CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 19-670/S-020

Name: Claritin-D® 12 hour (5 mg loratadine /120 mg pseudoephedrine sulfate) Extended-release Tablets

Sponsor: Schering-Plough Healthcare Products

Approval Date: April 23, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-670/S-020

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-670/S-020

Schering-Plough Healthcare Products
Attention: Charles Lanese
Manager, Regulatory Affairs
56 Livingston Avenue
Roseland, NJ 07068

Dear Mr. Lanese:

Please refer to your supplemental new drug application dated December 22, 2008, received December 23, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Claritin-D® 12 hour (5 mg loratadine /120 mg pseudoephedrine sulfate) extended-release tablets.

This supplemental new drug application provides for a new formulation for Claritin-D® 12 hour, replacing the previously approved formulation. This formulation is identical to the 5 mg loratadine/ 120 mg pseudoephedrine sulfate extended release formulation approved under ANDA 76-070 (Impax Labs). This supplemental NDA also provides for the manufacturing, packaging, and analytical testing (release and stability) operations for this formulation at the Schering-Plough facilities in Kenilworth and Union, New Jersey.

We have completed our review of this supplemental application. This application is approved, effective on the date of this letter, for use as recommended in the agreed upon labeling text.

Submit final printed labeling as soon as they are available, but no more than 30 days after they are printed. The final printed labeling (FPL) must be identical to the enclosed labels (Claritin-D 12 Hour 10-, 20- and 30-count carton and blister foil labels submitted December 22, 2009), and must be in the "Drug Facts" format (21 CFR 201.66), where applicable.

The final printed labeling should be submitted electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Labeling for approved NDA 19-670/S-020**." Approval of this submission by FDA is not required before the labeling is used.

We note your request for the Agency to reinstate Claritin-D 12 Hour as the reference listed drug. It is not appropriate to request this type of change in a supplement to an approved application (see 21 CFR 314.70) Therefore, this request was not reviewed as part of this supplement. You should contact the Orange Book Staff, Mary Ann Holovac, at 240-276-8971 for further information regarding any issues concerning designation as a reference listed drug.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to both this NDA and the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Janice Adams-King, Regulatory Project Manager, at (301) 796-3713.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure

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/s/

Janice Adams-King

4/23/2009 12:37:46 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-670/S-020

LABELING


Claritin-D 12
10 EXTENDED RELEASE TABLETS
Non-Drowsy
Claritin-D 12
Allergy & Congestion
10 EXTENDED RELEASE TABLETS
Claritin-D 12


Claritin-D 12
20 EXTENDED RELEASE TABLETS
Non-Drowsy
Claritin-D 12
Allergy & Congestion
20 EXTENDED RELEASE TABLETS
Claritin-D 12


Claritin-D 12
30 EXTENDED RELEASE TABLETS
Non-Drowsy
Claritin-D 12 hour
Allergy & Congestion
30 EXTENDED RELEASE TABLETS
Claritin-D 12

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-670/S-020

LABELING REVIEW

OTC Drug Labeling Review

Office of Nonprescription Drug Products
Center for Drug Evaluation and Research • Food and Drug Administration

SUBMISSION DATE: January 20, 2009 REVIEW DATE: February 3, 2009

NDA: 19-670

SUBMISSION TYPE: SCF 020

SPONSOR/CONTACT: Charles Lanese
Manager, Regulatory Affairs

56 Livingston Avenue
Roseland, NJ 07068

DRUG PRODUCT (BRAND NAME): Claritin-D 12 Hour Extended

ACTIVE INGREDIENT(S) [ESTABLISHED NAME(S)]:

loratadine 5 mg, pseudoephedrine sulfate 120 mg

PHARMACOLOGICAL CATEGORY: antihistamine/nasal decongestant

LABELING SUBMITTED (SKU): 10, 20, 30-count carton and blister pack foil labels

PROJECT MANAGER: Janice Adams-King, RN

REVIEWER'S NAME: Ayana K. Rowley, Pharm.D

BACKGROUND

The most recently approved labeling was submitted on March 9, 2004 and approved on July 30, 2004 under SLR 019. In this submission (SCF 020), Schering-Plough HealthCare Products seeks approval for proposed draft labels Claritin-D 12 Hour ER (10, 20 and 30-count).

Reinstatement of Reference Listed Drug Status

In 2003, the sponsor stopped manufacturing Claritin-D 12 hour ER tablets under the NDA 19-670 and began distributing the drug product under ANDA 76-050. This change in manufacturing also switch the reference listed drug (RLD) from the NDA 19-670 to the ANDA 76-050. In this submission, the sponsor is also requesting to reinstate NDA 19-670 as the RLD because they are now using a new formulation for Claritin D-12 Hour ER tablets. This new formulation under NDA 19-670 is identical to the currently approved formulation under ANDA 76-050.

REVIEWER'S COMMENT

I. Carton label
   A. Principal Display Panel
      - In upper left hand corner sponsor states product is "Original Prescription Strength." PDP is acceptable because Claritin-D was completely switched from RX to OTC, and there is no longer prescription strength.

   B. Other Panels
      - Location of expiration date and control/lot number is not identified on the carton label as in accordance to 21 CFR 201.17 and 201.18. Sponsor needs to make provision for expiration date and control/lot number in final printed labeling.

   C. Drug Facts Panel
      - Subheading: Other Information: Manufacture added additional bullet "each tablet contains: calcium 30 mg". This is acceptable as stated in 21 CFR 201.70(b), the calcium content per unit dosage shall be expressed on the drug facts label.

II. Immediate container/Blister pack label
   A. Individual blister foil label is acceptable.

III. Reinstatement as the RLD
The sponsor has requested a reinstatement of NDA 19-670 as the RLD. This review is a labeling review. The request for reinstatement will be addressed by Regulatory Management Staff (RMS).

RECOMMENDATIONS:

1. An "Approved" letter can be issued to the sponsor for the 10, 20, and 30- carton labels and blister foil label submitted on January 20, 2009 and request final printed labels, when available.

2. Remind the sponsor that provisions for a control number and expiration date for 10, 20 and 30- count carton labels need to be provided for the final printed labels.

3. RMS: This is to inform you that the sponsor has requested a reinstatement of this NDA as the RLD.

Ayana K. Rowley, Pharm.D.
Reviewer's name

Marina Chang, R.Ph.
Team Leader concurrence

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/s/

Ayana Rowley
2/18/2009 09:58:49 AM
PHARMACIST

Marina Chang
2/19/2009 08:13:30 AM
INTERDISCIPLINARY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-670/S-020

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation (DNCE)

Date: April 6, 2009

From: Linda Hu, MD
Medical Officer, DNCE

Subject: NDA 19-670 (S-020),Claritin-D 12 hour extended release tablets
Loratadine 5 mg / Pseudoephedrine Sulfate 120 mg

Sponsor: Schering-Plough Health Care Products.

PDUFA: April 22, 2009

1 Introduction and Regulatory Background

Schering-Plough HealthCare Products (SPHCP) is submitting supplement S-020 to NDA 19-670 to include a new formulation under NDA 19-670 for Claritin-D 12 Hour Extended Release Tablets (loratadine 5 mg/ pseudoephedrine sulfate 120 mg). This product was previously marketed by SPHCP under NDA 19-670 which was approved for prescription use in 1994. The product was later approved for OTC marketing on November 27, 2002. In 2003, Schering-Plough stopped distributing product manufactured under NDA 19-670 and began marketing the OTC Claritin-D® 12 Hour formulation manufactured by Impax Laboratories under ANDA 76-050. SPHCP now intends to manufacture a loratadine 5 mg / pseudoephedrine sulfate 120 mg formulation within its own facilities located in Kenilworth, New Jersey.

The present supplemental application to NDA 19-670 for Claritin-D® 12 Hour Extended Release Tablets relies on the Agency's previous approval of ANDA 76-050 for the loratadine 5 mg / pseudoephedrine sulfate 120 mg formulation sponsored by Impax Laboratories (b) (4) .

A Briefing Document for a Type C Meeting was submitted to FDA on April 13, 2007. The purpose of that meeting was to discuss and gain agreement on the requirements for the submission of a CMC supplement to add the new formulation, manufacturing process, packaging and analytical methods for Claritin-D® 12 Hour Extended Release Tablets into the SPHCP

sponsored NDA 19-670. The meeting also sought the Agency's concurrence regarding the design of the proposed bioequivalence study to be conducted in support of these changes.

The Agency sent a preliminary response via fax dated May 15, 2007 which documented agreement with SPHCP's proposed filing strategy of the CMC supplement. The Agency also agreed with the design of the proposed bioequivalence study. The Type C meeting was subsequently canceled.

SPONSOR REQUEST FOR REINSTATEMENT OF REFERENCE LISTED DRUG STATUS

Prior to 2003, NDA 19-670 was the reference listed drug for the approved drug product Claritin-D 12 Hour Tablets (loratadine 5mg/pseudoephedrine sulfate 120 mg). In 2003, Schering-Plough stopped distributing product approved under NDA 19-670 and began distributing instead the formulation manufactured by Impax under ANDA 76-050. As there was no commercially available product manufactured under NDA 19-670, ANDA 76-050 became the reference listed drug (RLD).

Within the present supplement, SPHCP requests that a new formulation for NDA 19-670 be approved. This formulation is identical and bioequivalent to the approved drug product in ANDA 76-050.

Since ANDA 76-050 relied on the safety and efficacy trials conducted by Schering-Plough for NDA 19-670, and since the test product is bioequivalent to the current RLD listed in the Orange Book, ANDA 76-050, SPHCP proposes that NDA 19-670 be reinstated as the RLD upon the commercial introduction of the subject formula.

1.1 Product Information

Claritin-D 12 Hour Extended Release Tablets (loratadine 5 mg/pseudoephedrine 120 mg) has been marketed in the US without a prescription since November 27, 2002 with the following indications:

- temporarily relieves the following symptoms due to hay fever or other respiratory allergies: sneezing; runny nose; itchy, watery eyes; itching of the nose or throat;
- temporarily relieves congestion due to the common cold, hay fever and other upper respiratory allergies;
- reduces swelling of nasal passages;
- temporarily reduces sinus congestion and pressure
- temporarily restores freer breathing through the nose.

2 Chemistry

The submission includes a description of the analytical methods used for sample analysis. See the chemistry review for further detail and comments.

3 Clinical Pharmacology

The Sponsor submitted one clinical trial, Protocol CL2006-08 (PRACS R06-1634)"A Single Dose, Comparative, Randomized, Two-Way Crossover Bioequivalence Study of Loratadine/Pseudoephedrine Administered as a Claritin-D® 12 Hour Extended Release Tablet From Two Manufacturing Sites" to support the manufacturing site transfer of Claritin-D 12 Hour Extended Release Tablets to the Schering-Plough facility rather than sourcing it from Impax Laboratories.

Study Objective: The objective of this study was to evaluate the bioequivalence of one extended release combination tablet (loratadine 5 mg/pseudoephedrine sulfate 120 mg) manufactured at Schering Corporation (test treatment) to one extended release combination tablet (loratadine 5 mg/pseudoephedrine sulfate 120 mg) manufactured at Impax Pharmaceuticals (reference treatment).

Procedure:
Thirty-six non-smoking, healthy adult subjects (27 males, 9 females; 34 Caucasian, 1 Hawaiian or other Pacific Islanders/Caucasian and 1 American Indian or Alaska Native) were enrolled in this study. The subjects were between the ages of 19 and 43 inclusive (mean = 26.1 years). The study treatments are shown in Table 1.

Table 1: Study Treatments

Test Preparation:	Treatment A	Treatment B
Name:	CLARITIN-D 12 Hour Extended Release Tablet	CLARITIN-D 12 Hour Extended Release Tablet
Batch/Lot no.:	Lot # 7-SP1-11	Lot # 7J07AR
Manufacturer	Schering Corporation	Impax Laboratories

All subjects fasted for at least 10 hours before dosing and another four hours after 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 the two dosing periods, Period 1 and Period 2. Eighteen subjects were randomized to dosing sequence A-B (one did not complete the study) for the dosing periods, and eighteen subjects were randomized to B-A.

Pharmacokinetic blood sampling and safety monitoring continued for up to 120 hours following study drug administration. Subjects had a post study physical examination, ECG, and clinical laboratory (including pregnancy test for women of childbearing potential) and urinalysis evaluations prior to discharge from the clinic at the end of Period 2 or upon early discontinuation from the study. In addition to screening, baseline, and exit labs, serum loratadine, desloratadine, and pseudoephedrine concentrations were obtained at 0 hour/pre-dose, 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 after dosing in each period. Safety evaluations included assessments of adverse experiences, ECG, physical exam and periodic monitoring of vital signs, and clinical laboratory results (including hematology, serum chemistry, and urinalysis).

Table 2 shows the study procedure.

Table 2. Schematic of study procedure

Evaluation	Screening Day -14 to Day -2	Period[a] I & 2						
		Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Obtain Informed Consent[b]	X							
Eligibility (Inclusion/Exclusion)	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 (females only)	X	X						X[h]
Vital Signs[e]	X	X	X	X	X	X	X	X
Volunteer Confinement[f]		X	X	X	X	X	X	X
Treatment Administration			X					
Blood Samples[g]			X	X	X	X	X	X

[a] A washout period of at least 14 days separated each dose administration. [b] Written informed consent 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, respiration, oral body temperature screening, Day -1, prior to first blood draw each day (Days 1-6, Period 1 & 2) and after the 120 hour post-dose blood draw (Period 2 only). [f] Subjects arrived at the study site at least 12 hours prior to dosing and remained at the site until after the 120-hour post-dose blood draw. [g] Blood samples for determination of plasma loratadine, desloratadine, pseudoephedrine 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.

Inclusion Criteria were as follows:

1. Healthy, male or female subjects between the ages of 18 and 45 years, inclusive, with a Body Mass Index (BMI) between 19-30 inclusive [BMI = weight(kg)/height(m^2)]

2. Clinical laboratory tests (CBC, blood chemistries, urinalysis) were within normal limits or were clinically acceptable to the Investigator/Sponsor.

3. Drug screen for drugs with a high potential for abuse were negative at screening and on admission to the study site (Day -1 of each period).

4. Subjects were free of any clinically significant disease that required a physician's care and/or would have interfered with study evaluations, procedures or participation.

5. Subjects agreed not to take monoamine oxidase inhibitor (MAOI) for two weeks after the end of the study.

6. Subjects were willing to give written informed consent (prior to any study related procedures being performed) and were able to adhere to restrictions and examination schedules.

7. Subjects had normal or clinically acceptable physical exam and ECG intervals (PR, QRS, QT and QTc) on 12-lead ECG (recorded at 25 mm/s).

Exclusion Criteria were as follows:

1. Subjects who had a history of any clinically significant local or systemic infectious disease within four weeks prior to initial treatment administration.

2. Subjects who did not comply with the requirement to abstain from the use of any drugs (except acetaminophen) within 14 days prior to the study and alcohol or xanthine-containing substances within 72 hours prior to study drug administration.

3. Subjects who had participated in a clinical trial of an investigational drug within 30 days prior to the start of the study (Day 1).

4. Subjects who were, appeared to be, or were known to be, current or former drug addicts or alcoholics.

5. Subjects who were positive for hepatitis B surface antigen or hepatitis C antibody.

6. Subjects who were positive for HIV antibodies.

7. Subjects who had a clinically significant history of food or drug allergy.

8. Subjects who had a known allergy or intolerance to loratadine, Clarinex® (desloratadine), or pseudoephedrine sulfate.

9. Subjects who had donated blood or plasma within the preceding 30 days.

10. Females who were pregnant, nursing or unwilling to use/practice adequate contraception (I.U.D., barrier method, etc.).

11. Subjects who had used a loratadine, desloratadine, or pseudoephedrine-containing product within two weeks prior to the start of the study or during the washout period.

12. Subjects who had smoked tobacco, used tobacco products, or used an adjunct to smoking cessation within the past six months; or subject with a positive cotinine test result at screening.

MO Comment: The inclusion and exclusion criteria are standard and acceptable from the safety point of view.

Discontinuation of Subject From Therapy or Study Observation
Subject no. 06 withdrew consent due to a family emergency and discontinued from the study (sequence AB, prior to hour 98 of Period II). No subjects were discontinued due to an adverse experience.

Pharmacokinetic Results
The pharmacokinetic parameters are displayed in Table 3 below.

Table 3 Summary of Pharmacokinetic Parameters (Protocol No. CL2006-08)

Parameter	Geometric Mean Ln - Transformed Data			90% CI
	Claritin-D 12 Hour Extended Release Tablet (Schering Corporation) Test	Claritin-D 12 Hour Extended Release Tablet (Impax Laboratories) Reference	% Ratio	
Loratadine N=36				
AUC_{0-t} (pg-hr/mL)	1882.91	1824.96	103.18	(94.84,112.24)
$AUC_{0-\infty}$ (pg-hr/mL)	2001.61	1955.38	102.36	(94.3, 111.11)
C_{max} (pg/mL)	722.61	708.97	101.92	(93.29, 111.35)
Desloratadine N=36				
AUC_{0-t} (pg-hr/mL)	15993.43	15845.62	100.93	(95.94, 106.18)
$AUC_{0-\infty}$ (pg-hr/mL)	17082.05	16936.62	100.86	(96.35, 105.58)
C_{max} (pg/mL)	1382.85	1364.37	101.35	(95.17, 107.94)
Pseudoephedrine N=36				
AUC_{0-t} (pg-hr/mL)	3418.59	3235.24	105.67	(101.33, 110.18)
$AUC_{0-\infty}$ (pg-hr/mL)	3465.97	3275.61	105.81	(101.52, 110.28)
C_{max} (pg/mL)	309.59	303.99	101.84	(97.83, 106.01)

MO Comment: The results of this study demonstrate bioequivalence between these two products. Specifically, 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 loratadine, desloratadine and pseudoephedrine were within the bioequivalence 80-125% limits for the pharmacokinetic parameters.

4 Safety Summary

Analysis of Adverse Events

Thirty-five (97.2%) subjects successfully completed this randomized, two-way, fasted, crossover comparative bioavailability study testing for bioequivalence. Subject no. 06 withdrew consent due to a family emergency and discontinued from the study. **No serious adverse events were reported in this study.** Four subjects reported a total of 4 adverse events (headache, epistaxis, rash and hyperaesthesia). Three subjects reported adverse events after receiving Treatment A (Test Product) and one subject experienced an adverse event after receiving the Treatment B (Reference Product).

All adverse events were mild in severity. Both treatments were well tolerated (see Table 4 below).

Table 4: Summary of Adverse Events

Subject No.	System Organ Class	Preferred Name	Treatment	Severity	Relationship to drug	Outcome	Action Taken	Serious AE?
10	Nervous system disorders	Hyperaesthesia	Treatment B (Reference)	Mild	Unlikely related	Resolved	None	No
15	Nervous system disorders	Headache	Treatment A (Test)	Mild	Probably related	Resolved	None	No
21	Respiratory, thoracic and mediastinal disorders	Epistaxis	Treatment A (Test)	Mild	Unlikely related	Resolved	None	No
27	Skin and subcutaneous tissue disorders	Rash	Treatment A (Test)	Mild	Unlikely related	Resolved	None	No

Clinical Laboratory Evaluations

Laboratory evaluations were performed at Screening, Day-1 of each Period and at End of Study. These evaluations consisted of chemistry, hematology and urinalysis. No clinically significant changes in laboratory evaluations were observed.

Vital Signs, Physical findings, and Other Observations Related to Safety

Physical examinations and electrocardiograms (ECGs) were conducted at Screening and End of Study (Period 2). Vital signs were measured at Screening, Day-1 (at check-in), before the first blood draw each day and at end of study. No clinically significant changes for physical examinations, ECGs and vital signs were observed.

MO Comment: The results of this study do not raise any new safety issues.

See the biopharmacology review for further detail and comments on this study.

5 Efficacy Summary

No new clinical trial data for efficacy were submitted for this supplement.

6 Pediatrics

The Pediatric Research Equity Act (PREA) requirements do not apply, as this is still a tablet formulation and there was no change in dosing or indication.

7 Labeling

The label is consistent with prior approved labeling for Claritin-D. See the interdisciplinary scientist review for further comments.

8 Conclusion and Recommendation

The submitted study provides adequate evidence for bioequivalence between the SPHCP and Impax formulations of Claritin-D 12 Hour Extended Release Tablets (loratadine 5 mg/pseudoephedrine 120 mg). Approval of the supplemental NDA is recommended.

The Sponsor will be referred to the Orange Book staff in the Office of Generic Drugs regarding their question as to whether this product can be reinstituted as the reference listed drug.

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/s/

Linda Hu
4/10/2009 10:31:05 AM
MEDICAL OFFICER

Daiva Shetty
4/10/2009 10:34:20 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-670/S-020

CHEMISTRY REVIEW

CHEMIST'S REVIEW

1. ORGANIZATION CDER/ONDQA Division of Post-Marketing Evaluation HFD-560	**2. NDA #** 19-670 Original NDA approved:
3. NAME AND ADDRESS OF APPLICANT Schering-Plough 556 Morris Avenue Summit, NJ 07901	**4. SUPPLEMENT** SCF-020 22-DEC-2008 (Rec. 23-DEC-2008)
	5. Name of the Drug Claritin-D 24 Hour ER Tablets
	6. Nonproprietary Name loratadine Pseudoephedrine sulfate
7. SUPPLEMENT PROVIDES for new manufacturing, packaging, and analytical testing sites for Claritin-D 24 Hour ER Tablets	**8. AMENDMENT** --

9. PHARMACOLOGICAL CATEGORY Antihistamine/Nasal decongestant	**10. HOW DISPENSED** Rx	**11. RELATED** DMF (b) (4) DMF (b) (4)
12. DOSAGE FORM extended release tablets	**13. POTENCY** loratadine 10 mg Pseudoephedrine sulfate 240 mg	

14. CHEMICAL NAME AND STRUCTURE See Chemistry Review

Loratadine: 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-, ethyl ester; Ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate

$C_{22}H_{23}ClN_2O_2$ 382.88

Pseudoephedrine sulfate: Benzenemethanol, α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate (2:1) (salt).

$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$ 428.54

15. COMMENTS This application is submitted as a PA Supplement. See Chemistry Assessment. Since microbial limits are being proposed as a release and stability specification for the drug product, a Microbiology Consult was requested. The Microbiology Review was Satisfactory (02-APR-2009) The overall EER recommendation was Acceptable. The Office of Nonprescription Drug Products performed the Labeling review for 10, 20, 30-count carton and blister pack foil labels submitted on January 20, 2009, and recommended Approval (18-FEB-2009). The Medical Officer Review concluded there was adequate evidence for bioequivalence between the drug product formulation manufactured by IMPAX and the formulation manufactured by Schering Plough, and recommended Approval (10-APR-2009).

NOTE: Schering-Plough HealthCare Products (SPHCP), in this Supplement, provides for the drug product formulation (b) (4). In addition, it provides for the manufacturing, packaging and analytical testing (release and stability) operations for this formulation at SPHCP facilities in Kenilworth and Union, NJ. Currently, and since 2003, SPHCP markets the drug product approved under ANDA 76-050.

16. CONCLUSIONS AND RECOMMENDATIONS The (b) (4) Batch 8-SP2-5 and the primary stability/bio-equivalency batch 7-SP1-11 confirms the ability of the manufacturing site at Kenilworth, NJ to produce a consistent product of desired quality attributes. The stability data through 6 months is Acceptable. The approved, 24-month shelf life (b) (4) is also granted to the Schering product. The CMC recommendation is Approval. OND will issue the Action Letter.

17. REVIEWER NAME (AND SIGNATURE) **DATE COMPLETED** 17-APR-2009
Sharon Kelly, PhD **R/D INITIATED BY** **filename:** 19-670#020 NDA

DISTRIBUTION: Original: NDA 19-670#020 cc: Division File CSO Reviewer

AP

1

Following this page, 28 pages withheld in full - (b)(4), Chemistry Review

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-JAN-09
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 2210048 FEI : 2210048
SCHERING CORP
2000 GALLOPING HILL RD
KENILWORTH, NJ 070330530

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile : TTR OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 26-JAN-09
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 2211256 FEI : 2211256
SCHERING CORP
1011 MORRIS AVE
UNION, NJ 070837120

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 22-JAN-09
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

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/s/

Sharon Kelly
4/21/2009 03:56:47 PM
CHEMIST

Hasmukh Patel
4/21/2009 03:58:27 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-670/S-020

MICROBIOLOGY REVIEW

Product Quality Microbiology Review

02 April 2009

NDA: **19-670/SCF-020**

Drug Product Name
Proprietary: Claritin-D® 12-hour Extended Release
Non-proprietary: Loratadine, USP
Pseudoephedrine Sulfate, USP

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
22-DEC-2008	23-DEC-2008	21-JAN-2009	26-FEB-2009

Submission History (for amendments only) – N/A

Applicant/Sponsor
Name: Schering Plough
Address: 56 Livingston Avenue
Roseland, NJ 07068
Representative: Charles Lanese
Telephone: (862) 245-5127

Name of Reviewer: Denise Miller

Conclusion: Approve

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior Approval

2. SUBMISSION PROVIDES FOR: This supplement provides for the transfer of the manufacturing, packaging and analytical testing for the new formulations to Schering Plough facilities in Kenilworth and Union New Jersey. The sponsor is also adding microbial testing to their specification.

3. MANUFACTURING SITE:

Schering Corporation
2000 Galloping Hill Road
Kenilworth, N.J. 07033

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Tablet
- Oral
- Loratidine 5mg, Pseudoephedrine sulfate 120 mg

5. METHOD(S) OF STERILIZATION: N/A, this is a non-sterile drug product.

6. PHARMACOLOGICAL CATEGORY: Antihistamine/Decongestant for the relief of seasonal allergic rhinitis.

B. SUPPORTING/RELATED DOCUMENTS:
ANDA 76-050

C. REMARKS:

- This was a paper submission in CTD format and was comprised of 15 black folder bound volumes. Modules 1, 2 and 3 were reviewed.
- This submission included (b) (4).

filename: N019670S020R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend to approve from a quality microbiology standpoint

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4) formulation to NDA 019-670 (b) (4) with manufacturing to be done at Schering Plough. The submission also added microbiological testing to the release and stability specifications.

B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____
Denise Miller, Microbiologist

B. Endorsement Block _____
Bryan S. Riley, Ph.D.

C. CC Block
N/A

Following this page, 3 pages withheld in full - (b)(4), Microbiology Review

- Microbial Limits – tested (b) (4)

P.8.3 Stability Data – See section P.8.1

-Acceptable-

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT – N/A

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

No deficiencies noted based on the microbiology information submitted

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/s/

Denise Miller
4/2/2009 08:22:03 AM
MICROBIOLOGIST

Bryan Riley
4/2/2009 08:54:14 AM
MICROBIOLOGIST
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-670/S-020

CLINICAL PHARMACOLOGY REVIEW

CLINICAL PHARMACOLOGY REVIEW

NDA:	19-670 S020
Generic Name:	Loratadine/ Pseudoephedrine Extended Release Tablets
Proprietary Drug Name:	**Claritin-D® 12 Hour Extended Release Tablets**
Indication:	Antihistamine
Dosage Form:	Extended Release Tablets
Strengths:	5 mg/120mg
Route of Administration:	Oral
Applicant:	Schering-Plough
OCP Division:	Division of Clinical Pharmacology-2
Clinical Division:	Office of Nonprescription Drug Products
Type of Submission:	Prior approval supplement
Submission Date:	December 22, 2008
Date of Assignment:	January 27, 2008
Reviewer:	Sandra S. Sharp, Ph.D.
Team Leader:	Sally Choe, Ph. D.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Claritin-D® 12 Hour (loratadine/pseudoephedrine, 5 mg/120 mg) Extended Release (ER) Tablet has been marketed in the US without a prescription (OTC product) under NDA 19-670 since November 27, 2002. In 2003, Schering-Plough stopped distributing the product manufactured under NDA 19-670 and began marketing the OTC product Claritin-D® 12 Hour Tablets by distributing Loratadine 5 mg/Pseudoephedrine Sulfate 120 mg Extended Release Tablet (generic product) manufactured under ANDA 76-050 (Impax Labs).

The purpose of this prior approval supplement (S020) is to provide data supporting a change in formulation for Claritin-D® 12 Hour ER. This new formulation is identical to Loratadine/Pseudoephedrine Extended Release Tablet approved under ANDA 76-050 (Impax Laboratories). It is the sponsor's intention to manufacture Claritin-D 12 Hour Extended Release Tablets at the Kenilworth facility rather than sourcing it from Impax Laboratories.

In support of this application, the sponsor included the results of one bioequivalence (BE) study entitled "A Single Dose, Comparative, Randomized, Two-Way Crossover Bioequivalence Study of Loratadine/Pseudoephedrine Administered as a Claritin-D 12 Hour Extended Release Tablet from Two Manufacturing Sites". The purpose of this study was to demonstrate bioequivalence of Claritin–D 12 Hour ER tablet (formulation approved under ANDA 76-050) manufactured at Impax Labs (Reference) vs. Claritin-D 12 Hour ER Tablet (formulation (b) (4) (b) (4) manufacture at the Kenilworth facility (Test).

The 90% confidence intervals for the geometric means test/reference ratios for the area under the curve (AUC) and peak concentration (Cmax) for loratadine, desloratadine and pseudoephedrine are within the bioequivalence interval of 80-125. Therefore, Loratadine/pseudoephedrine 5/120 mg ER Tablets manufacture at the Impax Labs and Claritin-D 12 Hour ER Tablets manufacture at Schering Corporation are bioequivalent.

The effect of food on the pharmacokinetics of Claritin-D 12 Hour ER Tablet was not reported in this submission. It is noted that a bioequivalence study (fasting vs. non-fasting conditions) was

conducted for the (b) (4) formulation under ANDA 76-050[1]. The reviewer stated that IMPAX's Loratadine/ Pseudoephedrine Sulfate Extended Release Tablet under fasting conditions was bioequivalent to IMPAX's Loratadine/ Pseudoephedrine Sulfate Extended Release Tablet under non-fasting conditions.

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 2 (OCP / DCP-2) has reviewed the prior approval supplement (S020) submitted to NDA 19-670 on December 22, 2008 and found this supplement acceptable from an OCP standpoint. There are no labeling comments to the proposed carton labeling for this product.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings

The sponsor conducted a single dose, crossover bioequivalence study under fasting conditions (Protocol No. CL2006-08) in 36 healthy volunteers to support the change in formulation/manufacturing site transfer of Claritin-D 12 Hour Extended Release Tablets from Impax Laboratories to Kenilworth facility at Schering Corporation. This BE study is entitled "A Single Dose, Comparative, Randomized, Two-Way Crossover Bioequivalence Study of Loratadine/Pseudoephedrine Administered as a Claritin-D 12 Hour Extended Release Tablet from Two Manufacturing Sites". The objective of this study was to evaluate the bioequivalence of loratadine/pseudoephedrine combination administered as one extended release combination (loratadine 5 mg/pseudoephedrine sulfate 120 mg) tablet manufactured at Schering Corporation (test treatment) to one extended release combination (loratadine 5 mg/pseudoephedrine sulfate 120 mg) tablet manufactured at Impax Laboratories (reference treatment). Subjects received the following treatments in a randomized manner after at least 10 hrs of fasting:

> **Treatment A:** CLARITIN-D 12 Hour Tablet. Batch/Lot no.: Lot#7-SP1-11. Manufacturer: Schering Corporation.
>
> **Treatment B:** CLARITIN-D 12 Hour Tablet. Batch/Lot no.: Lot # 7J07AR. Manufacturer: Impax Laboratories.

A washout period of 14 days separated each dosing period.

Claritin-D 12 Hour Extended Release Tablet at Schering Corporation (test treatment) was considered bioequivalent to one extended release combination (Loratadine 5 mg/Pseudoephedrine sulfate 120 mg) tablet manufactured at Impax Laboratories (reference treatment) if the 90% confidence intervals around the ratio of the geometric means for loratadine, desloratadine (loratadine's active metabolite), and pseudoephedrine ln-transformed AUC0-t, AUC0-inf and Cmax values fall within 80-125%. 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 loratadine, desloratadine, and pseudoephedrine were within the bioequivalence interval of 80-125 (Table 1). Therefore, Claritin-D 12 Hour ER tablet

[1] Office of Generic Drugs review for ANDA 76-050 by Dr. Z. Wahba dated December 12, 2000. (V:\firmsam\IMPAX\ltrs&rev\76050sd.d00)

manufactured at Schering Corp. is bioequivalent to Claritin-D 12 Hour ER tablet manufactured at Impax Labs.

Table 1. 90% confidence intervals (CIs) for the geometric means test-to-reference ratios for relevant PK parameters for loratadine, desloratadine, and pseudoephedrine

Formulation		**Point estimates (%)**		**90% Confidence Intervals**	
		Loratadine			
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's
Trt A/ Trt B	AUCt	103.18	103.17	(94.84, 112.24)	(94.8-112.24)
	AUCinf	102.36	102.36	(94.3, 111.11)	(94.3-111.11))
	Cmax	101.92	101.90	(93.29, 111.35)	(93.9-111.34)
		Desloratadine			
Trt A/ Trt B	AUCt	100.93	101.10	(95.94, 106.18)	(96.2-106.4)
	AUCinf	100.86	101.64	(96.35, 105.58)	(95.4-108.2)
	Cmax	101.35	101.60	(95.17, 107.94)	(95.4-108.2)
		Pseudoephedrine			
Trt A/ Trt B	AUCt	105.67	105.7	(101.33, 110.18)	101.3-110.2
	AUCinf	105.81	105.6	(101.52, 110.28)	(101.4-110.05)
	Cmax	101.84	101.8	(97.83, 106.01)	(97.04-106.01

2. QUESTION BASED REVIEW

2.1 General Attributes

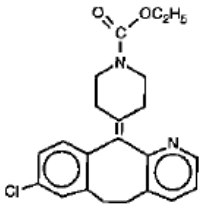
2.1.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Claritin-D® 12 Hour (loratadine/pseudoephedrine 5 mg/120 mg) ER Tablet was approved on November 14, 1994 under NDA 19-670 for the relieve of symptoms due to hay fever or respiratory allergies and for the relieve of congestion due to the common cold. Claritin-D® 12 Hour ER Tablet has been marketed in the US without a prescription (OTC product) under NDA 19-670 since November 27, 2002 for the same indication. The recommended dose in adults and children 12 years and older is one tablet taken twice a day. In 2003, Schering-Plough (SPHCP) stopped distributing the product manufactured under NDA 19-670 and began marketing the OTC product Claritin-D® 12 Hour Tablets by distributing loratadine 5 mg/pseudoephedrine sulfate 120 mg (generic product) manufactured under ANDA 76- 050 (Impax Labs). The extended release tablet under ANDA 76-050 was bioequivalent to the ER tablet under NDA 19-670 and therefore, relied on the safety and efficacy trials conducted by SPHCP for NDA 19-670.

Within this supplement, the sponsor requests that a new formulation for NDA 19-670 be approved. This formulation is identical to the approved drug product under ANDA 76-050. It is the sponsor's intention to manufacture Claritin-D 12 Hour Extended Release Tablets at the Kenilworth facility rather than sourcing it from Impax Laboratories. While Impax Laboratories will continue to produce product under their own ANDA, they have (b) (4) (b) (4).

2.1.2 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Drug Substance: The active pharmaceutical ingredients in Claritin®-D 12 Hour ER Tablets are Loratadine USP and Pseudoephedrine Sulfate. Loratadine is a white to off-white powder not soluble in water, but very soluble in acetone, alcohol, and chloroform. It has a molecular weight of 382.89, and empirical formula of $C_{22}H_{23}ClN_2O_2$. Its chemical name is ethyl 4-(8-chloro-5, 6-dihydro- 11 *H*-benzo[5,6]cyclohepta [1,2- *b*]pyridin-11- ylidene)-1-piperidinecarboxylate. It has the following formula:



Pseudoephedrine sulfate is the synthetic salt of one of the naturally occurring dextrorotatory diastereomers of ephedrine and is classified as an indirect sympathomimetic amine. The empirical formula for pseudoephedrine sulfate is $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$; the chemical name is a-[1-(methylamino) ethyl]-[S-(R*,R*)]- is a-[1-(methylamino) ethyl]-[S-(R*,R*)]-benzenemethanol sulfate (2:1) (salt). The molecular weight of pseudoephedrine sulfate is 428.54. It is a white powder, freely soluble in water and methanol and sparingly soluble in chloroform.

Drug Product

Claritin®-D 12 Hour Extended Release Tablets contain 5 mg of Loratadine USP and 60 mg of Pseudoephedrine Sulfate USP for immediate release and 60 mg of Pseudoephedrine Sulfate USP oral administration for extended release for 12 hours of nasal decongestion. The quantitative formula for Claritin-D 12 Hour Extended Release Tablets is provided in Table 2.1.2.1.

Table 2.1.2.1. Quantitative formula for Claritin-D 12 Hour Extended Release Tablets

Component	Amount per unit (mg/tablet)	Function
Loratadine	5.00	Drug Substance
Pseudoephedrine Sulfate	120.00	Drug Substance
Lactose Monohydrate	(b) (4)	(b) (4)
Dibasic Calcium Phosphate (b) (4)		
Hypromellose (b) (4)		
(b) (4)		
Povidone (b) (4)		
Croscarmellose Sodium		
Magnesium Stearate (b) (4) (b) (4)		
Titanium Dioxide		
Ink (b) (4)		

(b) (4)

The manufacture of Claritin-D 12 Hour Extended Release Tablets is based on technology (b) (4)

[redacted]

(b) (4)

[redacted]

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?
Mechanism of Action:
Loratadine is an antihistamine, and is available in several approved products as OTC medications.

INDICATION, DOSAGE AND ADMINISTRATION (as per proposed labeling for the carton)
The sponsor's proposed indication for Claritin® D-12 Hour ER Tablets is for the temporary relief symptoms due to hay fever or other upper respiratory allergies, such as runny nose, itchy and watery eyes, sneezing, and itching of the nose or throat and for nasal congestion in adults and children 12 years and older. The recommended dose is 1 tablet taken twice daily by oral administration.

[2] Office of Generic Drugs review by Dr. U.S. Atwal, Ph.D. dated May 18, 2001.
V:\FIRMSAM\IMPAX\LTRS&REV\76050.RV1

2.2 General Biopharmaceutics

2.2.1 Was Claritin-D 12 Hour ER Tablets (new formulation) manufactured at Schering Corporation bioequivalent to Loratadine/pseudoephedrine extended release tablet manufactured at IMPAX Labs?

Yes, Loratadine/pseudoephedrine 5 mg/120 mg ER Tablets (ANDA 76-050) manufactured at Impax Labs and Claritin-D 12 Hour ER Tablets manufactured at Schering Corporation were bioequivalent. The 90% confidence intervals for the geometric means Test/Reference ratios for the area under the curve (AUC) and peak concentration (Cmax) for loratadine, desloratadine and pseudoephedrine are within the bioequivalence interval of 80-125.

These results come from study Protocol No. CL2006-08. This study was a single dose, crossover bioequivalence study under fasting conditions entitled "A Single Dose, Comparative, Randomized, Two-Way Crossover Bioequivalence Study of Loratadine/Pseudoephedrine Administered as a Claritin-D 12 Hour Extended Release Tablet from Two Manufacturing Sites". The objective of this study was to evaluate the BE of loratadine/pseudoephedrine combination administered as one extended release combination (loratadine 5 mg/pseudoephedrine sulfate 120 mg) tablet manufactured at Schering Corporation (test treatment) to one extended release combination (loratadine 5 mg/pseudoephedrine sulfate 120 mg) tablet manufactured at Impax Laboratories (reference treatment).

Thirty-six non-smoking, healthy subjects (27 males, 9 females; 34 Caucasian, 1 Hawaiian or other Pacific Islanders/Caucasian and 1 American Indian or Alaska Native) were enrolled in this study and 35 completed the study. One subject withdrew consent due to a family emergency and discontinued from the study (prior to 96 hour, Period II). Subjects received the following treatment after at least 10 hrs of fasting:

> **Treatment A:** CLARITIN-D 12 Hour Tablet. Batch/Lot no.: Lot#7-SP1-11. Manufacturer: Schering Corporation.
>
> **Treatment B:** CLARITIN-D 12 Hour Tablet. Batch/Lot no.: Lot # 7J07AR. Manufacturer: Impax Laboratories.

Each dose was separated by a 14-day washout interval. Blood samples were collected at pre-dose (0 hour) and post-dose at study hours 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 for loratadine, pseudoephedrine, and desloratadine (active metabolite of loratadine) determination. Loratadine and desloratadine were analyzed using a LC-MS/MS method.

A total of 36 subjects were enrolled in the study and 36 subjects completed the study. Individual loratadine Cmax and AUCt values following the administration of the treatments are shown in Figures 2.2.1.1 and 2.2.1.2, respectively. Individual desloratadine Cmax and AUCt following administration of the treatments are represented in Figures 2.2.1.3 and 2.2.1.4, respectively. Likewise, individual pseudoephedrine Cmax and AUCt following administration of the treatments are represented in Figures 2.2.1.5 and 2.2.1.6, respectively. It is noted that the presence of outlier is closely consistent between treatments. This reviewer ran bioequivalence testing with and without the outliers using WinNonlin software (data not shown). The elimination of outliers did not change the outcome of the overall conclusion: bioequivalence between the test and reference products.

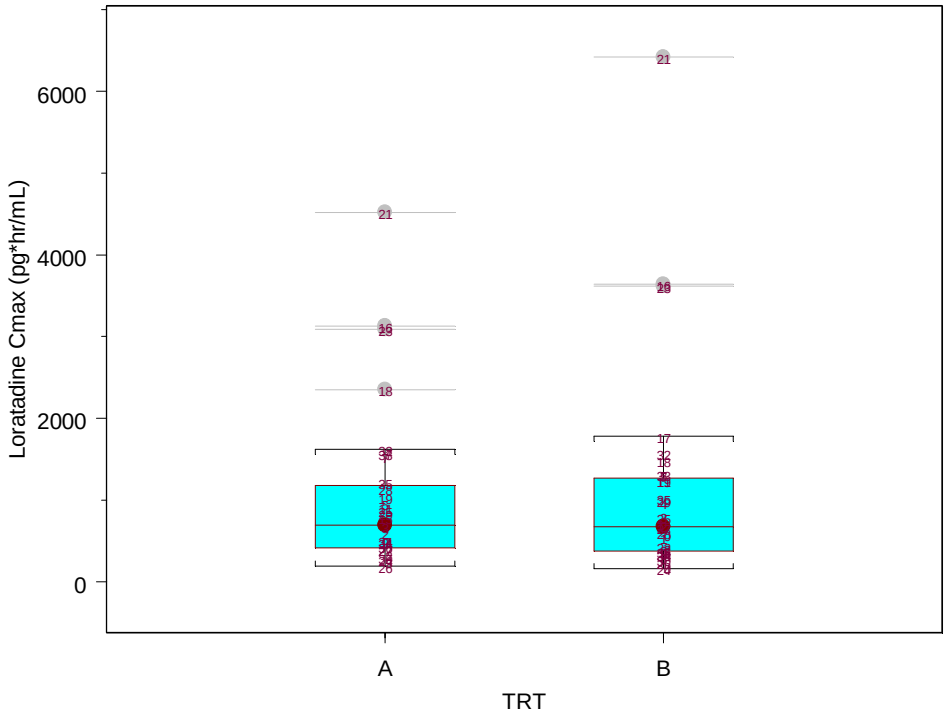


Figure 2.2.1.1**.** Loratadine Cmax box plot following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

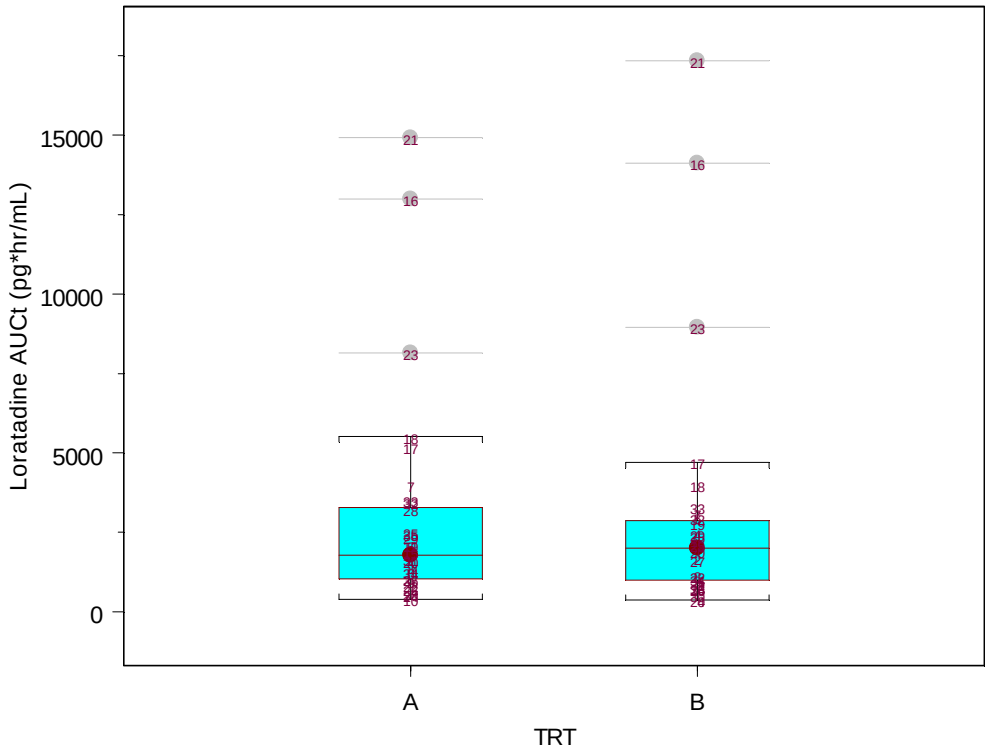


Figure 2.2.1.2**.** Loratadine AUCt box plot following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

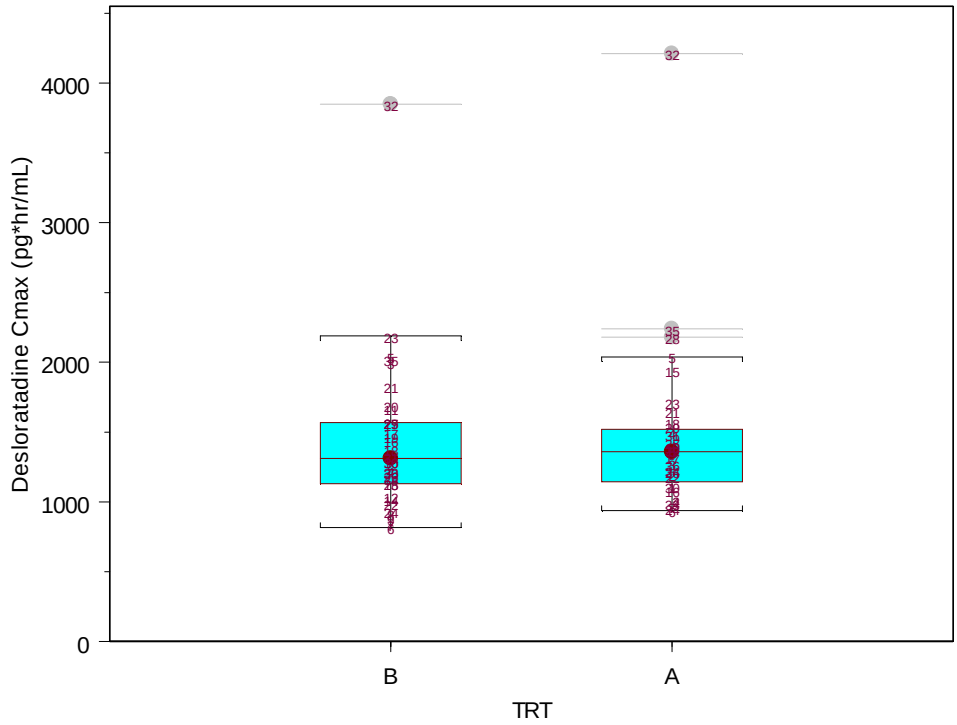


Figure 2.2.1.3**.** Desloratadine Cmax box plot following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

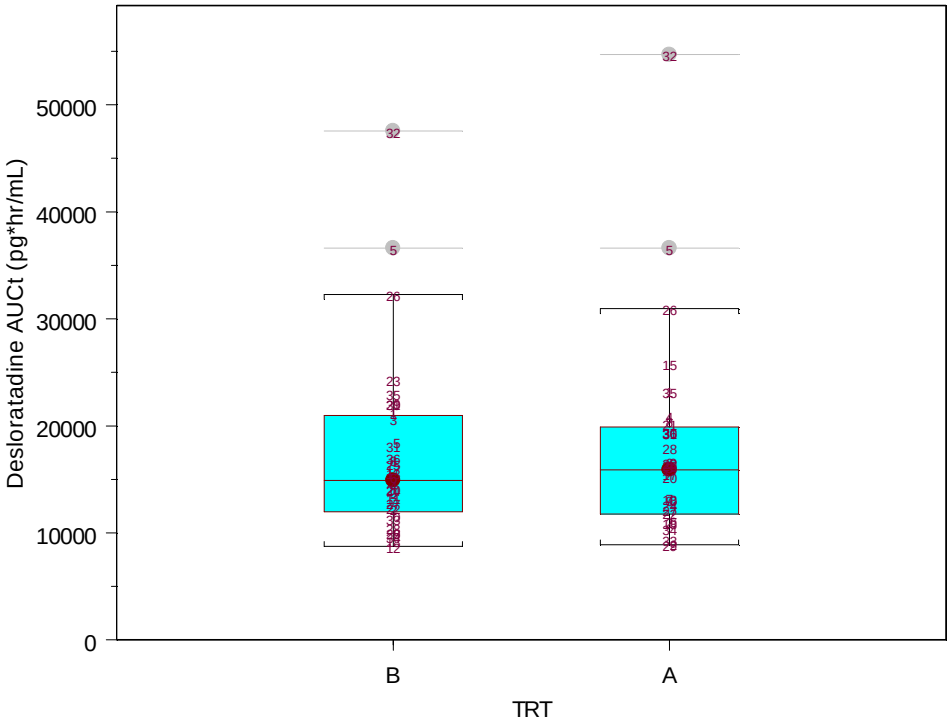


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Figure 2.2.1.4**.** Desloratadine AUCt box plot following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

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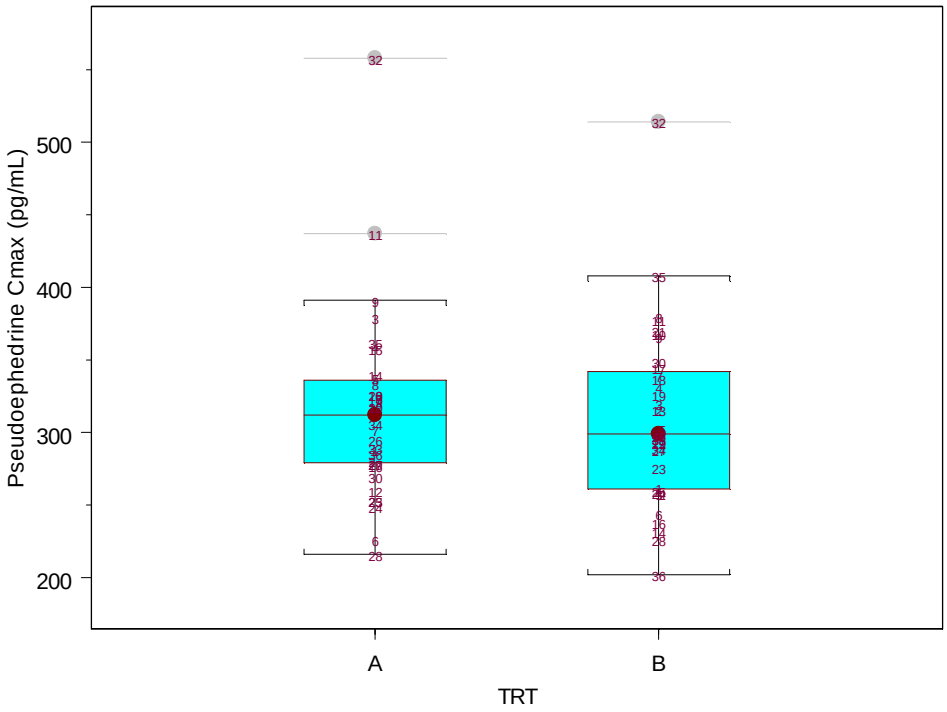

Figure 2.2.1.5**.** Pseudoephedrine Cmax box plot following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

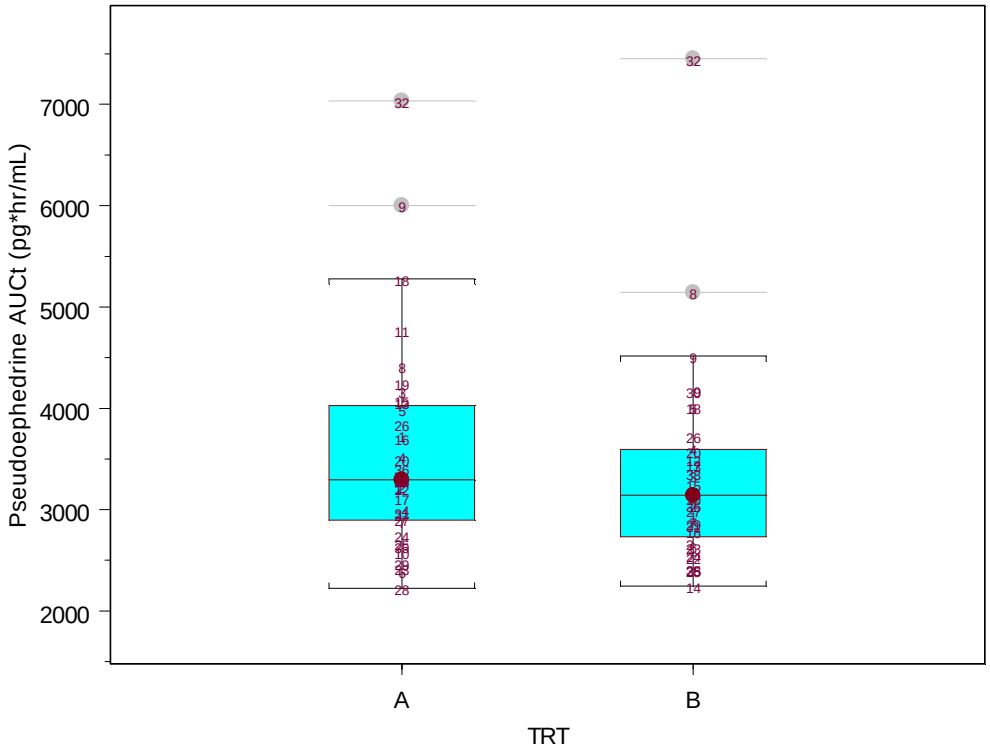

Figure 2.2.1.6**.** Pseudoephedrine AUCt box plot following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

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 loratadine, desloratadine, and pseudoephedrine were within the bioequivalence interval of 80-125 (Table 2.2.1.1).

Table 2.2.1.1. Comparative point estimates and 90% CI reported by the sponsor and calculated by this reviewer

Formulation		**Point estimates (%)**		**90% Confidence Intervals**	
		Loratadine			
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's findings
Trt A/ Trt B	AUCt	103.18	103.17	(94.84, 112.24)	(94.8-112.24)
	AUCinf	102.36	102.36	(94.3, 111.11)	(94.3-111.11))
	Cmax	101.92	101.90	(93.29, 111.35)	(93.9-111.34)
		Desloratadine			
Trt A/ Trt B	AUCt	100.93	101.10	(95.94, 106.18)	(96.2-106.4)
	AUCinf	100.86	101.64	(96.35, 105.58)	(95.4-108.2)
	Cmax	101.35	101.60	(95.17, 107.94)	(95.4-108.2)
		Pseudoephedrine			
Trt A/ Trt B	AUCt	105.67	105.70	(101.33, 110.18)	101.3-110.2
	AUCinf	105.81	105.60	(101.52, 110.28)	(101.4-110.05)
	Cmax	101.84	101.80	(97.83, 106.01)	(97.04-106.01

2.5.4 What is the effect of food on the BA of the drug?

The effect of food on the pharmacokinetics of Claritin-D 12 Hour ER Tablet was not reported in this submission. From a regulatory perspective, a fed BE study is not required when a change in manufacturing site is being considered. It is noted, however, that a bioequivalence study (fasting vs. non-fasting conditions) was conducted for the same formulation under ANDA 76-050. The reviewer for ANDA 76-050 stated that IMPAX's Loratadine/ Pseudoephedrine Sulfate Extended Release Tablet under fasting conditions was bioequivalent to IMPAX's Loratadine/ Pseudoephedrine Sulfate Extended Release Tablet under non-fasting conditions.

2.6 Analytical Section

2.6.1 Was the suitability of the analytical method supported by the submitted information?

Yes. The accuracy and precision for calibration standards and QCs were acceptable for all the methods (<10% Diff or %CV) for in-study validation information (see Tables 2.6.1.1 to 2.6.1.3).

Table 2.6.1.1: In-Study Validation for Loratadine

Matrix	Human Plasma	
Concentration Range	25 to 10000 pg/mL	
HPLC Procedure	LC/MS/MS	
Coefficient of Determination	$r^2 \geq 0.990$	
Between-Batch Accuracy (%Diff)	standards (25, 50, 75, 250, 1000, 3000, 8000, 10000 pg/mL) QCs (60, 150, 500, 1500, 7500 pg/mL)	-1.44 to 0.9 -0.8 to 2
Between-Batch (% CV)	standards QCs	1.8 to 6.4 2.2-4.8
Stability in human plasma	Long term	311 days

Table 2.6.1.2: In-Study Validation for Desloratadine

Matrix	Human Plasma	
Concentration Range	25 to 10000 pg/mL	
HPLC Procedure	LC/MS/MS	
Coefficient of Determination	$r^2 \geq 0.990$	
Between-Batch Accuracy (%Diff)	standards (25, 50, 75, 250, 1000, 3000, 8000, 10000 pg/mL) QCs (60, 150, 500, 1500, 7500 pg/mL)	-1.9 to 2.4 -3.3-0.6
Between-Batch (% CV)	standards QCs	2.3 to 8.5 4.1-7.6
Stability in human plasma	Long term	311 days
Dilution Integrity (QC 3 dil 4 500 ngmL)	%CV=3.6	%Diff=-7.9

Table 2.6.1.3: In-Study Validation for Pseudoephedrine

Matrix	Human Plasma	
Concentration Range	2.5 ng/mL to 500 ng/mL	
HPLC Procedure	LC/MS/MS	
Coefficient of Determination	$r^2 \geq 0.990$	
Between-Batch Accuracy (%Diff)	standards (2.5, 5, 10, 25, 50, 100, 250, 500 ng/mL) QCs (5, 12, 40, 120,	-0.188 to 0.6 -0.4 to 5.1

	400 ng/mL)	
Between-Batch (% CV)	standards QCs	3 to 7.8 3 to 8.1
Within-Batch	Accuracy CV	<10% <10%
Stability in human plasma	Long term	414 days
Dilution Integrity (QC 6 dil 4 1250 ngmL)	%CV=2.7	%Diff=-2.15

Clinical Site (name, address, phone, fax, contact person, if available)	**Analytical Site (name, address, phone, fax, contact person, if available)**
PRACS Institute, Ltd., Cetero Research, 625 DeMers Ave., East Grand Forks, MN 57721. Principal Investigator: Alan K. Copa, Pharm. D.	(b) (4) Principal Analytical Investigator: (b) (6), B.S.

3. Labeling Comments

There are no labeling comments to the proposed carton labeling for this product.

4. APPENDIX 4.1 Individual Study Reports

"A Single Dose, Comparative, Randomized, Two-Way Crossover Bioequivalence Study of loratadine/Pseudoephedrine Administered as a Claritin-D 12 Hour Extended Release Tablet from Two Manufacturing Sites".

Study no.: CL2006-08
Development Phase of Study: Phase I
Principal investigator: Alan K. Copa, Pharm. D.
625 De Mers Avenue
East Grand Forks, MN 56721

Study Dates: February 26, 2007- March 17, 2007

Objectives
Primary:

- to evaluate the BE of loratadine/pseudoephedrine combination administered as one extended release combination (loratadine 5 mg/pseudoephedrine sulfate 120 mg) tablet manufactured at Schering Corporation (test treatment) to one extended release combination (loratadine 5 mg/pseudoephedrine sulfate 120 mg) tablet manufactured at Impax Laboratories (reference treatment).

Study Population

The mean demographic data for subjects included in the study, including standard deviations, subjects, and for all subjects grouped by gender is shown in Table 1.

Table 1. Summary of Mean Demographic Data (±SD)

	All Subjects (N=36)	Males (N=27)	Females (N=9)
Age	26.1 (±7.5)	29.1 (±8.5)	25.1 (±6.4)
Weight (lbs)	170.3 (±24.2)	158.9 (±22.8)	174.1 (±23.8)
Height (in.)	69.8 (±3.1)	66.4 (±2.9)	71 (±2.6)
BMI	24.5 (±2.9)	25.3 (±3)	24.3 (±2.9)

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This single dose, randomized, two-period, two-treatment, two-sequence, crossover study was conducted to compare. Subjects received the following treatments:

Treatment A: CLARITIN-D 12 Hour Tablet. Batch/Lot no.: Lot#7-SP1-11. Manufacturer: Schering Corporation.

Treatment B: CLARITIN-D 12 Hour Tablet. Batch/Lot no.: Lot # 7J07AR. Manufacturer: Impax Laboratories.

Each dose was separated by a 14-day washout interval.

PHARMACOKINETIC MEASUREMENTS

In each study period, blood samples were collected at pre-dose (0 hour) and post-dose at study hours 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 for loratadine, desloratadine, and pseudoephedrine determination.

SAFETY MEASUREMENTS

Safety was evaluated from the results of spontaneously reported signs and symptoms, scheduled physical examinations, measurements of vital signs, 12-lead ECGs, and clinical laboratory evaluations. All adverse events were recorded.

Concomitant therapy

There were no concomitant medications reported.

DATA ANALYSIS

Pharmacokinetic Data Analysis

The analytical data were used to calculate the pharmacokinetic parameters: AUC0-t, AUC0-inf, Cmax, Tmax, ke, and t1/2. Pharmacokinetic variables were calculated from the plasma concentration data using the WinNonLin software for a non-compartmental model.

Statistical Analysis

Summary statistics were provided for the pharmacokinetic parameters and plasma concentrations at each time point. The derived pharmacokinetic parameters were statistically analyzed using a crossover analysis of variance model. The effects due to sequence, subject within sequence, period and treatment were extracted. Following In-transformation, AUC0-t, AUC0-inf, and Cmax results was compared between treatment groups using the two one-sided test procedure. The analysis procedure utilized the following analysis of variance model:
Response = treatment + period + sequence + subject (sequence).

The error term 'subject within sequence' was utilized for the test of sequence effect. One Claritin-D 12 Hour Extended Release Tablet at Schering Corporation (test treatment) was considered bioequivalent to one extended release combination (loratadine 5 mg/pseudoephedrine sulfate 120 mg) tablet manufactured at Impax Laboratories (reference treatment) if the 90% confidence intervals around the ratio of the geometric means for loratadine, desloratadine, and pseudoephedrine ln-transformed AUC0-t, AUC0-inf and Cmax values fall within 80-125%. Preliminary analysis included examining the pharmacokinetic parameters for extreme values.

RESULTS

Analytical Method

In-Study Validation for Loratadine

Matrix	Human Plasma	
Concentration Range	25 to 10000 pg/mL	
HPLC Procedure	LC/MS/MS	
Coefficient of Determination	$r^2 \geq 0.990$	
Between-Batch Accuracy (%Diff)	standards (25, 50, 75,	-1.44 to 0.9

	250, 1000, 3000, 8000, 10000 pg/mL) QCs (60, 150, 500, 1500, 7500 pg/mL)	-0.8 to 2
Between-Batch (% CV)	standards QCs	1.8 to 6.4 2.2-4.8
Stability in human plasma	Long term	311 days

In-Study Validation for Desloratadine

Matrix	Human Plasma	
Concentration Range	25 to 10000 pg/mL	
HPLC Procedure	LC/MS/MS	
Coefficient of Determination	$r^2 \geq 0.990$	
Between-Batch Accuracy (%Diff)	standards (25, 50, 75, 250, 1000, 3000, 8000, 10000 pg/mL) QCs (60, 150, 500, 1500, 7500 pg/mL)	-1.9 to 2.4 -3.3-0.6
Between-Batch (% CV)	standards QCs	2.3 to 8.5 4.1-7.6
Stability in human plasma	Long term	311 days
Dilution Integrity (QC 3 dil 4 500 ngmL)	%CV=3.6	%Diff=-7.9

In-Study Validation for Pseudoephedrine

Matrix	Human Plasma	
Concentration Range	2.5 ng/mL to 500 ng/mL	
HPLC Procedure	LC/MS/MS	
Coefficient of Determination	$r^2 \geq 0.990$	
Between-Batch Accuracy (%Diff)	standards (2.5, 5, 10, 25, 50, 100, 250, 500 ng/mL) QCs (5, 12, 40, 120, 400 ng/mL)	-0.188 to 0.6 -0.4 to 5.1
Between-Batch (% CV)	standards QCs	3 to 7.8 3 to 8.1
Within-Batch	Accuracy CV	<10% <10%

Stability in human plasma	Long term	414 days
Dilution Integrity (QC 6 dil 4 1250 ngmL)	%CV=2.7	%Diff=-2.15

Clinical Site (name, address, phone, fax, contact person, if available)	**Analytical Site (name, address, phone, fax, contact person, if available)**
PRACS Institute, Ltd., Cetero Research, 625 DeMers Ave., East Grand Forks, MN 57721. Principal Investigator: Alan K. Copa, Pharm. D.	(b) (4) Principal Analytical Investigator: (b) (6), B.S.

Reviewer's Remarks

It is noted that information on pre-study validation information was not provided in the analytical report (such as % recovery, short term stability, freeze/thaw stability, etc.). However, since the analytical methodology for loratadine, desloratadine, and pseudoephedrine is well understood, the lack of this information is not critical to the acceptability of the analytical methodology.

A request for inspection of the analytical and clinical sites listed above was sent to DSI. However, due to time constrains, the DSI indicated that an inspection could not be conducted on time (see email below).

-----Original Message-----
From: CDER DSI Bioequivalence
Sent: Friday, February 27, 2009 2:57 PM
To: Adams-King, Janice; CDER DSI Bioequivalence
Cc: Suarez, Sandra; Choe, Sally; Furness, Melissa
Subject: RE: DFS Email - N 019670 SCF 020 22-Dec-2008 - Forms

Our routine policy is to have 4 months from request to completion. Your request came at a particularly difficult time, when our schedules are already full of PDUFA, ForCause, and foreign inspections, all difficult or impossible to reschedule, so we cannot make an exception.

When an audit or inspection is important to a regulatory decision, please be sure to request the inspection promptly, so that we can complete it in time to be useful to you.

Best regards,

Michael F. Skelly, Ph.D.
Pharmacologist
GLP & Bioequivalence Investigations Branch
Division of Scientific Investigations
Office of Compliance/CDER
Food and Drug Administration

The PM for this NDA requested information on the outcome of the latest inspections performed for the clinical and analytical sites. DSI provided this information (see email below) which indicated acceptable overall performance of the sites for different related NDAs.

-----Original Message-----

From: Adams-King, Janice
Sent: Wednesday, March 11, 2009 10:14 AM
To: CDER DSI Bioequivalence
Cc: Furness, Melissa; Choe, Sally; Suarez, Sandra
Subject: RE: DFS Email - N 019670 SCF 020 22-Dec-2008 - Forms

We understand that DSI is unable to conduct an assessment of the facility within the requested timeframe. However, we would appreciate your letting us know the date and findings of the last inspection for this facility? Thank you, Janice

---

-----Original Message-----
From: CDER DSI Bioequivalence
Sent: Wednesday, March 11, 2009 1:43 PM
To: Adams-King, Janice; CDER DSI Bioequivalence
Cc: Furness, Melissa; Choe, Sally; Suarez, Sandra
Subject: RE: DFS Email - N 019670 SCF 020 22-Dec-2008 - Forms

The "EIR Reviews" for these inspections can be found in DFS, associted with the application. Note that some of the applications involved products with loratadine or pseudoephedrine. We hope that in the future we can serve you well by having sufficient notice when inspections are needed.

Inspection history in the last five years:
Start Date Application Classification Comments

PRACS-Cetero/East Grand Forks
(b) (4) *NAI*
NAI
VAI Records audited in Fargo
VAI Records audit in Fargo and also in East Grand Forks

(b) (4)

Upon review of the analytical method results and the history of inspections conducted for the clinical and analytical sites involved in this NDA, the clinical pharmacology review team decided that the clinical pharmacology review could be finalized without the DSI audit (see email below).

-----Original Message-----
From: Suarez, Sandra
Sent: Thursday, March 19, 2009 10:18 PM
To: Choe, Sally
Cc: Adams-King, Janice
Subject: RE: DFS Email - N 019670 SCF 020 22-Dec-2008 - Forms

Sally,
I think that you captured very nicely what we discussed. I just would like to add that, in my opinion, it will be the ONP's last call to decide if an inspection is imperative.

Thanks,
Sandra

-----Original Message-----
From: Choe, Sally
Sent: Thursday, March 19, 2009 9:09 PM
To: Adams-King, Janice
Cc: Suarez, Sandra
Subject: RE: DFS Email - N 019670 SCF 020 22-Dec-2008 - Forms
Hello Janice,
Sandra and I have discussed this and we concluded that we are comfortable finalizing our review and give our recommendation on this NDA without the DSI audit.
As we mentioned, typically we request DSI audit on pivotal BE studies. However, this is not mandatory. When Sandra looked at the study and their bioanalytical reports as well as looking at the DSI audit history below, we felt that we were fine with finalizing the review discussing the acceptability of the NDA.

Sandra,
Please comment if I did not cover our discussion correctly.

Thank you!
Sally-

Pharmacokinetic Results

A total of 36 subjects were enrolled in the study and 35 subjects completed the study. Subject 06 elected to withdraw prior to study hours 98 during period two. Plasma concentration data from 36 subjects were used in the statistical analysis.

The mean plasma concentration-time profiles for loratadine, desloratadine, and pseudoephedrine following administration of the treatments are shown in Figures 1, 2, and 3, respectively. The mean pharmacokinetic parameters for loratadine, desloratadine and pseudoephedrine are summarized in Table 2. Individual loratadine Cmax and AUCt values following the administration of the treatments are shown in Figures 4 and 5, respectively. Individual desloratadine Cmax and AUCt following administration of the treatments are represented in Figures 6 and 7, respectively. Likewise, individual PSE Cmax and AUCt following administration of the treatments are represented in Figures 8 and 9, respectively.

This reviewer ran bioequivalence testing without the outliers using WinNonlin software (data not shown). The elimination of outliers did not change the outcome of the overall conclusion: bioequivalence between the test and reference products.

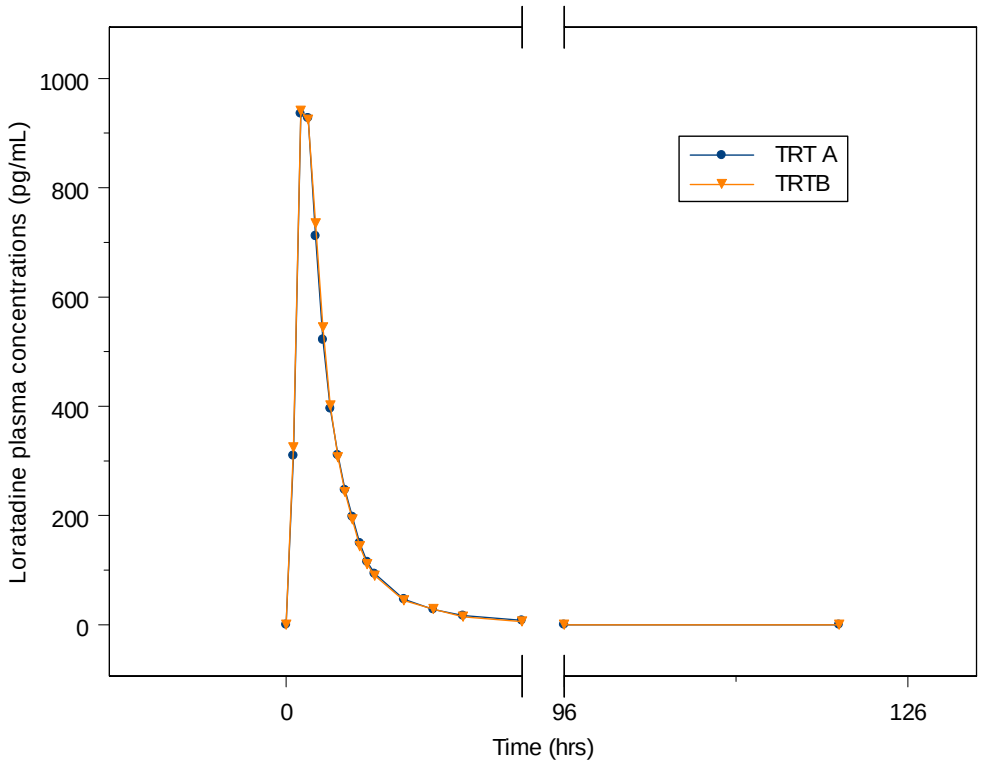

Figure 1. Mean loratadine plasma concentration-time profiles following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

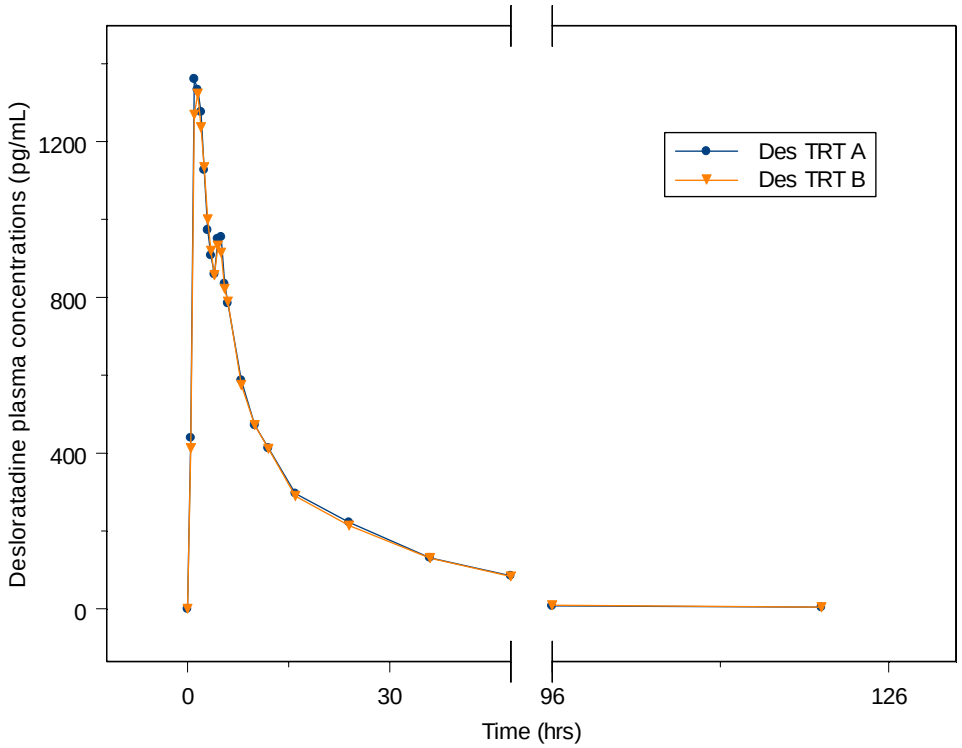

Figure 2. Mean desloratadine plasma concentration-time profiles following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

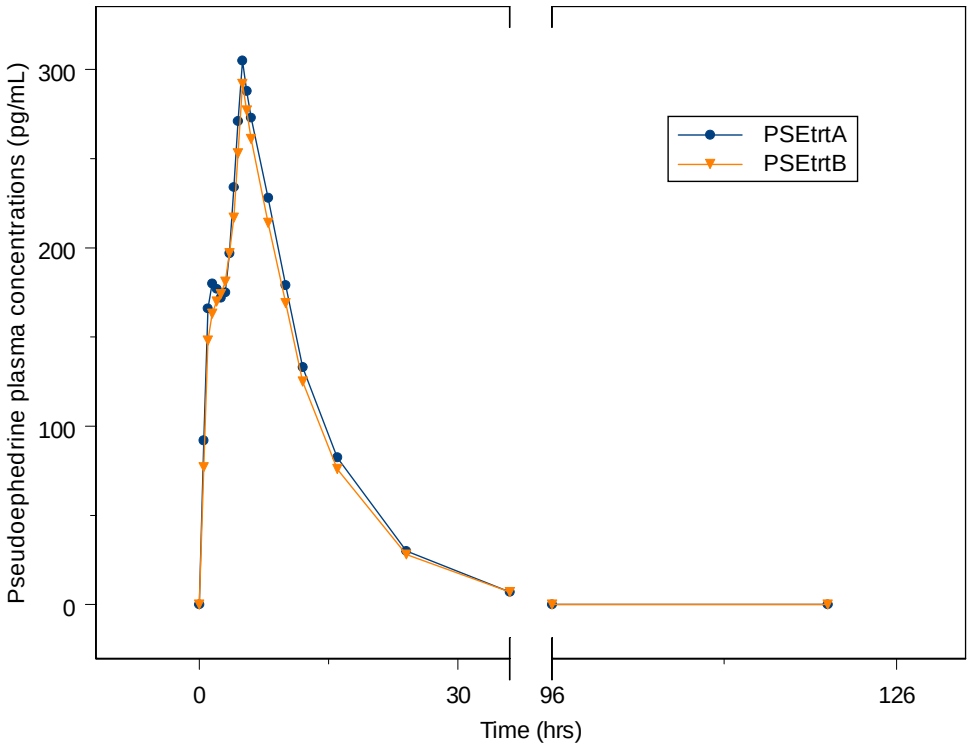

Figure 3. Mean pseudoephedrine plasma concentration-time profiles following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

Table 2. Mean (%CV) pharmacokinetic parameters of loratadine and desloratadine following single administration of the treatments

	Mean (SD) PK Parameters				
Treatment	**Cmax (ng/mL)**	**Tmax (hr)**	**AUCt (ng*hr/mL)**	**AUCinf (ng*hr/mL)**	**T1/2 (hr)**
	Loratadine (n=36)				
TRT T TRT R	998.8 (94.2) 1052 (126.5)	1.26 1.28	2801 (113) 2817 (126.5)	2961 (113) 3005 (126.8)	3.4 (121) 4.35 (193)
	Desloratadine (n=3)				
TRT T TRT R	1454 (39.6) 1440.4 (38)	1.53 1.47	17475 (50.6) 17270 (48)	18603 (50) 18331 (46)	18.81 (34) 18.5 (24)
	Pseudoephedrine (n=32)				
TRT T TRT R	314.8 (20) 309 (19)	4.97 4.97	3538 (29) 3338 (29)	3585 (29) 3378 (28)	5.4 (16) 5.46 (18)

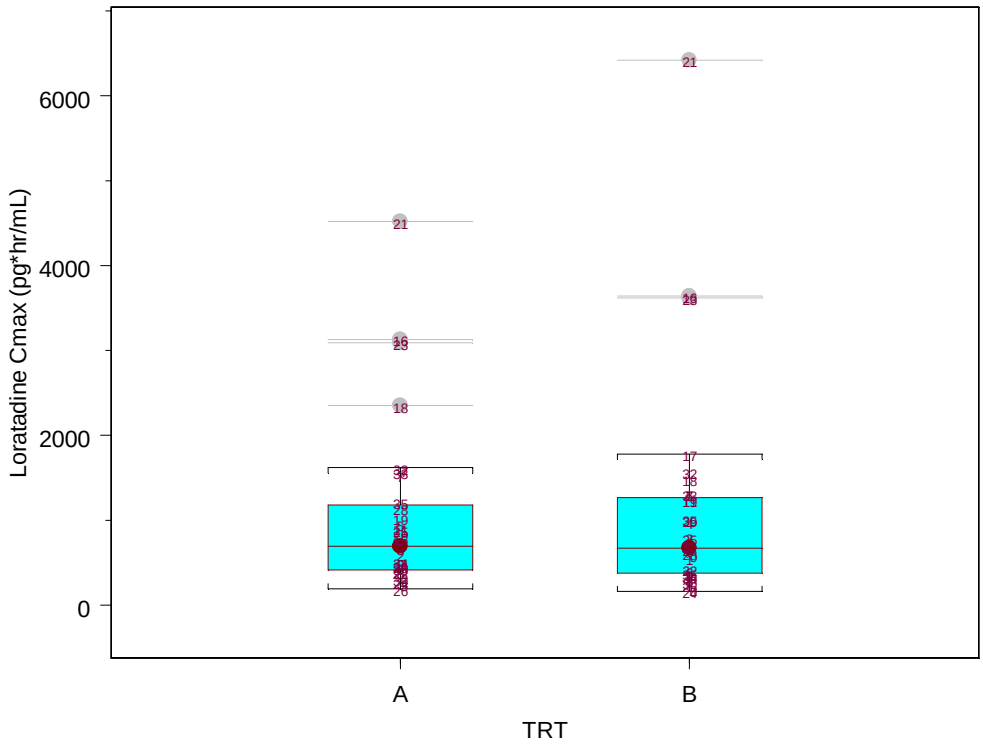

Figure 3. Loratadine Cmax box plot following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

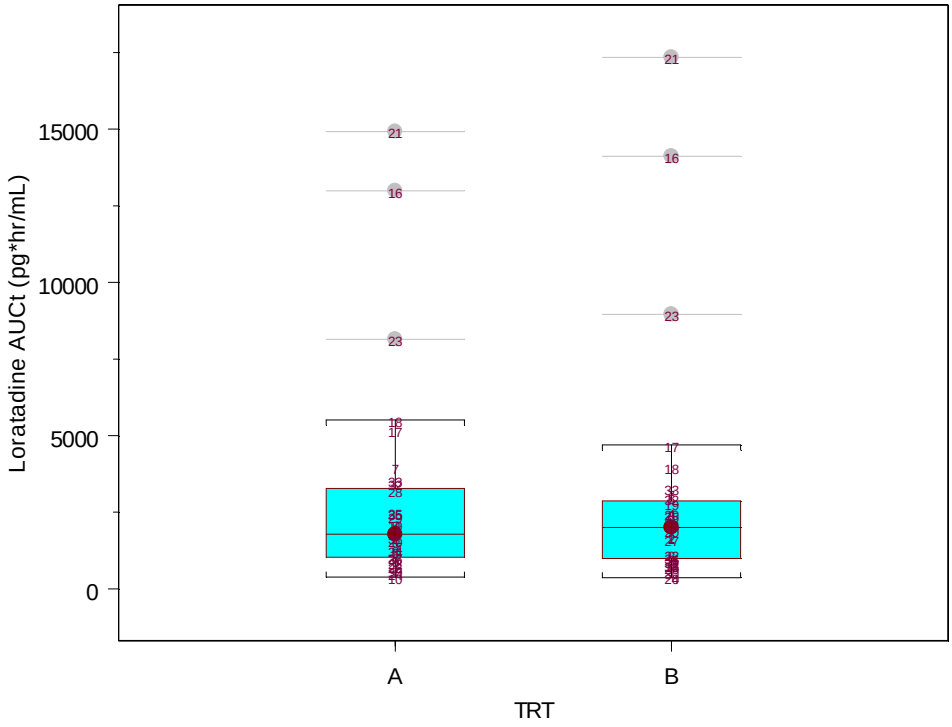

Figure 4. Loratadine AUCt box plot following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

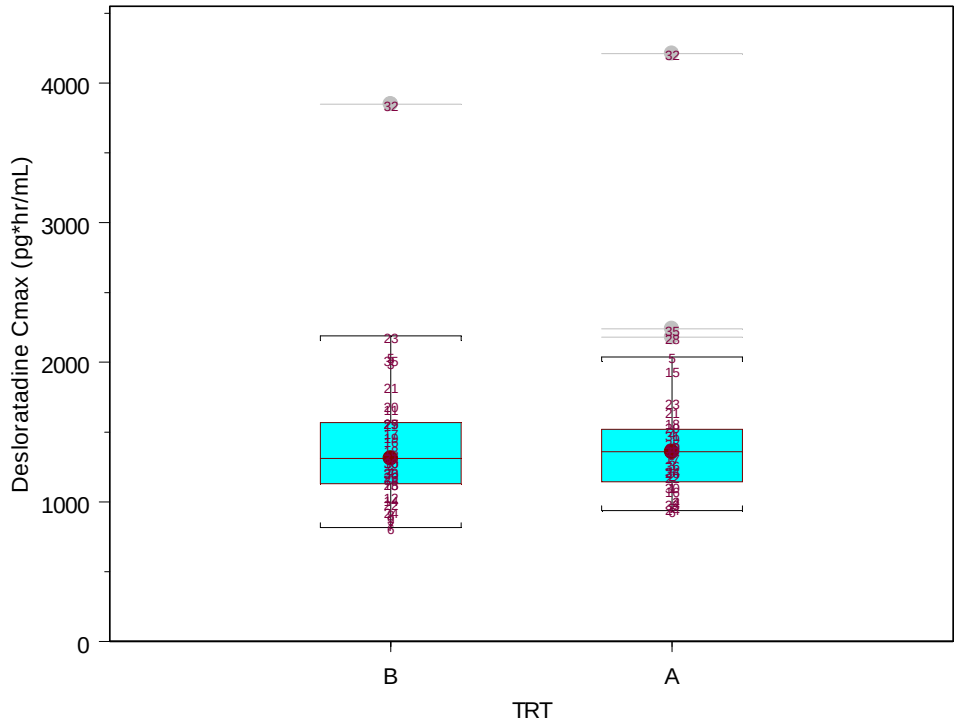

Figure 5. Desloratadine Cmax box plot following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

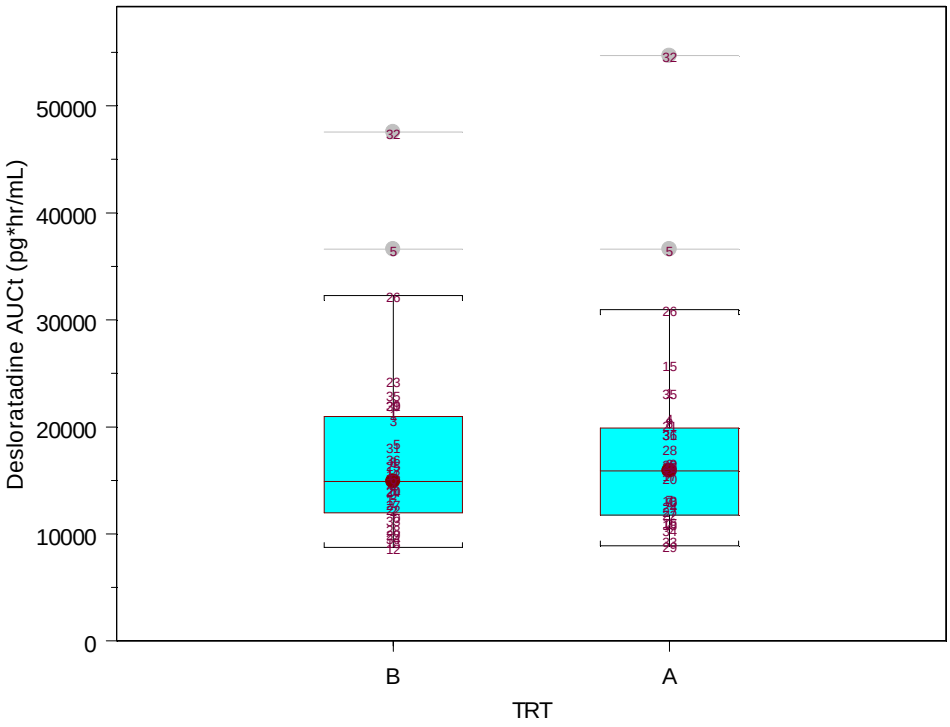

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Figure 6. Desloratadine AUCt box plot following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

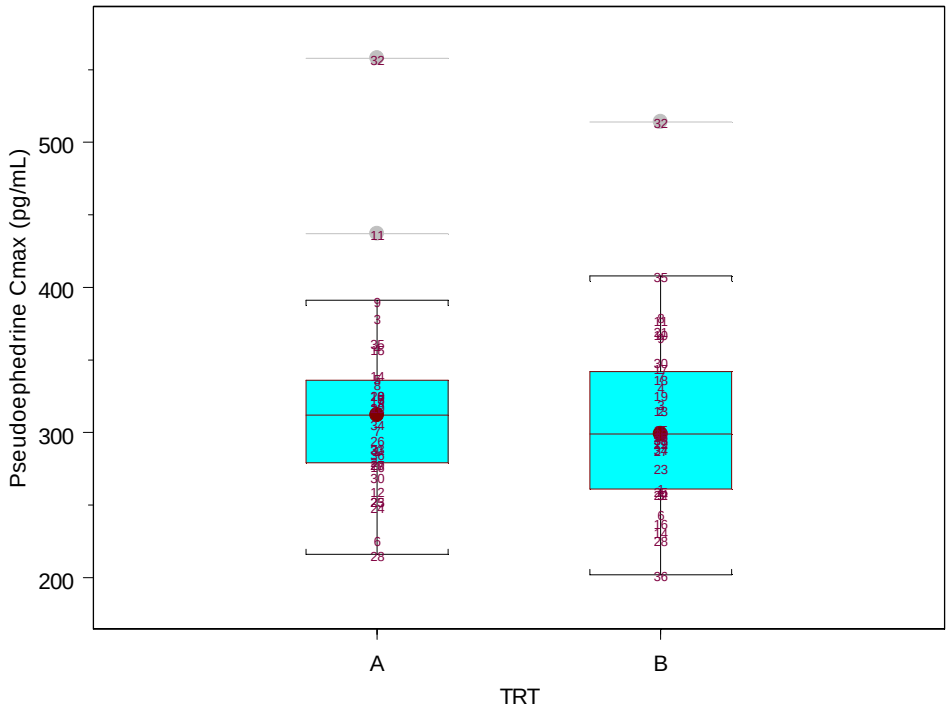

Figure 7. Pseudoephedrine Cmax box plot following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

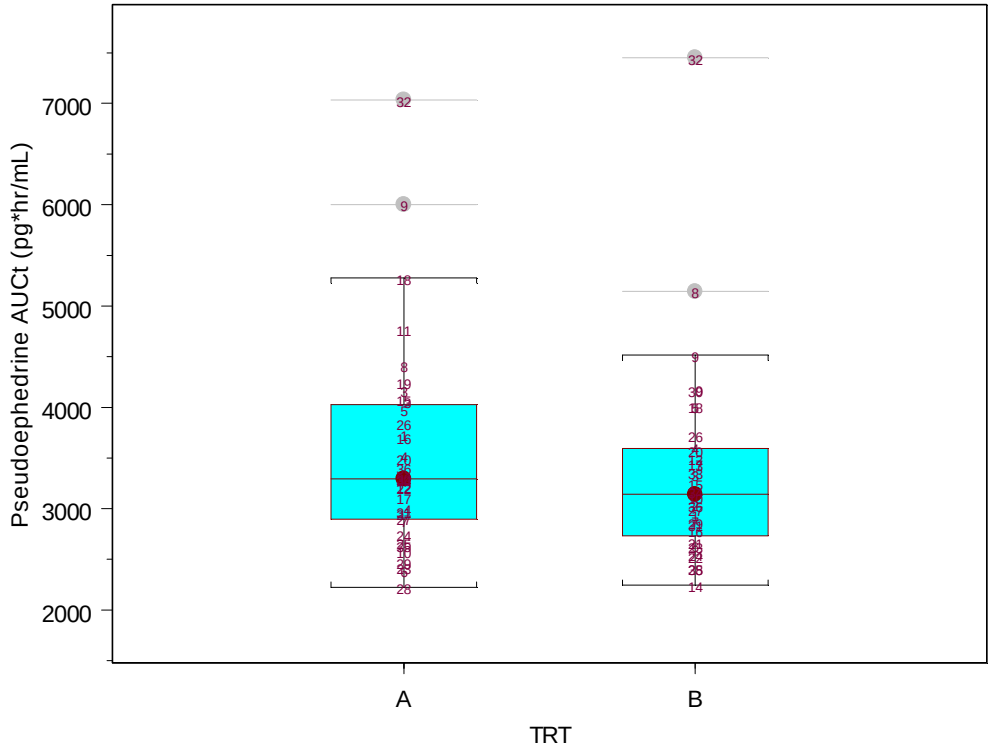

Figure 7. Pseudoephedrine AUCt box plot following single administration of **TRT A:** CLARITIN-D 12 Hour Tablet manufactured at Schering Corporation and **TRT B:** CLARITIN-D 12 Hour Tablet manufactured at Impax Laboratories to 36 male/female healthy volunteers.

Plasma concentrations from 36 subjects were used in the statistical analysis of loratadine, desloratadine and PSE. Cmax and AUC geometric means values of loratadine, desloratadine, and pseudoephedrine following single administration of the treatments are summarized in Table 3. The point estimates and the 90% CIs for the log-transformed Cmax, AUCt and AUCinf for loratadine, desloratadine, and PSE are presented in Table 4. The AUC(t), AUCinf, and Cmax CI for loratadine, desloratadine and PSE of R vs. T met the 80-125% bioequivalence guideline.

Table 3. Cmax and AUC geometric means values of loratadine, desloratadine, and pseudoephedrine following single administration of the treatments

Parameter	Geometric Mean		
	Claritin-D 12 Hour Extended Release Tablet (Schering Corporation) Test	Claritin-D 12 Hour Extended Release Tablet (Impax Laboratories) Reference	% Ratio
Loratadine N=36			
AUC0-t (pg-hr/mL)	1882.91	1824.96	103.18
AUC0-inf (pg-hr/mL)	2001.61	1955.38	102.36
Cmax (pg/mL)	722.61	708.97	101.92
Desloratadine N=36			
AUC0-t (pg-hr/mL)	15993043	15845.62	100.93
AUC0-inf (pg-hr/mL)	17082.05	16936.62	100.86
Cmax (pg/mL)	1382.85	1364.37	101.35
Pseudoephedrine N=36			
AUC0-t (pg-hr/mL)	3418.59	3235.24	105.67
AUC0-inf (pg-hr/mL)	3465.97	3275.61	105.81
Cmax (pg/mL)	309.59	303.99	101.84

Table 4. Comparative point estimates and 90% CI reported by the sponsor and calculated by this reviewer

Formulation		**Point estimates (%)**		**90% Confidence Intervals**	
		Loratadine			
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's
Trt A/ Trt B	AUCt	103.18	103.17	(94.84, 112.24)	(94.8-112.24)
	AUCinf	102.36	102.36	(94.3, 111.11)	(94.3-111.11))
	Cmax	101.92	101.9	(93.29, 111.35)	(93.9-111.34)
		Desloratadine			
Trt A/ Trt B	AUCt	100.93	101.1	(95.94, 106.18)	(96.2-106.4)
	AUCinf	100.86	101.64	(96.35, 105.58)	(95.4-108.2)
	Cmax	101.35	101.6	(95.17, 107.94)	(95.4-108.2)
		Pseudoephedrine			
Trt A/ Trt B	AUCt	105.67	105.7	(101.33, 110.18)	(101.3-110.2)
	AUCinf	105.81	105.6	(101.52, 110.28)	(101.4-110.05)
	Cmax	101.84	101.8	(97.83, 106.01)	(97.04-106.01

Summary of Findings/Conclusion

- Loratadine 5 mg/pseudoephedrine sulfate 120 mg extended release tablet manufactured at Schering Corporation (test treatment) is bioequivalent to loratadine 5 mg/pseudoephedrine sulfate 120 mg extended release tablet manufactured at Impax Laboratories (reference treatment).

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

/s/

Sandra Suarez
4/21/2009 01:54:02 PM
BIOPHARMACEUTICS

Sally Choe
4/21/2009 09:43:47 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-670/S-020

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ORIGINAL

Schering-Plough
HealthCare Products

56 Livingston Avenue
Roseland, NJ 07068
Telephone (862) 245-5127
Fax (862) 245-5127
charles.lanese@spcorp.com

December 22, 2008

Andrea Leonard-Segal, MD, Director
Division of Nonprescription Drug Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 19-670, S-020
Claritin-D® 12 Hour Extended Release Tablets
(loratadine 5 mg, pseudoephedrine sulfate 120 mg)

SCF

SUBJECT: PRIOR APPROVAL SUPPLEMENT: TO INCLUDE A NEW FORMULATION TO NDA 19-670 FOR CLARITIN-D® 12 HOUR EXTENDED RELEASE TABLETS

Dear Dr. Leonard-Segal,

Schering-Plough HealthCare Products (SPHCP) is herein submitting a Supplemental New Drug Application to include (b) (4) Loratadine 5 mg / Pseudoephedrine Sulfate 120 mg to NDA 19-670 for Claritin-D® 12 Hour Extended Release Tablets. In addition, Schering-Plough has transferred the manufacturing, packaging and analytical testing (release and stability) operations of the new formulation to our company facilities in Kenilworth and Union New Jersey.

This supplemental application to NDA 19-670 for Claritin-D® 12 Hour Extended Release Tablets relies on the Agency's previous approval of ANDA 76-050 for the loratadine 5 mg / pseudoephedrine sulfate 120 mg formulation sponsored by Impax Laboratories and the (b) (4) (b) (4)

A Briefing Document for a Type C Meeting was submitted to FDA on April 13, 2007. The purpose of the meeting was to discuss and gain agreement on the requirements for the submission of a CMC supplement to add the new formulation, manufacturing process, packaging and analytical methods for Claritin-D® 12 Hour Extended Release Tablets into the SPHCP sponsored NDA 19-670. The meeting also sought the Agency's concurrence regarding the design of the proposed bioequivalence study to be conducted in support of these changes.

The Agency sent a preliminary response via fax dated May 15, 2007 which documented agreement with SPHCP's proposed filing strategy of the CMC supplement. The Agency also agreed with the design of the proposed bioequivalence study. A copy of the preliminary response is included in Module 1, Section 1.6.3. The Type C meeting was subsequently canceled and the preliminary response was included in FDA's Documentation File System under NDA 19-670.

Module 5 contains the study report from Protocol CL2006-08, "A Single Dose, Comparative, Randomized, Two-Way Crossover Bioequivalence Study of Loratadine/Pseudoephedrine Administered as a Claritin-D® 12 Hour Extended Release Tablet From Two Manufacturing Sites." This study supports the inclusion of this formulation in the subject NDA. Discussion of the results of this study can be found in Section 2.5 Clinical Overview and Section 2.7 Clinical Summary.

The Claritin-D® 12 Hour Extended Release Tablets will be packaged in blister packages consisting of a foil based lidding structure (b) (4) sealed to a (b) (4) blister film and placed in fully labeled cartons. The proposed labeling for the subject product is based on the currently approved labeling for Claritin-D® 12 Hour Extended Release Tablets manufactured under Impax Laboratories ANDA 76-050 and marketed by SPHCP. Draft labeling is provided in Module 1.

The enclosed supplemental new drug application provides the following items in CTD format per the current FDA guidance.

Archival Copy (blue jackets)
- CTD Module 1 – Administrative
- CTD Module 2 – Summaries
- CTD Module 3 – Quality
- CTD Module 5 – Clinical

CMC Review Copy (red jackets)
- CTD Module 1 – Administrative
- CTD Module 2 – Summaries
- CTD Module 3 – Quality

Phmarmacokinetics Review Copy (orange jackets)
- CTD Module 1 – Administrative
- CTD Module 2 – Summaries
- CTD Module 5 – Clinical

Clinical Review Copy (tan jackets)
- CTD Module 1 – Administrative
- CTD Module 2 – Summaries
- CTD Module 5 – Clinical

Patent information, also provided in Module 1 Section 1.3.5.1 of this submission, has been previously provided on December 18, 2008 to the Center for Drug Evaluation and Research Central Documentation Room via facsimile and courier. The patent information submission references this filing to NDA 19-670 under Supplement S-020.

In accordance with 21 CFR 314.70(a)(5) Schering-Plough HealthCare Products certifies that a copy of this supplement is being sent to FDA's New Jersey District Office.

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If you have any questions regarding this submission, please contact me at (862) 245-5127.

Sincerely,

Charles Lanese

Charles Lanese
Manager, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Sylvia Gantt, HFD-003, 301-796-2123. WO51 Rm. 4195	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Tu-Van Lambert, ONDQA, Division of Post-Marketing Assessment, 301-796-4246, WO21 Rm. 2625

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 21, 2009		19-670	SCF-020	December 22, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Claritin-D			April 1, 2009

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☒ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Supplement provides for transferring the manufacturing, packaging and analytica testing (release and stability) operations fo the new formulations to company facilities in Kenilworth and Union, NJ. The sponsor is adding microbial testing to their specifications.

PDUFA date is April 23, 2009.

SIGNATURE OF REQUESTOR Tu-Van Lambert	METHOD OF DELIVERY (Check one) ☐ DFS ☐ EMAIL ☐ MAIL ☒ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Tu-Van Lambert

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