CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-952

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-952
Submission Code	000
Letter Date	December 19, 2007
Stamp Date	December 20, 2007
PDUFA Goal Date	June 20, 2008
Reviewer Name	Lolita A. Lopez, M.D.
Team Leader	Daiva Shetty, M.D.
Review Completion Date	May 1, 2008
Established Name	Loratadine 10 mg
(Proposed) Trade Name	Claritin® Liqui-Gels Capsules 10 mg
Therapeutic Class	Antihistamine
Applicant	Schering-Plough Healthcare Products, Inc.
Priority Designation	Standard
Formulation	Softgel Capsule
Dosing Regimen	One Capsule Every 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	Adults and Children ≥ 6 y/o

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The proposed loratadine (Claritin® Liqui-Gels™) capsule 10 mg for the indication of 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 has an acceptable safety profile for OTC marketing. Therefore, this application should be approved from a clinical safety standpoint.

1.2 Risk Benefit Assessment

This softgel formulation will be an additional formulation to the Claritin® brand products and is expected to be an easy swallow product for consumers 6 years and older who find tablets or other formulations to be difficult to swallow or are unpalatable. The proposed indication for this product is similar to the already approved indications for Claritin® tablets 10 mg. The risk from taking this new formulation is no different from the currently marketed loratadine products for OTC use. Therefore, the risk benefit profile of this proposed product is acceptable.

1.3 Recommendations for Postmarketing Risk Management Activities

No special risk management activities are recommended for this NDA.

1.4 Recommendations for other Post Marketing Study Commitments

No required post marketing commitments are recommended.

2 Introduction and Regulatory Background

The purpose of this NDA 21-952 resubmission review is mainly to evaluate the food effect study conducted by the sponsor comparing the bioavailability of the proposed Claritin Liqui-Gels™ capsule 10 mg to the reference drug, Claritin Tablet 10 mg. This study was conducted in response to the approvable letter dated January 12, 2007 for this NDA during its initial submission (on March 16, 2006). The Clinical Review for the initial NDA 21-952 submission can be found in DFS entered on December 11, 2006.

2.1 Product Information

Loratadine (Claritin®) is an oral second generation, non-sedating antihistamine initially approved for prescription use by the FDA on April 12, 1993 for the relief of hay fever and upper respiratory allergy symptoms in adults and children 6 years of age and older. Later, in December 2000, it was approved for use in children as young as 2 years of age. On November 27, 2002, all formulations of Claritin® were approved for nonprescription or over-the-counter (OTC) use.

Loratadine is an oral non-sedating H1-blocker that is similar in structure to cyproheptadine and azatadine. It does not readily cross the blood brain barrier, and preferentially binds at H-1 receptors in the periphery rather than within the brain, which probably accounts for some of this nonsedating character.[1] After oral administration, loratadine is rapidly metabolized to desloratadine, a pharmacologically active metabolite. Its onset of action occurs within 1-3 hours, the half-life of loratadine is 8 to 15 hours and the half-life of desloratadine is 12 to 24 hours.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are other currently available medical treatments for the relief of allergic rhinitis symptoms. These are the first and second generation H_1-antagonist antihistamines marketed both prescription and OTC. The first generation antihistamine products available for OTC use are either drugs in which the active ingredients are included in the list of OTC monograph[2] or drugs approved under an NDA. The table below lists the second-generation and some of the most commonly used first-generation antihistamines.

Table 1: Currently Available Treatments for Proposed Indications

Active ingredients	Examples of Trade Names
First generation Antihistamines	
brompheniramine	Dimetapp®, Dimetane®
chlorpheniramine	Chlor-Trimeton®
doxylamine	Vicks NyQuil®
clemastine	Tavist®
triprolidine	Actifed®
Second-generation Antihistamines	
loratadine	Claritin®, Alavert®
cetirizine	Zyrtec®
fexofenadine (Rx only)	Allegra®

2.3 Availability of Proposed Active Ingredient in the United States

Loratadine has been available in the United States since 1993, and a loratadine/pseudoephedrine combination product since 1994. There are several other marketed products containing loratadine hydrochloride for OTC use in the United States currently available for OTC marketing: 10 mg tablet, 10 mg reditab, 5 mg chewable tablet, and 1mg/mL syrup. The combination products containing loratadine and pseudoephedrine have an additional indication of temporary relief of sinus congestion and pressure.

1 Clinical Pharmacology Online accessed 4-1-08 (http://www.clinicalpharmacology-ip.com/Default.aspx).
2 21CFR 341.12

2.4 Important Safety Issues With Consideration to Related Drugs

Antihistamines are known for their sedative effects; however, the second generation antihistamines (cetirizine, fexofenadine and loratadine) cause a much lesser degree of somnolence compared to older antihistamines. Cetirizine, at recommended doses, may cause a higher incidence of somnolence when compared to fexofenadine and loratadine. Terfenadine (withdrawn in 1998) and astemizole (discontinued 1999) are two non-sedating second generation antihistamines with similar structures that have been removed from the market due to the associated risk of causing cardiac arrhythmia, Torsades de Pointes secondary to QT prolongation at high serum concentrations. So far, there has been no reports of the Torsades de Pointes with loratadine as the single suspect drug.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Schering-Plough HealthCare Products, Inc. (SPHCP) is seeking approval to market Claritin® Liqui-Gels™ capsule10 mg, an immediate release, liquid-filled capsule containing 10 mg of loratadine. This softgel formulation will be an additional formulation to the Claritin® brand products and is expected to be an easy swallow product for consumers 6 years and older who find tablets or other formulations to be difficult to swallow or are unpalatable. The proposed indication for this product is similar to the already approved indications for Claritin® tablets 10 mg.

On March 16, 2006, the sponsor submitted NDA 21-952, seeking to market Claritin Liqui-Gels 10 mg capsules. To support this NDA, the sponsor conducted a bioequivalence study (CL2004-02) comparing the pharmacokinetics (PK) of a single dose of the proposed Claritin® Liqui-Gels® capsule 10 mg and the currently marketed Claritin® tablet 10 mg, the reference listed drug (RLD) under fasting conditions in 48 healthy subjects. The result of this study showed that Claritin® Liqui-Gels™ capsules did not meet bioequivalence (BE) criteria for loratadine Cmax (90% CI = 0.7875-0.9996) but met the BE criteria for loratadine AUC as well as for the Cmax and AUC of its active metabolite, desloratadine (see Table A-1 in the Appendix section of this review). A food effect study (CL2005-17) was also conducted. This study showed that Claritin® Liqui-Gels™ capsules 10 mg, when administered with food, increased the loratadine Cmax by 53%, AUC_{0-t} by 121%, and $AUC_{0-\infty}$ by 118% but no significant change in desloratadine PK (see Table A-2 in the Appendix section of this review). There was no reference product included in the study; therefore, comparison to a reference drug cannot be assessed adequately. Previous PK studies with loratadine formulations have shown that food increased the bioavailability (AUC) of loratadine by approximately 11 to 48%.[3] However, the clinical significance of the magnitude of food effect shown from the food effect study CL2005-17 is unknown.

A teleconference was held with the sponsor on November 30, 2006 with regards to the food effect and labeling of the proposed product (see Meeting Minutes in DFS). The Agency expressed the need for labeling to address the food effect and the potential for AEs, including unexpected drowsiness. The statement "take on an empty stomach," as suggested by the sponsor, was not sufficient to convey the potential safety concerns such as unexpected drowsiness when the proposed product was taken with food, which is a safety issue. The sponsor may be able to remove the food effect information from the

3 Prescription Information for Claritin, Physicians Desk Reference (PDR) 2003.

label if they can present sufficient data to either show that the food effect for this formulation is similar to the food effect of other approved Claritin formulations, or that the systemic levels that may be reached when taken with food do not adversely affect the safety profile of the product.[4] The sponsor and the Agency were not able to come to an agreement regarding the appropriate language on the label to address the food effect concerns.

On January 12, 2007, the sponsor was sent an approvable letter for this NDA. The letter stated that before the application may be approved, the sponsor must send revised draft labeling with the bulleted statement "• *take on an empty stomach. Taking with food may cause drowsiness.*" This was supposed to be incorporated in the Directions section of the "Drug Facts" labeling. The sponsor responded that it intended to conduct a bioequivalence study comparing Claritin® Liqui-Gels™ capsule to Claritin tablet, 10 mg under fed conditions and demonstrate that the statement would not be necessary.

On January 20, 2008, the sponsor submitted this resubmission in response to the Claritin Liqui-Gels Capsules, NDA 21-952 approvable letter.

2.6 Other Relevant Background Information

There are no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No DSI inspection was requested for this resubmission. A DSI inspection was done for the pivotal bioequivalence study (CL-2004-02) submitted during the initial NDA submission[5].

3.2 Compliance with Good Clinical Practices

The sponsor stated that this study was conducted in accordance with the guidelines set forth by the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (ICH Guideline E6), the U.S. Code of Federal Regulations Guidelines for Good Clinical Practice (21 CFR Parts 50 and 56) and the Declaration of Helsinki regarding the treatment of human subjects in a study. The study was initiated on February 26, 2007 and completed on March 17, 2007.

3.3 Financial Disclosures

The Sponsor conducted one bioequivalence study in this submission, Protocol #CL2006-09, that involved only one clinical site with one principal investigator, four sub-investigators and five medical investigators. An FDA form 3454 was submitted certifying that as a sponsor of the submitted studies, it

4 See Deputy Division Director Memorandum dated January 15, 2007.
5 See DSI Review by J. Kadavil, Ph.D. entered in DFS on December 6, 2006.

has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The sponsor also certified that each listed clinical investigator did not disclose any proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) and that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). There were no financial disclosures that would cast doubt on the findings of the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The sponsor makes reference to the applications from the original NDA submissions of the single-ingredient prescription loratadine products for the Chemistry, Manufacturing and Controls (CMC) information. See Chemistry review for details.

4.2 Clinical Microbiology

Microbiology review was not necessary for this application.

4.3 Preclinical Pharmacology/Toxicology

There are no new data or toxicology information submitted with this NDA. The sponsor refers to the Nonclinical Pharmacology and Toxicology information in their previously submitted NDAs for the single-ingredient loratadine products.

The sponsor searched the worldwide, peer-reviewed literature to identify pre-clinical studies relevant to the safety of loratadine between January 1, 2007 and November 1, 2007. There were no pre-clinical studies relevant to the safety of loratadine identified in the literature during the reporting period.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Loratadine, like other H1-blockers, does not prevent the release of histamine as do cromolyn and nedocromil, but competes with free histamine for binding at the H1-receptor. This competitive antagonism blocks the effects of histamine on H1-receptors in the GI tract, uterus, large blood vessels, and bronchial muscle. This drug does not readily cross the blood-brain barrier; it preferentially binds at H1-receptors in the periphery rather than within the brain, which probably accounts for some of its non-sedating character. Loratadine does not exert significant anticholinergic effects at therapeutic concentrations. In vitro studies have shown that loratadine has a weak affinity for acetylcholine and

alpha-adrenergic receptors.[6]

4.4.2 Pharmacodynamics

There are no new pharmacodynamic data submitted with this NDA. The following information is included in the prescription label for loratadine[7]:

> Human skin wheal studies following single and repeated 10 mg oral doses of loratadine have shown that the drug exhibits an antihistaminic effect beginning within 1 to 3 hours, reaching a maximum at 8 to 12 hours, and lasting in excess of 24 hours.

4.4.3 Pharmacokinetics

Loratadine is administered orally, its onset of action occurs within 1-3 hours, with peak effects in 8-12 hours, and a duration of action greater than 24 hours. Administration with food increases absorption and systemic bioavailability (AUC) up to 40% for the syrup or tablets, and up to 48% for the rapidly disintegrating tablets; the time to peak concentrations (Tmax) is delayed by administration with food by one hour. [8] However, peak plasma concentrations (Cmax) are not affected by food. It has a high first pass effect and is almost completely metabolized in the liver to the minimally active metabolite, descarboethoxyloratadine. The normal mean elimination half-lives of loratadine and its metabolite, descarboethoxyloratadine, are 8.4 hours (range 3-20 hours) and 28 hours, respectively. There is considerable variability in the pk data in all studies of Claritin® tablets and syrup probably because of extensive first-pass metabolism.[9] Elimination occurs through the fecal and renal routes.[10]

In this submission, the sponsor conducted one bioavailability study comparing the PK profile of one dose of Claritin Liqui-Gels™ capsule 10 mg to one Claritin® tablet 10 mg, the reference listed drug (RLD) under fed conditions. The study showed that the tablet and Liqui-Gels capsule formulations for Claritin were not bioequivalent; in the presence of food, loratadine Cmax was observed to be 16% higher for the Liqui-Gels formulation compared to that of the tablet. However, this higher Cmax for the Liqui-Gels formulation may not be clinically relevant because loratadine is classified as a highly variable drug. In addition, there were two subjects taking Claritin tablet whose Cmax values were higher than the highest Cmax observed for the subject taking Claritin Liqui-Gels, both taken with food.[11]

---

6 Clinical Pharmacology Online (http://cpip.gsm.com) accessed on 4-2-08.
7 Prescription Information for Claritin, Physicians Desk Reference (PDR) 2003.
8 Clinical Pharmacology Online (http://cpip.gsm.com) accessed on 2-15-08.
9 Prescription Information for Claritin, Physicians Desk Reference (PDR) 2003.
10 Clinical Pharmacology Online (http://cpip.gsm.com) accessed on 2-15-08.
11 See Biopharm review by Sandra Suarez-Sharp, Ph.D. entered in DFS

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The sponsor submitted one bioquivalence study (CL2006-09) to this NDA resubmission. This was an open-label, single dose, randomized, two-period, two-treatment, two-sequence, crossover study of one Claritin Liqui-Gels™ capsule to one Claritin® tablet, loratadine 10 mg, conducted in 36 healthy adult subjects under fed conditions.

5.2 Review Strategy

One bioavailability study (CL2006-09) submitted by the sponsor comparing the PK profile of one 10 mg dose of Claritin Liqui-Gels™ capsule to one Claritin® tablet (loratadine 10 mg) under fed conditions was mainly utilized in the review of this NDA resubmission. This reviewer will evaluate the safety of the proposed Claritin Liqui-Gels™ capsule 10 mg for OTC use as well as the postmarketing safety update for all Claritin formulations submitted by the sponsor. The Biopharmaceutics reviewer will review the relative bioavailability study in detail. A reviewer from the Division of Nonprescription Regulation Development (DNRD) will review the OTC label in detail.

5.3 Discussion of Individual Studies

Brief Summary of Study CL2006-09
This was an open-label, single dose, randomized, two-period, two-treatment, two-sequence, crossover study conducted to compare the relative bioavailability of two formulations of loratadine 10 mg, Claritin® Liqui-Gels™ capsule and 10 mg Claritin® tablet under fed conditions (after a standardized high fat breakfast). Personnel at the analytical laboratory were blinded to the randomization code to prevent bias during analysis. A total of 36 subjects were enrolled. Subjects received each of the following treatments (A→B or B→A).

Study Treatments

Treatment A	Treatment B
Claritin® Liqui-Gel™ Capsule 10 mg	Claritin® 10 mg Tablet

All subjects fasted for at least 10 hours and then ate a standardized high fat breakfast[12] 30 minutes before dosing. Each treatment was administered with 240 mL of room temperature water; 18 subjects were randomly assigned to dosing sequence A→B and 18 subjects were assigned to dosing sequence B→A. There was a 14-day washout interval between treatments. Approximately 276 mL of blood was collected from each subject for PK samples over the course of both study periods.

12 The FDA standardized high fat breakfast served to each subject consisted of the following: 2-eggs fried in butter, 2-slices of toast with butter, 2-strips of bacon, 4-ounces of hash brown potatoes, 8-fl. oz. (240 mL) of whole milk.

At 4 and 9 hours after dose administration, standardized meals and beverages were provided to each subject. In addition, a standardized snack was served at approximately 14.5 hours postdose. All meals were free from grapefruit, xanthine-, and caffeine-containing products.

Table 2: Table of Events (CL2006-09)

Evaluation	Screening	Periods[a] I & 2						
	(Day –14 to –2)	Day –1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Obtain Informed Consent[b]	X							
Inclusion/Exclusion 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.
b: Written informed consent was obtained prior to any study evaluations being performed.
c. CBC and differential, chemistry panel, urinalysis (including microscopic examination).
d: ECG – standard 12 lead reporting ventricular rate, PR, QRS, QT and QTc interval.
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 14.5 hours prior to dosing and remain 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.

The results of the bioequivalence study are shown in the table 3 below.

APPEARS THIS WAY ON ORIGINAL

Table 3: Summary of PK Parameters Food Effect Study CL2006-09

Parameter	Claritin® 10 mg Liqui-Gels™ Capsule Fed	Claritin® 10 mg Tablets Fed	% Ratio	90% CI
Loratadine N=33				
AUC_{0-t} (pg-hr/mL)	10421.41	10318.84	100.99	(90.11, 113.19)
$AUC_{0-\infty}$ (pg-hr/mL)	11102.52	11097.47	100.05	(89.3, 112.08)
C_{max} (pg/mL)	3338.16	2864.80	116.52	(94.42, 143.8)
Desloratadine N=32				
AUC_{0-t} (pg-hr/mL)	43569.34	44347.17	98.25	(93.35, 103.4)
$AUC_{0-\infty}$ (pg-hr/mL)	44593.38	45408.58	98.20	(93.37, 103.29)
C_{max} (pg/mL)	3946.90	3697.23	106.75	(95.89, 118.85)

Sponsor's submission Mod. 2, section 2.0

The study showed that under fed conditions:

- The 90% confidence intervals around the ratio of the [geometric] mean for Treatment A (Claritin® Liqui-Gels™ Capsule 10 mg) to the mean of Treatment B (Claritin® Tablet 10 mg) met the criteria for bioequivalence for AUC_{0-inf} [100.05 (89.3, 112.08)] for loratadine.
- The upper limit of the 90% confidence interval around the ratio of the [geometric] mean for Treatment A to the mean of Treatment B for loratadine Cmax [**116.52** (94.42, **143.8**)] was above the 125% limit under fed conditions.
- The 90% confidence intervals (CI) for the geometric means test-to reference ratios for AUC_{0-inf} [98.20 (93.37, 103.29)] and Cmax [106.75 (95.89, 118.85)] desloratadine were within the bioequivalence interval of 80-125.

Medical Officer Comments: A 16.5% increase in the geometric mean ratio in Cmax for the parent drug loratadine with this new Liqui-Gels formulation compared to the currently marketed Claritin® tablet 10 mg formulation is probably not clinically significant. The Biopharm reviewer who reviewed the study in detail shares the same opinion (see review entered in DFS).

The prescribing information for loratadine, under the Clinical Pharmacology section, under Pharmacokinetics[13] subsection, states that the Cmax of Claritin Reditabs was 6% greater than that of Claritin tablets following administration of 10 mg loratadine once daily in 24 normal adult subjects (AUC was 11% greater).

In addition, under the Precautions section, Drug Interactions subsection, it states that the plasma concentrations ($AUC_{0-24\ hrs}$) of loratadine and desloratadine were increased after 10 days of coadministration of loratadine 10 mg with three other drugs (erythromycin by 40%, cimetidine by 103%

[13] Prescription Information for Claritin, Physicians Desk Reference (PDR) 2003.

and ketoconazole by 307%) in normal volunteers (N=24). It is further stated that there were no clinically relevant changes in the safety profile of loratadine, as assessed by electrocardiographic parameters, clinical laboratory tests, vital signs and adverse events. There were no significant effects on QTc intervals, and no reports of sedation or syncope.

This Medical Officer believes that the increase in Cmax (of 16.5%) for the Liqui-Gel formulation observed in this study will unlikely cause significant serious adverse events or common adverse events experienced when taking this product with food.

6 Review of Efficacy

There were no efficacy trials conducted for this NDA except for PK evaluation. Reference is made by the sponsor to their previously submitted NDA 19-658 (Claritin® 10 mg tablets Rx-to-OTC switch application) for efficacy information. Efficacy of this Liqui-Gel formulation is extrapolated based on PK data from the single-dose relative bioavailability studies assessing the proposed Claritin® Liqui-Gels capsule 10 mg and the currently marketed Claritin® tablet 10 mg (RLD) under fasted (Study CL2004-02, previously submitted) and fed (Study CL2004-09) conditions. The adequacy of these relative bioavailability studies will be reviewed by the Office of Clinical Pharmacology (OCP).

7 Review of Safety

Safety Summary

The sponsor relies on the safety information being referenced from their previously submitted NDA 19-658 (Claritin® tablets 10 mg Rx-to-OTC switch application), RLD. The safety of the proposed formulation has been evaluated in detail during the initial submission of this NDA (see Medical Officer's Review in DFS).

A total of 97 subjects were exposed to the proposed Claritin® Liqui-Gels10 mg capsule formulation in the studies submitted to NDA 21-952 (original and resubmission). All studies evaluated single dose of the drug.

Thirty six (36) subjects were exposed to the proposed Claritin® Liqui-Gels™ in the food effect bioequivalence study (CL2006-09) conducted for this resubmission; 33 subjects received 2 doses of loratadine and completed the study. A total of 9 (16%) subjects experienced 21 adverse events (AEs): 3 (8%) subjects in the Claritin® Liqui-Gels™ capsule group experienced 7 AEs, and 7 (20%) subjects in the Claritin® tablet group. There was one subject (#02) who experienced AEs in each treatment period. The most common adverse events reported for both treatments was headache. Headache, reported by 1/35 (2.86%) subjects after administration of Claritin® Liqui-Gels™ capsule and 4/34 (11.76%) subjects after administration of Claritin tablets, 10 mg, were considered treatment-related adverse events. Headache is a known common AE of loratadine; this is consistent with the already well-characterized adverse event profile for loratadine.

In addition, during the original submission of this NDA, a total of 61 subjects were exposed to Claritin® Liqui-Gels capsule. In the fasting study CL2004-02, 50 subjects received at least one dose of study drug and were analyzed for safety, 48 completed the study. In this study, the most commonly reported adverse events were headache (3/50, 6%), pyrexia (3/50, 6%), and pharyngopharyngeal pain (3/50, 6%). The most commonly reported treatment-emergent adverse events after administration of loratadine gelatin capsules (test drug) were headache and pyrexia. In the food effect study CL2005-17, 11 subjects received the test drug. There were 4 adverse events reported in this study: dysmenorrhea (1 patient), headache (1 patient), and menstrual disorder (1 patient); all were considered not related to the test drug. See Clinical Review of this NDA entered in DFS.

Loratadine (Claritin®) has been marketed with a well-characterized safety profile in the United States since its approval for prescription use in April 12, 1993 and OTC switch since November 27, 2002. An extensive safety database exists for loratadine postmarketing experience. The safety update since the original NDA submission and an evaluation of the adverse events from the food effect study included in this resubmission do not raise any new safety concern, and establish the safety of Claritin® Liqui-Gels™ capsule 10 mg for OTC use when taken as directed.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

There were no studies conducted to specifically evaluate the safety of Claritin® Liqui-Gels capsules. This NDA relies on the safety information from the sponsor's previously submitted NDA 19-658 (Claritin® 10 mg tablets Rx-to-OTC switch application). Safety data from bioequivalence study CL2004-09 conducted with this resubmission was also evaluated.

7.1.2 Adequacy of Data

Loratadine has been proven safe and effective under prescription use at a daily dose up to 10 mg in the U.S. for almost 15 years; it is approved for use at a higher dose for up to 20 mg in other countries. The safety profile of loratadine is well-characterized and clinical experience is adequate from both prescription and OTC use. The data from the bioequivalence studies conducted by the sponsor (during the original submission and resubmission) for this NDA do not raise any new safety concern. Therefore, the clinical experience from loratadine and the data from this NDA are adequate to assess the safety of Claritin® Liqui-Gels™ capsule 10 mg for OTC use.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

This section is not applicable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 36 healthy subjects (25 males, 11 females; 32 Caucasian, 4 African Americans; 32 not Hispanic or Latino, 4 Hispanic or Latino) between the ages of 18 and 44 were enrolled, treated and analyzed for safety.

The study medication was administered to all 36 enrolled subjects, 33 subjects (92%) received two doses of loratadine and completed the study.

- 18 subjects were assigned to receive the study medication according to Sequence 1
  - loratadine 1 x 10 mg Liqui-Gels capsule in Period 1 followed by 1 x loratadine 10 mg Tablet in Period 2
- 18 subjects were assigned to receive the study medication according to Sequence 2
  - loratadine 1 x 10 mg tablet in Period 1 followed by loratadine 10 mg Liqui-Gels capsule in Period 2

Three subjects (14, 16 and 29) received only one dose of loratadine10 mg, and discontinued from the study.

7.2.2 Explorations for Dose Response

This section is not applicable.

7.2.3 Special Animal and/or In Vitro Testing

There are no new animal studies submitted with this NDA resubmission. The sponsor relies on the information from the sponsor's previously submitted NDA 19-658 (Claritin® 10 mg tablets Rx-to-OTC switch application).

7.2.4 Routine Clinical Testing

The following assessments were completed during screening, within 28 days prior to Period I dose administration: medical and medication history, physical examination, sitting blood pressure and heart rate, oral temperature, respiratory rate, electrocardiogram; clinical laboratory evaluations, screens for HIV antibody, hepatitis B surface antigen, hepatitis C antibody, drugs of abuse, and pregnancy (females only). All subjects were briefly evaluated before each confinement period to assess whether they continued to meet the inclusion/exclusion criteria. Demographic data (including height, weight, age, gender, ethnicity, and race) were also collected for each subject.

Study exit procedures were completed within 14 days after the last scheduled blood sample collection. The exit procedures included general observations, a physical examination, blood

pressure, heart rate and temperature evaluations, clinical laboratory tests (hematology and clinical chemistry testing), 12-lead ECG, and a pregnancy screen (females only).

Routine clinical testing was appropriate and adequate for the study.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new information on metabolic, clearance and interaction was submitted with this NDA.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

This section is not applicable.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in this study.

7.3.2 Nonfatal Serious Adverse Events

There were no other serious adverse events, or other significant adverse events occurred over the course of the study.

7.3.3 Dropouts and/or Discontinuations

Subject #14 discontinued from the study during Period I and received only one 10 mg dose of study drug (Liqui-Gels capsule); subject #16 discontinued from the study prior to Period II dosing and received only one 10 mg dose of study drug (Liqui-Gels); and subject #29 withdrew prior to Period II and received only one dose of 10 mg tablet. See table 4 below.

Table 4: Discontinued Subjects

Subject No.	Subject Initials	Reason
14	—	Subject withdrew consent prior to Period II dosing due to adverse event (vomiting) *(received Liqui-Gels only)*
16	—	Subject withdrew consent prior to study hour 11.5 during Period I due to a family emergency *(received Liqui-Gels only)*
29	—	Subject withdrew consent prior to Period II check-in due to personal reasons *(received tablet only)*

b(4)

Table 5: Summary of Subject Disposition

	Sequence		Total
	AB	BA	
Subjects Randomized	18	18	36
Subjects Who Successfully Completed the Study	16	17	33
Subjects Who Withdrew Consent	2	1	3
Subjects Dropped by the Investigator or Sponsor	0	0	0

Treatment A: Claritin 10 mg Liqui-Gel™ Capsules (loratadine 10 mg)
Treatment B: Claritin 10 mg Tablets

Table 6: Disposition for All Dosed Subjects by Treatment

	Treatment	
	A Liqui-Gels	B Tablets
Number of subjects who received study treatment	35	34
Subjects who withdrew consent	2	0
Subjects who withdrew or were dismissed due to AEs	0	1

Adapted from Sponsor's submission, Mod. 5 p.4

7.3.4 Significant Adverse Events

There were no other significant adverse events reported in this study.

7.3.5 Submission Specific Primary Safety Concerns

This section is not applicable.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In this PK fed study, there were nine subjects (02, 14, 19, 20, 23, 24, 32, 33, 35) who experienced a total of 21 adverse events (AEs) over the course of the study. AEs were mild to moderate in severity, no severe AEs were reported. All of the AEs were considered related to loratadine. See table 7 below.

The most frequently reported AE from each treatment was headache.

- 1 subject (1/35, 2.86%) in Treatment A (Claritin 10 mg Liqui-Gels™ capsules) experienced moderate headache on more than one occasion

- 4 subjects (4/34, 11.76%) in Treatment B (Claritin 10 mg tablets) experienced 6 episodes of mild to moderate headache; 1 subject (#32) experienced more than one episode of mild headache and one episode of moderate headache.

Below is a table of AEs reported during the study.

Table 7: Number of Subjects Reporting an AEs (Rate), Subject Number(s) & Total Number of Episodes Reported

Treatment A Liqui-Gels™ Capsules (N=35)							
		Mild		Moderate		Total	
System Organ Class	Preferred Term	Related	Subject No.	Related	Subject No.	Related	Overall
Nervous system disorders	Dizziness	1 (2.86%)	33			1	1
	Headache			1 (2.86%)	02*	3	3
Respiratory, thoracic and mediastinal disorders	Cough	1 (2.86%)	02			1	1
	Epistaxis	1 (2.86%)	19			1	1
	Respiratory tract congestion	1 (2.86%)	02			1	1
Treatment B Tablets (N=34)							
Gastrointestinal disorders	Nausea	2 (5.88%)	24, 32			2	2
	Vomiting			1 (2.94%)	14*	3	3
Infections & Infestations	Gastroenteritis Viral			1 (2.94%)	35	1	1
Investigations	Heart rate Increased	1 (2.94%)	23*			2	2
Nervous system disorders	Headache	2 (5.88%)	02, 32*	3 (8.82%)	20, 24, 32	6	6

*Subject experienced adverse event on more than one occasion.
Adapted from sponsor's submission, Mod. 5, pp 40-41

7.4.2 Laboratory Findings

Laboratory tests were performed at Screening, Day-1 of each period and after 120 hours post-dose blood draw in Period 2 only (see Table 2), these included:

- CBC with differential count
- Serum chemistry panel
- Urinalysis including microscopic examination.

In addition, the following were completed during screening, within 28 days prior to Period I dose administration: screens for HIV antibody, hepatitis B surface antigen, hepatitis C antibody, drugs of abuse, and pregnancy (females only). Study exit procedures were completed within 14 days after the last scheduled blood sample collection. The exit procedures included clinical laboratory tests and a pregnancy screen (females only). All results were reviewed by the clinical investigators. Those values outside the reported reference range were either designated as not clinically significant or follow-up testing was required.

The clinical laboratory values were considered unremarkable and none of the values outside of the reference range at study exit were considered directly attributable to the product. There were no clinically significant changes in the clinical laboratory measurements over the course of the study which could be reasonably associated with the formulations under investigation.

7.4.3 Vital Signs

Blood pressure, heart rate, oral body temperature and respirations were measured at screening; on day -1 (baseline), on day 1 pre-dose; on days 2-6 before the first blood draw of the day; and on day 6 after the last blood draw. There were no reported clinically significant changes from baseline for vital signs. Physical examinations were also performed at screening and at the end of the study; there were no reported changes from baseline.

7.4.4 Electrocardiograms (ECGs)

A 12-lead ECG was recorded during the screening visit and at study exit. There were no reported clinically significant changes observed for ECGs in the study.

7.4.5 Special Safety Studies

There were no special safety studies conducted in this submission.

7.4.6 Immunogenicity

There was no immunogenic evaluation conducted in this submission; no known immunogenicity issues are related to loratadine.

7.5 Other Safety Explorations

There were no other safety explorations performed in this NDA resubmission.

7.6 Additional Safety Explorations

There were no additional safety explorations performed in this NDA resubmission.

7.7 Additional Submissions

On February 4, 2008, a postmarketing safety data that was included in the January 24, 2008 Sponsor's Annual periodic ADE report for the different formulations of Claritin® was submitted to this NDA resubmission. This covers the period from November 27, 2007 to November 27, 2008 for the following formulations: tablet (NDA 19-658), redi-tab (NDA 20-704) and oral solution (NDA 20-641). Also included was the postmarketing safety data for the chewable tablet formulation (NDA 21-891) that covers the period from November 23, 2006 and November 27, 2007. Safety information from the FDA Adverse Event Reporting System (AERS), World Health Organization (WHO) and Toxic Exposure Surveillance System (TESS) databases were already included during the initial NDA submission. No information from these safety databases was included in this resubmission.

On April 10, 2008, the sponsor submitted an amendment to the above Safety Update that provides for the analysis of the postmarketing serious adverse events for the different Claritin® formulations as requested by this reveiwer. There were no new significant safety issues identified in this reporting period. See (Postmarketing) section 8 of this review.

8 Postmarketing Experience

Loratadine (Claritin®) has been marketed with a well-characterized safety profile in the United States since its approval for prescription use on April 12, 1993 and its OTC switch since November 27, 2002. An extensive safety database exists for loratadine postmarketing experience. The sponsor currently markets the following single-ingredient loratadine products in the United States: Claritin® 24 hour Allergy Tablets (10 mg), Claritin® Hives Relief Tablets (10 mg), Claritin® RediTabs Tablets (10 mg), Children's Claritin® Allergy Oral Solution (5mg/5ml), and Claritin® Chewable Tablets (5 mg).

The safety information from postmarketing data was submitted and reviewed during the initial submission of this NDA.[14] The postmarketing review for this resubmission covers the information from November 27, 2007 to November 26, 2008 for the different Claritin® dosage formulations, and November 23, 2006 and November 22, 2007 for the Claritin® chewable tablets.

During the above reporting period, over ——— loratadine tablets (tablets and redi-tabs), over ——— chewable tablets and over ——— ounces of Claritin® oral solution were distributed worldwide. For all dosage forms, there were 2355 adverse event (serious and non-serious) cases

b(4)

14 See Clinical Review (section 7.1.17) by this Medical Officer for NDA 21-952 entered in DFS on December 8, 2006.

identified in the database; of these, there were 91 serious cases, 2214 initial non-serious cases and 50 follow-up non-serious cases. Serious cases were 3.8% of the total cases received during the reporting period. *(Comment: There is a discrepancy in the total number of serious AEs reported from the Safety Update dated February 4, 2008 and April 10, 2008, 91 vs. 84. It is possible that the 7 cases formerly categorized as serious cases were categorized as non-serious on follow-up.)*

The most common system organ class (SOCs) with reported serious AEs for all dosage forms include Nervous System, Psychiatric, General and Gastrointestinal Disorders. The tablet, with the highest number of doses distributed, had 63 serious cases (160 AEs) while the redi-tabs had 11 cases (51 AEs); the syrup had 8 cases (19 AEs) and the chewables had 2 cases (6 AEs).

The most frequently reported serious AEs ($\geq$ 3 times or 0.1%) are loss of consciousness, pharyngeal edema, convulsion, lip swelling and tachycardia (tablet); and confusional state (redi-tab).

Deaths

There were two reports of deaths during this reporting period:

- A 6 y/o male (U.S. case) had a medical history of chronic allergies, recurrent ENT infections, gastroesophageal reflux disease (GERD) and sleep apnea. He was on chronic loratadine therapy with concurrent pharmacotherapy including mebendazole, promethazine with codeine, pseudoephedrine, ranitidine and antibiotics. Report indicated recent history of pinworms and vomiting the evening prior to death. Details on how he died were not provided. Autopsy was inconclusive; laboratory results noted elevated descarboethoxyloratadine. The sponsor stated that although product association cannot be ruled out, underlying sleep apnea and concurrent pharmacotherapy with codeine and ranitidine were possibly contributing factors.
- A 16 y/o male (2007SP009395, Canada) with history of Attention Deficit Hyperactivity Disorder was on methylphenidate HCl 60 mg daily with recent increase to 70 mg daily. Approximately 3 days after the start of loratadine therapy, the patient collapsed while running during physical education and had ventricular fibrillation QT prolongation with loss of consciousness. Cardioversion was successful, but the patient died 4 days later. Although product association cannot be ruled out, recent increase of methylphenidate HCl was considered a confounder; adverse event profile include serious cardiovascular events and is considered contributory thus providing an alternative causality for the fatal outcome.

Medical Officer Comments: For the first case, elevated levels of descarboethoxyloratadine (although the exact level was not reported), the underlying medical conditions and concomitant pharmacotherapy are all possible contributing factors to the patient's death. For the second case, both loratadine and methylphenidate have known cardiovascular adverse events such syncope, tachycardia and cardiac arrhythmia. It is possible that concomitant intake of these medications contributed to the patient's outcome, as well as the recent increase in methylphenidate[15] dosage. Both cases were confounded with

15 The average dosage for methylphenidate in adults is 20 to 30 mg daily, some patients may require 40 to 60 mg daily; Drugs.com (http://www.drugs.com/pro/methylphenidate.html) accessed 4-28-08.

intake of concomitant medications, underlying medical conditions or had limited clinical information to definitely assess causality.

Below is a list of other serious adverse events reported in which a short narrative was provided:

- Suspected erythema multiforme in a 28 y/o female (2007SP015637, Japan) with atopic dermatitis since childhood a day after initiation of loratadine tablets. She was also on other medications for her dermatitis. Suspected condition was treated with steroids and clemastine. A chamber scarification patch test for loratadine was negative as well as oral rechallenge. The condition was assessed as unrelated to product use.
- Exfoliative dermatitis in a 63 y/o male (2007SP017780, Italy) 11 days after initiating loratadine tablets for eosinophilia. Concurrent medications include leflunomide (anti-inflammatory), finasteride and tamsulosin HCl (last 2 drugs are used for the treatment of benign prostatic hypertrophy). Although product association cannot be ruled out, concurrent therapy with levoflunomide has been associated with severe skin reactions including ulceration.
- Congestive cardiac failure and tachycardia in a 91 y/o female 19 days after starting loratadine tablets. She was treated with verapamil and digoxin. The reporting physician noted that a pre-existing cardiac failure cannot be ruled out.
- Angina pectoris reported in a 97 y/o male with a medical history of hypercholesterolemia and myocardial events who has a cardiac pacemaker and was taking clopidogrel, atorvastatin, and metoprolol. He was taking loratadine tablets for voice hoarseness; use of this product in the past was uneventful. The sponsor reports that the patient's advanced age and underlying medical history are confounders in this case, and limited information prevents further medical assessment.
- Dizziness and weakness (questionable diagnosis of transient ischemic attack vs. hypotensive episode) in a 29 y/o female (2007SP000858, Estonia) after the first dose of loratadine tablets. A similar reaction was noted with Theraflu® tablets. Loratadine was discontinued and the event resolved.
- Facial droop, dysarthria, speech disorder, oral hypoaesthesia, headache, paraesthesia, somnolence, eye disorder and nausea in a 13 y/o female (2007SP006142, U.S.) experienced shortly after the first dose of loratadine redi-tabs. No medical intervention was provided. Previous exposure to the product was uneventful. No further information was provided.
- Drowsiness with short term loss consciousness resulting in a minor traffic accident in a 65 y/o female (2007SP01 0056, U.S.) 3 days after taking loratadine redi-tabs. She had a medical history of overactive bladder, depression, hypercholesterolemia and was taking tolterodine (antimuscarinic), atorvastatin and citalopram. Concurrent wellbutrin and citalopram have been associated with somnolence. No additional information was provided.

Medical Officer Comments: The types of adverse events that were noted during the reporting period are generally similar to those reported in clinical trials and postmarketing. For any serious or life-threatening adverse events not previously identified or reported, there was either no conclusive evidence, limited information provided, or there was underlying medical condition(s) present to establish a causal relationship between the use of loratadine and the reported event(s). There were no trends or signals that indicate any new safety issue with loratadine for OTC use during this reporting period.

Literature Review

The sponsor searched the worldwide, peer-reviewed literature to identify publications relevant to the safety of loratadine for human use between January 1, 2007 and November 1, 2007. There were no new published prospective clinical trials or new published case reports relevant to the safety of loratadine for human use during this time period. There was one publication[16] of a clinical study that presented the results of the absorption, metabolism and excretion of a single oral dose of radiolabeled loratadine10 mg capsule administered to six healthy adult male volunteers. There were no deaths or serious adverse events reported and no clinically significant changes were noted on physical examinations and routine clinical laboratory safety tests.

Medical Officer Comments: The postmarketing safety update submitted and the review of literature during the reporting period did not reveal any new significant safety concerns that preclude the continued use of loratadine for OTC use.

9 Pediatrics

Loratadine is indicated for use in children 6 years of age and older. Pediatric patients were not evaluated in this NDA. The sponsor is requesting a waiver for children less than 6 years of age; this request should be granted.

Loratadine is already labeled for OTC use in children two years of age and older for the proposed indication. There are several loratadine formulations available OTC for allergic rhinitis symptoms including tablets (10 mg), orally disintegrating tablets (10 mg), chewable tablets (5 mg) and syrup (1 mg/1 mL). Approved formulations for children 2 to 5 years of age include chewable and orally disintegrating tablets, as well as the syrup. Thus, there are other currently marketed loratadine formulations that are appropriate for this age group.

The proposed product would not offer any additional meaningful therapeutic benefit over existing therapies for the pediatric population aged 2 to 5 years. For children less than 2 years of age, it is the Agency's decision not to label loratadine below this age based on the knowledge that children generally need to be exposed to allergens for at least two seasons before they develop a seasonal allergy.

In addition, there are other second-generation antihistamines available by prescription and labeled down to the age of 6 months to treat (perennial) allergic rhinitis. PREA[17] requirements for loratadine have been met for children 2 years and older, and a waiver would apply for those less than 2 years of age.

16 Ramanathan R, Reyderman L, Kulmatycki K, et.al. Schering-Plough Research Institute, Kenilworth, NY, USA Disposition of loratadine in healthy volunteers. Xenobiotica, July 2007; 37(7): 753-769.
17 Pediatric Research Equity Act

10 Appendices

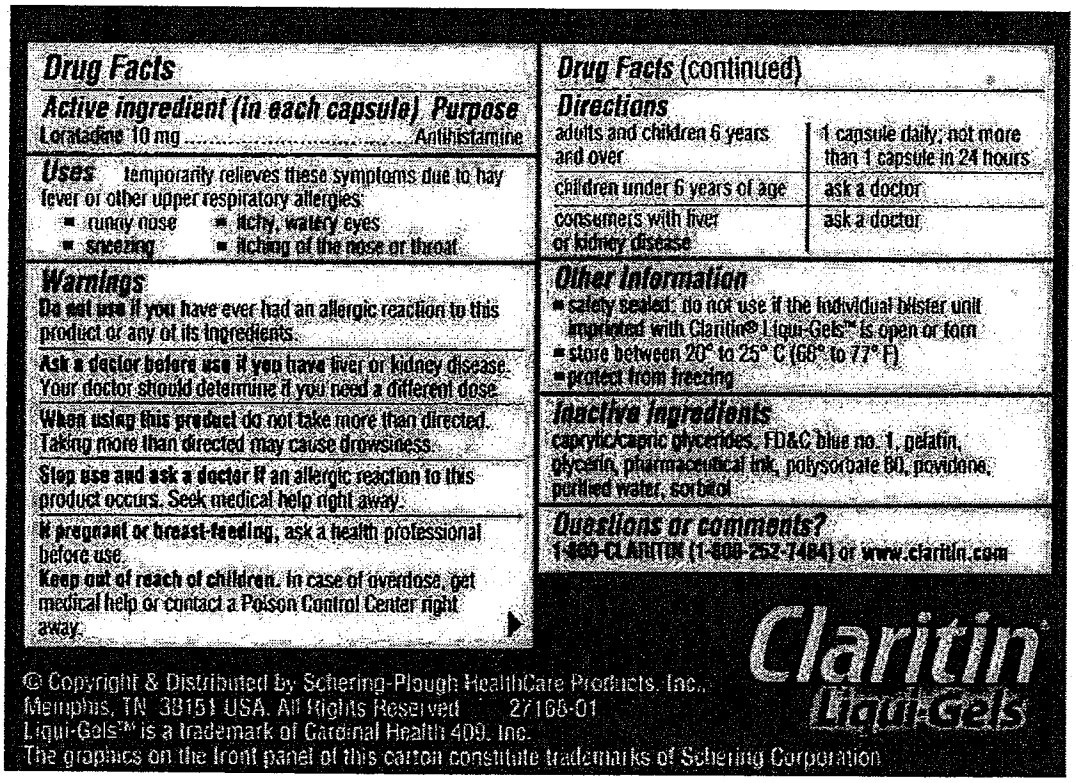
10.1 Literature Review/References

Ramanathan R. Reyderman L. Kulmatycki K. Su AD. et. al. 2007. Disposition of loratadine in healthy volunteers. Xenobiotica Jul; 37(7):753-69.

10.2 Labeling Recommendations

Below is the sponsor's proposed label. The sponsor is proposing a label very similar to the already approved Claritin Tablets label (including the Drug Facts, Uses, Warnings, and Directions). No additional directions regarding the effect of food and use of this product will be necessary. This reviewer has no further labeling recommendations and finds the proposed label acceptable from a clinical safety standpoint. A member of the Interdisciplinary Scientist (IDS) group in the Division of Nonprescription Regulation Development (DNRD) will be reviewing the proposed label.

Figure 1: Proposed Drug Facts Label for Claritin Liqui-Gels Capsule



10.3 Tables from Previous Bioequivalence Studies

Below are tables from bioequivalence studies previously submitted during the initial submission of NDA 21-952.

Table A-1: Analysis of Loratadine and Desloratadine Bioequivalence Fasting Study (CL2004-02)

Analyte Parameter	1 x 10 mg Claritin Liqui-Gel Capsule (Test)	1 x 10 mg Claritin Tablet (Reference)	Ratio (Test/Reference)	90% CI Lower	90% CI Upper
Loratadine					
AUC	6.9581	7.6683	0.9074	0.8135	1.0121
AUC_T	6.5545	7.1760	0.9134	0.8214	1.0156
Cmax	2.4688	2.7825	0.8873	**0.7875**	0.9996
Desloratadine					
AUC	38.9407	42.0624	0.9258	0.8668	0.9888
AUC_T	37.6661	40.7446	0.9244	0.8647	0.9883
Cmax	2.9756	3.2874	0.9051	0.8375	0.9783

Table A-2: Analysis of Loratadine and Desloratadine Bioavailability Food Effect Study (CL2005-17)

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data (N = 11)				
Parameter	Fed	Fasting	% Ratio	90% CI
Loratadine				
AUC_{0-t} (ng-hr/mL)	13.45	6.08	**221.13**	(191.02, 255.99)
$AUC_{0-\infty}$ (ng-hr/mL)	14.13	6.48	**218.03**	(187.84, 253.07)
Cmax (ng/mL)	3.91	2.55	**153.06**	(113.45, 206.5)
Desloratadine				
AUC_{0-t} (ng-hr/mL)	38.10	35.99	105.87	(95.98, 116.79)
$AUC_{0-\infty}$ (ng-hr/mL)	39.66	37.33	106.24	(96.3, 117.2)
Cmax (ng/mL)	3.03	3.19	94.81	(78.69, 114.24)

10.4 Advisory Committee Meeting

This section is not applicable for this submission.

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

/s/

Lolita Lopez
5/7/2008 11:30:03 AM
MEDICAL OFFICER

Daiva Shetty
5/12/2008 06:41:56 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-952
Submission Code	000
Letter Date	March 6, 2006
Stamp Date	March 16, 2006
PDUFA Goal Date	January 16, 2007
Reviewer Name	Lolita A. Lopez, M.D.
Review Completion Date	November 17, 2006
Established Name	Loratadine 10 mg
(Proposed) Trade Name	Claritin® Liqui-Gels™ Capsules 10 mg
Therapeutic Class	Antihistamine
Applicant	Schering-Plough Healthcare Products, Inc.
Priority Designation	Standard
Formulation	Softgel Capsule
Dosing Regimen	One Capsule Every 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 Years and Older

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The proposed loratadine (Claritin® Liqui-Gels™) capsule 10 mg for the indication of 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 has an acceptable safety profile for OTC marketing. Therefore, this application should be approved from a clinical safety standpoint. Final approvability depends on the adequacy of the bioavailability study #CL2004-02 conducted by the sponsor and the DSI inspection. In addition, the sponsor should incorporate the reviewing team's labeling recommendations for this product.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No special risk management activities are recommended for this NDA.

1.2.2 Required Phase 4 Commitments

No required phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

No other phase 4 requests are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Schering-Plough HealthCare Products, Inc. (SPHCP) is seeking approval to market Claritin® Liqui-Gels™ capsule10 mg, an immediate release, liquid-filled capsule containing 10 mg of loratadine. This softgel formulation will be an additional formulation to the Claritin® brand products and is expected to be an easy swallow product for consumers who find tablets or other formulations to be difficult to swallow or are unpalatable. The proposed indication for this product is similar to the already approved indications for Claritin® tablets 10 mg which are: 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. The proposed

dose is one 10 mg Liqui-Gel capsule every twenty-four hours for adults and children 6 years of age and older.

In support of this NDA, the sponsor conducted one bioequivalence study (CL2004-02) comparing the pharmacokinetics (PK) of a single dose of the proposed Claritin® Liqui-Gels® capsule 10 mg and the currently marketed Claritin® tablet 10 mg, the reference listed drug (RLD). No new food effect study was conducted on this Liqui-Gel® capsule formulation during the initial submission of this NDA. The sponsor states that the food effect of loratadine is well established and is not considered to affect clinical efficacy; therefore, no new food effect study was conducted on this capsule formulation during the initial submission of this NDA on March 6, 2006. In a Filing letter sent to the sponsor dated May 15, 2006, the sponsor was requested to submit additional data to support that the food effect for Claritin Liqui-Gels® capsules is expected to be the same as that seen for Claritin® tablets. The sponsor stated that subsequent to filing, it conducted a food effect study. A teleconference was held between the sponsor and the Agency on July 18, 2006 to discuss the results of the food effect study (see meeting minutes entered in DFS).

In this 505(b)(1) application, reference is made by the sponsor to their previously submitted NDA 19-658 (Claritin® 10 mg tablets Rx-to-OTC switch application) for clinical and pre-clinical information.

1.3.2 Efficacy

There were no efficacy trials conducted for this NDA except for a pharmacokinetic (PK) evaluation. Reference is made by the sponsor to their previously submitted NDA 19-658 (Claritin® tablets 10 mg Rx-to-OTC switch application) for efficacy information. Efficacy of this product is extrapolated based on PK data from the single-dose relative bioavailability study (CL2004-02) assessing the proposed Claritin® Liqui-Gel 10 mg capsule and the currently marketed Claritin® tablet 10 mg (RLD).

This bioequivalence study was an open-label, single dose, comparative, randomized, crossover study in healthy volunteers under fasting conditions with a 14-day wash-out period. A total of 48 subjects were planned; 50 subjects (24 males and 26 females) were enrolled, treated, and analyzed for safety; 48 subjects completed the study and were included in the analysis of bioequivalence. The results of the study have shown that the 90% confidence intervals (CIs) for the geometric means test-to-reference ratios for the area under the curve (AUC) and peak concentration (Cmax) for desloratadine (an active metabolite of loratadine) were within the bioequivalence interval guidelines of 0.80-1.25; AUC: 0.9258 (0.8668, 0.9888) and Cmax: 0.9051 (0.8375, 0.9783). This bioequivalence criterion was also met for the parent drug lotatadine, AUC: 0.9074 (0.8135, 1.0121). However, the lower boundary of the CI for the Cmax of loratadine fell below the bioequivalence limit of 0.80: [0.8873 (*0.7847*, 0.9996)].

A food effect study (CL2005-17) was also conducted by the sponsor for the proposed product and showed that administration of Claritin® Liqui-Gel 10 mg capsule with food increased loratadine Cmax by 53%, AUC_{0-t} by 121%, and $AUC_{0-\infty}$ by 118%; the change in desloratadine PK was not significant. The results showed a doubling of the AUC of the parent drug loratadine under fed conditions. Historically, a 30-40% increase in loratadine AUC has been shown for other Claritin® formulations.

The adequacy of relative bioavailability studies will be reviewed by the Office of Clinical Pharmacology (OCP).

1.3.3 Safety

The sponsor relies on the safety information being referenced from their previously submitted NDA 19-658 (Claritin® tablets 10 mg Rx-to-OTC switch application) and the safety data submitted to the recently approved NDA 21-891 (Claritin® chewable tablets 5 mg). In addition, the following were submitted to this application:

- Safety data from bioequivalence study CL2004-02
- Post Marketing Safety Surveillance (adverse event) data
  - Schering-Plough internal adverse event database from October 1, 2005 to June 28, 2006
  - World Health Organization (WHO) database from October 1, 2005 to February 2, 2006
- Toxic Exposure Surveillance System (TESS) database from the American Association of Poison Control Centers (AAPCC) from December 1, 2005 to May 31, 2006
- Worldwide human and pre-clinical peer-reviewed literature October 1, 2005 to July 14, 2006

A total of 61 subjects were exposed to the proposed Claritin® Liqui-Gel™ 10 mg capsule formulation in the PK studies during the clinical development program. In the fasting bioequivalence study conducted (CL2004-02, N=50), a total of 8 (16%) subjects experienced 10 adverse events (AEs): 6 (12%) subjects in the Claritin® Liqui-Gel™ capsule group and 4 (8.3%) subjects in the Claritin® tablet group. The most common adverse events reported for both treatments were headache (3/50, 6%), pyrexia (3/50, 6%) and pharyngolaryngeal pain (3/50, 6 %). Headache, reported by 2/50 (4%) subjects after administration of Claritin® Liqui-Gel™ capsule; and dizziness reported by 2/48 (4%) subjects after administration of Claritin® tablets were considered treatment-related adverse events. These are consistent with the already well-characterized adverse event profile of loratadine.

Loratadine (Claritin®) has been marketed with a well-characterized safety profile in the United States since its approval for prescription use in April 12, 1993 and its nonprescription or over-the-counter (OTC) switch since November 27, 2002. An extensive safety database exists for loratadine postmarketing experience. A new formulation, Claritin® chewable tablet 5 mg, was recently approved (August 26, 2006) for marketing. The combination of postmarketing data, previous clinical trials, literature review and adverse events information from the relative bioavailability studies conducted by the sponsor do not raise any new safety concern, and establish the safety of Claritin® Liqui-Gel™ capsule 10 mg when taken as directed.

The clinical significance of the magnitude of food effect (which is more than double the AUC of the parent drug, loratadine) with this new Liqui-Gel capsule formulation compared to other marketed Claritin® formulations (e.g., Claritin® Tablet 10 mg) is unknown. There is a possibility that due to the increased bioavailability of this drug, patients might have an increased in adverse events, specifically somnolence when taking this product even at the recommended dose of 10 mg. Therefore, for safety reasons, patients should be informed that drowsiness may occur when this formulation is taken with food.

1.3.4 Dosing Regimen and Administration

The sponsor is seeking for the already approved OTC indications and dosing regimen for loratadine one capsule daily. The proposed indication will be for the temporary relief of symptoms of runny nose, sneezing, itchy and watery eyes, 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.

1.3.5 Drug-Drug Interactions

There are no new significant drug-drug interactions that were evaluated in this submission that warrant a change in the label of loratadine for OTC use.

1.3.6 Special Populations

No new information regarding other patient populations was submitted with this NDA. The PK studies did not perform any analyses by ethnic group. The subjects in study CL2004-02 were predominantly comprised of Hispanic (84.0%), followed by African American (12%) then Caucasian (4%).

The current loratadine OTC label addresses patients with renal or hepatic impairment. The *Warnings* section of the label states:

- *Ask a doctor before use if you have liver or kidney disease. Your doctor should determine if you need a different dose.*
- *If pregnant or breastfeeding, ask a health professional before use.*

Pediatrics

Pediatric patients were not evaluated in this NDA. No new significant data were submitted by the sponsor regarding this population for the proposed indication.

The sponsor is requesting a waiver for children less than 6 years of age; this request should be granted. Loratadine is already labeled for use in children two years and older, and there are other currently marketed loratadine formulations that are appropriate for this age group such as syrup and the recently approved chewable formulation. Additional studies using the proposed capsule formulation will not offer meaningful therapeutic benefit over the existing loratadine formulations.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Loratadine (Claritin®) is an oral second generation, non-sedating antihistamine approved for prescription use by the FDA on April 12, 1993 for the relief of hay fever and upper respiratory allergy symptoms in adults and children 6 years of age and older. In December 2000, loratadine received FDA approval for use in children ≥ 2 years old. On November 27, 2002, all formulations of Claritin® were approved for nonprescription or over-the-counter (OTC) use.

Loratadine is a selective peripheral H_1-receptor antagonist with poor penetration into the central nervous system (CNS) and a low affinity for CNS H_1-receptors; the CNS effects are less with loratadine compared to the non-selective H_1-blockers. Therefore, it has less undesirable sedation and anticholinergic effects of first-generation antihistamines (e.g. diphenhydramine, chlopheniramine maleate, etc.). Unlike astemizole and terfenadine, which are both second generation H_1-receptor antagonists, loratadine has not been associated with QT prolongation or torsades de pointes.[1] After oral administration, loratadine is rapidly metabolized to desloratadine, a pharmacologically active metabolite. Its onset of action occurs within 1-3 hours, the half-life of loratadine is 8 to 15 hours and the half-life of desloratadine is 12 to 24 hours.

Claritin® is currently available OTC as a 10 mg tablet, 10 mg reditabs and 1mg/mL syrup; a 5 mg chewable tablet was recently approved for marketing. The current indications are for the temporary relief of symptoms of runny nose, sneezing, itchy and watery eyes, and itching of the nose or throat due to hay fever or other upper respiratory allergies; and for the relief of hives. Also available are separate combination products of loratadine and pseudoephedrine, Claritin-D Non-Drowsy 12-Hour® tablets (loratadine 5 mg and pseudoephedrine 120 mg) and Claritin-D Non-Drowsy 24-Hour® tablets (loratadine 10 mg and pseudoephedrine 240 mg) with an additional indication of temporary relief of sinus congestion and pressure. The most common adverse events reported with the use of loratadine are headache, somnolence, fatigue, and dry mouth.

In this submission, Schering-Plough HealthCare Products, Inc. (SPHCP) is seeking for the approval of Claritin® Liqui-Gels™ 10 mg capsule, an immediate release, liquid-filled capsule containing 10 mg of loratadine to offer consumers additional convenient options for treatment. This softgel formulation will be an additional formulation to the Claritin® brand products and is expected to be an easy swallow product for consumers who find tablets or other formulations to be difficult to swallow or are unpalatable. The proposed indication for this product is similar to the already approved indications for Claritin® tablets 10 mg. The proposed dose is one 10 mg Liqui-Gel capsule every 24-hours for adults and children 6 years of age and older.

2.2 Currently Available Treatment for Indications

There are other currently available medical treatment for the sponsor's proposed indications; these are the currently marketed first and second-generation OTC H_1-antagonist antihistamines. The only second-generation antihistamine available for OTC use is loratadine, marketed brand names such as Claritin® [(10

1 Pharmacology Online, accessed on 10-12-06 (http://cpip.gsm.com)

mg tablet, 10-mg reditabs, 1mg/mL syrup, 5-mg chewables (recently approved)] and Alavert® (10 mg tablet or 10 mg quick dissolving tablet) or as a generic loratadine product.

The first generation antihistamines available for OTC use are: brompheniramine (e.g. Dimetapp Cold® & Allergy Elixir®, Robitussin Allergy & Cough Liquid®), chlorpheniramine (Singlet®), diphenhydramine (Benadryl Allergy®, Nytol®, Sominex®), and doxylamine (Vicks NyQuil®, Alka-Seltzer Plus Night-Time Cold Medicine®). The active ingredients in these products are included in the list of OTC monograph drugs.

2.3 Availability of Proposed Active Ingredient in the United States

Another loratadine brand, Alavert™ 10 mg tablet or 10 mg orally disintegrating tablets were FDA approved in December 2002. Generic formulations of Claritin® tablets and Claritin® Reditabs were approved in February 2003. The following are the approved Claritin® brand OTC products:

Table 1: Claritin® Products

NDA #	Product
19-658/S-018	Claritin Tablets OTC
20-704/S-008	Claritin RediTabs OTC
20-641/S-009	Claritin Syrup
21-891	Claritin Chewable Tablets
19-670/S-018	Claritin-D 12 Hour Tablets (discontinued) (5 mg lora/120 mg PSE)
20-470/S-016	Claritin-D 24 Hour Tablets (10 mg lora/240mg PSE)

2.4 Important Issues With Pharmacologically Related Products

Antihistamines are known for their sedative effects. Second generation antihistamines (cetirizine, fexofenadine and loratadine) cause a much lesser degree of somnolence compared to older antihistamines. Cetirizine, at recommended doses, may cause a higher incidence of somnolence when compared to fexofenadine and loratadine.

Terfenadine (withdrawn in 1998) and astemizole (discontinued 1999) are two non-sedating second generation antihistamines with similar structures that have been removed from the market due to the associated risk of causing cardiac arrhythmia, Torsades de Pointes secondary to QT prolongation at high serum concentrations. The metabolism of each drug may decrease (hence increase serum concentration) given concomitantly with certain drugs such as antifungals (e.g. ketoconazole and fluconazole), macrolides (erythromycin), antivirals and those with the potential to inhibit hepatic microsomal enzymes, particularly isozyme CYP3A4. So far, there has been no reports of the Torsades de Pointes with loratadine as the single suspect drug.

2.5 Presubmission Regulatory Activity

On September 8, 2005, a teleconference was held between the sponsor and the FDA to discuss the proposed capsule formulation, their reference listed drug, and the results of the bioequivalence study completed that compared the proposed new dosage form, Claritin Liqui-Gel® capsules and the currently marketed Claritin® tablets, 10 mg. In this study conducted, Claritin Liqui-Gels capsules were found to be bioequivalent to Claritin Tablets for both AUC and Cmax parameters of desloratadine, and AUC parameter of loratadine. However, the lower boundary of the 90% confidence interval of the ratio for the Cmax parameter for loratadine was less than 80%. The sponsor further stated, that in a previous multiple dose PK study comparing Clarinex® tablets (desloratadine 5 mg, test dose) to Claritin tablets (loratadine 10 mg, RLD), the Clarinex® 5 mg tablet was found to be bioequivalent to the Claritin 10 mg Tablet with regard to desloratadine AUC, but the lower boundary of the 90% confidence interval for the ratio for the desloratadine Cmax parameter was less than 80%. A subsequent allergy clinical studies found Clarinex® 5 mg tablet to be safe and effective for relief of allergy symptoms. The sponsor states that the Claritin® 10 mg Liqui-Gels Capsule is bioequivalent to the Claritin® 10 mg Tablet for both Cmax and AUC for desloratadine, and deliver a dose of desloratadine that is at least bioequivalent to the Clarinex® 5 mg Tablet; therefore, Claritin® Liqui- Gels Capsule 10 mg should be an effective dose for the relief of allergy symptoms. See meeting minutes of this teleconference dated September 8, 2005 in the Division File System (DFS) under PIND 63,803.

On March 15, 2006, the sponsor submitted NDA 21-952, Claritin® Liqui-Gels® capsules 10 mg under a 505(b)(1) application. The sponsor refers to the following NDAs they previously submitted:

- NDA 19-658/S-018 for complete marketing history, nonclinical information, clinical information
- NDA 20-704 for human pharmacokinetics and bioavailability
- NDA 21-993 for efficacy
- NDA 21-891 for safety update

Table 2 below lists the product approvals for the Claritin products.

Table 2: Claritin® Product Approvals

NDA #	Trade Name	Dosage Form	Strength	Rx Approval Date	OTC Approval Date	
					Allergic Rhinitis	Hives
19-658	Claritin	tablet	10 mg	4/12/93	11/27/02	11/19/03
19-670	Claritin-D 12 Hour	tablet (ER)	5 mg/ 120mg (PSE)	11/14/94	11/27/02 (discontinued)	
20-470	Claritin-D 24 Hour	tablet (ER)	10 mg/ 240mg (PSE)	8/23/96	11/27/02	
20-641	Claritin	syrup	1mg/1mL	10/10/96	11/27/02	11/19/03 (discontinued)
20-704	Claritin Reditab	orally disintegrating tablet	10 mg	12/23/96	11/27/02	11/19/03
21-891	Children's Claritin	chewable tablet	5 mg		8/26/06	

No new food effect study was conducted on this Liqui-Gel™ capsule formulation during the initial submission of this NDA; the sponsor states that the food effect of loratadine is well established and is not considered to effect clinical efficacy. In a Filing letter sent to the sponsor dated May 15, 2006, the sponsor was requested to submit additional data to support that the food effect for Claritin® Liqui-Gel™ capsule 10 mg is expected to be the same as that seen for Claritin® tablets 10 mg. The sponsor stated that subsequent to filing, a food effect study (CL2005-17) was conducted. A teleconference was held between the sponsor and the Agency on July 18, 2006 to discuss the results of this food effect study (see meeting minutes in DFS).

2.6 Other Relevant Background Information

Loratadine is marketed worldwide in over 100 countries as either prescription or OTC product. No approved formulation has ever been withdrawn from any market for safety reasons. The safety profile of loratadine is well-characterized both as a prescription and OTC product. So far, no serious unexpected adverse events have been reported with any of its formulations.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The proposed Claritin® Liqui-Gels™ capsules 10 mg is a clear blue liquid filled gelatin oval-shape capsule imprinted with a unique identifier in white ink. The 10 mg dose of loratadine is in solution in the liquid material. See Chemistry review for details.

3.2 Animal Pharmacology/Toxicology

There are no new data or toxicology information submitted with this NDA. The sponsor refers to the Nonclinical Pharmacology and Toxicology information in their previously submitted NDA 19-658. In chronic oral toxicity studies up to 12 months in rats and up to 17 months in monkeys, the targeted organs were the testes, liver and lymphocytes. Loratadine was not genotoxic, and in reproductive studies, loratadine was not teratogenic but decreased male fertility which was reversible with cessation of dosing. In carcinogenicity studies, loratadine caused an increase in hepatocellular tumors in rats and mice. The clinical significance of these tumor findings during long term use is unknown. The Pharm/Tox reviewer concludes that loratadine is a potent orally active and selective H_1 receptor antagonist, and from a preclinical standpoint, there are no safety issues that would prevent Claritin Liqui-Gels capsules from being an OTC product for children and adults. The levels of the excipients in the proposed suspension are acceptable. See Pharmacology/Toxicology review entered in DFS on 9-18-06.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data utilized in this review were the results from the sponsor's open-label, single dose, comparative, randomized, crossover bioequivalence study of one Claritin Liqui-Gels™ capsule 10 mg to one Claritin® tablet 10 mg conducted in 48 healthy adult subjects (Protocol No. CL2004-02). The OTC and previous prescription labels of the different formulations of Claritin, the proposed label, and a safety update were also utilized in this review. The sponsor also referenced their approved applications for their Claritin products: NDAs 19-658/S-018, 20-704, 21-993 and 21-891 21-993 for marketing history, nonclinical and clinical information, human pharmacokinetics and bioavailability, efficacy, and safety update.

4.2 Tables of Clinical Studies

The sponsor submitted one bioquivalence study (Protocol No. CL2004-02) to this NDA. This was an open-label, single dose, comparative, randomized, crossover bioequivalence study of one Claritin Liqui-Gels™ capsule (loratadine 10 mg) to one Claritin® tablet (loratadine 10 mg) conducted in 48 healthy adult subjects. A food effect study was also conducted in 11 healthy volunteers.

4.3 Review Strategy

One bioavailability study submitted by the sponsor comparing the pharmacokinetic profile of one 10 mg dose of Claritin Liqui-Gel™ capsule to one Claritin® tablet (loratadine 10 mg) was mainly utilized in the review of this NDA. This review covers the safety update. The Biopharmaceutics reviewer will review the relative bioavailability studies in detail.

4.4 Data Quality and Integrity

A DSI inspection was requested for study CL2004-02 and the result of the inspection is pending at the time this review was written.

4.5 Compliance with Good Clinical Practices

The sponsor states that this study was conducted in compliance with the Declaration of Helsinki and its amendments, FDA principles of Good Clinical Practice, and ICH guidelines. The study was initiated on February 1, 2005 and completed on April 4, 2005.

4.6 Financial Disclosures

The Sponsor conducted one bioequivalence study in this submission, Protocol #CL2004-02, that involved only one clinical site with one investigator and four sub-investigators. An FDA form 3454 was submitted certifying that as a sponsor of the submitted studies, it has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The sponsor also certified that each listed clinical

investigator did not disclose any proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) and that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). There were no financial disclosures that would cast doubt on the findings.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Loratadine is administered orally, its onset of action occurs within 1-3 hours, with peak effects in 8-12 hours and a duration of action greater than 24 hours. Administration with food increases absorption and systemic bioavailability (AUC) up to 40% for the syrup or tablets, and up to 48% for the rapidly disintegrating tablets; the time to peak concentrations (Tmax) is also delayed by administration with food by one hour. However, peak plasma concentrations (Cmax) are not affected by food. Loratadine is 97% protein-bound and is excreted into breast milk. It has a high first pass effect and is almost completely metabolized in the liver to the minimally active metabolite, descarboethoxyloratadine. *In vitro* studies indicate that loratadine is metabolized to descarboethoxyloratadine predominantly by CYP3A4 and to a lesser extent, by cytochrome CYP2D6. In the presence of a CYP3A4 inhibitor, loratadine is metabolized to descarboethoxyloratadine predominantly by CYP2D6. Concurrent administration of loratadine with either ketoconazole, erythromycin (both CYP3A4 inhibitors), or cimetidine (CYP2D6 and CYP3A4 inhibitor) to healthy volunteers was associated with increased plasma concentrations of loratadine. The normal mean elimination half-lives of loratadine and its metabolite are 8.4 hours (range 3-20 hours) and 28 hours, respectively. Elimination occurs through the fecal and renal routes.[2]

The sponsor submitted one bioavailability study comparing the pharmacokinetic profile of one dose of Claritin Liqui-Gel™ capsule 10 mg to one Claritin® tablet 10 mg, the reference listed drug (RLD). The sponsor did not initially submit a new food effect study on the 10 mg Claritin Liqui-Gel capsules. The sponsor states that the food effect of loratadine is well-established and it is not considered to effect clinical efficacy. However, in a filing letter sent to the sponsor, the Agency requested the Sponsor to submit additional data to support that the food effect for Claritin Liqui-Gel capsules 10 mg is expected to be the same as that seen for Claritin® tablets. Subsequent to filing the NDA, the sponsor conducted a single-dose food effect study.

Brief Summary of Study CL2004-02.

Study CL2004-02 was an open-label, single dose, comparative, randomized, crossover bioequivalence study of two dosage forms of loratadine, 10 mg Claritin® Liqui-Gel™ Capsule and 10 mg Claritin® Tablet under fasting conditions. A total of 50 healthy male and female subjects between the ages of 18 and 45 were enrolled; 48 completed the study. Personnel at the analytical laboratory were blinded to the treatment sequence.
Subjects were screened for eligibility within 14 days of receiving the first dose of study medication and those eligible reported to the study clinic at least 12 hours prior to the first dose of study medication.
Subjects received each of the following treatments (A→B or B→A) provided in Table 3.

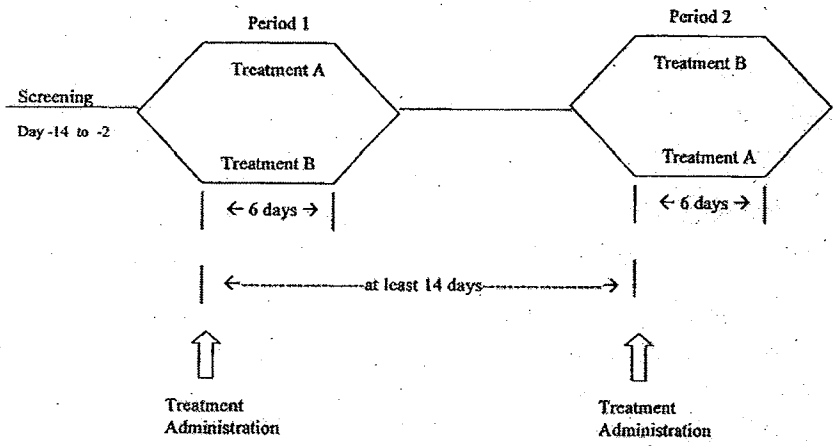
2 Clinical Pharmacology Online (http://cpip.gsm.com)

Table 3: Study Treatments

Treatment A	Treatment B
Claritin® Liqui-Gel™ Capsule 10 mg	Claritin® 10 mg Tablet

Subjects fasted for at least 10 hours before dosing and 4 hours post drug treatment. Each treatment was administered with 240 mL of room temperature water and a mouth check was performed. A washout period of 14 days separated each dosing period. A total of 26 subjects were randomly assigned to dosing sequence A→B and 24 subjects were assigned to dosing sequence B→A. Subjects were confined to the study site on the day prior to and for 120 hours (5 days) following administration of study drug for collection of pharmacokinetic blood samples and safety monitoring. Subjects who discontinued the study prematurely were replaced at the sponsor's discretion.

Figure 1: Study Design Schematic



Treatment A: One loratadine 10 mg soft gelatin capsule following a ten-hour fast.
Treatment B: One loratadine 10 mg tablet following a ten-hour fast.

Subjects were randomly assigned to one of two treatment sequences as follows:

- Sequence 1: 1 x 10 mg loratadine soft gelatin capsule → 1 x 10 mg loratadine tablet
- Sequence 2: 1 x 10 mg loratadine tablet → 1 x 10 mg loratadine soft gelatin capsule.

Following a 10-hour fast, all subjects received a single dose of each treatment during each of two study periods.

Table 4: Study Assessments and Procedures

Evaluation	Screening	Periods[a] 1 & 2						
	(Day –32 to –2)	Day –1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Informed Consent[b]	X							
Inclusion/Exclusion 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

Sponsor's table Module. 5 *p.25*

a: A washout period of at least 14 days separated the two doses of study medication.
b: Written informed consent must have been obtained prior to any study evaluations being performed.
c. CBC and differential, serum chemistry, urinalysis (including microscopic examination).
d: ECG - standard 12-lead reporting ventricular rate, PR, QRS, QT and QTc interval.
e: Seated blood pressure, respiration rate, pulse, oral body temperature screening, Day -1, prior to first blood draw each day (Days 1-6, Periods 1 and 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/predose 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.

A total of 48 subjects completed both study periods and were included in the analysis of bioequivalence; 50 subjects were enrolled, treated, and analyzed for safety. Subject no. 12 was lost to follow-up after Period 1 and subject no. 13 was discontinued from the study due to protocol violation (positive drug screen prior to Period 2). These two subjects did not have sufficient data in both periods and were not included in the PK population. No serious adverse events were reported in this study. Eight (8) subjects each reported a total of 14 adverse events, all mild in severity: headache (3), pyrexia (3), dizziness (2), pharyngolaryngeal pain (3), nasal congestion, coughing and dyspnea.

The result of the bioequivalence study is shown in the two tables below. Respective median loratadine t_{max} occurred at 1.5 and 1.0 hours after dosing of the 1 x 10 mg capsule and 1 x 10 mg tablet, respectively (ranged: 1.0 to 3.5 hours). Half-life values ranged from 1.13 to 62.73 hours, and mean half-lives were 5.09 and 5.62 hours for the test and reference treatments, respectively.

Table 5: Summary of Mean (SD) Loratadine Pharmacokinetic Parameters

	1 x 10 mg Capsule (n=50)	1 x 10 mg Tablet (n=48)
Parameter	Arithmetic Mean (SD)	
Cmax (ng/mL)	3.65 (3.80)	4.26 (4.52)
tmax (hr)[a]	1.0 (1.00-3.00)	1.00 (1.00-3.50)
AUC_T (ng.hr/mL)	11.03 (12.83)	12.29 (14.94)
AUC (ng.hr/mL)	11.63 (13.42)	12.93 (15.45)
λ_Z (Ke) (hr^{-1})	0.1363 (0.1112)	0.1234 (0.1350)
$T_{1/2}$, (hr)[b]	5.09 (4.23)	5.62 (6.51)

Sponsor's table Mod. 5, vol.1, p.38

The results of the study have shown that the 90% confidence intervals (CIs) for the geometric means test-to-reference ratios for the area under, the cure (AUC) and peak concentration (Cmax) for desloratadine were within the bioequivalence interval guidelines of 0.80-1.25; AUC: 0.9258 (0.8668, 0.9888) and Cmax: 0.9051 (0.8375, 0.9783). This bioequivalence criterion was also met for lotatadine's AUC: 0.9074 (0.8135, 1.0121). However, the lower boundary of the CI for the Cmax of loratadine fell below the bioequivalence limit of 0.80: [0.8873 (*0.7875*, 0.9996)].

Table 6: Analysis of Loratadine and Desloratadine Bioequivalence (CL2004-02)

Analyte Parameter	1 x 10 mg Claritin Liqui-Gel Capsule (Test)	1 x 10 mg Claritin Tablet (Reference)	Ratio (Test/Reference)	90% CI Lower	90% CI Upper
Loratadine					
AUC	6.9581	7.6683	0.9074	0.8135	1.0121
AUC_T	6.5545	7.1760	0.9134	0.8214	1.0156
Cmax	2.4688	2.7825	0.8873	**0.7875**	0.9996
Desloratadine					
AUC	38.9407	42.0624	0.9258	0.8668	0.9888
AUC_T	37.6661	40.7446	0.9244	0.8647	0.9883
Cmax	2.9756	3.2874	0.9051	0.8375	0.9783

Sponsor's submission Module 2 sec. 2.7.1

The sponsor subsequently performed a re-analysis of the bioequivalence data as a result of the observations from the Division of Scientific Investigations (DSI) audit of the clinical site. The re-analysis did not change the overall findings; however, the lower boundary of the 90% CI for the Cmax of loratadine remains below 0.80, 0.7847, slightly lower than the previously calculated 0.7875.

Summary of Food Effect Study

The food effect study was a single-dose, comparative, randomized, crossover bioequivalence study to evaluate the effect of food on Claritin® Liqui-Gel capsule 10 mg in 11 subjects. Each subject received the

treatments (A→B or B→A) based on his/her subject number, as assigned by the computer generated randomization code. For the fed treatment, all subjects received a standardized high fat breakfast after fasting for at least 10 hours and then fasted for 4 hours post drug treatment. All subject in the fasting group, fasted for at least 10 hours prior to dosing and then fasted for 4 hours post drug treatment. Each treatment was administered with 240 mL of room temperature water and a mouth check was performed. A washout period of 21 days separated each dosing period. See results in the table below.

Table 7: Analysis of Loratadine and Desloratadine Bioavailability Food Effect Study (CL2005-17)

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data (N = 11)				
Parameter	Fed	Fasting	% Ratio	90% CI
Loratadine				
AUC_{0-t} (ng-hr/mL)	13.45	6.08	**221.13**	(191.02, 255.99)
$AUC_{0-\infty}$ (ng-hr/mL)	14.13	6.48	**218.03**	(187.84, 253.07)
Cmax (ng/mL)	3.91	2.55	**153.06**	(113.45, 206.5)
Desloratadine				
AUC_{0-t} (ng-hr/mL)	38.10	35.99	105.87	(95.98, 116.79)
$AUC_{0-\infty}$ (ng-hr/mL)	39.66	37.33	106.24	(96.3, 117.2)
Cmax (ng/mL)	3.03	3.19	94.81	(78.69, 114.24)

- Administration with food increased the loratadine capsule Cmax by 53%, AUC_{0-t} by 121%, and $AUC_{0-\infty}$ by 118%; the change in desloratadine PK was not significant.
- Previous studies conducted with loratadine have shown that food increases its bioavailability. The results showed a doubling of the bioavailability of the parent drug under fed conditions; while normally a 30-40% increase has been shown for other Claritin® formulations.

Four (4) adverse events: dysmenorrhea (two episodes in 1patient), headache (1 patient), and menstrual disorder (1 patient) were reported during the food effect study. All four AEs occurred after the oral administration of Claritin® Liqui-Gels Capsules under fasting conditions and none after administration of the test drug under fed conditions. All of these AEs resolved and were considered not related to the test drug.

Medical Officer Comments: The clinical significance of the magnitude of food effect (which is more than double the AUC of the parent drug, loratadine) with this new Liqui-Gel formulation compared to other marketed formulations (e.g., Claritin® Tablet 10 mg) is unknown.

There are several drug-drug interactions listed in the prescribing information for Claritin[3] under the Precautions section, Drug Interactions subsection. The plasma concentrations ($AUC_{0-24\ hrs}$) of loratadine and desloratadine were increased (see below) after 10 days of coadministration of loratadine 10 mg with three other drugs in normal volunteers (N=24).

[3] Prescrition Infromation for Claritin, Physicians Desk Reference (PDR) 2003.

	Loratadine	Descarboethoxyloratadine
Erythromycin (500 mg q8h)	+40%	+46%
Cimetidine (300 mg qid)	+103%	+6%
Ketoconazole (200 mg q12 h)	+307%	+73%

It is further stated that there were no clinically relevant changes in the safety profile of loratadine, as assessed by electrocardiographic parameters, clinical laboratory tests, vital signs and adverse events. There were ***no significant*** *effects on QTc intervals, and no reports of sedation or syncope. This Medical Officer believes that doubling AUC of loratadine will unlikely cause* ***significant*** *serious adverse events. However, for adverse events commonly experienced when taking this product such as dry mouth, headache, and most importantly, somnolence, a sample size of 24 volunteers is not adequate to further assess the most common adverse event profile of loratadine when the AUC is doubled or tripled.*

It is possible that because the AUC of the parent drug, patients might experience an increase in adverse events such as headache, dry mouth, and most importantly, drowsiness even at the recommended dose of 10 mg. Therefore patients should be informed that taking this formulation with food may cause drowsiness; this should be communicated in the product's label. Alternatively, the sponsor should provide data that characterize the safety and adverse event profile loratadine if the AUC is doubled.

5.2 Pharmacodynamics

There are no new pharmacodynamic data submitted with this NDA.

5.3 Exposure-Response Relationships

There is no new exposure-response relationship data submitted with this NDA.

6 INTEGRATED REVIEW OF EFFICACY

There were no efficacy trials conducted for this NDA except for a PK evaluation. Reference is made by the sponsor to their previously submitted NDA 19-658 (Claritin® 10 mg tablets Rx-to-OTC switch application) for efficacy information. Efficacy of this product is extrapolated based on PK data from the single-dose relative bioavailability study (CL2004-02) assessing the proposed Claritin® Liqui-Gel capsule 10 mg and the currently marketed Claritin® tablet 10 mg (RLD). The adequacy of relative bioavailability studies will be reviewed by the Office of Clinical Pharmacology (OCP).

7 INTEGRATED REVIEW OF SAFETY

Safety data reviewed for this NDA includes safety information being referenced from the sponsor's previously submitted NDA 19-658 (Claritin® 10 mg tablets Rx-to-OTC switch application) and the safety data submitted to the recently approved NDA 21-891 (Claritin® chewable tablets 5 mg). In addition, the following were submitted to this application:

- Safety data from bioequivalence study CL2004-02

- Post Marketing Safety Surveillance (adverse event) data
  - Schering-Plough internal adverse event database from October 1, 2005 to June 28, 2006
  - World Health Organization (WHO) database from October 1, 2005 to February 2, 2006
- Toxic Exposure Surveillance System (TESS) database from the American Association of Poison Control Centers from December 1, 2005 to May 31, 2006
- Worldwide human and pre-clinical peer-reviewed literature October 1, 2005 to July 14, 2006

7.1 Methods and Findings

All of the subjects in the PK study CL2004-02 conducted by the sponsor were healthy adults. All 50 subjects received at least one dose of study drug in Study CL2004-02, and were analyzed for safety. Safety 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), physical examinations, and 12-lead ECG results. Physical examination was conducted at screening and at the end of the study, see Study Assessments and Procedures in table 4.

7.1.1 Deaths

There were no reported deaths in this study.

7.1.2 Other Serious Adverse Events

There were no serious adverse events reported in this study.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Two of the 48 subjects (12 and 13) originally enrolled did not complete the study. Subject no.12 was lost to follow-up and subject no.13 was discontinued from the study. Subject no.12 received a 10 mg loratadine capsule during Period 1, but did not return to the clinic for Period 2 and was considered lost to follow-up. Subject no. 13 had a positive urine drug screen at check-in to the clinic for Period 2 and was discontinued for a protocol violation. Subjects 112 and 113 were then enrolled to replace Subjects 012 and 013, respectively. The replacement subjects were assigned to the same treatment sequence as the subjects they replaced. Thus, 48 subjects were planned; a total of 50 subjects were enrolled, treated, and analyzed for safety; 48 subjects completed the study and were included in the analysis of bioequivalence.

7.1.3.2 Adverse events associated with dropouts

There were no subjects who dropped out due to an adverse event.

7.1.3.3 Other significant adverse events

There were no other significant adverse events.

7.1.4 Other Search Strategies

This section is not applicable.

7.1.5 Common Adverse Events

Historically, the most common adverse events associated with the use of loratadine include the following:

(In patients 12 years and older)

- Headache
- Somnolence
- Fatigue
- Dry mouth, nose and throat

(In patients 6 to 12 years old)

- Nervousness (restlessness)
- Wheezing
- Fatigue
- Hyperkinesia
- Abdominal Pain

In adults, somnolence (drowsiness), headache, and sinus tachycardia have been reported with doses greater than 10 mg (doses of 40-180 mg) with loratadine tablet formulation. Extrapyramidal signs and palpitations have been reported in children with doses greater than 10 mg of Claritin syrup.[4]

In study CL2004-02, the most commonly adverse events reported were headache (3/50, 6%), pyrexia (3/50, 6%), and pharyngopharyngeal pain(3/50, 6%). The most commonly reported treatment-emergent adverse events after administration of loratadine gelatin capsules (test drug) were headache and pyrexia.

7.1.5.1 Eliciting adverse events data in the development program

At each visit after the subjects signs the informed consent, the Investigator inquired about adverse events (AEs) and intercurrent illnesses during the visit and since the last visit. Subjects were questioned for evidence of AEs and the questioning of subjects with regard to the possible occurrence of AEs was generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs was not to be solicited from subjects.

AEs were monitored throughout the study until resolution or stabilization and were described in terms of seriousness (serious or non-serious), severity (mild, moderate, severe or life-threatening) and relationship (unlikely, possible or probably related) to treatment.

[4] Physicians Desk Reference (PDR), 2003 edition.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The adverse event categorization and preferred terms used in the study were appropriate.

7.1.5.3 Incidence of common adverse events

The most commonly reported adverse events for both treatments in the CL2004-02 trial were headache (3/50, 6%), pyrexia (3/50, 6%) and pharyngolaryngeal pain (3/50, 6 %). A total of 8 (16%) subjects experienced a total of 10 adverse events (AEs): 6 (12%) subjects in the Claritin® Liqui-gel *capsule* group and 4 (8.3%) subjects in the Claritin® *tablet* group. Two subjects (005 and 113) experienced headache after receiving loratadine capsules, and dizziness after receiving loratadine tablets.

The most commonly reported treatment-emergent adverse events after administration of Claritin® Liqui-Gel capsule (test drug) were headache (3/50, 6%) and pyrexia (3/50, 6%). The most commonly reported treatment-emergent adverse event after administration of Claritin® tablets was dizziness (2/48, 4.2%).

7.1.5.4 Common adverse event tables

Table 8 below lists the number and percentage of subjects with adverse events by treatment group and system organ class from Study CL2004-02.

Table 8: Incidence of Treatment-Emergent Adverse Events (CL2004-02)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects		
	(Test) Capsules N=50	(Reference) Tablets N=48	Overall N=50
Number of Subjects with an AE	**6 (12.0)**	**4 (8.3)**	**8 (16.0)***
Total AEs	**9**	**4**	**13**
General Disorders and Administration Site Conditions	3 (6.0)	0	3 (6.0)
Pyrexia	3 (6.0)	0	3 (6.0)
Nervous System Disorders	3 (6.0)	2 (4.2)	5 (10.0)
Dizziness*	0	2 (4.2)	2 (4.0)
Headache*	3 (6.0)	0	3 (6.0)
Respiratory, Thoracic, and Mediastinal Disorders	3 (6.0)	2 (4.2)	5 (10.0)
Cough	1 (2.0)	0	1 (2.0)
Dyspnea	1 (2.0)	0	1 (2.0)
Nasal Congestion	0	1 (2.1)	1 (2.0)
Pharyngolaryngeal Pain	2 (4.0)	1 (2.1)	3 (6.0)

Adapted from the sponsor's table

* Two subjects (005 and 113) experienced headache after receiving loratadine capsules and dizziness after receiving loratadine tablets.

7.1.5.5 Identifying common and drug-related adverse events

The AEs considered possibly or probably related to treatment were headache, reported by 2/50, 4% subjects (036 and 113) after administration of Claritin® Liqui-Gel capsule; and dizziness reported by 2/48 (4%) subjects (005 and 113) after administration of Claritin® tablets. These AEs are consistent with the known effects of loratadine.

7.1.5.6 Additional analyses and explorations

There were no additional analyses and explorations performed by the sponsor.

7.1.6 Less Common Adverse Events

There are no significant less common adverse events in the study conducted. In addition, the number of subjects in the study is too small to assess the incidence of the less common adverse events.

7.1.7 Laboratory Findings

Mean values for serum chemistry, hematology, and urinalysis parameters remained within normal range at every time point during the study. There were no detected clinically meaningful treatment-related trends. Any abnormal laboratory values reported during this study were considered not clinically significant, and none were associated with an AE. The most common abnormality was elevated cholesterol, with 34% of the subjects entering the study with values above the reference range.

7.1.7.1 Overview of laboratory testing in the development program

Laboratory tests were performed at Screening, Day-1 of each period and after 120 hours post-dose blood draw in Period 2 only (see table 4). Clinical laboratory tests included:

- CBC with differential 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)

- Urinalysis including microscopic examination.

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

There was no control group in the study conducted; therefore, drug-control comparisons were not performed.

7.1.7.3 Standard analyses and explorations of laboratory data

This section is not applicable.

7.1.7.4 Additional analyses and explorations

This section is not applicable.

7.1.7.5 Special assessments

This section is not applicable.

7.1.8 Vital Signs

The sponsor measured the following vital signs during the screening period: blood pressure, pulse rate, respiratory rate, and temperature. Mean vital signs values were within normal ranges throughout the study. While no clinically significant vital signs results were reported, 3 subjects did experience AEs of pyrexia (unlikely related to loratadine administration) during the study which resolved after one or two days of treatment with acetaminophen.

7.1.9 Electrocardiograms (ECGs)

No clinically significant electrocardiogram findings were reported for any subjects at screening or at the end of the study assessment. 12-lead ECGs were recorded at 25 mm/s and included results for ventricular rate, PR, QRS, QT, and QTc intervals.

7.1.10 Immunogenicity

There was no immunogenic evaluation conducted in this submission; no known immunogenicity issues are related to loratadine.

7.1.11 Human Carcinogenicity

No new animal or toxicology studies were submitted with this NDA. References have been made to its toxicological profile in NDA 19-658. In carcinogenicity studies, loratadine caused an increase in

hepatocellular tumors in rats and mice. The clinical significance of these tumor findings during long term use is unknown. See Pharm/Tox review.

7.1.12 Special Safety Studies

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

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Loratadine has no known withdrawal phenomena and/or abuse potential and is not regulated under the Controlled Substance Act. It is not likely to present a substantial risk for medical abuse, lead to addiction or misused for illegal purposes.

7.1.14 Human Reproduction and Pregnancy Data

This application has no new information regarding pregnant women. Loratadine is currently listed as Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women. Loratadine should be used during pregnancy only if clearly indicated.

7.1.15 Assessment of Effect on Growth

No information was submitted regarding the effect of loratadine on growth. Loratadine is not indicated in children <2 years old.

7.1.16 Overdose Experience

In adults, somnolence, tachycardia, and headache have been reported with overdoses greater than 10 mg with the tablet formulation (40-180 mg). Extrapyramidal signs and palpitations have been reported in children with overdoses of >10 mg of Claritin syrup. In the event of overdosage, general symptomatic and supportive measures should be instituted promptly and maintained for as long as necessary.[5]

Toxic Exposure Surveillance System (TESS) Database

Data from the TESS, which is compiled by the American Association of Poison Control Centers (AAPCC) from December 1, 2005 to May 31, 2006 were reviewed for exposures to loratadine containing products. There were over 3,300 exposures to loratadine reported to a poison control center, > 2/3 these exposures included exposure to loratadine only. Majority of exposures (>80% cases) were unintentional as expected, while a smaller percentage were due to adverse drug reactions or intentional exposures. More than 90% remained asymptomatic or had minimal/minor effects; approximately 2% (67) of all patients became critically ill and required ICU admission, and approximately 2.5% (86) required noncritical care bed or a psychiatric in-patient facility. Those admitted to a critical care setting ingested a higher number of concomitant medications.

5 Prescribing Information for Claritin, PDR 2003 edition.

There was one reported death which resulted from a suspected suicide attempt using multiple drugs by a 44 year old female. Details for this case are scant, but indicate that she underwent multiple invasive support procedures and experienced seizures as a result of her overdose.
Accidental or intentional overdoses with loratadine generally do not require treatment or hospitalization and result in a good clinical outcome. The above data presented support the continued OTC use of loratadine.

7.1.17 Postmarketing Experience

Loratadine (Claritin®) has been marketed with a well-characterized safety profile in the United States since its approval for prescription use in April 12, 1993 and its OTC switch since November 27, 2002. An extensive safety database exists for loratadine postmarketing experience.

The sponsor refers to the comprehensive review of all available recent safety data completed for all loratadine-only products submitted under NDA 21-891 (Claritin® chewable tablets 5 mg). The postmarketing data and review of the literature submitted under NDA 21-891 did not reveal any new safety concerns for the OTC marketing of loratadine.[6] This application was approved on August 26, 2006 and the following safety information was reviewed:

- Sponsor-received adverse events for the period November 27, 2004-November 26, 2005
- Update of the FDA Adverse Event Reporting System (AERS) database for the period November 1, 2003-January 31, 2006.
- Literature update for loratadine for the period November 1, 2003-December 31, 2005.

In addition to the above safety information referenced, postmarketing data submitted to this NDA come from the following sources:

- Post Marketing Safety Surveillance (adverse event) data
  - Schering-Plough internal adverse event database from October 1, 2005 to June 28, 2006
  - World Health Organization (WHO) database from October 1, 2005 to February 2, 2006
- Toxic Exposure Surveillance System (TESS) database from the American Association of Poison Control Centers from December 1, 2005 to May 31, 2006
- Worldwide human and pre-clinical peer-reviewed literature October 1, 2005 to July 14, 2006 (The literature review can be found in section 8.6).

During the reporting period, over ——— doses of loratadine were distributed worldwide. b(4)

Sponsor's Database

This safety update received on August 9, 2006 contains a worldwide summary of all AE data reported to Schering-Plough (SP) from October 1, 2005 to June 28, 2006. Data were obtained by searching the sponsor's database for adverse events occurring temporally with the use of loratadine-only products (when loratadine was considered to be a suspect or co-suspect drug) from worldwide sources during the reporting period. The sponsor currently markets the following single ingredient loratadine formulations in the United States: Claritin®24 hour Allergy Tablets (10 mg loratadine), Claritin® Hives Relief Tablets

[6] See Clinical Review of NDA 21-891 by Dr. Steven Osborne entered in DFS on 3-30-06.

(10 mg loratadine), Claritin® RediTabs Tablets (10 mg loratadine orally disintegrating tablets), and Children's Claritin® Allergy Oral Solution (5mg loratadine/5ml).

During the above reporting period, more than 3,000 AEs (98 serious and 3,141 non-serious) from more than 2,300 total worldwide cases where loratadine was considered to be a suspect or co-suspect drug were identified in the database. One death was reported from the U.K. during this period. This was a terminally ill man with rapid progression of lung cancer with metastasis who was receiving Claritin Allergy Syrup to reduce fluid secretions. He experienced a cough every time he took the syrup, concomitant medications were unknown and were reported to change quickly because of the rapid progression of his disease. It was unlikely that the product was related to disease progression inevitable.

For all Schering-Plough loratadine worldwide dosage forms, a combined 98 serious adverse events from 42 serious cases in which loratadine was considered a suspect or co-suspect drug were identified in the AE database during the reporting period. Serious cases were less than 2% of the total cases received during the reporting period.

The most common system organ class (SOCs) for serious AEs for all dosage forms included Nervous System Disorders, Psychiatric Disorders and Skin and Subcutaneous tissue disorders. The tablet, with the highest number of doses distributed, had 71 serious AEs while the syrup/oral solution had 19 serious AEs, and the orally disintegrating tablets had 8 serious AEs. See the Appendix section of this review for the tabulated serious adverse events for each dosage form.

In addition to the common SOCs described above, the tablet formulation also had gastrointestinal (GI bleeding) serious AEs case reports summarized below:

- A 92 y/o male on allopurinol, olmesartan and amlodipine. Claritin Tablets therapy was initiated for itchy skin; he then noted melena and decreased platelet count. Patient was treated, and rechallenged with Claritin after 3 months, decreased platelet count recurred. The reporter ascribed the decreased platelet count to Claritin.
- A 61-year-old male who reported previous bleeding from aspirin ingestion took Claritin Tablets for 5 days; no concomitant medications reported. He then had abdominal pain and two episodes of diarrhea with bright red blood. Claritin was discontinued and did not return the product for evaluation. No further information was provided in the report.
- A 51-year-old male reported blood in his stool 4 months after taking Claritin Tablets; this resolved after discontinuing the tablet. No other information provided.

The last two reports of GI bleeding were not confirmed by a health care professional; neither patient sought medical care. More information is needed to assess if there is a trend or signal that suggests the exacerbation or predisposition of gastrointestinal bleeding with loratadine use.

Below is a list of other reported serious adverse events:

- Suicide gesture in a 24 y/o female who took unknown amount of Claritin tablets with two other cold/sinus medications. No other information was provided.
- A rise in blood pressure (systolic >200mmHg) in a female after taking Claritin Tablets and higher than the therapeutic dose of naproxen for arthritis pain. Patient was on medications for hypertension,

hyperlipidemia, and thyroid disorder. Naproxen and Claritin Tablets were discontinued; blood pressure normalized. Schering-Plough considered naproxen to be a co-suspect in the event.

- Angioneurotic edema and anaphylaxis in a 67 y/o female after taking Claritin Tablets and a pseudoephedrine product. Skin tests with sympathomimetic agents and oral challenge tests with increasing doses of loratadine did not show a positive allergic response. The cause of the reaction is unknown and the event resolved.
- Several reports of allergic reactions, rash, uricaria and hepatic dysfunction in patients taking multiple medications or having chronic disease states such as Chikungunya disease. One case of hepatitis and increased eosinophilia count reported in a 48 y/o male possibly related to Claritin.
- Erythema multiforme secondary to a drug eruption, loratadine, viral infection or brown tussock moth toxin. The event resolved; no other information was provided.
- Eye movement disorder and asthenopia (eye strain) after taking Claritin Tablets and Lexapro in a 42 y/o female with depression, anxiety, GERD and hyperlipidemia. Lexapro and Claritin were discontinued and the events resolved. Symptoms returned after restarting Lexapro. SP considered Lexapro to be a co-suspect for the event.
- Thrombocytopenia in an 81 y/o male with hypertension, deep vein thrombosis (DVT) and chronic renal failure requiring dialysis. The patient was on multiple medications, including loratadine tablets. Claritin was considered to be doubtfully related to the event.
- Hallucinations: 2 cases. An 83 y/o female after receiving Claritin Oral Solution for a rash, no additional information provided. A 2 y/o female who took one dose of Claritin oral solution for sneezing and rhinorrhea. The child's mother reported that her daughter experienced "psychotic episodes" in which she was hysterical and inconsolable as well as hallucinating. A second dose was given and the child experienced the same events.
- New onset seizure-like activity in an 11 y/o male after 5 hours ingesting Claritin RediTabs. The event reappeared after the second dose of Claritin. Underlying cause was not determined; patient recovered without sequalae.
- New onset Type I diabetes mellitus (DM) in a 31 y/o five days after taking Claritin RediTabs; patient has a family history of DM. Her HbA1c was 9.5 which implies that her blood sugar has been elevated the preceding months.
- Panic attack with agitation and left sided numbness of the face and arm in a 34 y/o female who concomitantly ingested Claritin RediTabs and Ativan. The event resolved within 3 hours.
- Two cases of seizure after taking Claritin Oral Solution:
    - A 6 y/o male developed seizure 8 hrs. after receiving 2 tsp of Claritin Oral Solution for rhinorrhea, sneezing and nasal congestion. Diagnostic tests did not reveal an underlying cause. Claritin was discontinued.
    - An 8 y/o male had a seizure activity 14 hours after receiving 2 tsp of Claritin Oral Solution; no other medications were taken. CT scan was normal; no other information was available for this case.

Medical Officer Comments: Thrombocytopenia, hepatitis, erythema multiforme, seizures, and agitation have been previously reported with the use of loratadine (see Claritin prescription information).
The majority of the remaining serious cases for Claritin Allergy tablets were reported in patients with multiple, chronic co-morbid conditions.

For the non-serious adverse events reported for Claritin for all dosage forms, the most frequently reported AEs include lack of acceptable product efficacy reported by consumer, worsening of allergic symptoms, fatigue, headache, cough, epistaxis, rash and pruritus. Some of these events may be considered extensions of the disease states for which the product is being used. Lack of efficacy have also been reported in a certain percentage of patients. It is reported that in more than 3 years that Claritin products have been marketed as OTC products, the lack of efficacy reports have remained consistent and average between 40-50% of all reported AEs and the data from these reporting periods are similar.

Other common AEs associated with certain system organ class (SOC) are:

- Injury, Nervous System Disorder, and Skin and Subcutaneous disorders: fatigue and/or malaise, headache, cough, epistaxis, rash and pruritis.
- Gastrointestinal disorders: abdominal pain, nausea, and diarrhea
- Psychiatric Disorders: insomnia, somnolence, and jitteriness (all dose forms), nightmares and behavior changes such as crying, agitation and anxiety in children (for oral solution)

Overdose and misuse of loratadine products was also one of the most commonly reported AEs for the Injury system organ class for all dosage forms worldwide. As previously reported (quarterly PSUR for NDAs 19-658, 20-641 and 20-704, 2002-2005) the majority of adult and pediatric overdose, either intentional or accidental, were not symptomatic and did not require medical treatment. There was also a higher percentage of reported overdoses with the oral solution when compared to the other dosage forms. A review of the post-marketing data suggest that overdose of loratadine in children is frequently related to more than one care-giver each administering a dose of the product to a child, recognizing the overdose situation and subsequently inquiring about the safety of the overdose.

Medical Officer Comments: Overall, the postmarketing experience with the already approved loratadine did not identify any new serious, unusual or specific safety concern or significant trend suggestive of a new safety issue associated with exposure to loratadine from the previous safety update.

World Health Organization (WHO) Database

The sponsor evaluated the worldwide post-marketing data for all dosage forms of a single-active drug product containing loratadine based upon the records of the post-marketing adverse events as documented in the WHO database from October 1, 2005 to February 2, 2006. There were 90 adverse events involving 37 cases reported to WHO (over 17 System-Organ Classes). No deaths or serious outcome events were reported. The most commonly occurring AEs are tachycardia (5) and convulsions (4).

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

7.2.1.1 Study type and design/patient enumeration

The sponsor submitted bioequivalence study (CL2004-02) to support this application. This was an open-label, single dose, comparative, randomized, crossover bioequivalence study of two dosage forms of loratadine, 10 mg Claritin Liqui-Gel™ Capsule and 10 mg Claritin® Tablet. A total of 50 healthy male and female subjects between the ages of 18 and 45 were enrolled; 48 completed both treatment periods of the study. Personnel at the analytical laboratory were blinded to the treatment sequence.

7.2.1.2 Demographics

Fifty subjects enrolled in the study, 26 females (52.0%) and 24 males (48.0%). The majority of subjects were Hispanic (42/50, 84.0%), followed by African American (6/50, 12%) then Caucasian (2/50, 4%). The overall mean (SD) age of subjects in the study was 31.8 (range: 18 to 45 years) and the overall mean (SD) BMI for subjects was 24.4 (range: 21-28). Below is a demographic summary for all subjects for Study CL2004-02.

Table 9: Demographics (CL2004-02)

Characteristic	Sequence 1 (n=26)	Sequence 2 (n=24)	Overall (n=50)
Gender			
Female	14 (53.8%)	12 (50.0%)	26 (52.0%)
Male	12 (46.2%)	12 (50.0%)	24 (48.0%)
Ethnic Group			
Hispanic	20 (76.9%)	22 (91.7%)	42 (84.0%)
African American	4 (15.4%)	2 (8.3%)	6 (12.0%)
Caucasian	2 (7.7%)	0 (0.0%)	2 (4.0%)
Age (years)			
Mean (SD)	31.7 (8.24)	32.0 (8.25)	31.8 (8.16)
Median	30.0	30.5	30.0
Minimum-Maximum	18-45	19-45	18-45
Height (cm)			
Mean (SD)	166.2 (9.17)	163.8 (8.47)	165.1 (8.83)
Median	162.6	162.6	162.6
Minimum-Maximum	155-185	150-183	150-185
Weight (kg)			
Mean (SD)	66.8 (8.81)	66.1 (9.96)	66.5 (9.29)
Median	65.5	66.2	65.9
Minimum-Maximum	53-95	48-83	48-95
BMI			
Mean (SD)	24.1 (1.60)	24.5 (2.24)	24.3 (1.92)
Median	24.0	24.8	24.4
Minimum-Maximum	22-28	21-28	21-28

Medical Officer Comments: The demographics of this study population is not reflective of the overall U.S. population but is acceptable for a PK evaluation.

7.2.1.3 Extent of exposure (dose/duration)

Study medication was administered to all 50 enrolled subjects, 48 subjects (96%) completed the study.

- 26 subjects were assigned to receive the study medication according to Sequence 1
  - loratadine 1 x 10 mg liqui-gel capsule in Period 1 followed by 1 x loratadine 10 mg tablet in Period 2
- 24 subjects were assigned to receive the study medication according to Sequence 2
  - loratadine 1 x 10 mg tablet in Period 1 followed by loratadine 10 mg liqui-gel capsule in Period 2

Subjects 012 and 013 (both in Sequence 1) discontinued from the study and received only one 10 mg dose of study drug (soft gelatin capsules). See section 7.1.3.1 of this review.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Postmarketing safety data is discussed in section 7.1.17 and safety data from published literature is discussed in section 8.6 of this review.

7.2.3 Adequacy of Overall Clinical Experience

Loratadine has been proven safe and effective in the U.S. for over 13 years, and has been available for OTC use for almost four years now. Therefore, there is an adequate clinical experience with loratadine from both prescription and OTC use.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There are no new animal studies submitted with this NDA.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing which included vital signs, physical exam, EKG, urinalysis and laboratory evaluation including hematology and chemistry were adequate for this pharmacokinetic study.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new information on metabolic, clearance and interaction was submitted with this 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

This section is not applicable.

7.2.8 Assessment of Quality and Completeness of Data

A consult to the Division of Scientific Investigation was requested and the result of their evaluation is still pending at the time this review was written.

7.2.9 Additional Submissions, Including Safety Update

A Safety Update was submitted that covers the period from October 2005 to July 2006, see (Postmarketing) section 7.1.17 of this review. There are no new significant safety issues identified in this reporting period.

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

Not applicable.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

No pooled data analyses were done by the sponsor. The sponsor submitted one PK study comparing Claritin Liqui-gel capsule 10 mg to Claritin tablet 10 mg.

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

No explorations for predictive factors were done by the sponsor for this NDA.

7.4.3 Causality Determination

This section is not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor is seeking for the already approved OTC indications and dosing regimen for loratadine. The proposed indication will be for the temporary relief of symptoms of runny nose, sneezing, itchy and watery eyes, 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 following are the product's uses and directions for use:

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

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

Directions:

- Adults and children 6 years and over: 1 capsule daily; not more than 1 capsule in 24 hours
- Children under 6 years of age: ask a doctor
- Consumers with liver or kidney disease: ask a doctor

8.2 Drug-Drug Interactions

No new drug-drug interactions were evaluated in this submission. Increased concentrations ($AUC_{0\text{-}24\ hours}$) of loratadine and/or descarboethoxyloratadine were observed following coadministration of erythromycin, cimetidine, ketoconazole in adult volunteers. There were no clinically relevant changes in the safety profile of loratadine as assessed by ECG parameters, clinical laboratory tests, vital signs and adverse events. There were no reported significant effects on QTc intervals and no reports of sedation or syncope.[7]

8.3 Special Populations

No new information regarding other patient populations was submitted with this NDA. The pharmacokinetic studies did not perform any analyses by ethnic group. The subjects predominantly comprised of Hispanic (84.0%), followed by African American (12%) then Caucasian (4%). The prescribing information for loratadinereflects the following information regarding special population:

Pregnancy
Loratadine is classified as pregnancy category B. Animal studies have not demonstrated a risk to the fetus; however, there are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only when the potential benefits outweigh the risks to the fetus.

7 Prescribing Information for Claritin, Physicians Desk Reference (PDR), 2003 ed.

Medical Officer Comments: There was previously a concern regarding a reported signal of an increased risk of hypospadias among male infants born to women who had taken loratadine during pregnancy by the Swedish Medical Birth Registry in 2001-2002. Investigations into this signal have been undertaken since this first report and none of these follow up studies have suggested a possible teratogenic effect of loratadine. This is further discussed in section 8.6 of this review.

Nursing Mothers
Loratadine and its metabolite pass easily into breast milk. Caution should be exercised when loratadine is administered to a nursing mother, taking into account the importance of the drug to the mother.

Renal Impairment
The AUC and Cmax of loratadine and its metabolite are elevated in patients with chronic renal impairment (creatinine clearance $\leq$ 30 mL/min). Loratadine should be used cautiously in those with renal failure or impairment. The recommended starting dose in these patients is 10 mg every other day.

Hepatic Impairment
The AUC and Cmax of loratadine were double in patients with chronic alcoholic liver disease. Loratadine should be used cautiously in those with hepatic disease. The recommended starting dose in patients with liver failure is 10 mg every other day.

The current loratadine OTC label Warnings section include:

- *Ask a doctor before use if with liver or kidney disease. Your doctor should determine if you need a different dose.*
- *If pregnant or breastfeeding, ask a health professional before use.*

8.4 Pediatrics

Pediatric patients were not evaluated in this NDA. No data were submitted by the sponsor regarding this population for the proposed indication. Loratadine is indicated for use in children 6 years of age and older. The safety and efficacy of loratadine has not been established in children under two years of age.

The sponsor is requesting a waiver for children less than 6 years of age; this request should be granted. Loratadine is already labeled for use in children two years and older, and there are other currently marketed loratadine formulations that are appropriate for this age group such as the syrup and the recently approved chewable formulation. Additional studies using the proposed capsule formulation will not offer meaningful therapeutic benefit over the existing loratadine formulations.

8.5 Advisory Committee Meeting

This section is not applicable for this submission.

8.6 Literature Review

The sponsor submitted a safety update report of worldwide human and pre-clinical peer-reviewed literature related to the safety of loratadine from January 2006 to July 2006. The sponsor also refers to the safety information submitted to their recently approved NDA 21-891 (Claritin chewable 5 mg tablet), see the Medical Officer review for this NDA entered in DFS.

There were eight publications of clinical studies or case reports during the reporting period that provided information regarding the safety of loratadine. These publications presented the results of exposures to loratadine in a total of 72 subjects (in three clinical trials) and five case reports. There were no new published pre-clinical studies relevant to the safety of loratadine identified in the literature during the reporting period.

In the three clinical trials conducted, loratadine was well-tolerated and the adverse events reported were consistent with the known adverse event profile for loratadine which were headache, fatigue, dry mucous membranes of eyes, mouth and throat.

There was a concern regarding the a reported signal of a two-fold (vs. general population) increased risk of hypospadias among male infants born to women who while pregnant had taken loratadine by the Swedish Medical Birth Registry in 2001-2002. Investigations into this signal have been undertaken since this first report and none of these follow up studies have suggested a possible teratogenic effect of loratadine.

Recently, Schering-Plough commissioned a larger study of the Danish birth registry and the entire Danish population (5.2 million) was evaluated. Data were obtained from two sources (Danish Medical Birth Registry and the Hospital Discharge Registry) for the period of January 1, 1995 to December 31, 2004. Preliminary results identified 1575 hypospadias cases and, compared to a local control group, revealed a relative risk estimate for loratadine exposure of 0.6 (95% confidence interval: 0.1-1.5) and for other antihistamines 1.3 (95% confidence interval 0.9-1.9). The local control group consisted of 30% of the total population. The fact that the loratadine exposed group had a lower point estimate of relative risk than the other antihistamine-exposed group is supportive of a lack of risk of hypospadias following maternal exposure to loratadine. Neither the loratadine nor other antihistamine exposed groups had confidence intervals that encompassed a two-fold risk which is the most important finding of the study. The sponsor states that these results are preliminary and will report the final results to FDA as they become available.

Medical Officer Comments: A worldwide review of the published literature during the reporting period of January 2006 to July 14, 2006, including adverse reactions from case reports, prospective and retrospective clinical studies using loratadine did not reveal any new serious, unusual, significant or new safety concerns associated with the OTC use of loratadine. The available literature continue to support the safety of loratadine as an OTC product.

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan recommended for this NDA.

8.8 Other Relevant Materials

There are no other relevant materials submitted for the review.

9 OVERALL ASSESSMENT

9.1 Conclusions

The results of the bioequivalence study CL2002-02 which compared a single dose of each 10 mg of Claritin® Liqui-Gels™ Capsule to Claritin® tablet under fasting conditions have shown that the 90% confidence interval for the geometric means test-to-reference ratios for the AUC and Cmax for the metabolite of loratadine, desloratadine, were within the bioequivalence interval guidelines of 0.80-1.25. This bioequivalence criterion was also met for the AUC of the parent drug loratadine; however, the lower boundary of the CI for the Cmax of loratadine fell below the bioequivalence limit of 0.80: [0.8873 (**0.7847**, 0.9996)]. The adequacy of relative bioavailability study will be reviewed by the Office of Clinical Pharmacology (OCP).

In addition, a food effect study conducted by the sponsor have shown that when the proposed product was administered with food, loratadine Cmax was increased by 53%, AUC_{0-t} by 121%, and $AUC_{0-\infty}$ by 118%; the change in desloratadine PK was not significant. Historically, a 30-40% increase in loratadine AUC has been shown for other Claritin® formulations. The clinical significance of the magnitude of this food effect with this new Liqui-Gel formulation is unknown. There is a possibility that due to the increased bioavailability of this drug, patients might experience an increase in adverse events, specifically somnolence when taking this product even at the recommended dose of 10 mg. Therefore, for safety reasons, patients should be informed that drowsiness may occur when this formulation is taken with food. This should be communicated to patients through the label.

Both Claritin treatments were well-tolerated in the PK studies conducted and there were a few adverse events reported which are consistent with the already known adverse event profile for loratadine. There were neither deaths nor serious adverse events reported. The clinical experience with the already approved loratadine for OTC use, literature review, and the adverse event data from the studies conducted by the sponsor do not identify any new safety concerns. The safety profile of loratadine is well-characterized as an OTC drug and so far, no serious unexpected adverse events have been reported with any of its formulations. From a clinical safety standpoint, this application should be approved.

9.2 Recommendation on Regulatory Action

The proposed loratadine (Claritin® Liqui-Gels™) capsules 10 mg for the indication of 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 has an acceptable safety profile for OTC marketing. Therefore, this application should be approved from a clinical safety standpoint. Final approvability depends on the adequacy of the bioavailability study CL2004-02 conducted by the sponsor, which the reviewer in the Clinical Pharmacology team is reviewing, and the DSI inspection. In addition, the sponsor should incorporate the reviewing team's labeling recommendations for this product.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No special risk management activities are recommended for this NDA.

9.3.2 Required Phase 4 Commitments

No required phase 4 commitments are recommended.

9.3.3 Other Phase 4 Requests

No other phase 4 requests are recommended.

9.4 Labeling Review

Below are the sponsor's proposed labels and product insert. A member of the Interdisciplinary Scientist (IDS) group in the Division of Nonprescription Regulation Development (DNRD) will be reviewing the proposed label. The sponsor is proposing a label very similar to the already approved Claritin Tablets label (including the Drug Facts, Uses, Warnings, and Directions). The sponsor incorporated all the important warnings for loratadine.

However, the clinical significance of the magnitude of food effect (which is more than double the AUC of the parent drug, loratadine) with this new Liqui-Gel capsule formulation compared to other marketed Claritin® formulations (e.g., Claritin® Tablet 10 mg) is unknown. There is a possibility that due to the increased bioavailability of this drug, patients might experience an increase in adverse events, specifically somnolence (drowsiness) when taking this product even at the recommended dose of 10 mg. Therefore, it should be communicated in the label that taking this formulation with food may cause drowsiness.
The Directions section of the "Drug Facts" labeling should be revised to include the following bulleted statement:

- *Take on an empty stomach. Taking with food may cause drowsiness.*

In addition, the sponsor should delete the phrase [redacted] in the carton label because there is no data to support this claim and is purely promotional in nature. Studies to support this claim will be difficult to interpret as well. b(4)

The proposed label is otherwise acceptable from a clinical safety perspective. Below is the sponsor's proposed label:

CLARITIN LIQUI-GELS CAPSULES (10 AND 30 COUNT)

Principal Display Panel

NDC

New! Original Prescription Strength

Non-Drowsy*
Claritin®
loratadine 10 mg/antihistamine

24 Hour
Relief of:
- Sneezing
- Runny Nose
- Itchy, Watery Eyes
- Itchy Throat or Nose

Allergy

10 *or* 30 LIQUID FILLED CAPSULES

ACTUAL SIZE [graphic of the capsule]
Liqui-Gels™ capsules

b(4)

*When taken as directed. See Drug Facts Panel.

Top Panel

Claritin® Liqui-Gels ™capsules [graphic of the capsule]

10 *or* 30 CAPSULES FOR 10 or 30 DAYS OF RELIEF

b(4)

Side Panel

lot number and expiration dating code area

Claritin®

Bottom Panel

Claritin®

Liqui-Gels ™capsules [graphic of the capsule]

[This text does not appear on the 10 count]

b(4)

The graphics on the front panel of this carton constitute trademarks

10 or 30 CAPSULES
FOR 10 *or* 30 DAYS OF RELIEF

Back Panel

Drug Facts

Active ingredient (in each capsule)	*Purpose*
Loratadine 10 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. ▶

Drug Facts (continued)

Directions

adults and children 6 years and over	1 capsule daily; not more than 1 capsule in 24 hours
children under 6 years of age	ask a doctor
consumers with liver or kidney disease	ask a doctor

Other information

- safety sealed: do not use if the individual blister unit imprinted with Claritin® Liqui-Gels™ is open or torn

APPEARS THIS WAY ON ORIGINAL

- store between 20° to 25°C (68° to 77°F)
- protect from freezing

Inactive ingredients
caprylic/capric glycerides, FD&C blue no.1, gelatin, glycerin, pharmaceutical ink, polysorbate 80, povidone, purified water, sorbitol

Questions or comments?
1-800-CLARITIN (1-800-252-7484) or **www.claritin.com**

9.5 Comments to Applicant

Revise your proposed label as recommended by the NDA's reviewing team to include the following text under **Directions** in the **Drug Facts** section of the label to include the following bulleted statement:

- *Take on an empty stomach. Taking with food may cause drowsiness.*

Alternatively, if you do not want this language to be include in the label, additional data should be provided to prove that this product does not cause drowsiness despite increasing the loratadine $AUC_{0-\infty}$ by 118%.

10 APPENDICES

10.1 Review of Individual Study Reports

Not applicable.

10.2 Line-by-Line Labeling Review

See section 9.4.

10.3 Table of Serious Adverse Events (SAE)

APPEARS THIS WAY ON ORIGINAL

Table A-1. SAEs Loratadine tablets (10mg) from Oct 1, 2005-Jun 28, 2006

Body System and Preferred Term	Count	Rate
Blood and lymphatic system disorders	**2**	**0.00017**
Eosinophilia	1	
Thrombocytopenia	1	
Cardiac disorders	**2**	**0.00017**
Atrial fibrillation	1	
Palpitations	1	
Endocrine disorders	**1**	**0.00008**
Hypothyroidism	1	
Eye disorders	**2**	**0.00017**
Eye pain	1	
Glaucoma	1	

Continued on the next pages...

Table A-1 continued…

Gastrointestinal disorders	**7**	**0.00058**
Gastrointestinal haemorrhage	1	
Diarrhea haemorrhagic	1	
Haematochezia	1	
Melaena	1	
Nausea	2	
Vomiting	1	
General disorders and administration site conditions	**4**	**0.0003**
Drug ineffective	1	
Face oedema	1	
Fatigue	1	
Ulcer	1	
Hepatobiliary disorders	**5**	**0.0004**
Hepatic function abnormal	2	
Hepatitis	1	
Hepatocellular damage	2	
Immune system disorders	**2**	**0.00017**
Anaphylactic reaction	2	
Injury, poisoning and procedural complications	**3**	**0.00025**
Compression fracture	1	
Intentional overdose	1	
Road traffic accident	1	
Investigations	**6**	**0.0005**
Blood pressure increased	1	
Coagulation factor VIII level decreased	1	
Eosinophil count increased	1	
Platelet count decreased	1	
Thyroid function test abnormal	1	
Weight decreased	1	
Metabolism and nutrition disorders	**3**	**0.00025**
Hypoalbuminaemia	1	
Hypocalcaemia	1	
Hypoproteinaemia	1	
Musculoskeletal and connective tissue disorders	**2**	**0.00017**
Back pain	1	
Spinal osteoarthritis	1	
Nervous system disorders	**8**	**0.00066**
Dizziness	1	
Epilepsy	1	
Grand mal convulsion	2	
Paraesthesia	1	
Parosmia	1	
Syncope	1	
Visual field defect	1	
Psychiatric disorders	**4**	**0.00033**
Depression	1	
Hallucination	1	
Insomnia	1	
Suicide attempt	1	
Renal and urinary disorders	**1**	**0.00008**
Urinary retention	1	
Reproductive system and breast disorders	**1**	**0.00008**
Benign prostatic hyperplasia	1	
Respiratory, thoracic and mediastinal disorders	**1**	**0.00008**
Epistaxis	1	
Skin and subcutaneous tissue disorders	**15**	**0.00099**
Alopecia	3	
Angioneurotic oedema	1	
Decubitus ulcer	1	
Eczema	1	

Table A-1 continued…

Epidermal necrosis	1	
Erythema multiforme	1	
Leukocytoclastic vasculitis	1	
Pruritus	2	
Purpura	1	
Rash	1	
Rash vesicular	1	
Urticaria generalised	1	
Surgical and medical procedures	**2**	**0.00017**
Bladder catheterisation	1	
Thyroidectomy	1	
Total	**71**	**0.0059**

APPEARS THIS WAY ON ORIGINAL

Table A-2: Serious Adverse Events for Loratadine oral solution (5mg/5ml) Oct 1, 2005-Jun 28, 2006

Body System and Preferred Term	Count	Rate
General disorders and administration site conditions	**1**	**0.00082**
Disease progression	1	
Immune system disorders	**1**	**0.00082**
Hypersensitivity	1	
Injury, poisoning and procedural complications	**1**	**0.00082**
Poor quality drug administered	1	
Nervous system disorders	**6**	**0.0049**
Amnesia	1	
Convulsion	1	
Loss of consciousness	2	
Syncope	1	
Tremor	1	
Psychiatric disorders	**8**	**0.0065**
Abnormal behaviour	3	
Crying	1	
Fear	1	
Hallucination	2	
Psychotic disorder	1	
Respiratory, thoracic and mediastinal disorders	**1**	**0.00082**
Cough	1	
Skin and subcutaneous tissue disorders	**1**	**0.00082**
Urticaria	1	
Total	**19**	**0.0155**

Table A-3: SAEs Loratadine Orally Disintegrating Tablets (10mg) Oct 1, 2005-Jun 28, 2006

Body System and Preferred Term	Count	Rate
Injury, poisoning and procedural complications	**1**	**0.0015**
Fall	1	
Metabolism and nutrition disorders	**1**	**0.0015**
Diabetes mellitus insulin-dependent	1	
Nervous system disorders	**5**	**0.0075**
Amnesia	1	
Dizziness	1	
Grand mal convulsion	1	
Hypoaesthesia	1	
Monoplegia	1	
Psychiatric disorders	**1**	**0.0015**
Agitation	1	
Total	**8**	**0.012**

REFERENCES

1) Gonzalez de Olano D, Raon Roan J, de la Hoz Caballer B, et.al. Urticaria induced by antihistamines. J Investig Allergol Clin Immunol, 2006. 16: 144-146.

2) Harahsheh, A. and Al-ansari, N. Cough in a teenager. Clin Pediatr 2006, 45:377-380.

3) 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. An. Allergy Asthma Immunol, 2005. 94: 457-464.

4) Kallen B, Olausson PO. No Increased Risk of Infant Hypospadias after maternal use of loratadine in early pregnancy. International Journal of Medical Sciences, 2006. (3)3: 106-107.

5) Noehr-Jensen L, Damkier P, Bidstrup JB, et. al. The relative bioavailability of loratadine administered as a chewing gum formulation in healthy volunteers. Eur J Clin Pharmacol, 2006. 62: 437-445.

6) Piñeyro-López A, Piñeyro-Garza E, Torres-Alanís 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: 11-115.

7) Montero A, Durán Quintana JA, Jiménez Sáenz M, et. Al. A strategy to improve the detection of drug-induced hepatotoxicity. Rev Esp Enferm Dig, 2005. 97: 155-160.

8) Casale TB, Blaiss MS, Gelfand E, et al. First do no harm: managing antihistamine impairment in patients with allergic rhinitis. J Allergy Clin Immunol 2003; ILL: 835-842.

9) Plaut M, Valentine MD. Clinical practice. Allergic rhinitis. N Engl J Med 2005; Nov 3; 353(18): 1934-
44.

10) Overgaard AB, Hojsted J, Hansen R, et al. Patient's evaluation of shape, size and colour of solid dosages forms. Pharma World Sci 2001; 23(5): 185-8.

11) Prenner BM, Schenkel E. Allergic rhinitis: treatment based on patient profiles. Am J Med 2006; Mar 119 (3): 230-7.

12) Richter A, Anton SE, Koch P, Dennett SL. The impact of reducing dose frequency on health outcomes. Clin Ther 2003; 25(8): 2307-35.

13) Sohi H, Sultana Y, Khar RK. Taste masking technologies in oral pharmaceuticals: recent developments and approaches. Drug Dev Ind Pharm 2004; 30(5): 429-48.

14) Spangler DL, Brunton S. Efficacy and central nervous system impairment of newer-generation prescription antihistamines in seasonal allergic rhinitis. South Med J. 2006. Jun; 99(6):593-9

15) Philpot EE. Safety of second generation antihistamines. Allergy Asthma Proc. 2000 Jan-Feb; 21(1): 15-20.

16) Ten Eick AP, Blumer JL, Reed MD. Safety of antihistamines in children. Drug Saf. 2001; 24(2): 119-47.

17) Prescribing Information for Claritin tablets®, Physician's Desk Reference (PDR), 2003.

18) Medical Officer Review of NDA 21-891, Claritin Chewable tablets 5 mg.

19) Safety Assessment of the Antihistamines Loratadine and Fexofenadine. Memorandum from the FDA OTC Switch Review Team to Robert Meyer, M.D. (FDA Director, Division of Pulmonary and Allergy Drug Products). May 12, 2000 .

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

/s/

Lolita Lopez
12/11/2006 08:33:32 AM
MEDICAL OFFICER

Daiva Shetty
12/11/2006 09:31:25 AM
MEDICAL OFFICER