10 mg.

Reference is also made to the facsimile correspondence from Steven Mazella, Project Manager, dated January 4, 2002 providing comments from the Division of Bioequivalence in response to our request for changing the dissolution specifications. Our response to those comments follows:

BIOEQUIVALENCY COMMENTS

Your request to change the dissolution specification to "Not less than —% (Q) of loratadine in the dosage is dissolved in 10 minutes" is denied.

Therefore the current dissolution conditions will still remain the same. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37° using apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications.

Not less than —% (Q) of loratadine in the dosage is dissolved in 6 minutes.

CENTER FOR DRUG
JAN 2 8 2002
EVALUATION AND RESEARCH

RESPONSE

We acknowledge your comments and we accept the current dissolution specification. Dissolution testing will be conducted in 900 mL of 0.1N HCl at 37° using apparatus 2 (paddle) at 50 rpm. ESI Lederle's Loratadine Orally Disintegrating Tablets, 10 mg will have to meet the following specifications: Not less than — % (Q) of loratadine in the dosage is dissolved in 6 minutes.

401 North Middletown Rd., Pearl River, NY 10965-1299 Tel: (914) 732-5000 Fax: (914) 732-5114

ANDA 75-822 January 21, 2002

As Mr. Mazella requested, a copy of the agency's January 4, 2002 facsimile correspondence is included with this response.

If you have any questions, please contact the undersigned by telephone at 845 602-4137, or by facsimile at 845 602 5689.

Sincerely,

Nicholas Tantillo
Senior Director, Regulatory Affairs
ESI Lederle

enc.

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY AMENDMENT

NDA 75-822

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JAN - 4 2002

TO: APPLICANT: ESI Lederle

ATTN: Nicholas C. Tantillo

FROM: Steven Mazzella

TEL: 845-602-4137

FAX: 845-602-5689

PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on December 5, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine Orally Disintegrating Tablets, 10 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

CENTER FOR DRUG
JAN 2 8 2002
EVALUATION AND RESEARCH

JAN - 4 2002

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-822 APPLICANT: ESI Lederle

DRUG PRODUCT: Loratadine Orally Disintegrating Tablets, 10 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following comment is provided in response to your request for changing the dissolution specifications:

You request to change the dissolution specification to "Not less than — % (Q) of loratadine in the dosage is dissolved in 10 minutes" is denied.

Therefore, the current dissolution conditions will still remain the same. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications.

Not less than — % (Q) of loratadine in the dosage is dissolved in 6 minutes.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ESi LEDERLE

LABELING SUBMISSION

January 22, 2002

NDA [illegible] AMENDMENT

AF

Mr. Gary Buehler, Director
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Loratadine Orally Disintegrating
Tablets, 10 mg
ANDA 75-822

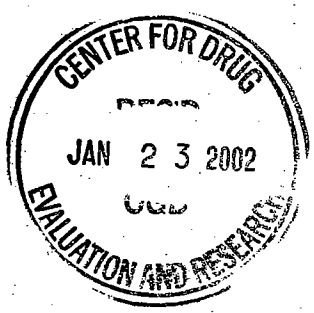
Dear Mr. Buehler,

Reference is made to our abbreviated new drug application submitted on March 9, 2000 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Loratadine Orally Disintegrating Tablets, 10 mg.

Reference is also made to the facsimile correspondence from Debra M. Catterson, Labeling Reviewer dated July 25, 2001 providing labeling comments. A copy of this correspondence is attached.

Also attached are four copies of draft labeling for the unit dose blister container, carton, and package insert revised according to your recommendations. A comparison of the new proposed labeling to the previous labeling is included with this submission. The unit dose container and carton labeling have been revised based on the mocked-up copy of draft labeling you provided, and the package insert labeling has been revised based on the new labeling you provided (changes to the approved labeling for the reference listed drug - revised Sept., 2000 and approved Dec., 2000.)

If you have any questions, please contact the undersigned by telephone at 845 602-4137, or by facsimile at 845 602 5689.



Sincerely,

Nicholas Tantillo
Senior Director, Regulatory Affairs
ESI Lederle

enc.

401 North Middletown Rd., Pearl River, NY 10965-1299 Tel: (914) 732-5000 Fax: (914) 732-5114

Wyeth Pharmaceuticals
P.O. Box 8299
Philadelphia, PA 19101-8299

Worldwide Regulatory Affairs

3.1

Wyeth

NEW CORRESP
NC

July 3, 2002

75-822 (55)

ANDA No. ~~75-882~~
Loratadine Orally Disintegrating Tablets, 10 mg

Gary Buehler, Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Attn: Document Control Room 150
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

General Correspondence

Dear Mr. Buehler:

75822 (55)

Reference is made to our abbreviated new drug application for Loratadine Orally Disintegrating Tablets, 10 mg, ANDA No. ~~75-882.~~ This ANDA is pending approval and was submitted by Lederle Laboratories, Pearl River, NY. Worldwide Regulatory Affairs at the above address is the parent organization overseeing this application. We hereby notify you of a change in the name of the holder of this ANDA from Lederle Laboratories to Wyeth Consumer Healthcare.

Please direct all future correspondence to:

Wyeth Consumer Healthcare
5 Giralda Farms
Madison, NJ 07940

The contact information is as follows:

Ms. Lauren Quinn (primary contact)
Associate Director, Regulatory Affairs
Telephone: (973) 660-6167
Facsimile: (973) 660-8761

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JUL 05 2002
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Wyeth

Dr. David Smith (secondary contact)
Director, Regulatory Affairs
Telephone: (973) 660-6806
Facsimile: (973) 660-8698

Mr. Ken Warner
Director, CMC Regulatory Affairs
Telephone: (973) 660-8696
Facsimile: (973) 660-8673

If you have any further questions, please contact Dr. Warren L. Sunshine at (610) 902-5236.

Sincerely,

WYETH-AYERST LABORATORIES

Diane Mitrione

Diane Mitrione
Assistant Vice-President
Worldwide Regulatory Affairs

MINOR AMENDMENT

ANDA 75-822

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUL 8 2002

TO: APPLICANT: ESI Lederle

ATTN: ~~Nicholas C. Tantillo~~ Diane Mitrione

TEL: 845-602-4137

FAX: ~~845-602-5689~~ 610-964-5686 per Rosalba Rortman on July 8, 2002. RW

FROM: Ruby Wu

PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 9, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine Orally Disintegrating Tablets, 10 mg.

Reference is also made to your amendment(s) dated: December 5, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__1__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided. Labeling comments, if any, will be provided under separate cover.

7/01/02

38. CHEMISTRY COMMENTS To Be PROVIDED To The APPLICANT JUL 8 2002

ANDA: **75-822** APPLICANT: **ESI Lederle**

DRUG PRODUCT: **Loratadine Orally Disintegrating Tablets, 10 mg**

A. The deficiencies presented below represent **MINOR** deficiencies.

1. Regarding your **drug substance** specifications:

a. [redacted]

b. [redacted]

c. [redacted]

2. Regarding your specifications for the **finished product** and **stability:**

a. [redacted]

b. [redacted]

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

The labeling portion of your application is under review. Any deficiencies will be conveyed to you in a separate letter.

Sincerely yours,

Paul Shweiter for

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

David S. Smith, PhD
Director, Regulatory Affairs
973-660-6806
SmithD16@wyeth.com

Wyeth

July 9, 2002

NC

NEW CORRES

ANDA 75-822
NDA 21-375
Alavert (loratadine 10mg orally disintegrating tablets)
General Correspondence: Type A Meeting Request – Administrative Issues

Gary J. Buehler, Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Document Control Room 150
7500 Standish Place
Rockville, MD, 20855

Robert Meyer, MD, Director
Office of Drug Evaluation II, HFD-102
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Central Document Room
9210 Corporate Boulevard
Rockville, MD 20857

S. ~ 2/13/03

Dear Mr. Buehler and Dr. Meyer:

Reference is made to ANDA 75-822 submitted by ESI/Lederle Pharmaceuticals on March 9, 2000 and NDA 21-375 for Alavert (loratadine 10mg Orally Disintegrating Tablets), submitted by Wyeth Consumer Healthcare (WCH) on August 23, 2001. Reference is also made to the Type B meeting request submitted to NDA 21-375 on June 7, 2002, and the approvable letter received on July 3, 2002. Based on the consideration that there has been no formal response to our June 7 request, and because the outcome of this meeting is essential to the approval and marketing of our product, we are hereby amending our questions and are resubmitting our meeting request to change it to a Type A meeting.

As noted in the original request, Wyeth has several questions concerning both the administrative procedures for our applications, and the contents of a potential amendment, which are critical to the approval and marketing of this product.

It should be noted that Wyeth has two active applications for the same dosage form of loratadine. ANDA 75-822 was originally filed by Wyeth's generic division, ESI Lederle, for a generic prescription version of loratadine. Wyeth Consumer Healthcare filed NDA 21-375 as a 505(b)(2) application to switch loratadine to Over-the-Counter status. Based

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Wyeth

on our corporate re-structuring, both applications are now managed through Wyeth Consumer Healthcare.

Since Schering has indicated that it has filed an NDA to switch Claritin to OTC status, several of our issues concerning our 505(b)(2) application are becoming intertwined with our 505(j) application. Because there is the possibility that there will continue to be a prescription market for loratadine with the CIU indication, the company intends to keep both applications active. We therefore request the participation of both the Division of Pulmonary and Allergy Drug Products and the Office of Generic Drugs. Furthermore, since our issues concern the OTC labeling for our product, we also request the participation of the OTC Division.

We are requesting answers to the following questions.

Question 1. The published action date for Schering's Claritin Rx to OTC switch NDA is November 28, 2002, and the Waxman-Hatch exclusivity for Claritin expires December 19, 2002. If ongoing patent litigation is resolved in favor of Wyeth, we intend to immediately launch an OTC loratadine. Could representatives of the appropriate Divisions explain the administrative procedure for obtaining the Claritin OTC labeling, amending our ANDA with the revised labeling and obtaining final approval of the ANDA by the expiration of the Claritin exclusivity period?

Question 2. Considering the guidance Wyeth received concerning our 505(b)(2) application, and the results of the recent Non-Prescription Drug Advisory Committee Meeting on CIU, we are proposing that an update of publicly available safety data to amend or supplement our NDA as all that is required to add the CIU indication. We request your concurrence that this type of safety data would be adequate to add the indication to our label. We also seek confirmation that essential data required to add the CIU indication would not constitute the basis of 3-years exclusivity for the product.

Question 3. We seek FDA confirmation that if any urticaria-related exclusivity were to be granted, that the exclusivity would be limited to the urticaria indication and will not collaterally prevent ANDA applicants from achieving approval for the remaining non-exclusive uses.

Wyeth

Question 4. If no decision has been reached regarding an OTC urticaria/hives indication by the time Claritin or Wyeth's 505(b)(2) NDA receives final approval for rhinitis, will FDA permit Schering's NDA for the approval and continued marketing of prescription loratadine products for urticaria only, or for urticaria and rhinitis indications, or will FDA prohibit prescription loratadine products altogether?

Also, will rhinitis be maintained as an approved prescription-only indication for children 5 years and younger?

Question 5. Will FDA immediately terminate the 30-month approval stay on Wyeth's 505(b)(2) NDA upon the issuance of a district court decision that the patents for which Wyeth filed a Paragraph IV Certification are invalid, unenforceable, or not infringed?

Question 6. Assuming patent suit resolution in favor of Wyeth, could FDA explain if there would be any restrictions or limitations on approval and marketing of our loratadine products that would be marketed based on both of our 505(b)(2), and 505(j) applications. It is conceivable that based on the current status of our 505(b)(2) application, and potential revision to include CIU for our ANDA product, we could have two identical products with different labeling.

Question 7. It is our understanding that FDA will act on the Wellpoint Citizen's Petition to switch non-sedating antihistamines to OTC status. We would like clarification on FDA administrative procedures related to approval of the Petition that potentially affect our applications. For example, if the Wellpoint petition is granted before approval of our NDAs, how will Wyeth negotiate OTC labeling with the FDA? Will labeling still be based on our submission, or Wellpoint or Schering actions?

We look forward to discussing these questions with you. While we prefer to have this meeting in person, we could also accommodate a teleconference. Should you have any

Wyeth

questions or comments, please do not hesitate to contact the undersigned at (973) 660-6806 or Sharon Heddish at (973) 660-5767.

Regards,
WYETH CONSUMER HEALTHCARE

David S Smith

David S. Smith PhD
Director, Regulatory Affairs

Cc: Badrul Chowdhury, MD, PhD HFD-550
Charles Ganley, MD HFD-560

Wyeth Consumer Healthcare
5 Giralda Farms
Madison NJ 07940

David S. Smith, PhD
Director, Regulatory Affairs
973-660-6806
SmithD16@wyeth.com

Wyeth

July 12, 2002

NC

NEW CORRESP

ANDA 75-822
Loratadine 10mg orally disintegrating tablets (Alavert)
Notice of Intent to Amend the Application

Gary J. Buehler, Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Document Control Room 150
7500 Standish Place
Rockville, MD, 20855

Dear Mr. Buehler:

Reference is made to ANDA 75-822 submitted by ESI/Lederle Pharmaceuticals on March 9, 2000 and the Not Approvable letter received on July 8, 2002. Based on the Corporate restructuring of Wyeth, this ANDA is now managed by Wyeth Consumer Healthcare. This submission informs the Office of Generic Drugs of the intention of Wyeth Consumer Healthcare to amend the application, as specified by 21CFR 314.120.

Reference is also made to NDA 21-375 for Alavert (loratadine 10mg Orally Disintegrating Tablets), submitted by Wyeth Consumer Healthcare on August 23, 2001. Wyeth intends to sell loratadine tablets as both Rx and OTC products, and NDA 21-375 is for the OTC version. Since we intend to manufacture the tablets for both Rx and OTC versions according to a single set of specifications, Wyeth would like to agree on this single set of specifications with both OGD and Pulmonary. In letters to The Office of Generic Drugs, and the Office of Allergy and Pulmonary Drugs dated July 8, 2002, Wyeth requested a Type A meeting with both Divisions to agree on the specifications.

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S.N.
2/13/03

Wyeth

It is our intention that the specifications will be agreed at that meeting, that has been requested for mid-August. The ANDA would then be formally amended with the agreed specifications immediately after the meeting.

We look forward to discussing this application with you. Should you have any questions or comments, please do not hesitate to contact the undersigned at (973) 660-6806 or Sharon Heddish at (973) 660-5767.

Regards,
WYETH CONSUMER HEALTHCARE

David S Smith

David S. Smith PhD
Director, Regulatory Affairs

cc: Badrul Chowdhury, MD, PhD HFD-550

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Wyeth

Lauren Quinn
Associate Director
Regulatory Affairs
973-660-6167 tel
QuinnL4@wyeth.com

VAT 10/11/02
- Copy of Court Case - 716 found invalid
P.M. VP

September 5, 2002

ANDA 75-822
Loratadine Orally Disintegrating Tablets, 10mg
Amendment to Original Application: Notice of Final Judgment

NEW CORRESP

NC

Mr. Gary Buehler, Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Dear Mr. Buehler:

Reference is made to ANDA 75-822 for Loratadine Orally Disintegrating Tablets, 10mg, submitted on March 9, 2000, and to the patent litigation pertaining to this application..

In the original ANDA for Loratadine Orally Disintegrating Tablets 10mg, Wyeth Consumer Healthcare (WCH)(formerly ESI/Lederle) provided Paragraph IV certifications pertaining to US Patents 4,659,716 and 4,863,931. WCH served notice to Schering Plough of that certification on May 1, 2000 and May 17, 2000, and submitted an amendment to the ANDA on June 8, 2000 providing proof of receipt by Schering-Plough. Schering-Plough brought suit against WCH on June 15, 2000, with regard to patent 4,659,716 only. No action was brought against WCH with regard to patent 4,863,931. On August 1, 2000, WCH submitted an amendment providing documentation evidencing the filing of the lawsuit by Schering-Plough.

In accordance with 21 CFR 314.107(e), this amendment serves to notify the Agency that the United States District Court for the District of New Jersey has entered a final judgment in favor of WCH finding that all of the asserted claims of the Schering-Plough patent listed for loratadine (US patent 4,659,716) are invalid. Enclosed in Attachments 1, 2 and 3 respectively are copies of the decision, order and final judgment.

Based on Schering's May 18, 2000 receipt of WCH's Paragraph IV notification, the 30-month stay expires on November 18, 2002. Accordingly, WCH will be eligible for effective

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OGD / CDER

Wyeth

approval when the "pediatric exclusivity" related to U.S. Patent 4,282,233 expires on December 19, 2002.

Thank you for your consideration of this matter. If you have any questions or concerns, please contact the undersigned at (973) 660-6167 or David Smith at (973) 660-6806.

Sincerely,

WYETH CONSUMER HEALTHCARE

Lauren Quinn

Lauren Quinn
Associate Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Julia L. Kim, Ph.D.
Associate Director
Regulatory Affairs CMC
973-660-5139 tel
kimj2@wyeth.com

Wyeth

ORIG AMENDMENT
N/AM

October 17, 2002

ANDA 75-822
Loratadine 10 mg Orally Disintegrating Tablets

MINOR AMENDMENT - Chemistry, Manufacturing and Controls

Rashmikant M. Patel, Ph.D, Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research, Food and Drug Administration
ATTENTION: Document Control Room, Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Dear Dr. Patel:

Reference is made to abbreviated new drug application (ANDA) 75-822 sponsored by Wyeth Consumer Healthcare for Loratadine 10 mg Orally Disintegrating Tablets (ODT). The subject ANDA was submitted on March 9, 2000. Additional reference is made to the teleconference conducted on May 8, 2002 and to the Not Approvable letter (by facsimile) dated July 8, 2002 in which the FDA requested that the ANDA be amended with tightened individual and total impurity specifications for both drug substance and drug product. Wyeth Consumer Healthcare is hereby submitting this minor amendment responding to the request in the July 8, 2002 facsimile.

Wyeth Consumer Healthcare submitted a 505(b)(2) application to the Division of Pulmonary and Allergy Drug Products (DPADP) for an OTC version of this same product. The tablets for both Rx and OTC use are identical in formulation, manufacturing process and primary packaging components; labeling and the outer carton will be different. Therefore, Wyeth proposes that a single set of specifications and methods be applied to the manufacture and release of both the Rx and OTC tablets.

Similar to the request from OGD, the DPADP also requested revisions to the proposed specifications for the product in an Approvable letter of September 19,

Wyeth

2002. Wyeth discussed and agreed on final methods and specifications with Dr. Poochikian and Dr. Kim in a meeting held September 26, and a telecon held October 4. The resubmission in response to the Approvable letter was received by DPADP on October 16, 2002.

We also refer to a telephone conversation held on October 15, 2002 between Dr. Devinder Gill, the Review Team Leader for this ANDA, and Dr. David Smith of Wyeth. The Wyeth proposal to have a single set of specifications and methods was discussed and it was agreed that Wyeth should amend the ANDA accordingly. In addition, it was agreed that this Minor Amendment to OGD contain the exact same information that was provided in the resubmission to DPADP.

Wyeth Consumer Healthcare certifies that a copy of this submission will be provided to the FDA District Offices in North Brunswick, NJ and Minneapolis, MN.

We trust that this amendment addresses the Agency's concerns relative to these issues. If you have any questions or comments regarding any CMC related issues, please feel free to contact the undersigned at (973) 660-5139 or Susan Beavis at (973) 660-5068. Thank you.

Sincerely,
WYETH CONSUMER HEALTHCARE

Julia L. Kim, Ph.D.
Associate Director, Regulatory Affairs CMC

cc: Ms. Sarah Kim (HFD-620)
Dr. Devinder Gill (HFD-620)

ANDA 75-822

DEC 3 2002

Wyeth Consumer Healthcare
Attention: Susan Beavis
5 Giralda Farms
Madison, NJ 07940

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 9, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine Orally Disintegrating Tablets, 10 mg.

On November 27, 2002, the FDA approved Schering's supplemental new drug application providing for the over-the-counter (OTC) use of Claritin® (loratadine) Tablets, Syrup, and RediTabs®. With this approval, the approved indications for these products are "for the temporary relief of symptoms of hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat." Please note that the use of these products for the treatment of chronic idiopathic urticaria (CIU) is not included in the approved OTC labeling. The agency has been informed that with the introduction of products labeled for OTC use, these products will no longer be marketed with prescription (Rx) labeling. Thus, since your ANDA currently references the former product with prescription only labeling, your application cannot be approved.

You may submit a revised Form FDA 356h along with appropriate information to this ANDA to indicate the correct reference listed drug (RLD). In addition, we request that you withdraw your former labeling and submit for our review revised final-printed labeling which is consistent in content and format with that which provides for the OTC use of the RLD.

Furthermore, the agency is unaware of any new patent or patent information submitted by Schering to the NDA supplements providing for the switch from prescription to OTC marketing status for loratadine drug products. As a result, ANDA applicants who submit an amendment to their pending ANDA providing only to amend their proposed labeling to conform with the labeling for the approved reference listed drug will not be required to submit new patent certifications. Please be advised, however, that submission of additional patents by Schering for the RLD may require you to submit additional ANDA patent certifications.

If you have any questions, please contact: Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at 301-827-5845.

Sincerely yours,

Gary J. Buehler 12/3/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Claritin Labeling

APPEARS THIS WAY
ON ORIGINAL

~~q:\issues\loratadine\otcanda.doc~~

Drafted by: C. Parise 11/15/02
Comments by: L. Dickinson 11/22/02

Endorsement(s):

HFD-617/S. Kim/ S. Kim 11/29/02 Loratadine OTC.doc

V:\FIRMSAM\ESILEDER\LTRS&REV\75822.~~OTCANDA.doc~~
F/T by: sk/11/29/02

APPEARS THIS WAY
ON ORIGINAL

Pre-Printed Pouch

TOP FRONT

10 Orally Disintegrating Tablets

Claritin® RediTabs®

Loratadine Orally Disintegrating Tablets 10 mg/Antihistamine

- Each tablet contains: 10 mg loratadine.
- Adults and children 6 years and over: 1 RediTabs® tablet daily. See carton.
- Do not give to children under 6 years of age unless directed by a doctor.
- Read carton directions carefully.
- Keep in a dry place. Store between 2° and 25°C (36° and 77°F).
- Use within 6 months of opening foil pouch and immediately upon opening individual blister.

Date foil pouch opened: _____

Do not use if individual blister unit inside the foil pouch is open or torn.

DO NOT ATTEMPT TO PUSH TABLET THROUGH FOIL.

 26092400/26190-00

SEAL AREA, NO TEXT

TOP BACK

10 Orally Disintegrating Tablets

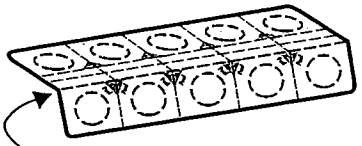
Claritin® RediTabs®

Loratadine Orally Disintegrating Tablets 10 mg/Antihistamine

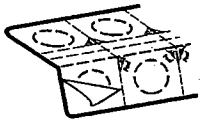
INSTRUCTIONS FOR OPENING

DO NOT ATTEMPT TO PUSH TABLET THROUGH FOIL.

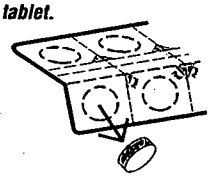
Read these instructions before attempting to remove tablet.



1. Bend or tear here.



2. Peel back foil at corner tab.



3. Gently push tablet out.

4. Place the tablet on tongue and close mouth. The tablet will disintegrate.

CODE AREA

30 days of relief 30 Orally Disintegrating Tablets

Claritin® RediTabs® 24 hour

Original Prescription Strength

NEW!

Non-Drowsy*

Claritin® RediTabs®

Loratadine Orally Disintegrating Tablets 10 mg/Antihistamine

For Adults and Children six years and older

24 hour Allergy

Relief of:
Sneezing, Runny Nose
Itchy, Watery Eyes
Itchy Throat or Nose

30 ORALLY DISINTEGRATING TABLETS

Actual Size

*When taken as directed. See Drug Facts Panel.

CODE AREA
NO VARNISH

30 Orally Disintegrating Tablets

Claritin® RediTabs® 24 hour

Directions

- place 1 tablet on tongue; tablet disintegrates, with or without water

adults and children 6 years and over	1 tablet daily; not more than 1 tablet in 24 hours
children under 6 years of age	ask a doctor
consumers with liver or kidney disease	ask a doctor

1. Bend or tear blister card at perforation.
2. Peel back foil at corner tab.
3. Gently push tablet out.
4. Place the tablet on tongue and close mouth. The tablet will disintegrate.

0 41100 81634 4

NO VARNISH

Claritin® RediTabs® 24 hour

30 Orally Disintegrating Tablets

Drug Facts

Active ingredient (in each tablet) — **Purpose**

Loratadine 10 mg ..... Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:

- runny nose
- sneezing
- itchy, watery eyes
- itching of the nose or throat

Warnings

Do not use if you have ever had an allergic reaction to this product or any of its ingredients.

Ask a doctor before use if you have liver or kidney disease. Your doctor should determine if you need a different dose.

When using this product do not take more than directed. Taking more than directed may cause drowsiness.

Stop use and ask a doctor if an allergic reaction to this product occurs. Seek medical help right away.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- place 1 tablet on tongue; tablet disintegrates, with or without water

adults and children 6 years and over	1 tablet daily; not more than 1 tablet in 24 hours
children under 6 years of age	ask a doctor
consumers with liver or kidney disease	ask a doctor

Drug Facts (continued)

Other information

- safety sealed: do not use if interior foil pouch or individual blister unit imprinted with Claritin® RediTabs® inside the foil pouch is open or torn
- store between 2° and 25° C (36° and 77° F)
- keep in a dry place
- use within 6 months of opening foil pouch
- use tablet immediately after opening individual blister

Inactive ingredients

citric acid, gelatin, mannitol, mint flavor

Questions or comments?

1-800-CLARITIN (1-800-252-7484) or www.claritin.com

Follow these directions carefully. Do not attempt to push the tablet through the foil.

1. Bend or tear blister card at perforation.
2. Peel back foil at corner tab.
3. Gently push tablet out.
4. Place the tablet on tongue and close mouth. The tablet will disintegrate.

NO VARNISH

FPO 26247314

NO VARNISH

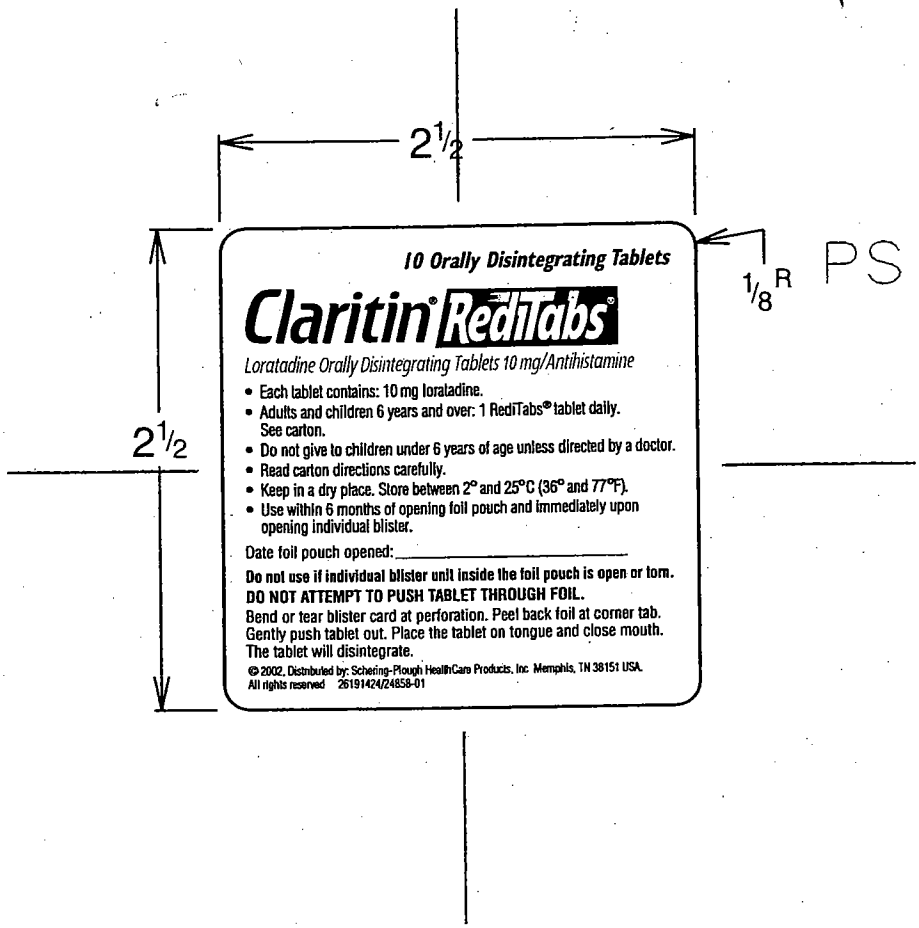
FPO 26247314

ATTACH LEGEND ON ALL DIGITAL MECHANICALS

STANDARD FORMAT
Helvetica Condensed
Variable horizontal scale adheres to 39 characters per inch
Drug Facts - 10.35 pt Helvetica Cnd. Bold Italic
Drug Facts (continued)
Drug Facts - 9.2 pt Helvetica Cnd. Bold Italic (continued) - 9.2 pt Helvetica Cnd.
Headings - 9.2 pt Helvetica Cnd. Bold Italic
Sub Heads -6.9 pt Helvetica Cnd. Bold
Text - 6.9 pt Helvetica Cnd. minimum leading 7.48
Square Bullets - 4.03 pt Zaph Dingbats no compression
Border - 1 pt rule, 3/64" gap all around
Barline - 1 pt rule
Hairline - .5 pt rule

Certified by: VM

Launch Pouch Sticker



er. Schering Plough
M8903
+1/2 x 2+1/ 2x0

Material:– Sachet Sticker
Description: Claritin Adult 10s Sachet
Side Shown: Printside
Date: 10/24/2002

Wyeth Consumer Healthcare
5 Giralda Farms
Madison NJ 07940

David S. Smith, PhD
Director, Regulatory Affairs
973.660.6806
smithd16@wyeth.com

Wyeth

December 10, 2002

ORIG AMENDMENT
N/AF

Abbreviated New Drug Application 75-822
Loratadine Orally Disintegrating Tablets, 10mg (OTC)
Minor Amendment: Labeling

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RECEIVED
DEC 1 1 2002
OGD / CDER

Dear Mr. Buehler:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act Wyeth Consumer Healthcare (WCH) is hereby submitting an amendment to our Abbreviated New Drug Application 75-822 for Loratadine Orally Disintegrating Tablets, 10mg, OTC.

WCH is the sponsor of pending ANDA 75-822 for Loratadine Orally Disintegrating Tablets 10mg Rx, for the indications Chronic Idiopathic Urticaria (CIU) and Allergic Rhinitis. Schering-Plough has been granted approval for OTC use in Allergic Rhinitis, which has resulted in a change to the labeling of the Reference Listed Drug, Claritin® RediTabs, 10mg manufactured by Schering-Plough, approved under NDA 20,704. As requested in the December 3 letter from Mr. Buehler, WCH is filing this amendment informing the Office of Generic Drugs that WCH withdraws the labeling previously submitted to the ANDA, and providing new labeling for only the OTC indication of allergic rhinitis.

All other aspects of the ANDA remain unchanged. The active ingredient, dosage form, strength, and route of administration of the proposed product are

Wyeth

the same as those of the reference listed drug. As indicated in the ANDA, the manufacture, processing, testing, labeling and packaging of the dosage form will take place at [redacted] a third party contract facility.

A side-by-side comparison of the proposed labeling to the listed drug product labeling is included in this application. In addition, we are providing a copy of the final printed labeling for our product.

Should you have any questions concerning this application, please contact the undersigned, or Lauren Quinn at (973) 660-6167.

Sincerely,
WYETH CONSUMER HEALTHCARE

David S Smith

David S. Smith, PhD
Director, Regulatory Affairs

Wyeth Consumer Healthcare
5 Giralda Farms
Madison NJ 07940

David S. Smith, PhD
Director, Regulatory Affairs
973.660.6806
smithd16@wyeth.com

Wyeth

DRUG AMENDMENT
N/AM

December 13, 2002

ANDA 75-822
Loratadine Orally Disintegrating Tablets, 10mg (OTC)
Telephone Amendment: CMC

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Dear Mr. Buehler:

Reference is made to ANDA 75-822 for Loratadine Orally Disintegrating Tablets 10mg. A request was made by Sarah Kim of your office to provide a citation to the volume and page number of the ANDA where the tamper evident features of the packaging are discussed.

Please refer to Volume 16, pages 6749 to 6751 of ANDA 75-822 for information concerning the container closure. While the ANDA does not specifically state that there is a tamper evident feature on the packaging, you will note that the primary packaging is a blister card of 6, which meets the requirements for tamper evident packaging per 21 CFR 211.132. In order to access the blister, the consumer must tear the foil/paper lidding material and peel it back. In doing so, fibre tear becomes evident along the perforation. Furthermore, special equipment would be required to re-seal the blister once opened.

Should you have any questions concerning this amendment, please contact the undersigned, or Lauren Quinn at (973) 660-6167.

Wyeth

Sincerely,
WYETH CONSUMER HEALTHCARE

David S Smith

David S. Smith, PhD
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Lauren Quinn
Associate Director
Regulatory Affairs
(973) 660-6167 tel
QuinnL4@wyeth.com

Wyeth

December 18, 2002

ANDA 75-822
Loratadine Orally Disintegrating Tablets, 10mg (OTC)
Telephone Amendment: CMC

ORIG AMENDMENT
N/AM

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Dear Mr. Buehler,

Reference is made to Wyeth Consumer Healthcare (WCH) ANDA 75-822 for loratadine orally disintegrating tablets, 10mg (OTC). Reference is also made to a telephone contact with Sarah Kim of your office requesting WCH to reconcile the inactive ingredients listed on the Final Printed Labeling submitted and the ingredient listing in the application.

To clarify, it is WCH practice to include some of the ingredients of the flavoring or coloring that are of interest to the consumer for potential safety reasons, such as hypersensitivity. The inactive ingredients Corn Syrup Solids and Modified Food Starch are components of Natural and Artificial Mint ——— manufactured by ———————————. The DMF for this product is 202 and can be found in volume 17 on page 7086.

If you have any questions or concerns, please contact the undersigned or David Smith at (973) 660-6806.

Sincerely,

Lauren Quinn

Lauren Quinn
Associate Director, Regulatory Affairs

RECEIVED
DEC 19 2002
OGD / CDER

Wyeth Consumer Healthcare
5 Giralda Farms
Madison NJ 07940

Lauren Quinn
Associate Director, Regulatory Affairs
973.660.6167
quinnL4@wyeth.com

Wyeth

January 10, 2003

Abbreviated New Drug Application 75-822
Loratadine Orally Disintegrating Tablets, 10mg (OTC)
Minor Amendment: Labeling

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

N/AF

FPL

Dear Mr. Buehler:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act Wyeth Consumer Healthcare (WCH) is hereby submitting an amendment to our Abbreviated New Drug Application 75-822 for Loratadine Orally Disintegrating Tablets, 10mg, OTC.

As requested by Dr. Catterson of your office, enclosed please find 12 copies of the blister back labeling for this product.

Should you have any questions concerning this application, please contact the undersigned, or David Smith at (973) 660-6806.

Sincerely,
WYETH CONSUMER HEALTHCARE

Lauren Quinn

Lauren Quinn
Associate Director, Regulatory Affairs