CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-993

MEDICAL REVIEW(S)

MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation

Date: **December 5, 2006**

From: **Andrea Leonard-Segal, M.D.**
Director

Subject: **NDA 21-993**
Claritin® RediTabs 12 Hour Tablets
(loratadine 5 mg)

Sponsor: **Schering-Plough HealthCare Products**

Background:
Claritin® (loratadine) first became available as a nonprescription drug in the United States in 2002. Loratadine is a H_1 receptor antagonist. The sponsor is seeking OTC approval to market Claritin® RediTabs 12 Hour Tablets. These are orally disintegrating tablets containing loratadine 5 mg to be dosed as one tablet every 12 hours not to exceed 2 tablets in 24 hours. The indication is the temporary relief of symptoms of runny nose, itchy, watery eyes, sneezing, and itching of the nose or throat, due to hay fever or other upper respiratory allergies in adults and children 6 years of age and older.

Currently, Claritin® 10 mg tablets and Claritin®10 mg RediTabs orally disintegrating tablets are approved OTC for once a day dosing for adults and children 6 years and older for the same indication as the proposed 5 mg RediTab. A 5-mg /teaspoon loratadine syrup and a 5-mg loratadine chewable tablet are approved for OTC use in adults and children 2 years and older for this indication. Loratadine is also marketed as an OTC drug to treat hives in adults and children 6 years of age and older.

Loratadine is marketed OTC in combination with pseudoephedrine as Claritin-D® 12 and Claritin-D® 24 for the treatment of allergic rhinitis and nasal congestion. Claritin-D® 12 contains 5 mg of loratadine plus 120 mg of pseudoephedrine and Claritin-D® 24 contains 10 mg of loratadine plus 240 mg of pseudoephedrine.

Chemistry:
Refer to the chemistry review dated 11/29/06 by Tarun Mehta. The reviewer concludes that the chemistry data supports the approval of the Claritin® RediTab NDA. The inspection of the drug-product manufacturing site found the site to be acceptable.

On page 43 of his review, Tarun Mehta states, *"The applicant has agreed to revise the release as well as the stability specifications as a post approval commitment (prior approval supplement) to include disintegration test and acceptance criterion, once sufficient data (are) collected from the commercial batches."* I acknowledge this recommendation.

Pharmacology/Toxicology:
Refer to the September 19, 2006 review by Drs. Lawrence Sancilio and Joseph Sun. The sponsor referenced the toxicology data for loratadine in NDA 19-658 and NDA 20-704 and did not submit additional data with this NDA. The excipients in this new formulation are acceptable. The reviewers conclude that from a preclinical standpoint, there are no safety issues that would prevent Claritin® RediTabs tablets from being an OTC product for children and adults and they recommend approval.

Clinical Pharmacology:
The sponsor submitted two bioequivalence pharmacokinetics studies to support this application. The subjects in these studies were ages 18 - 45 years old. The data from study CL2005-02 showed that one 5 mg Claritin® RediTab is not bioequivalent to the loratadine component of Claritin-D® 12. The systemic exposure (area under the curve) was higher from the test product compared with the reference product. Desloratadine, the active metabolite of loratadine, from the test product and from the RLD were bioequivalent.

However, study CL2004-01 demonstrated that two 5 mg Claritin® RediTabs are bioequivalent to the approved 1 X 10 mg Claritin® RediTab both for loratadine and desloratadine.

In their October 18, 2006 review of the clinical pharmacology data, Drs. Shinja Kim and Emmanuel Fadiran concluded that study CL2004-01 supports the approval of this NDA.

The Division of Scientific Investigation investigated the two bioequivalence studies. For Study CL2005-02 the investigators recommended that data for 4 subjects for desloratadine be excluded from the bioequivalence determination. For Study CL2004-01 the investigators recommended that data for 3 subjects for loratadine be excluded and that data for 6 subjects for desloratadine be excluded from the bioequivalence determination.

A reanalysis of the data from the bioequivalence studies was performed because of the recommendations of the Division of Scientific Investigation. In their review dated November 29, 2006, Drs. Kim and Fadiran conclude that based upon the data reanalysis that they can still recommend that this NDA be approved.

Clinical:
Efficacy:
The efficacy for this product is extrapolated based upon the pharmacokinetics data.

Safety:
Refer to the review by Dr. Stephen Osborne. An integrated review of safety was conducted at the time of the approval of Claritin® for hives relief on November 19, 2003 and was updated at for NDA 21-891 Children's Claritin® Chewable Tablets 5 mg which was approved in August, 2006. Safety data submitted with this new 5 mg orally disintegrating loratadine tablet application consists of:

- Adverse event data from the two bioequivalence trials
- Overdose and abuse data from the Toxic Exposure Surveillance System database of the American Association of Poison Control Centers from December 1, 2005-May 31, 2006
- Postmarketing adverse event data on loratadine from October 1, 2005 – March 31, 2006
- World Health Organization database from October 1, 2005 – February 2, 2006
- FDA AERS data for the period February 1, 2006 – August 1, 2006
- Literature review from October 1, 2005 – April 30, 2006.

No deaths or serious adverse events were reported with the clinical pharmacology studies and the safety data from these studies did not raise new safety concerns for loratadine. Also, a review of the safety data submitted from the other sources listed above did not raise new safety concerns for loratadine in adults or children.

Pediatrics:
In 1998, FDA issued a written request to Schering Plough for pediatric studies for loratadine. Children down to 6 months of age (N20-641 SE8-008) were studied and it was found that there was a higher exposure of loratadine and its metabolites in children ages 6 months to 2 yrs. The Agency did not label the approved Claritin® products to allow use in children below 2 years of age.

The sponsor requested a waiver for studies in children under the age of 2 years for NDA 21-993. The FDA granted this because Claritin® RediTabs 5 mg does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients. The sponsor has fulfilled the pediatric study requirement for this application in children greater than 2 years of age. Refer to the June 27, 2006 letter.

Labeling:
There are no outstanding labeling issues to be resolved before this product can be approved. The Division of Medication Errors and Technical Support (DMETS) consulted on this application to assess the descriptor "12 Hour" in conjunction with the proprietary name, Claritin® RediTabs. The DMETS recommends that the descriptor should appear in close proximity to the proprietary name wherever it appears on the

carton. I, along with the labeling reviewers, agree with this recommendation. The sponsor can make this change post-approval within 180 days or at the time of the next printing, whichever occurs first.

Additional labeling revisions, as laid out in the October 12, 2006 review by Dr. Cazemiro Martin, have been addressed by the sponsor. The 5- and 10-count blister card labels submitted on February 10, 2006 and resubmitted on June 20, 2006 should be discontinued no later than 6 months post-approval. The 5- and 10-count blister card labels submitted on September 8, 2006 and resubmitted on October 4, 2006 should be implemented no later than 6 months post approval. The flag "New 12 Hour!" on the 5- and 10-count alternate graphics cartons should be deleted from the principal display panel six months after introduction into the marketplace.

Conclusions:
The data suggest that this would be a safe and effective drug for nonprescription marketing. There are no issues to be resolved before this NDA could be approved. The sponsor will implement labeling as described above.

Recommendations:

- NDA 21-993 should be approved with the agreed upon labeling.
- As a post approval commitment (prior approval supplement) the applicant has agreed to revise the release as well as the stability specifications to include disintegration test and acceptance criterion, once sufficient data collected from the commercial batches.
- The descriptor "12 Hour" should appear in close proximity to the proprietary name wherever it appears on the carton. The sponsor can make this labeling change post-approval within 180 days or at the time of the next printing, whichever occurs first.
- The 5- and 10-count blister card labels submitted on February 10, 2006 and resubmitted on June 20, 2006 should be discontinued no later than 6 months post-approval. The 5- and 10-count blister card labels submitted on September 8, 2006 and resubmitted on October 4, 2006 will be implemented no later than 6 months post approval.
- The flag "New 12 Hour!" must be deleted from the PDP six months after introduction into the marketplace.

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/s/

Andrea Segal
12/5/2006 03:20:14 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-993, S-000
Submission Code	
Letter Date	February 10, 2006
Stamp Date	February 15, 2006
PDUFA Goal Date	December 13, 2006
Reviewer Name	Steven F. Osborne, M.D.
Review Completion Date	September 19, 2006
Established Name	loratadine
(Proposed) Trade Name	Claritin RediTabs 12 Hour Tablets
Therapeutic Class	antihistamine
Applicant	Schering Plough Healthcare Products
Priority Designation	Standard
Formulation	Disintegrating tablet
Dosing Regimen	for adults and children 6 years of age and older, one 5-mg tablet every 12 hours; not more than two tablets in 24 hours
Indication	Temporary relief of symptoms of runny nose, itchy, watery eyes, sneezing, and itching of the nose or throat, due to hay fever or other respiratory allergies
Intended Population	age 6 and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The proposed 5-mg loratadine orally disintegrating tablet for the indication of the relief of upper respiratory allergy symptoms in adults and children 6 years of age and older has an acceptable safety profile for OTC marketing. Therefore, this application is approvable from the safety standpoint. Final approvability depends on the outcome of the biopharmaceutical equivalence studies #CL2005-02 and #CL2004-01, which the biopharmaceutics reviewer is reviewing.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No special post-marketing risk management activities are recommended.

1.2.2 Required Phase 4

No special Phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

None.

Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Schering Plough Healthcare Products is seeking approval to market an orally disintegrating tablet dosage form containing 5 mg of loratadine for the indication of relief of hay fever and upper respiratory allergy symptoms in adults and children 6 years of age and older. The Sponsor currently markets an over-the-counter (OTC) 10-mg loratadine tablet and a 10-mg loratadine orally disintegrating tablet for adults and children 6 years and older for the same indication. The Sponsor also markets a 5-mg loratadine per teaspoon syrup and a 5-mg loratadine chewable tablet for use in adults and children 2 years and older for the same indication.

1.3.2 Efficacy

No controlled clinical efficacy trials were conducted. In support of efficacy, the Sponsor conducted two pharmacokinetic studies comparing two formulations of loratadine (1 x 5 mg

orally disintegrating tablet versus 1 combination tablet of loratadine 5 mg plus pseudoephedrine 60 mg in an extended release formulation; 2 x loratadine 5 mg orally disintegrating tablets versus 1 x loratadine 10 mg orally disintegrating tablet). The biopharmaceutical reviewer is reviewing the results of these bioequivalence trials.

Briefly, Study #CL2005-02 was a randomized, open-label, single-dose, two-way crossover bioequivalence study of two formulations of loratadine (1 x 5 mg disintegrating tablet versus 1 combination tablet of loratadine 5 mg plus pseudoephedrine 120 mg in an extended release formulation—(*Claritin-D Non-Drowsy 12-Hour Tablets*) in 91 healthy adult subjects. The subjects were randomly assigned to one of two treatment sequences (1 x 5 mg loratadine disintegrating tablet, followed by 1 *Claritin-D Non-Drowsy 12-Hour Tablets*; or 1 *Claritin-D Non-Drowsy 12-Hour Tablets*, followed by 1 x 5 mg loratadine disintegrating tablet), with single dose administration in each period. A 14-day washout period separated the two doses of study medication. For 120 hours following study drug administration the investigators collected blood for pharmacokinetic and safety monitoring, including plasma loratadine and desloratadine levels (active metabolite). The loratadine results did not meet the bioequivalence criteria for AUC, with the 90% CI for AUC falling *above* the bioequivalence limit of 1.25. However, the active metabolite, desloratadine, was equivalent between the two treatments.

Study #CL2004-01 was submitted to demonstrate safety after Study #CL2005-02 showed the AUC of the loratadine component in the disintegrating tablet was higher than that of the reference product. Study #CL2004-01 was a randomized, open-label, single-dose, two-way crossover bioequivalence study of two formulations of loratadine alone (2 x 5 mg disintegrating tablets versus 1 x 10 mg disintegrating tablet) in 48 healthy adult subjects. The subjects were randomly assigned to one of two treatment sequences (2 x 5 mg disintegrating tablets, followed by 1 x 10 mg disintegrating tablet; or 1 x 10 mg disintegrating tablet, followed by 2 x 5 mg disintegrating tablets), with single dose administration in each period. A 14-day washout period separated the two doses of study medication. For 120 hours following study drug administration the investigators collected blood for pharmacokinetic and safety monitoring, including plasma loratadine and desloratadine levels (active metabolite). The 2 treatments were found to be bioequivalent for both loratadine and desloratadine with the C_{max} and AUC falling completely within the range of 0.8 to 1.25.

1.3.3 Safety

An integrated review of safety was conducted at the time of the approval of Claritin for hives relief on November 19, 2003, and was updated at the time of approval for Children's Claritin Chewable Tablets 5 mg in June 2006. Safety data submitted to the current application consists of safety data from the current bioequivalence trials, overdose and abuse data, postmarketing adverse event data, and a literature review. Safety in Study #CL2005-02 and #CL2004-01 was assessed through the monitoring of adverse events (AEs), vital signs (blood pressure, respiration rate, pulse, and oral body temperature), clinical laboratory evaluations (CBC and differential, serum chemistry, and urinalyses including microscopic examination), physical examinations, and 12-lead ECG results.

In Study #CL2005-02 single oral doses of 5 mg loratadine disintegrating tablet and loratadine 5 mg plus pseudoephedrine 120 mg in an extended release formulation were well tolerated. The overall number of subjects reporting AEs was low (5 of 91 subjects, 5.5%). Headache was the most commonly reported treatment-related AE, occurring in 2 subjects each following administration of 5 mg loratadine disintegrating tablet. Only one subject reported all other AEs. No deaths or other serious adverse events (SAE) were reported for any subjects during the study. No clinically meaningful trends were observed in clinical laboratory results, vital sign measurements, physical examination findings, or ECG results.

In Study #CL2004-01 the number of subjects reporting treatment-emergent AEs was low for both treatment groups (3 of 46 subjects, 6.5% for the 2 x 5 mg group; and 6 of 48 subjects, 12.5% for the 1 x 10 mg group). In the 2 x 5 mg group, 2 subjects reported headache – 1 occurrence was considered treatment-related and 1 was not related. Two subjects reported chest pain that was not considered treatment-related. In the 1 x 10 mg group, 3 subjects reported headache that was considered treatment related and 1 subject each reported constipation, dry mouth, influenza-like illness, pyrexia, vaginal infection, dizziness, and rhonchi, of which only dry mouth and dizziness were considered related to treatment. All AEs were mild, and all treatment-related AEs resolved within 1 day of onset. One subject discontinued from the study 14 days after administration of 1 x 10 mg loratadine due to pyrexia and rhonchi that were not considered related to treatment. No deaths or serious adverse events (SAEs) were reported. No clinically meaningful trends were observed in clinical laboratory results, vital signs measurements, physical examination findings, or ECG results.

The Sponsor's 2005 Claritin product update did not show any new safety concerns during the period November 27, 2004-November 26, 2005. Postmarketing data submitted to the Sponsor or FDA, and a review of the literature, did not reveal any new safety concerns. In particular there were no cases of Torsade de Pointes, severe cardiac arrhythmias, or male congenital hypospadias that could be clearly related to loratadine. An additional safety update from the Sponsor on June 19, 2006 did not reveal any safety concerns.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen for this orally disintegrating tablet is one 5 mg tablet every 12 hours for adults and children 6 years of age and older.

1.3.5 Drug-Drug Interactions

No drug-drug interactions were evaluated in this safety update or in the current trials, Study # CL2005-02 and Study # CL2004-01. However, in a FDA safety assessment for the OTC switch (May 12, 2000, reference 5) the potential interaction between loratadine with erythromycin, cimetidine, and ketoconazole was reviewed. The latter three drugs combined with loratadine were not associated with adverse events, though an increase was noted in the area under the curve (AUC) values for loratadine and the active metabolite, descarboethoxyloratadine (desloratadine).

1.3.6 Special Populations

The proposed labeling has all the appropriate warnings for consumers of certain age categories, with underlying medical conditions, and for those taking interacting medications.

2 INTRODUCTION AND BACKGROUND

Claritin Tablets (loratadine 10 mg or loratadine 10 mg orally disintegrating tablet) are marketed for the relief of hay fever and upper respiratory allergy symptoms in adults and children 6 years of age and older and are available in the United States without a prescription. The Sponsor also markets Claritin Syrup (loratadine 5 mg per teaspoon) for the same indication in adults and children 2 years of age and older. In addition, the Sponsor markets an OTC 10-mg tablet for relief of hives in adults and children 6 years and older. A separate combination product with pseudoephedrine and loratadine, Claritin-D Non-Drowsy 12-Hour (and 24-Hour) Tablet, is available for the same indication. A 5 mg loratadine chewable tablet was approved in August 2006.

Loratadine has been shown in animals and in man to be an orally effective, long-acting antihistamine devoid of central nervous system effects. Following oral administration, loratadine is rapidly metabolized to desloratadine, a pharmacologically active metabolite. The half-life of loratadine is 8 to 15 hours and the half-life of desloratadine is 12 to 24 hours.

The Sponsor has developed a 5 mg loratadine tablet that is orally disintegrating. The proposed dosing regimen for this orally disintegrating tablet is one 5 mg tablet every 12 hours for adults and children 6 years and older. Study #CL2005-02 is designed to evaluate the bioequivalence of the test product (1 x 5 mg loratadine orally disintegrating tablets) and the reference product (Claritin-D Non-Drowsy 12-Hour tablet consisting of loratadine 5 mg / pseudoephedrine 120 mg). An additional study, submitted to support safety, Study #CL2004-01, is designed to evaluate the bioequivalence of the test product (2 x 5 mg loratadine orally disintegrating tablets) and the reference product (1 x 10 mg loratadine orally disintegrating tablet).

Product Information

Schering Plough Healthcare Products is seeking approval to market a 5-mg loratadine orally disintegrating tablet for the indication of the temporary relief of symptoms of runny nose, itchy, watery eyes, sneezing, and itching of the nose or throat, due to hay fever or other upper respiratory allergies in adults and children 6 years of age and older. The proposed dosing directions are:

- adults and children 6 years and over: place 1 tablet on tongue; tablet disintegrates, with or without water; 1 tablet every 12 hours; not more than 2 tablets in 24 hours
- children under 6 years of age: ask a doctor
- consumers with liver or kidney disease: ask a doctor

2.2 Currently Available Treatment for Indications

Loratadine is available OTC in a 10-mg tablet, a 10-mg orally disintegrating tablet, and a 5-mg/teaspoon syrup for the relief of upper respiratory allergy symptoms. A 5-mg chewable table was approved in August 2006. In addition, other antihistamines, both sedating and non-sedating, are available for the indication of the relief of upper respiratory allergy symptoms in adults and children 2 years of age and older.

Availability of Proposed Active Ingredient in the United States

See section 2.1 and 2.2.

2.4 Important Issues With Pharmacologically Related Products

Two other non-sedating antihistamines, terfenadine and astemizole, have been removed from the market due to the occurrence of a cardiac arrhythmia (Torsade de Pointes) that can occur when the blood level of terfenadine or astemizole is elevated. The blood level can become elevated beyond the therapeutic range when the respective drug is co-administered with another drug such as ketoconazole or erythromycin. To date, there have not been reports of the Torsade de Pointes cardiac arrhythmia with loratadine as the single suspect drug. See sections 7.2.9 and 8.6 for additional discussion on this topic.

The OTC label for loratadine warns consumers to avoid use if they ever had an allergic reaction to the product (Claritin) or any of its ingredients. Those with liver or kidney disease are advised to ask a doctor before use. Consumers are warned against taking more than directed, which may cause drowsiness.

2.5 Presubmission Regulatory Activity

The original NDA 19-658 for loratadine (Claritin Tablets) was approved on April 12, 1993. Since then, NDAs have been approved for Claritin-D (loratadine-pseudoephedrine), Claritin syrup, Claritin RediTabs Orally Disintegrating Tablets, and Claritin Chewable Tablets. On November 12, 2002 Claritin tablets were approved in a prescription-to-over-the-counter (Rx-OTC) switch. Since then, all Claritin products have been approved for OTC use. Table 1 below shows these products.

Table 1. Claritin product approvals

NDA #	Product Name	Year of Approval
19-658	Claritin Tablets 10 mg	1993
19-670	Claritin-D 12 Hour Tablets	2002 (now discontinued)
20-470	Claritin-D 24 Hour Tablets	2002
20-641	Claritin Syrup 5 mg/teaspoon	2002
20-704	Claritin RediTabs Orally Disintegrating Tablets 10 mg	2003

21-891	Children's Claritin Chewable Tablets 5 mg	2006

2.6 Other Relevant Background Information

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Not applicable.

3.2 Animal Pharmacology/Toxicology

No new animal data or toxicology data were submitted.

4.1 Sources of Clinical Data

The Sponsor provided results of one biopharmaceutical equivalence trial, Study #CL2005-02, a second biopharmaceutical equivalence trial in support of safety, Study #CL2004-01, a loratadine safety update, and the proposed OTC labeling, all of which are considered in this review. The Sponsor referenced data from the original NDA. These data included the original NDA 19-658 for Claritin Tablets 10 mg, NDA 20-704 for Claritin RediTabs Tablets 10 mg, and NDA 19-670 for Claritin-D 12-Hour Extended Release Tablets as shown below. This New Drug Application references the following approved applications:

Reference is made to:

1. The Original New Drug Application NDA 19-658 for Claritin Tablets dated October 31, 1986, approved April 12, 1993. Nonclinical Pharmacology and Toxicology.

2. The Original New Drug Application NDA 20-704 in its entirety for Claritin RediTabs Tablets dated February 29, 1996, approved December 23, 1996.

3. The Original New Drug Application NDA 19-670 in its entirety for Claritin-D 12-Hour Extended Release Tablets dated March 30, 1987, approved November 14, 1994.

4. NDA 19-658 Rx-to-OTC Switch Supplement S-018 for Claritin Tablets dated January 25, 2002, approved November 27, 2002.

5. PIND 63,797 Claritin RediTabs Tablets 12 Hour (loratadine 5 mg orally disintegrating tablets) Briefing Document for January 5, 2005 Pre-IND Meeting, submitted December 3, 2004.

4.2 Tables of Clinical Studies

The Sponsor submitted two biopharmaceutical equivalence trial studies to this NDA submission: Study #CL2005-02 and #CL2004-01. The Sponsor referenced studies from prior submissions to NDA 19-658, the currently-marketed Claritin Tablets for Nonclinical Pharmacology and Toxicology. The Sponsor also referenced NDA 19-670, the currently marketed OTC Claritin-D 12-Hour Extended Release Tablets (loratadine 5 mg / pseudoephedrine 120 mg) that was used as the reference listed drug in Study #CL2005-02. The Sponsor also referenced PIND 63,797 (Briefing Document) and NDA 20-704 in its entirety, for Claritin RediTabs Tablets that was used as the reference listed drug in Study #CL2004-01.

4.3 Review Strategy

This review covers the safety update. The efficacy portion of Study #CL2005-02 and #2004-01 will be reviewed by the biopharmaceutics reviewer.

4.4 Data Quality and Integrity

Not applicable. There were no DSI audits conducted for the study site or data analyses.

4.5 Compliance with Good Clinical Practices

Not applicable to this review.

Financial Disclosures

The Sponsor conducted two studies, #CL2005-02 and #CL2004-01, each involving only one clinical site and only one investigator. The Sponsor submitted Form 3454 certifying no financial interest by the investigators. There were no financial disclosures that would cast doubt on the findings.

5 CLINICAL PHARMACOLOGY

5.1 PHARMACOKINETICS

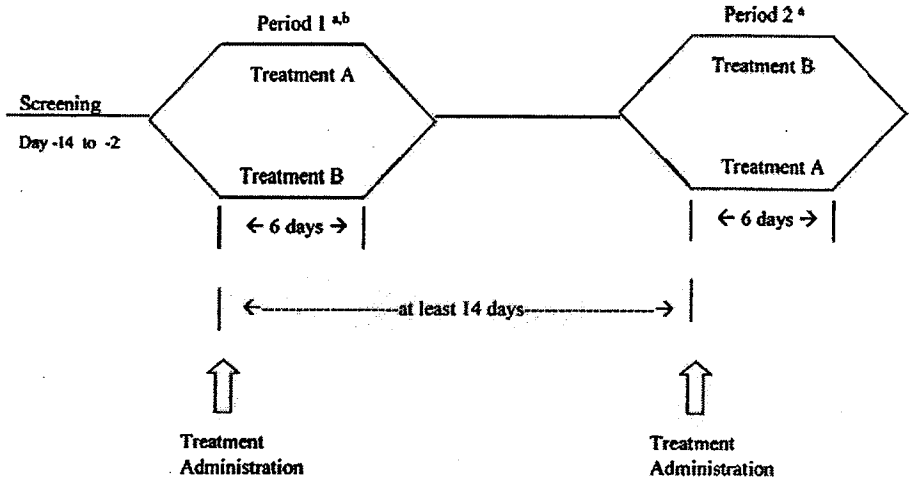
The proposed indication for Claritin RediTabs 12 Hour Tablets is the temporary relief of symptoms due to hay fever or other respiratory allergies. The biopharmaceutical reviewer is reviewing the efficacy study for this review, Study #CL2005-02, which assessed the bioequivalence of orally administered Claritin RediTabs 12 Hour Tablets (1 x 5 mg loratadine orally disintegrating tablets) and the reference product, Claritin-D 12-Hour Extended ReleaseTablet (loratadine 5 mg / pseudoephedrine 120 mg). In addition, the biopharmaceutics reviewer is reviewing the efficacy portion of the supplemental bioequivalence Study #CL2004-01, which assessed the bioequivalence of orally administered Claritin RediTabs 12-Hour Tablets

(2 x 5 mg loratadine orally disintegrating tablets) and the reference product, Claritin RediTabs Tablets 10 mg (1 x loratadine 10 mg orally disintegrating tablet) . Below is a brief summary of these studies.

Study #CL2005-02:

Study #CL2005-02 was a randomized, open-label, single-dose, two-way crossover bioequivalence study of two formulations of loratadine (1 x 5 mg disintegrating tablet versus 1 tablet of loratadine 5 mg plus pseudoephedrine 60 mg in an extended release formulation—(*Claritin-D Non-Drowsy 12-Hour Tablets*) in 91 healthy adult subjects. The study was not blinded to the subjects or the investigator; however, laboratory personnel were blinded to the treatment sequence. Subjects were screened for eligibility within 32 days of receiving the first dose of study medication. Eligible subjects reported to the study clinic at least 12 hours prior to the first dose of study medication. The subjects were randomly assigned to one of two treatment sequences (1 x 5 mg loratadine disintegrating tablet, followed by 1 *Claritin-D Non-Drowsy 12-Hour Tablets*; or 1 *Claritin-D Non-Drowsy 12-Hour Tablets*, followed by 1 x 5 mg loratadine disintegrating tablet), with single dose administration in each period. A 14-day washout period separated the two doses of study medication. For 120 hours following study drug administration the investigators collected blood for pharmacokinetic and safety monitoring, including plasma loratadine and desloratadine levels (active metabolite). Figure 1 and Table 2 show the study design and study assessments and procedures, respectively.

Figure 1. Study Design Schematic



Treatment A: One loratadine 5 mg orally disintegrating tablet administered without water following a 10-hour fast.
Treatment B: One loratadine 5 mg/pseudoephedrine sulfate 120 mg extended release tablet administered with water following a 10-hour fast.

a Pharmacokinetic analysis for 120 hours following treatment administration.

b A period of at least 14 days will separate dosing.

Table 2. Study assessments and procedures

Evaluation	Screening (Day –14 to –2)	Period[a] 1 & 2 Day –1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Obtain Informed Consent[b]	X							
Entry Criteria Review	X							
Concomitant Medication Review	X	X						
Medical History	X							
Physical Exam	X							X[h]
Body Weight (kg)	X							
Height (cm)	X							
Laboratory Tests[c]	X	X						X[h]
HIV/HbsAg/Hep C Antibody	X							
Urine Cotinine Test	X							
Urine Drug Screen	X	X						
ECG[d]	X							X[h]
Serum/Urine Pregnancy Test	X	X						X[h]
Vital Signs[e]	X	X	X	X	X	X	X	X
Volunteer Confinement[f]		X	X	X	X	X	X	X
Treatment Administration			X					
Blood Samples[g]			X	X	X	X	X	X

a A washout period of at least 14 days separated each dose administration.

b Written informed consent must have been obtained prior to any study evaluations being performed.

c CBC and differential, chemistry panel, urinalysis (including microscopic examination).

d Standard 12-lead ECG reporting ventricular rate, PR, QRS, QT and QTc intervals.

e Seated blood pressure, pulse rate, oral body temperature screening, Day -1, prior to first blood draw each day (Days 1-6, Periods 1 & 2) and after the 120 hour post-dose blood draw (Period 2 only).

f Subjects arrived at the study site at least 12 hours prior to dosing and remained at the site until after the 120-hour post-dose blood draw.

g Blood samples for determination of plasma loratadine and desloratadine levels were collected at 0 hours/pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours post-dose.

h Following collection of the 120-hour blood sample in Period 2 only.

Subject 006 (lost to follow-up after Period 1) did not have sufficient data in both periods and was not included in the analysis of bioavailability. In addition, 4 subjects (Subjects 003,037,049, and 082) with pre-dose concentrations of loratadine or desloratadine greater than 5% of Cmax, were also excluded from the analysis of bioavailability. As a result, bioavailability was assessed on a sample size of 86 subjects. The results showed that loratadine did not meet the bioequivalence criteria for AUC, with the 90% CI for AUC falling *above* the bioequivalence limit of 1.25. However, desloratadine was bioequivalent between the two treatments, with 90% confidence intervals around the ratio of the geometric least squares means for AUC and C_{max} all falling completely within the range of 0.8 to 1.25.

Study #CL2004-01:

Study #CL2004-01 was submitted to demonstrate safety after Study #CL2005-02 showed the AUC of the loratadine component in the disintegrating tablet was higher than that of the reference product. Study #CL2004-01 was a randomized, open-label, single-dose, two-way crossover bioequivalence study of two formulations of loratadine alone (2 x 5 mg disintegrating tablets versus 1 x 10 mg disintegrating tablet) in 48 healthy adult subjects. The subjects were

randomly assigned to one of two treatment sequences (2 x 5 mg disintegrating tablets, followed by 1 x 10 mg disintegrating tablet; or 1 x 10 mg disintegrating tablet, followed by 2 x 5 mg disintegrating tablets), with single dose administration in each period, as shown below:

- Sequence 1: 2 x 5 mg loratadine orally disintegrating tablets → 1 x 10 mg orally disintegrating loratadine tablet

- Sequence 2: 1 x 10 mg loratadine orally disintegrating tablet → 2 x 5 mg loratadine orally disintegrating tablets.

A 14-day washout period separated the two doses of study medication. For 120 hours following study drug administration the investigators collected blood for pharmacokinetic and safety monitoring, including plasma loratadine and desloratadine levels (active metabolite). The 2 treatments were found to be bioequivalent, with 90% confidence intervals around the ratio of the least squares means for loratadine and desloratadine C_{max} and AUC all falling completely within the range of 0.8 to 1.25. The geometric mean ratios (90% CIs) for loratadine AUC and C_{max} were 0.9629 (0.8868, 1.0454) and 0.9584 (0.8608, 1.0670). For desloratadine, the ratios (90% CIs) were 0.9895 (0.9401, 1.0414) and 0.9969 (0.9466, 1.0499) for AUC and C_{max}, respectively.

The basic Study Design Schematic and Study Assessments and Procedures are the same as in Figure 1 and Table 2 above for Study #CL2005-02 except for the actual study drugs.

5.2 Pharmacodynamics

No new pharmacodynamcis data were submitted with this application.

5.3 Exposure-Response Relationships

No new exposure-response relationship data were submitted with this application.

6 INTEGRATED REVIEW OF EFFICACY

Efficacy of the product is extrapolated based on the PK data. No new efficacy studies were performed with this formulation. The PK data is briefly shown below.

Study #CL2005-02:

Of the 91 subjects enrolled, 90 subjects (99%) completed the study. Subject 006 (Sequence 1) was lost to follow-up after receiving ClaritinB RediTabsB Tablet during Period 1. The loratadine results did not meet the bioequivalence criteria for AUC, with the 90% CI for AUC falling *above* the bioequivalence limit of 1.25. However, the active metabolite, desloratadine, was equivalent between the two treatments. The 2 treatments were found to be bioequivalent, with 90% confidence intervals around the ratio of the least squares means for loratadine and desloratadine C_{max} and AUC all falling completely within the range of 0.8 to 1.25. The geometric mean ratios

(90% CIs) for loratadine AUC and C_{max} were 0.9629 (0.8868, 1.0454) and 0.9584 (0.8608, 1.0670). For desloratadine, the ratios (90% CIs) were 0.9895 (0.9401, 1.0414) and 0.9969 (0.9466, 1.0499) for AUC and C_{max}, respectively.

Study #CL2004-01:

Of the 48 subjects enrolled, 46 subjects (95.8%) completed the study. Subject 033 discontinued due to adverse events (pyrexia and rhonchi) 14 days after receiving 1 dose of 10 mg loratadine, and Subject 039 withdrew consent due to a family emergency after receiving 1 dose of 10 mg loratadine. The test product (2 x 5 mg loratadine chewable tablets) was considered bioequivalent to the reference product (1 x 10 mg loratadine tablet) with 90% confidence intervals around the ratio of the least squares means for the C_{max} and AUC for loratadine and desloratadine all falling within the bioequivalence interval of 0.8 to 1.25. Of note, the Sponsor performed a fasted study, but not a fed study.

Comment:

Both Study #CL2005-02 and #CL2004-01 should have included a fed study. The biopharmaceutics reviewer will address how this will impact the approvability of the submission.

7 INTEGRATED REVIEW OF SAFETY

The following sections of the Integrated Summary of Safety (ISS) are being updated:

- Sponsor-received adverse events for the period October 1, 2005-March 31, 2006
- World Health Organization (WHO) database from October 1, 2005-February 2, 2006
- Update of the FDA Adverse Event Reporting System (AERS) database for the period February 1, 2006-August 1, 2006.
- Update of the Toxic Exposure Surveillance System (TESS) database from the American Association of Poison Control Centers for loratadine-containing products from December 1, 2005-May 31, 2006
- Literature update for loratadine for the period October 1, 2005-April 30, 2006.

7.1 Methods and Findings

The Sponsor defined an adverse event (AE) as any untoward medical occurrence or unfavorable and unintended sign in a subject administered a pharmaceutical product, whether or not considered related to the use of that product. This included the onset of new illness and the exacerbation of pre-existing conditions. A serious adverse event (SAE) was any adverse drug experience occurring at any dose that resulted in any of the following outcomes:

- death
- life-threatening AE (i.e., one that placed the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurred)

- persistent or significant disability/incapacity
- required in-patient hospitalization, or prolonged hospitalization
- congenital anomaly or birth defect

From clinical trials the most common AEs reported with the use of loratadine (for RediTabs in both Study #CL2005-02 and #CL2004-01) are headache, somnolence, fatigue, and dry mouth. The most common AEs reported with the use of Claritin-D@ 12-Hour Extended Release Tablet are headache, insomnia, somnolence, nervousness, dizziness, fatigue, dyspepsia, nausea, pharyngitis, anorexia, and thirst. The occurrence of these of these and other events was recorded in the subject's medical records and on the CRF, regardless of causality. All AEs were followed to satisfactory resolution or stabilization of the event(s).

All subjects who received at least one dose of study drug were included in the safety analyses. There were no reported serious adverse events in Study# CL2005-02 or in Study #CL2004-01.

7.1.1 Deaths

There were no reported deaths in Study# CL2005-02 or in Study #CL004-01. The proposed product is a new formulation and there are no reported deaths with its use. Worldwide, there were no reported deaths in the AERS Database for loratadine during the period November 1, 2003-December 31, 2005. One death was reported overseas. A consumer in the United Kingdom reported that her husband was receiving Clarityn Allergy Syrup (same dosage as the US OTC Children's Claritin Allergy Oral Solution) to reduce fluid secretions during his illness with lung cancer. He experienced a cough every time he took the Syrup. The family believed that his cough was due to the lung cancer. His cancer metastasized and he died of disease progression. Concomitant medications were unknown and were reported to change quickly because of the rapid progression of his disease. The consumer was being cared for at his home. The Sponsor notes that a quality analysis of the product did not reveal any reason for the cough or disease progression.

Comment:

1. The details of this case indicate that it is likely the product was not related to disease progression.

Fatalities associated with the intentional overdose or abuses of the active ingredient, loratadine, are discussed in sections 7.1.16 and 7.1.17 of this review.

7.12 Other Serious Adverse Events

No serious AEs occurred during Study #CL2004-01 or in Study #CL2004-01.

7.1.3 Dropouts and Other Significant Adverse Events

In Study #CL2005-02 subjects number 16 and 43 were dropped due to a withdrawal of consent (no stated reason) and noncompliance (failed drug test), respectively. In Study #CL2004-01 subject number 33 discontinued due to a nonserious AE (pyrexia and rhonchi) and subject number 39 withdrew due to a family emergency.

7.1.3.1 Overall profile of dropouts

In Study #CL2005-02 subject #16, a 22 year old female, withdrew consent on Day 18 of sequence two (see Figure 1 for sequence). Subject # 43, a 37 year old female, was removed from study #CL2005-02 on Day 15 of sequence one due to a positive drug screen. In Study #CL2004-01 both subjects who withdrew did so in sequence 2 (after receiving 1 x 10 mg loratadine). Subject number 33 was a 25 year old male and subject number 39 was a 23 year old female.

7.1.3.2 Adverse events associated with dropouts

The two dropouts in study # CL2005-02 were not associated with adverse events. In Study #CL2004-01 one of the dropouts (subject number 33) experienced pyrexia and rhonchi which were not considered related to treatment.

7.1.3.3 Other significant adverse events

Not applicable.

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

Study #CL-2005-02:

Of 91 subjects, 5 subjects (6%) reported at least one treatment-emergent AE: 3 subjects (3%) following administration of Claritin RediTabs Tablet and 3 subjects (3%) following administration of Claritin-D 12 Hour Extended Release Tablet. Most AEs were treatment-related AEs. No deaths, other SAEs, AEs causing discontinuation or adjustment of study medication, or severe AEs were reported for any subjects in this study. See Table 3 on the next page.

Table 3. Overall summary of adverse events in Study #CL2005-02.

Category	Number (%) of Subjects		
	Claritin® RediTabs® Tablet (N=91)	Claritin-D® 12 Hour Extended Release Tablet (N=90)	Overall (N=91)
Any AE	3 (3.3)	3 (3.3)	5 (5.5)
Treatment-emergent AE	3 (3.3)	3 (3.3)	5 (5.5)
Treatment-related AE	2 (2.2)	3 (3.3)	4 (4.4)
SAEs, including death	0	0	0
AE causing discontinuation of study medication	0	0	0
AE causing interruption of study medication or dosing change	0	0	0
Severe adverse event	0	0	0

AE=Adverse event; SAE=Serious adverse event

Note: Claritin® RediTabs® Tablet=Test product; Claritin-D® 12 Hour Extended Release Tablet=Reference product

Treatment–emergent AEs in MedDRA terminology are shown in Table 4 below. The most commonly reported treatment-emergent AE was headache, which was reported by 2 subjects (2%) following administration of Claritins RediTabs Tablet. All other AEs were reported by only one subject and included nausea and vaginal discharge following administration of Claritins RediTabs Tablet and upper abdominal pain, vomiting, dizziness, syncope, and macular rash following administration of Claritin-D@ 12 Hour Extended Release Tablet. All AEs were mild, and all AEs except for vaginal discharge were considered by the investigator to be treatment-related.

Table 4. Incidence of treatment-emergent AEs in Study #CL2005-02.

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects		
	Claritin® RediTabs® Tablet (N=91)	Claritin-D® 12 Hour Extended Release Tablet (N=90)	Overall (N=91)
Number of Subjects with an AE	3 (3.3)	3 (3.3)	5 (5.5)
Nervous System Disorders	2 (2.2)	1 (1.1)	3 (3.3)
Dizziness	0	1 (1.1)	1 (1.1)
Headache	2 (2.2)	0	2 (2.2)
Syncope	0	1 (1.1)	1 (1.1)
Gastrointestinal Disorders	1 (1.1)	2 (2.2)	3 (3.3)
Upper abdominal pain	0	1 (1.1)	1 (1.1)
Nausea	1 (1.1)	0	1 (1.1)
Vomiting NOS	0	1 (1.1)	1 (1.1)
Reproductive System and Breast Disorders	1 (1.1)	0	1 (1.1)
Vaginal discharge	1 (1.1)	0	1 (1.1)
Skin and Subcutaneous Disorders	0	1 (1.1)	1 (1.1)
Macular rash	0	1 (1.1)	1 (1.1)

Note: Claritin® RediTabs® Tablet=Test product;
Claritin-D® 12 Hour Extended Release Tablet=Reference product

Study #CL2004-01:

Of 48 subjects the number of subjects reporting treatment-emergent AEs was low for both treatment groups (3/46, 6.5% for the 2 x 5 mg group and 6/48, 12.5% for the 1 x 10 mg group). These results are shown in Table 5 below.

Table 5. Overall summary of adverse events in Study #CL2004-01.

	Number (%) of Subjects		
Category	2 x 5 mg N=46	1 x 10 N=48	Overall N=48
Any AE	3 (6.5)	6 (12.5)	9 (18.8)
Treatment-emergent AE	3 (6.5)	6 (12.5)	9 (18.8)
Treatment-related AE	1 (2.2)	3 (6.3)	4 (8.3)
SAEs, including death	0	0	0
AE causing discontinuation of study medication	0	1 (2.1)	1 (2.1)
AE causing interruption of study medication or dosing change	0	0	0
Severe adverse event	0	0	0

AE=Adverse event; SAE=Serious adverse event
Note: 2 x 5 mg=test product; 1 x 10 mg=reference product

In the 2 x 5 mg group, 2 subjects reported headache, with 1 occurrence considered treatment-related and 1 occurrence not related. Two subjects reported chest pain that was not considered treatment-related. Subject 16, a 40-year old female, reported an 18-minute episode of mild chest pain which resolved spontaneously and for which no action was taken. Subject 18, a 42-year old female, reported a 3-day episode of mild chest pain which resolved spontaneously and for which no action was taken.

In the 1 x 10 mg group, 3 subjects reported headache that was considered treatment related and 1 subject each reported constipation, dry mouth, influenza-like illness, pyrexia, vaginal infection, dizziness, and rhonchi of which only dry mouth and dizziness were considered related to treatment. All AEs were mild, and all treatment-related AEs resolved within 1 day of onset. No deaths, other SAEs, AEs causing discontinuation or adjustment of study medication, or severe AEs were reported for any subjects in this study. These results are shown by MedDRA system organ class and preferred term in Table 6 on the next page.

Comment:

The Sponsor believes that the chest pain episodes reported by subjects 16 and 18, females ages 40 and 42 years old respectively, were unrelated to the study drug 2 x 5 mg loratadine. It is not possible to be certain the chest pain was not related to the study drug, as no cardiac-related studies were done at the time. However, loratadine is not known to precipitate chest pain and 40-42 year old females are at low risk for chest pain related to a cardiac cause. End of Study ECGs were unchanged. Thus, the Sponsor's conclusion appears reasonable.

Table 6. Incidence of treatment-emergent AEs in Study #CL2004-01.

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects 2 x 5 mg N=47	 1 x 10 mg N=46	 Overall N=48
Number of Subjects with an AE	3 (6.5)	6 (12.5)	9 (18.8)
Gastrointestinal Disorders	0	2 (4.2)	2 (4.2)
Constipation	0	1 (2.1)	1 (2.1)
Dry Mouth	0	1 (2.1)	1 (2.1)
General Disorders and Administration Site Conditions	2 (4.3)	2 (4.2)	4 (8.3)
Chest Pain	2 (4.3)	0	2 (4.2)
Influenza Like Illness	0	1 (2.1)	1 (2.1)
Pyrexia	0	1 (2.1)	1 (2.1)
Infections and Infestations	0	1 (2.1)	1 (2.1)
Vaginal Infection NOS	0	1 (2.1)	1 (2.1)
Nervous System Disorders	2 (4.3)	3 (6.3)	5 (10.4)
Dizziness	0	1 (2.1)	1 (2.1)
Headache	2 (4.3)	3 (6.3)	5 (10.4)
Respiratory, Thoracic, and Mediastinal Disorders	0	1 (2.1)	1 (2.1)
Rhonchi	0	1 (2.1)	1 (2.1)

NOS=Not otherwise specified
Note: 2 x 5 mg=test product; 1 x 10 mg=reference product

7.1.5.1 Eliciting adverse events data in the development program

Safety was assessed through the monitoring of adverse events (AEs), vital signs, clinical laboratory evaluations, physical examinations, and 12-lead electrocardiograms (see Table 2). Subjects were questioned or examined by the investigator for evidence of AEs. A diary was not kept by the subjects.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and preferred terms were appropriate. MedDRA terminology was used.

7.1.5.3 Incidence of common adverse events

There were only four adverse events with loratadine use in Study #CL2005-02, of which two were cases of headache. In Study #CL2004-01 there were six adverse events, of which five were headache, and one was pyrexia and cough. Two incidents of chest pain, in subjects who also reported headache, were considered not treatment-related. There were no serious adverse events.

7.1.5.4 Common adverse event tables

See section 7.1.5.

7.1.5.5 Identifying common and drug-related adverse events

Five events were considered treatment-related in Study #CL2005-02 and four events were considered treatment-related in Study #CL2004-01. Most adverse events were headache in both studies. All AEs were mild.

7.1.5.6 Additional analyses and explorations

Not applicable.

7.1.6 Less Common Adverse Events

In Study #CL2005-02 and #CL2004-01 the number of subjects exposed and the number of adverse events were too few to assess the incidence of the more common or less common adverse events.

7.1.7 Laboratory Findings

Study #CL2005-02:

Mean values for serum chemistry, hematology, and urinalysis parameters remained within the normal range at every time point during the study. However, individual subjects had some abnormal serum chemistry values, including abnormal results for BUN, uric acid, and total cholesterol. Most of abnormalities did not persist from screening to end-of-study. Other parameters which increased in the number of abnormalities from screening to end-of-study included phosphorus and triglycerides (Table 9). Mean triglyceride levels increased from the time of screening (107.8 mg/dL) to the End of Study (128.3 mg/dL). See the Comments on the next page.

Table 9. Summary of Serum Chemistry Abnormalities (Number (%) of Subjects) in Study #CL2005-02.

	Number (%) of Subjects			
Parameter	Screening (N=91)	Period 1, Day -1 (N=91)	Period 2, Day -1 (N=90)	End of Study (N=90)
Sodium (mEq/L)	0	0	1 (1.1)	0
Potassium (mEq/L)	0	1 (1.1)	0	1 (1.1)
Chloride (mEq/L)	0	0	1 (1.1)	0
Glucose (mg/dL)	1 (1.1)	0	2 (2.2)	1 (1.1)
BUN (mg/dL)	12 (13.2)	9 (9.9)	8 (8.9)	9 (10.0)
Creatinine (mg/dL)	0	0	1 (1.1)	0
Phosphorus (mg/dL)	0	4 (4.4)	6 (6.7)	2 (2.2)
Uric Acid (mg/dL)	10 (11.0)	10 (11.0)	13 (14.4)	10 (11.1)
Calcium (mg/dL)	1 (1.1)	1 (1.1)	0	0
SGOT (U/L)	1 (1.1)	2 (2.2)	0	0
SGPT (U/L)	2 (2.2)	0	0	1 (1.1)
GGTP (U/L)	1 (1.1)	0	3 (3.3)	3 (3.3)
Bilirubin Total (mg/dL)	5 (5.5)	4 (4.4)	3 (3.3)	0
LDH (U/L)	2 (2.2)	3 (3.3)	1 (1.1)	1 (1.1)
Alkaline Phosphatase (U/L)	0	0	0	0
Total Protein (g/dL)	3 (3.3)	4 (4.4)	5 (5.6)	5 (5.6)
Albumin (g/dL)	1 (1.1)	2 (2.2)	1 (1.1)	3 (3.3)
Total Cholesterol (mg/dL)	38 (41.8)	34 (37.4)	32 (35.6)	27 (30.0)
Triglycerides (mg/dL)	8 (8.8)	8 (8.8)	14 (15.6)	15 (16.7)

Comments:

1. Although mean triglyceride levels increased from the time of screening (107.8 mg/dL) to the End of Study (128.3 mg/dL), the values are still below 150 mg/dL, which is often considered the upper limit of normal.

2. Four subjects who had normal phosphorus values at screening had abnormal phosphorus levels at Day -1, making it clear this abnormality was not related to loratadine use. A similar unexplained finding was noted in a preview loratadine product review (Children's Claritin Chewable Tablet).

The number of abnormalities in hematology results increased between screening and end-of-study for hemoglobin, hematocrit, RBC, MCV, WBC, neutrophil count, and percentage of lymphocytes (Table 10). See the Comment after Table 12 on the next page.

Table 10. Summary of Hematology Abnormalities (Number (%) of Subjects) in Study #CL2005-02.

	Number (%) of Subjects			
Parameter	Screening (N=91)	Period 1, Day -1 (N=91)	Period 2, Day -1 (N=90)	End of Study (N=90)
Hemoglobin (g/dL)	9 (9.9)	15 (16.5)	33 (36.7)	21 (23.3)
Hematocrit (%)	4 (4.4)	8 (8.8)	19 (21.1)	10 (11.1)
RBC (10^6/uL)	12 (13.2)	25 (27.5)	27 (30.0)	26 (28.9)
MCH (pg)	2 (2.2)	1 (1.1)	3 (3.3)	3 (3.3)
MCHC (g/dL)	2 (2.2)	2 (2.2)	1 (1.1)	0
MCV (fl)	9 (9.9)	14 (15.4)	14 (15.6)	17 (18.9)
Platelet count (10^3/uL)	0	0	0	2 (2.2)
WBC (10^3/uL)	3 (3.3)	8 (8.8)	1 (1.1)	6 (6.7)
Neutrophils (10^3/uL)	1 (1.1)	7 (7.7)	2 (2.2)	3 (3.3)
Neutrophils (%)	3 (3.3)	5 (5.5)	4 (4.4)	3 (3.3)
Lymphocytes (10^3/uL)	0	1 (1.1)	0	0
Lymphocytes (%)	5 (5.5)	12 (13.2)	9 (10.0)	5 (5.6)

Study #CL2004-01:

The number of subjects with abnormal serum chemistry values was generally low throughout the study. Abnormal sodium, glucose, phosphorus, uric acid, SGOT, and triglycerides were observed (Table 11). The number of subjects with abnormal hematology values was generally low except for hemoglobin, hematocrit, and RBC count. The number of subjects with abnormal hematology values increased from Period 1, Day -1 to the end-of-study assessment for the following parameters: hemoglobin, hematocrit, RBC count, MCV, platelet count, neutrophils, % neutrophils, and % lymphocytes (Table 12).

Table 11. Summary of Serum Chemistry Abnormalities (Number (%) of Subjects) in Study #CL2004-01.

	Number (%) of Subjects			
Parameter	Screening N=48	Period 1, Day -1 N=47	Period 2, Day -1 N=47	End of Study N=48
Sodium	0	0	3(6.4)	1 (2.1)
Glucose	0	0	2 (4.3)	0
Phosphorus	1 (2.1)	2 (4.3)	0	2 (4.2)
Uric Acid	3 (6.3)	2 (4.3)	1 (2.1)	4 (8.3)
SGOT	0	1 (2.1)	1 (2.1)	2 (4.2)
Triglycerides	4 (8.3)	3 (6.4)	4 (8.5)	5 (10.4)

Table 12. Summary of Hematology Abnormalities (Number (%) of Subjects) in Study #CL2004-01

	Number (%) of Subjects			
Parameter	Screening N=48	Period 1, Day -1 N=47	Period 2, Day -2 N=47	End of Study N=48
Hemoglobin	5 (10.4)	3 (6.4)	11 (23.4)	14 (29.2)
Hematocrit	1 (2.1)	0	0	9 (18.8)
RBC	15 (31.3)	13 (27.7)	18 (38.3)	24 (50.0)
MCV	3 (6.3)	3 (6.4)	3 (6.4)	5 (10.4)
Platelet Count	1 (2.1)	1 (2.1)	1 (2.1)	2 (4.2)
Neutrophils	5 (10.4)	3 (6.4)	4 (8.5)	0
Neutrophils (%)	2 (4.2)	3 (6.4)	4 (8.5)	2 (4.2)
Lymphocytes (%)	3 (6.3)	5 (10.6)	7 (14.9)	4 (8.3)

Comment:

The Sponsor considered none of the abnormal laboratory values reported during Study #CL2005-02 or Study #CL2004-01 to be clinically significant, and the Sponsor noted no clinical laboratory-related adverse events during the studies. In particular, the decrease in hemoglobin and hematocrit in both Study #CL2005-02 and #CL2004-01 may be attributed to the 23 phlebotomy samplings.

7.1.7.1 Overview of laboratory testing in the development program

The safety and pharmacokinetic measures used in Study #CL2005-02 and #CL2004-01 are standard for Phase I bioequivalence studies. The criteria for bioequivalence (90% confidence intervals within 80 to 125% of the ratio of the LS Means for Cmax and AUC) are consistent with the FDA guidance for the establishment of bioequivalence of orally administered drug products.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Clinical laboratory tests in Study #CL2005-02 and #CL2004-01 included a CBC with differential white blood cell count and platelet count; serum chemistry (total protein, albumin, calcium, inorganic phosphorus, cholesterol, triglycerides, blood sugar (fasting at screening and at 120 hours post-dose in Period 2), blood urea nitrogen (BUN), uric acid, total bilirubin, alkaline phosphatase, lactic dehydrogenase ([LDH), serum glutamic oxaloacetic transaminase (SGOT/AST), serum glutamic pyruvic transaminase (SGPT/ALT), gamma glutamyl transpeptidase (GGT), serum creatinine, electrolytes (sodium, potassium, and chloride); and urinalysis including microscopic examination.

7.1.7.3 Standard analyses and explorations of laboratory data

Mean values for serum chemistry parameters and in Study #CL2005-02 and #CL2004-01 remained within the normal range at every time point during both studies. Red blood cell indices trended slightly lower through both studies (due to 23 phlebotomy tests). In Study #CL2005-02 the mean value for hemoglobin was 13.39 g/dL (s.d.1.421) at the End of Study time (normal range: 14.0-18.0 g/dL for males and 12.0-16.0 g/dL for females). In Study #CL2004-01 the mean value for hemoglobin was 13.415 g/dL (s.d.1.546) at the End of Study time.

7.17.3.1 Analyses focused on measures of central tendency

Not applicable.

7.1.7.3.1 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

None.

7.1.7.4 Additional analyses and explorations

12-Lead ECGs were recorded at 25 mm/s and included results for ventricular rate, PR, QRS, QT, and QTc intervals for both Study #CL-2005-02 and #CL2004-01.

7.1.7.5 Special assessments

Not applicable.

7.1.8 Vital Signs

Study #CL2005-02
Vital signs were obtained after the subject had been in a seated position for 3 minutes. No clinically significant changes in mean vital signs values were reported during the study. One subject (Subject 076, Sequence 2) had a clinically significant decrease from baseline in systolic blood pressure (from 100 mmHg to 79 mmHg) following administration of Claritin-D@ 12 Hour Extended Release Tablet.

Study #CL2004-01
Most mean values for vital sign measurements were within normal ranges. The only clinically significant change in vital sign measurements was a decrease in systolic blood pressure for 1 subject in the 2 x 5 mg group (Subject 046). The subject's systolic blood pressure was 89 mmHg on Day 2 of Period 1 compared to 113 mmHg on Day 1 and 114 mmHg on Day 3. (Appendix 16.2, Listing 12). No AE related to this change was reported.

7.1.8.1 Overview of vital signs testing in the development program
Vital signs were tested daily on Day-1 through Day 6 in Study #CL2005-02 and #CL2004-01.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

7.1.8.3 Standard analyses and explorations of vital signs data

Not applicable.

7.1.8.3.1 Analyses focused on measures of central tendencies

Not applicable.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no marked outliers or dropouts for vital sign abnormalities in Study #CL2005-02 and #CL2004-01

7.1.8.4 Additional analyses and explorations

Not applicable.

7.1.9 Electrocardiograms (ECGs)

In Study # CL2005-02, 82 of 91 subjects had normal ECGs. Of the remaining 9 subjects the ECG showed an abnormality that the Sponsor deemed clinically insignificant. No significant changes in mean values for ventricular rate, PR interval, QRS interval, or QTc interval were observed from screening to end-of-study.

In Study #CL2004-01, 44 of 48 subjects had normal ECGs. Of the remaining 4 subjects the ECG showed sinus arrhythmia, early repolarization, left axis deviation, and non-specific ST-T wave changes respectively, all of which the Sponsor determined to be clinically insignificant.

Comment:

The Sponsor did not list the specific abnormality in Study CL2005-02, but the ventricular rate, PR, QRS, QT, and QT corrected intervals were normal, which supports the Sponsor's position that these abnormalities were clinically insignificant.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG testing looked for abnormalities in cardiac rhythm, such as Torsade de Pointes, or in cardiac intervals, such as the QT interval. No clinically significant electrocardiogram findings were reported in studies #CL2005-02 and #CL2004-01.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable.

7.1.9.3.1 Analyses focused on measures of central tendency

Not applicable.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Not applicable.

7.1.9.4 Additional analyses and explorations

Not applicable.

7.1.10 Immunogenicity

No immunogenicity studies were performed for this submission. There are no known immunogenicity issues related to loratadine.

7.1.11 Human Carcinogenicity

There are no known carcinogenicity issues related to loratadine.

7.1.12 Special Safety Studies

There were no special safety studies requested or performed for this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no history of a withdrawal syndrome for loratadine. The TESS database for the period February 1, 2006-August 1, 2006 found one subject, a 44 year old female, who abused Claritin in a multidrug overdose completed suicide. She underwent multiple invasive procedures and experienced seizures prior to death.

7.1.14 Human Reproduction and Pregnancy Data

No human reproduction or pregnancy studies were performed for this submission.

7.1.15 Assessment of Effect on Growth

There were no data submitted on effects on growth.

7.1.16 Overdose Experience

The Sponsor submitted data regarding an overdose experience on June 19, 2006. This data is reviewed in section 7.2.9.

As noted in section 7.1.13 there was one subject, an 18-year-old female, in the FDA Adverse Event Reporting System (AERS) database for the period November 1, 2003-January 31, 2006 who overdosed on Claritin in a multi-drug overdose suicide attempt.

7.1.17 Postmarketing Experience

Postmarketing experience data submitted to this NDA comes from two different sources: the Sponsor's database and FDA's AERS database. With this submission the Sponsor submitted adverse event data for the bioequivalence studies #CL2005-02 and #CL2004-01.

Subsequently, the Sponsor submitted a safety update which included data from the WHO, the Tess database, and a literature search (see section 7.0 for the time periods). The Sponsor reported no new significant safety data as a result of the safety update for any loratadin-only products.

AERS Database

This reviewer queried the AERS Database for FDA individual safety reports (ISRs, MedWatch forms) describing all serious adverse events worldwide, expected and unexpected, reported for Claritin as a primary drug suspect since reviewing the NDA application for Children's Claritin Chewable Tablets 5 mg in June 2006. These loratadine products were manufactured by Schering Corporation or its subsidiaries (Schering Plough, Schering Pharmaceutical Corporation, Schering Plough Healthcare Products, Inc, Schering Plough Research Institute). This query excluded Claritin combination products (i.e. loratadine-pseudoephedrine) or generic loratadine manufactured by other Sponsors. See Appendix 1 at the end of this review for the complete search criteria. The query yielded a total of 21 reports for Claritin products from February 1, 2003-August 21, 2006 listing Schering Corporation's Claritin-loratadine as the suspect drug. There was 1 death listed (an apparent error, see Comments below) and 3 life-threatening reactions. Four of the 21 reports were domestic (USA) and 17 reports were foreign (non-USA). These results are shown for the referenced Claritin products in Table 8 below:

Table 8. Serious AEs with Schering Corporation*-manufactured loratadine as primary drug suspect. Cases by ISR type; domestic and foreign.

FDA - AERS DataMart
Cases By ISR Type
February 2006 to August 2006

ISR Type	Total	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
Expedited (5 Day)	21	1	19	15	2	0	3	0
Domestic	4	0	2	2	0	0	0	0
Foreign	17	1	17	15	2	0	3	0
	21	1	19	15	2	0	3	0

Table 9 below shows the breakdown of the AEs for each Claritin-referenced product.

Table 9. Serious AEs with Schering Corporation (or subsidiaries)-manufactured loratadine as primary drug suspect. Cases by formulation.

Claritin Tablets 10mg	93	2	59	6	5	21	0
Claritin syrup	2	0	8	0	0	0	0
Claritin							

Redi-tabs 10mg	7	0	6	0	0	0	0

Tables 10, and 11 below show the same data by year and quarter and by gender and age group, respectively.

Table 10. Serious AEs with Schering Corporation*-manufactured loratadine as primary drug suspect. Cases by year and quarter.

FDA - AERS DataMart
Cases By Year and Quarter
February 2006 to August 2006

Year	Quarter	Total	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
2006	1	7	0	7	7	0	0	1	0
	2	13	1	11	7	2	0	2	0
	3	1	0	1	1	0	0	0	0
	Yearly Totals:	21	1	19	15	2	0	3	0
	Grand Totals:	21	1	19	15	2	0	3	0

Table 11. Serious AEs with Schering Corporation*-manufactured loratadine as primary drug suspect. Cases by gender and age group.

FDA - AERS DataMart
Cases By Gender And Age Group
February 2006 to August 2006

Gender	Age Group	Total	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
Female	Null	0	0	0	0	0	0	0	0
	Neonate	0	0	0	0	0	0	0	0
	Infant	0	0	0	0	0	0	0	0
	Child	0	0	0	0	0	0	0	0
	Adolescent	0	0	0	0	0	0	0	0
	Adult	6	0	6	5	1	0	1	0
	Elderly	2	0	2	1	0	0	1	0
	Gender Total:	8	0	8	6	1	0	2	0
Male	Null	2	1	2	1	0	0	0	0
	Neonate	0	0	0	0	0	0	0	0
	Infant	0	0	0	0	0	0	0	0
	Child	2	0	1	1	0	0	0	0
	Adolescent	0	0	0	0	0	0	0	0
	Adult	3	0	3	2	1	0	1	0
	Elderly	6	0	5	5	0	0	0	0
	Gender Total:	13	1	11	9	1	0	1	0
Not Specified	Null	0	0	0	0	0	0	0	0
	Neonate	0	0	0	0	0	0	0	0
	Infant	0	0	0	0	0	0	0	0
	Child	0	0	0	0	0	0	0	0
	Adolescent	0	0	0	0	0	0	0	0
	Adult	0	0	0	0	0	0	0	0
	Elderly	0	0	0	0	0	0	0	0
	Gender Total:	0	0	0	0	0	0	0	0

Comments:

1. It is not clear why none of the cases in Tables 8, 10, and 11 are listed as having required intervention. The search criteria specified the outcomes: death, life-threatening, hospitalization, disability, congenital anomaly, and "required intervention to prevent permanent damage/impairment".

2. The sole death in Tables 8, 10, and 11 is listed as having occurred overseas in a male fetus. However, individual inspection of the 21 cases reports did not reveal a death; therefore, this entry is an apparent error.

Table 12 below shows the top ten categories of serious AEs by body system or organ class with particular types of AEs of interest noted, such as Torsade de Pointes.

Table 12. Serious adverse events from AERS database with loratadine as suspect medication*

Body System/Organ Class	*Number of Serious Cases*	*Particular Type of AE*
cardiac disorders	2	1 atrial fibrillation
gastrointestinal disorders	1	
general disorders	6	1 renal tubular necrosis
hepatobiliary disorders	1	
infections and infestations	1	
investigations (laboratory)	4	
nervous system disorders	3	2 convulsion
respiratory, thoracic, and mediastinal disorders	1	
skin and subcutaneous tissue disorders	4	1 hypersensitivity

*Top nine categories; each case may have multiple preferred terms

Comments:

1. Of note, there were no cases of Torsade de Pointes or hypospadias reported during the period February 1, 2003-August 21, 2006.

2. The 2 cases of convulsions were new seizure disorders that occurred in an 8 year old and in an 11 year old child who had taken Claritin syrup in recommended doses.

3. In the Sponsor's internal database review the cases of convulsions were in patients with known seizure disorders. Since there was no control group for comparison then, or now, we cannot make any conclusions about seizure causality from loratadine. However, it is possible that loratadine could lower the seizure threshold, so these data bear further watching.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The updated safety database comprised 91 subjects in Study #CL2005-02, in which four subjects had nonserious adverse events, and 48 subjects in study # CL2004-01 in which nine subjects had nonserious adverse events.

Protocol Deviations

In Study #CL2005-02, at check-in to Period 2, the urine drug screen for Subject 022 was positive for benzodiazepine. No waiver was granted; however, the subject was dosed on the following day and completed the study.

In Study #CL2004-01 six subjects did not have a BMI between 19 and 27 at the screening visit. Exemptions were granted for all 6 subjects. Subject 30 was granted an exemption for turning 46 years old on Day 2 of the study.

7.2.1.1 Study type and design/patient enumeration

The Sponsor submitted two studies, Study# CL2005-02 and Study# CL2004-01, to support the application. Both studies were randomized, open, and single-dose. Laboratory personnel were blinded.

7.2.1.2 Demographics

Study #CL2005-02
Ninety-one subjects (46 males, 55 females; 60 Hispanics, 11 African Americans, 20 Caucasian) were enrolled in this study. The subjects were between the ages of 18 and 45 inclusive (mean = 32.1 years). The subjects' mean height was 164.6 centimeters (range 140-193 centimeters) and the subjects' mean weight was 67.6 kilograms (range 45-100 kilograms). This data is shown in Table 7 on the next page.

Table 7. Demographics of Protocol # CL2005-02 by sequence and overall totals.

Characteristic	Sequence 1 (n=46)	Sequence 2 (n=45)	Overall (n=91)
Age (years)			
Mean (SD)	32.9 (7.41)	31.4 (7.70)	32.1 (7.55)
Median	33.0	30.0	32.0
Minimum, Maximum	20,45	18,45	18,45
Weight (kg)			
Mean (SD)	68.2 (9.52)	66.9 (10.91)	67.6 (10.20)
Median	65.6	65.9	65.6
Minimum, Maximum	50,89	45,100	45,100
BMI			
Mean (SD)	25.1 (2.54)	24.7 (2.55)	24.9 (2.54)
Median	25.1	24.3	24.9
Minimum, Maximum	21,30	20,30	20,30
Height (cm)			
Mean (SD)	164.8 (8.21)	164.4 (9.94)	164.6 (9.06)
Median	165.1	162.6	165.1
Minimum, Maximum	150,183	140,193	140,193
Gender: n (%)			
Female	29 (63.0)	26 (57.8)	55 (60.4)
Male	17 (37.0)	19 (42.2)	36 (39.6)
Ethnic Group: n (%)			
Hispanic	28 (60.9)	32 (71.1)	60 (65.9)
Caucasian	11 (23.9)	9 (20.0)	20 (22.0)
African American	7 (15.2)	4 (8.9)	11 (12.1)

BMI=Body mass index; SD=Standard deviation
Sequence 1: Claritin® RediTabs® Tablet ; Claritin-D® 12 Hour Extended Release Tablet;
Sequence 2: Claritin-D® 12 Hour Extended Release Tablet , Claritin® RediTabs® Tablet

Study #CL2004-01

Forty-eight subjects (18 males, 30 females; 36 Hispanics, 10 African Americans, 2 Caucasian) were enrolled in this study. The subjects were between the ages of 18 and 45 inclusive (mean = 33.6 years). The subjects' mean height was 164.1 centimeters (range 147-185 centimeters) and the subjects' mean weight was 64.9 kilograms (range 48-90 kilograms). This data is shown in Table 8 below.

Table 8. Demographics of Protocol # CL2004-01 by sequence and overall totals.

Characteristic	Sequence 1 (n=24)	Sequence 2 (n=24)	Overall (n=48)
Gender			
Female	16 (66.7%)	14 (58.3%)	30 (62.5%)
Male	8 (33.3%)	10 (41.7%)	18 (37.5%)
Ethnic Group			
Hispanic	21 (87.5%)	15 (62.5%)	36 (75.0%)
African American	2 (8.3%)	8 (33.3%)	10 (20.8%)
Caucasian	1 (4.2%)	1 (4.2%)	2 (4.2%)
Age (years)			
Mean (SD)	35.3 (6.95)	32.0 (8.35)	33.6 (7.78)
Median	35.0	34.5	35.0
Minimum-Maximum	18-45	19-45	18-45
Height (cm)			
Mean (SD)	163.0 (8.57)	165.2 (8.11)	164.1 (8.33)
Median	160.0	165.1	162.6
Minimum-Maximum	147-185	150-183	147-185
Weight (kg)			
Mean (SD)	63.3 (10.71)	66.6 (7.49)	64.9 (9.29)
Median	60.9	65.6	63.6
Minimum-Maximum	48-87	59-90	48-90
BMI			
Mean (SD)	23.7 (2.48)	24.4 (2.38)	24.1 (2.43)
Median	23.5	24.3	23.8
Minimum-Maximum	19-28	20-29	19-29

BMI=Body mass index; SD=Standard deviation

7.2.1.3 Extent of exposure (dose/duration)

In Study #CL2005-02 all 91 subjects received a dose of study medication during Period 1 and 90 subjects received a dose of study medication during Period 2. Subject 006 was lost to follow-up after receiving Claritin RediTabs Tablet during Period 1.

In Study #CL2004-01 forty-six of the 48 subjects received both single doses of study medication. Subject 033 (Sequence 1) was discontinued from the study due to adverse events (pyrexia and rhonchi) 14 days after receiving one dose of loratadine 10 mg. Subject 039 withdrew consent due to a family emergency.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Data from the Sponsor's safety update is discussed in section 7.1.17 and data from the AERS Database is discussed in section 7.2.9. Safety data from the literature is discussed in section 8.2 of this review.

7.2.3 Adequacy of Overall Clinical Experience

This is a supplemental application. The original submission of this NDA contained full safety data for the ingredient, loratadine. No safety issues were identified at the time of the original application.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Animal or in vitro data were not provided in this application.

7.2.5 Adequacy of Routine Clinical Testing

Not applicable for this supplemental safety data submission.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The Sponsor provided sufficient data to characterize the pharmacological profile of loratadine during the original submission of the NDA.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

From a clinical safety perspective there are no recommendations for further studies.

7.2.8 Assessment of Quality and Completeness of Data

From a clinical safety perspective, this application is adequate and complete.

7.2.9 Additional Submissions, Including Safety Update

On June 19, 2006 the Sponsor submitted the following additional data:

- Schering-Plough internal summary of adverse events for the period October 1, 2005-March 31, 2006
- World Health Organization (WHO) adverse events for the period October 1, 2005-February 2, 2006
- A review of the Toxic Exposure Surveillance System (TESS) database from the American Association of Poison Control Centers for loratadine-containing products from December 1, 2005-May 31, 2006
- Worldwide human and pre-clinical peer-reviewed literature related to the safety of loratadine from October 1, 2005-April 30, 2006

The Schering-Plough internal summary of adverse events for the period October 1, 2005-March 31, 2006 yielded 1739 adverse events from 1190 total cases worldwide. Of these 1692 cases were non-serious AEs and 47 serious AEs. The 47 serious AEs (29 total cases) were similar to the serious AEs discussed in section 7.1.17; however, there was 1 death (see Deaths, section 7.1.1), 5 psychiatric disorders, and 5 nervous system disorders that included two cases of loss of consciousness. Of note, there were no cardiac disorders and no cases of arrhythmia or Torsade de Pointes. Three cases of convulsions were noted, with two in children without a known seizure disorder, and one case was not further defined.

Serious Adverse Events from the Schering-Plough AE Database:
The trends for the 47 serious AEs in the current submission did not have marked differences among the products. For reference, from December 1, 2002-September 30, 2005 (analysis period for NDA 21-891), there were few differences when comparing the serious adverse events by System-Organ-Class terminology (SOC) between the dosage forms. The oral solution (syrup) had a higher number of AEs related to Psychiatric Disorders (38 instances of crying, hallucinations or nightmares) than the other dosage forms of loratadine. Orally disintegrating tablets had a higher rate of Hepatobiliary disorders (2 cases) that was not noted with other dosage forms. The Sponsor considered that neither one of these observations represented a safety signal but were related to the low absolute number of serious AEs with these two dosage forms (oral solution had 71 serious AEs, orally disintegrating tablets had 51).

For the period October 1, 2005-March 31, 2006 the oral solution and orally disintegrating tablets had 9 AEs and 5 AEs, respectively. The most common SOC for serious AEs among all dosage forms was Nervous System Disorders and Psychiatric Disorders. Claritin Allergy Tablets also had Gastrointestinal and Immune System Disorders as a common SOC for serious AEs. It should be noted that, for all dosage forms, the absolute number of serious AEs was very low for this period.

Non-Serious Adverse Events from the Schering-Plough AE Database:
Of these 1,692 nonserious AEs in which loratadine was considered to be a suspect or co-suspect drug (October 1, 2005- March 31, 2006) the common adverse events were headache and drowsiness. There was no new information that suggests a substantial change in the incidence of

common, less serious adverse events between the worldwide data for the previous reporting period December 1, 2002-September 30, 2005 and the period of October 1, 2005-March 31, 2006 presented in this Safety Update.

Comment:

The Sponsor's internal summary of adverse events for the period October 1, 2005-March 31, 2006 does not show a new safety signal for loratadine products. In particular, a review of these combined worldwide data (all loratadine-only formulations) as well as the data separated by Claritin dosage forms (tablet, oral solution, orally disintegrating tablet) for the two reporting periods did not suggest any new safety trends or signals for loratadine-only products.

From the period October 1, 2005-February 2, 2006 the WHO database revealed 90 AEs involving 37 cases. Of the 90 AEs, there were no deaths and no serious AEs. The most common AEs were 5 cases of tachycardia and 4 convulsions.

Comment:

The Sponsor did not report additional information about the cases of tachycardia or convulsions.

To evaluate overdose experience, the Sponsor analyzed data gathered from the Toxic Exposure Surveillance System (TESS) database from the American Association of Poison Control Centers for the period December 1, 2005- May 31, 2006. This search included all products, regardless of trade name, that contained loratadine as the only active ingredient. During this period, US Poison Control Centers received 3,385 reports in which loratadine was ingested in an overdose event. About 80% of cases were unintentional and 20% intentional. Two thirds involved exposure to loratidine alone. There were 67 patients admitted to a critical care setting and also 86 admitted to a non-critical care bed or a psychiatric inpatient facility. The range of estimated or confirmed tablets ingested was 0.5-300 tablets. The mean patient age was 12 years (when known), with a range of 1 month to 97 years old. The most common gastric decontamination performed was oral activated charcoal followed by gastric lavage or a cathartic. There was one death, in a 44-year-old female in a suspected suicide attempt involving multiple drug ingestion. The patient underwent multiple invasive support procedures and experienced seizures as a result of the overdose. No deaths occurred with loratadine-only exposure.

Comments:

1. The data showed only one case for May 2006 (on May 1, 2006), so the majority of the data is for a 5-month period, yielding about 677 cases per month. This is slightly below the 705 cases per month for 2005 as a whole, indicating no increase in the overdose case rate.

2. The Sponsor concluded that the overdose data do not show a safety signal or trend that indicates that loratadine is unsafe, even in an overdose. This conclusion appears to be correct.

The Sponsor's additional literature review is discussed in section 8.6.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The Sponsor submitted two studies with adverse event data. The Sponsor referenced three other NDAs for Claritin products: Claritin Tablets, Claritin-D 12 Hour tablets, and Claritin RediTabs. Safety data were evaluated in the medical reviews for the approval of these referenced NDAs.

7.4.1.1 Pooled data vs. individual study data

Not applicable.

7.4.1.2 Combining data

Not applicable.

7.4.2 Explorations for Predictive Factors

The submitted studies, #CL2005-02 and #CL2004-01, were single-dose trials. There was no analysis based upon dose, duration of use, or concomitant medication.

7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable, as studies #CL2005-02 and #CL2004-01 were single-dose trials.

7.4.2.2 Explorations for time dependency for adverse findings

Not applicable, as the product is single-dose.

7.4.2.3 Explorations for drug-demographic interactions

The Sponsor has not conducted any study exploring drug-demographic interactions for this product. There were only 5 AEs in study#CL2005-02 and 9 AEs in Study #CL2004-01, all nonserious. In the Sponsor's pediatric trials with loratadine syrup, dysphonia, nervousness, hyperkinesis, abdominal pain and conjunctivitis were noted at a slightly higher incidence in the 10-mg loratadine group vs. placebo. In adult loratadine trials fatigue, headache, dry mouth, dry nose, pruritus, and somnolence occurred at a greater incidence in the loratadine-treated groups. This data suggests that younger subjects might be more likely to experience nervousness or hyperkinesis while older subjects might be more likely to experience sedation with loratadine compared to placebo.

7.4.2.4 Explorations for drug-disease interactions

The Sponsor has not conducted any study exploring drug-disease interactions for this product. The current product label does not indicate any known drug-disease interactions; however, those with liver or kidney disease are advised to ask a doctor before use.

7.4.2.5 Explorations for drug-drug interactions

No drug-drug interactions were evaluated in this safety update or in the current trials, studies #CL2005-02 and #CL2004-01. However, in a FDA safety assessment for the OTC switch (May 12, 2000, reference 7, the potential interaction between loratadine with erythromycin, cimetidine, and ketoconazole was reviewed and found not to be associated with adverse events, though an increase was noted in the AUC (area under the curve) values for loratadine and and active metabolite (descarboethoxyloratadine or desloratadine).

7.4.3 Causality Determination

The Sponsor did not perform special causality assessments.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

For adults and children 6 years and over, one 5-mg tablet every 12 hours; not more than 2 tablets in 24 hours. For children under 6 years of age: ask a doctor.

8.2 Drug-Drug Interactions

See section 7.4.2.5.

8.3 Special Populations

The current label advises those who have ever had an allergic reaction to the product or any of its ingredients to not use the product.

8.4 Pediatrics

In the current submission the Sponsor studied subjects 18-45 years old. The Sponsor previously studied pediatric subjects, and FDA previously reviewed the data, for the approval of NDA 20-641, Claritin Syrup. From February 1, 2006-August 1, 2006 (the time frame from the last FDA AERS database query for a loratadine-only Claritin product review) a total 24 AEs have been reported to the FDA AERS database, none of which were in children younger than 36 months.

For reference, during the search period November 1, 2003-January 31, 2006 in the review of NDA 21-981 (Children's Claritin Chewable Tablets), there were a total of 105 AEs, with 8 of these in children younger than 36 months. The literature search for NDA 21-891 noted 3 articles discussing safety of loratadine in children and there has been no new information since then.

Based on the AE reports and literature review noted above, no new safety-related concerns were noted in children for the proposed use of loratadine for the indication of relief of hay fever and upper respiratory allergy symptoms in adults and children 6 years of age and older.

8.5 Advisory Committee Meeting

No advisory committee meetings addressed this application.

8.6 Literature Review

The Sponsor reviewed the worldwide literature relevant to the safety of loratadine from January 2006 to April 2006. In addition they included any literature references of human exposure from 2005 that were not previously reported to FDA. This literature review yielded five references. Three of these (Ruiz-Montero et al., Heller, and Patriarca et al.) were case reports and two were clinical trials (Hyo et al, Pineyro et al.). These are discussed below.

Case Reports:

In a study designed to improve the detection of hepatotoxic adverse drug reactions among hospitalized patients, Ruiz-Montero et al. (2005) used clinical chemistry "alert signals" to investigate potential hepatotoxicity among 519,381 patients treated in a university, urban teaching hospital over a 12-month period. The alert signals included the following: >76 U/L of SGPT, or >0.6 mg/dL of conjugated bilirubin, or >80 U/L SGOT, >2 mg/dL total bilirubin, and 516 U/L of alkaline phosphatase (simultaneously). In this study, the presence of a single alert signal was sufficient to generate an investigation of the patient's case. The authors reported 2 subjects (a 52-year old female and a 43-year old male) having mild hepatocellular toxicity potentially attributed to loratadine. No additional case information surrounding these subjects was reported by the authors.

Heller (2005) reported a case study of a 34-year old male treated with multiple therapies for hypopigmented macules (Bier spots). Loratadine (10 mg daily) was administered for an unspecified duration as a treatment, but was discontinued, due to drowsiness.

As part of a desensitization protocol for a patient with peanut allergy, Patriarca et al. (2006) instructed the patient (38-year old female) to use loratadine (10 mg/day) and ranitidine (300 mg/day) during the rush phase and for 2 weeks during the maintenance therapy. The authors reported that she did not manifest side effects.

Clinical Trials:

Hyo et al. (2005) conducted a randomized, double blind, placebo-controlled trial in 113 participants with Japanese cedar pollinosis for two days. Participants were divided into four groups that included daily doses of loratadine, cetirizine, fexofenadine, or placebo. The authors noted that all study medications were well tolerated. No serious adverse events were reported. The most frequent adverse event was drowsiness, which was seen in two subjects in the loratadine arm and one subject in the placebo arm. No other adverse events were reported.

Pineyro-Lopez et al. (2006) conducted an open-label, randomized, 2-period crossover study in 32 subjects to evaluate the comparative bioavailability and tolerability of two different loratadine formulations used in Mexico. Subjects were given 400 mg of ketoconazole one day before the test period. On the test day they were given 200 mg of ketoconazole and two 10 mg tablets (a 20 mg total dose) of loratadine. They assessed tolerability via vital signs and a subject interview during the study and one week after the study. A two week washout period separated the crossover period. The investigators found that the test formulation of loratadine was bioequivalent to the reference formulation and that no adverse events were reported.

Comment:

Other than saying that ketoconazole has been shown to increase loratadine levels, the investigators do not mention why they included dosing with ketoconazole in this bioequivalence trial. While the trial was small (32 subjects) and not designed to assess safety, and electrocardiograms were not reported, it appears that a single dose of loratadine 20 mg total might be safe with ketoconazole dosed for 2 days.

Additional Information from Worldwide Literature:

The Sponsor refers to the Worldwide Literature for the loratadine section of the 4-month safety update submitted March 3, 2006 to NDA 21-952, S-000, Amendment 4. In a discussion of prenatal exposure and risk of hypospadias in male infants, a preliminary epidemiology report by Kallen et al. was referenced (reference 6, Kallen and Olausson 2001). The March 3, 2006 submission also included a discussion of a followup, short research communication confirming that the initial signal for hypospadias has not been confirmed upon continuing review of available data. This research communication was published in the International Journal of Medical Sciences (reference 7, Kallen and Olausson 2006).

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan.

8.8 Other Relevant Materials

There are no other relevant materials submitted for this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

The Sponsor conducted two open- label, single- dose, two- way crossover, bioequivalence studies of loratadine 5 mg orally disintegrating tablets. Study #CL2005-02 compared 1 x 5 mg loratadine orally disintegrating tablets tablet with 1 Claritin-D tablet containing 5 mg of loratadine and 120 mg of pseudoephedrine in 91 healthy adult subjects. All 91 subjects received at least one dose of study drug and were assessed for safety; 91 subjects were included in the primary analysis of bioequivalence. The loratadine results did not meet the bioequivalence criteria for AUC, with the 90% CI for AUC falling *above* the bioequivalence limit of 1.25. However, the active metabolite, desloratadine, was equivalent between the two treatments.

Study #CL2004-01 compared 2 x 5 mg loratadine orally disintegrating tablets and the reference product 1 x 10 mg loratadine orally disintegrating tablets in 48 healthy adult subjects. Forty eight subjects received at least one dose of study drug and were assessed for safety; 46 subjects were included in the primary analysis of bioequivalence. In the analysis of bioequivalence, the 90% confidence intervals around the ratio (test to reference products) of the least squares means for both loratadine and desloratadine all fell within the bioequivalence interval of 0.80 to 1.25, demonstrating that the 2 x 5 mg chewable tablets were bioequivalent to the 1 x 10 mg tablet. The 2 x 5 mg treatment had a favorable safety profile when compared to the 1 x 10 mg treatment. Both treatments were well tolerated. Few AEs were reported during the study by a small number of subjects, and only one, a mild headache, was considered related to treatment. No deaths, serious AEs, discontinuations due to AEs, or other significant AEs were reported for subjects in this study. No clinically meaningful trends were observed in clinical laboratory results, vital sign measurements, physical examination findings, or ECG results.

This reviewer's FDA AERS Database search showed 24 serious AEs from February 1, 2006-August 1, 2006 but did not reveal any new or worrisome information about loratadine. Also, the Sponsor's internal AE reports, the Sponsor's WHO Database search, a TESS database search, the Sponsor's literature search and this reviewer's literature search also did not reveal any new or worrisome information about loratadine. In particular, there were no unconfounded cases of Torsade de Pointes. Also, a previous potential concern for congenital hypospadias, in male children of mothers with prenatal use of loratadine, was addressed by a CDC study (reference 8, MMWR 2004) that did not show a link between using loratadine and second or third degree hypospadias.

Three cases of convulsions were noted in the Sponsor's internal database from October 1, 2005-March 31, 2006 and four cases of convulsions were noted in the WHO database from October 1, 2005-February 2, 2006. At least 2 of these seizure cases were first presentations. Previously, the Sponsor had reported eight cases of convulsions from November 27, 2002-May 31, 2005, though all were in patients with known seizure disorders. Fourteen cases were noted in the Sponsor's AERS Database review in 2005, but none were found in this reviewer's AERS Database search from February 1, 2006-August 1, 2006. The lack of a control group not taking loratadine

precludes making any conclusion about seizure causality due to loratadine. However, it is possible that loratadine could lower the seizure threshold, so these data bear further watching.

9.2 Recommendation on Regulatory Action

The proposed 5-mg loratadine chewable tablet for the indication of the relief of upper respiratory allergy symptoms in adults and children 6 years of age and older has an acceptable safety profile for OTC marketing. Therefore, this application is approvable from the safety standpoint. Final approvability depends on the outcome of the biopharmaceutical equivalence study #CL2003-02, which the biopharmaceutics reviewer is reviewing.

Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No special postmarketing risk management activities are recommended.

9.3.2 Required Phase 4 Commitments

No special Phase 4 commitments are recommended.

9.3.3 Other Phase 4 Requests

None.

Labeling Review

The proposed label is presented below. An interdisciplinary scientist in the Office of Nonprescription Products is reviewing the proposed label. The Sponsor incorporated all the important warnings for loratadine. The label is acceptable from a clinical point of review.

1.0 CARTON LABEL – CLARITIN REDITABS 12 HOUR TABLETS (10 —— AND ——OUNT)

Principal Display Panel

Top Panel

Side Panel

Side Panel

Bottom Panel

Back Panel

Drug Facts

Active ingredient (in each tablet)	***Purpose***
Loratadine 5 mg	Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:

- runny nose
- itchy, watery eyes
- sneezing
- itching of the nose or throat

Warnings

Do not use if you 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 every 12 hours; not more than 2 tablets 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 the individual blister unit imprinted with Claritin® RediTabs® is open or torn[3]
- store between 20° to 25°C (68° to 77°F)[4]
- use tablet immediately after opening individual blister

Inactive ingredients

anhydrous 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.
[instructional diagrams]

1. **Peel back outer edge.**
2. **Gently push tablet out.**
3. **Place the tablet on tongue and close mouth. The tablet will disintegrate.**[5]

Comments to Applicant

No comments.

10 Appendices

Appendix 1 shows the search criteria for the AERS Database search.

Review of Individual Study Reports

Not applicable. The only pivotal study report, Protocol #Cl2003-02, is being reviewed by a reviewer in the Division of Biopharmaceutics.

10.2 Line-by-Line Labeling Review

An interdisciplinary scientist in the Office of Nonprescription Products is reviewing the proposed label. Labeling should not advise more than two tablets per day for adults and children 6 years and over, A higher dose would be off-label use without clinical data for support. Children under 6 years of age or consumers with liver or kidney disease should ask a doctor.

Appendix 1
Search Criteria for 105 cases in the FDA Reviewer's query of the FDA Adverse Event Reporting System (AERS) database:

Criteria: PRIMARY DRUG, PRIMARY INGREDIENT, MANU, FDA Received Date, OUTCOME, REPORT TYPE, DRUG ROLE, BEST REPRESENTATIVE

PRIMARY DRUG
N019658 / CLARITIN,
N019658 / CLARITIN HIVES RELIEF,
N020641 / CLARITIN,
N020641 / CLARITIN HIVES RELIEF,
N020704 / CLARITIN HIVES RELIEF REDITAB,
N020704 / CLARITIN REDITABS

PRIMARY INGREDIENT
LORATADINE

MANU
SCHERING CORP SUB SCHERING PLOUGH CORP,
SCHERING CORPORATION,
SCHERING PHARMACEUTICAL CORP,
SCHERING PLOUGH CORP,
SCHERING PLOUGH HEALTHCARE PRODUCTS INC,
SCHERING PLOUGH RESEARCH INSTITUTE,
SCHERING
FDA Received Date
2003NOV-2006JAN

OUTCOME
Death, Life-Threatening, Hospitalization - Initial or Prolonged, Disability, Congenital Anomaly, Required Intervention to Prevent Permanent Impairment/Damage

REPORT TYPE
Domestic 5 Day, Foreign 5 Day, Unknown 5 Day, Domestic 10 Day, Foreign 10 Day, Unknown 10 Day, Domestic Expedited (15-Day), Foreign Expedited (15-Day), Unknown Expedited (15-Day), Domestic Periodic, Foreign Periodic, Unknown Periodic

DRUG ROLE
PRIMARY

BEST REPRESENTATIVE
TRUE

References

1. Heller M.. Diffuse Bier spots. Dermatology Online J. 2005;11(4):2005.

2. Hyo S, Fujieda S, Kawada R, Kitazawa S, Takenaka H. The efficacy of short-term administration of 3 antihistamines vs placebo under natural exposure to Japanese cedar pollen. Ann Allergy Asthma Immunol. 2005; 94: 457-464.

3. Patriarca G, Nucera E, Pollanstrini E, de Pasquale T, et al. Oral rush desensitization in peanut allergy: a case report. Digest. Dis. Sci. 2006; 51: 471-473.

4. Pineyro-Lopez , A, Pineyro-Garza E, Torres- Alanis O, et al. Bioavailability of two oral formulations of loratadine 20 mg with concomitant ketoconazole: An open-label, randomized, two-period crossover comparison in healthy Mexican adult volunteers. Clin Therap 2006; 28: 110-115.

5. Montero A Ruiz, Quintana JA, and Saenz MJ et al. A strategy to improve the detection of drug- induced hepatotoxicity. Rev Esp Enferm Dig (Madrid) 2005; 155-160.

6. Kallen B and Olausson PO. (2001) Monitoring of maternal drug use and infant congenital malformations. Does loratadine cause hypospadias? Int. J. Risk Safety in Med. 14: 115-119.

7. Kallen B and Olausson PO. No increased risk of infant hypospadias after maternal use of loratadine in early pregnancy. Int J Med Sciences 2006; 3: 106-107.

8. Centers for Disease Control and Prevention (CDC). Evaluation of an association between loratadine and hypospadias--United States, 1997-2001. MMWR Morb Mortal Wkly Rep 2004 Mar 19;53(10):219-21.

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/s/

Steven Osborne
9/19/2006 06:20:31 AM
MEDICAL OFFICER

Bindi Nikhar
9/19/2006 10:39:05 AM
MEDICAL OFFICER
Biopharmaceutics review awaited. Final approval will take into account results from bioequivalence studies.