CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 077991

Name: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg (OTC)

Sponsor: Sandoz, Inc.

Approval Date: March 5, 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077991

CONTENTS

Reviews / Information Included in this Review

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Tentative Approval Letter	
Labeling	**X**
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Bioequivalence Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077991

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-991

Sandoz, Inc.
Attention: Beth Brannan
Director, Regulatory Affairs
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 15, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg (OTC).

Reference is also made to your amendments dated February 14, May 26, and December 14, 2006; November 30, and December 19, 2007; and January 31, and February 29, 2008. We also acknowledge receipt of your correspondence dated April 14, 2006, April 16, June 11, December 6, December 12, December 13, December 14, and December 17, 2007, pertaining to the patent issues associated with this ANDA.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted over-the-counter (OTC) labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg, to be bioequivalent to the reference listed drug (RLD), Zyrtec-D Extended-Release Tablets, (12-Hour), 5 mg/120 mg, of Pfizer Pharmaceuticals, Inc. (Pfizer).

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA. The "interim" dissolution specifications are as follows:

The dissolution testing should be conducted in 500 mL of 0.1 N HCl at 37°C, using USP Apparatus I (Basket) at 100 rpm. The test product should meet the following "interim" specifications:

Component	Time (hours)	Percent Dissolved
Cetirizine HCl	0.5	NLT 80%
Pseudoephedrine HCl	1	30-50
	2	50-70
	6	NLT 80

The "interim" dissolution tests and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement – Changes Being Effected" if there are no revisions to be made to the "interim" specifications, or if the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The RLD upon which you have based your ANDA, Pfizer's Zyrtec-D Extended-Release Tablets, is subject to periods of patent protection. The following patents with their expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
6,469,009 (the '009 patent)	July 13, 2019
6,489,329 (the '329 patent)	April 8, 2016
7,014,867 (the '867 patent)	June 10, 2022
7,226,614 (the '614 patent)	June 10, 2022

With respect to each of these patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg, under this

ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against Sandoz, Inc.(Sandoz) for infringement of one or more of these patents that were the subjects of the paragraph IV certifications. You have notified the agency that Sandoz complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement was brought against Sandoz within the statutory 45-day period, which action would have resulted in a 30-month stay of approval under section 505(j)(5)(B)(iii).

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

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

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Robert L. West
3/5/2008 12:54:05 PM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077991

LABELING

NDC 0781-5285-31

Cetirizine HCl and Pseudoephedrine HCl Extended Release Tablets

5 mg/120 mg

antihistamine/nasal decongestant

ALLERGY & CONGESTION Indoor & Outdoor Allergies

12 hour Relief of
- Runny Nose
- Itchy, Watery Eyes
- Sinus Pressure
- Sneezing
- Itchy Throat or Nose
- Nasal Congestion

SANDOZ

30 Tablets

S2 912

Open for Full Labeling →

Drug Facts

Active ingredients (in each extended release tablet) **Purpose**

Cetirizine HCl 5 mg	Antihistamine
Pseudoephedrine HCl 120 mg	Nasal decongestant

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

Sandoz Inc
Princeton, NJ 08540
12-2007M

LOT:
EXP:

N 3 0781-5285-31 9

Panel 1

Drug Facts (continued)

Warnings

Do not use
- if you have ever had an allergic reaction to this product or any of its ingredients or to an antihistamine containing hydroxyzine
- if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product

Ask a doctor before use if you have
- heart disease
- thyroid disease
- diabetes
- glaucoma
- high blood pressure
- trouble urinating due to an enlarged prostate gland
- liver or kidney disease. Your doctor should determine if you need a different dose

Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives

When using this product
- **do not use more than directed**
- drowsiness may occur
- avoid alcoholic drinks
- alcohol, sedatives, and tranquilizers may increase drowsiness
- be careful when driving a motor vehicle or operating machinery

Panel 2

Drug Facts (continued)

Stop use and ask a doctor if
- an allergic reaction to this product occurs. Seek medical help right away
- you get nervous, dizzy, or sleepless
- symptoms do not improve within 7 days or are accompanied by fever

If pregnant or breast-feeding:
- if breast-feeding: not recommended
- if pregnant: ask a health professional before use

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away

Directions
- do not break or chew tablet; swallow tablet whole

adults and children 12 years and over	take 1 tablet every 12 hours; do not take more than 2 tablets in 24 hours
adults 65 years and over	ask a doctor
children under 12 years of age	ask a doctor
consumers with liver or kidney disease	ask a doctor

Panel 3

Drug Facts (continued)

Other information

- Safety sealed: do not use if the imprinted bottle seal is open or torn
- Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature)

Inactive ingredients

Colloidal silicon dioxide, croscarmellose sodium, D & C yellow aluminum lake, hypromellose, iron oxide red, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate, povidone, and titanium dioxide

NDC 0781-5285-31

Cetirizine HCl and Pseudoephedrine HCl Extended Release Tablets

5 mg/120 mg

antihistamine/nasal decongestant

ALLERGY & CONGESTION **Indoor & Outdoor Allergies**

12 hour Relief of

- Runny Nose
- Itchy, Watery Eyes
- Sinus Pressure
- Sneezing
- Itchy Throat or Nose
- Nasal Congestion

SANDOZ

30 Tablets

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077991

LABELING REVIEWS

This labeling approval summary supersedes the labeling approval summary dated December 14, 2006.

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

ANDA Number: 77-991

Dates of Submission: December 19, 2007 and November 30, 2007

Applicant's Name: Sandoz Inc.

Established Name: Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets, 5 mg/120 mg (OTC)

BASIS OF APPROVAL:

APPROVAL SUMMARY

CONTAINER (bottles of 30)

Satisfactory in FPL as of December 19, 2007 e-submission.

REFERENCE LISTED DRUG:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Zyrtec-D 12 Hour Extended Release Tablets
NDA Number: 21-150
NDA Drug Name: Zyrtec-D 12 Hour Extended Release® Tablets
NDA Firm: Pfizer Pharmaceuticals
Date of Approval of NDA Insert and supplement: NDA 21-150/S-007, approved November 9, 2007
This supplement provided for the OTC switch
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison
Basis of Approval for the Package Insert: Side-by-side comparison

PATENTS/EXCLUSIVITIES for NDA 21-150

Patent Data

No	Expiration	Use Code	Use	File	Labeling Impact
6469009	JUL 13, 2019	U-295	Treatment of seasonal and perennial allergic rhinitis symptoms	IV	None
6489329	APR 8, 2016			IV	None
7014867	Jun 10, 2012			IV	None

Exclusivity Data

There is no unexpired exclusivity for this product.

FOR THE RECORD:

1. The following review is based on the on the labeling of Zyrtec-D 12 Hour Extended Release Tablets (NDA 21-150/S-007) approved November 9, 2007.

2. **PATENTS/EXCLUSIVITIES for NDA 21-150**
See above table.

3. MANUFACTURING FACILITY
Sandoz Inc.

West Midway Blvd.
Broomfield, CO 80038-0446
(pp. 440-1)

4. SCORING:
NDA - unscored
ANDA - unscored

5. STORAGE CONDITIONS:
NDA - Store at 20° to 25°C (68° to 77°F)
ANDA - Store at 20° to 25°C (68° to 77°F)

6. DISPENSING RECOMMENDATIONS:
NDA - Dispense in tight containers (USP).
ANDA - Dispense in a tight, light-resistant container.

7. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears IS NOT consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 96 (Volume 1.1). (b) (4)

8. PACKAGING CONFIGURATIONS:

NDA- packages of 24 blisters

ANDA- bottles of 30

9. CONTAINER/CLOSURE SYSTEM:

Size	Container	Closure
30 Count	120 cc, Round White, Opaque, HDPE	38 mm, Plastic CRC, w/ (b) (4) inner seal

CRC = child resistant closure (b) (4)

10. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

Round, film-coated yellow bilayer tablets, debossed SZ 912 on one side and plain on the reverse side

11. Firm submitted labeling for the (b) (4)

Date of Review: January 7, 2008

Dates of Submission: December 19, 2007 and November 30, 2007

Primary Reviewer: Postelle Birch-Smith

Team Leader: John Grace

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cc: ANDA: 77-991
DUP/DIVISION FILE

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/s/

Postelle Birch
1/7/2008 04:43:48 PM
LABELING REVIEWER

John Grace
1/8/2008 11:08:59 AM
LABELING REVIEWER
30 count bottles only are satisfactory for approval. The

(b) (4)

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

ANDA Number:	77-991	Date of Submission:	December 14, 2006
Applicant's Name:	Sandoz Inc.		
Established Name:	Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets, 5 mg/120 mg		

BASIS OF APPROVAL:

APPROVAL SUMMARY

1. CONTAINER (bottles of 30, (b) (4) tablets)

Satisfactory in FPL as of December 14, 2006 e-submission. (Vol. 5.1)

2. INSERT

Satisfactory in FPL as of December 14, 2006 e-submission. (Vol. 5.1)

REFERENCE LISTED DRUG:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Zyrtec-D 12 Hour Extended Release Tablets
NDA Number: 21-150
NDA Drug Name: Zyrtec-D 12 Hour Extended Release® Tablets
NDA Firm: Pfizer Pharmaceuticals
Date of Approval of NDA Insert and supplement: NDA; NDA 21-150/S-005, approved March 17, 2004
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison
Basis of Approval for the Package Insert: Side-by-side comparison

PATENTS/EXCLUSIVITIES for NDA 21-150

Patent Data

No	Expiration	Use Code	Use	File	Labeling Impact
4525358	JUN 25, 2007	U-295	Treatment of seasonal and perennial allergic rhinitis symptoms	III	None
4525358***PED**	DEC 25, 2007	U-295	Treatment of seasonal and perennial allergic rhinitis symptoms	III	None
6469009	JUL 13, 2019	U-295	Treatment of seasonal and perennial allergic rhinitis symptoms	IV	None
6489329	APR 8, 2016			IV	None
7014867	Jun 10, 2012			IV	None

Exclusivity Data

There is no unexpired exclusivity for this product.

FOR THE RECORD:

1. The following review is based on the on the labeling of Zyrtec-D 12 Hour Extended Release Tablets (NDA 21-150/S-005) approved March 17, 2004.

2. **PATENTS/EXCLUSIVITIES for NDA 21-150**

See above table.

3. MANUFACTURING FACILITY
Sandoz Inc.
West Midway Blvd.
Broomfield, CO 80038-0446
(pp. 440-1)

4. SCORING:
NDA - unscored
ANDA - unscored

5. STORAGE CONDITIONS:
NDA - Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]
ANDA - Store at 20° to 25°C (68° to 77°F) [See USP Controlled Rom Temperature]

6. DISPENSING RECOMMENDATIONS:
NDA - Dispense in tight containers (USP).
ANDA - Dispense in a tight, light-resistant container.

7. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears IS NOT consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 96 (Volume 1.1). (b) (4)

8. PACKAGING CONFIGURATIONS:

NDA- bottles of 100

ANDA- The applicant proposes to market its product in bottles of 30, (b) (4)

9. CONTAINER/CLOSURE SYSTEM:

Size	Container	Closure
30 Count	120 cc, Round White, Opaque, HDPE	38 mm, Plastic CRC, w/ (b) (4) inner seal
	(b) (4)	(b) (4)

CRC = child resistant closure (b) (4)
(p. 727)

10. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

Round, film-coated yellow bilayer tablets, debossed SZ 912 on one side and plain on the reverse side

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Date of Review: January 9, 2007

Date of Submission: December 14, 2006

Primary Reviewer: Postelle Birch-Smith

Team Leader: John Grace

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cc: ANDA: 77-991
DUP/DIVISION FILE

Following this page, 7 pages withheld in full (b)(4)

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

/s/

Postelle Birch
1/11/2007 05:33:28 PM
MEDICAL OFFICER

John Grace
1/12/2007 11:19:59 AM
MEDICAL OFFICER

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

ANDA Number:	77-991
Date of Submission:	November 15, 2005
Applicant's Name:	Sandoz Inc.
Established Name:	Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets, 5 mg/120 mg

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Labeling Deficiencies:

1. CONTAINER (bottles of 30, (b) (4) tablets)

Revise the (b) (4) to read, (b) (4)

2. INSERT

a. (b) (4)

b. Place all section headings on a single line.

c. Revise "Cetirizine Hydrochloride and Pseudophedrine Hydrochloride" to read "Cetirizine Hydrochloride and Pseudophedrine Hydrochloride Extended Release Tablets" (b) (4)

3. GENERAL COMMENT

Your submission did not address the 7014867 patent. Please comment.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

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

FOR THE RECORD:

1. The following review is based on the on the labeling of Zyrtec-D 12 Hour Extended Release Tablets (NDA 21-150/S-005) approved March 17, 2004.

2. **PATENTS/EXCLUSIVITIES for NDA 21-150**

Patent Data

No	Expiration	Use Code	Use	File	Labeling Impact
4525358	JUN 25, 2007	U-295	Treatment of seasonal and perennial allergic rhinitis symptoms	III	None
4525358***PED**	DEC 25, 2007	U-295	Treatment of seasonal and perennial allergic rhinitis symptoms	III	None
6469009	JUL 13, 2019	U-295	Treatment of seasonal and perennial allergic rhinitis symptoms	IV	None
6489329	APR 8, 2016			IV	None
7014867	Jun 10, 2012				Firm did not address

Exclusivity Data

There is no unexpired exclusivity for this product.

3. MANUFACTURING FACILITY
Sandoz Inc.
West Midway Blvd.
Broomfield, CO 80038-0446
(pp. 440-1)

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ANDA - unscored

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ANDA - Store at 20° to 25°C (68° to 77°F) [See USP Controlled Rom Temperature]

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The listing of inactive ingredients in the DESCRIPTION section of the package insert appears IS NOT consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 96 (Volume 1.1). (b) (4)

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NDA- bottles of 100

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9. CONTAINER/CLOSURE SYSTEM:

Size	Container	Closure
30 Count	120 cc, Round White, Opaque, HDPE	38 mm, Plastic CRC, w/ (b) (4) inner seal
	(b) (4)	

		(b) (4)

CRC = child resistant closure (b) (4)
(p. 727)

10. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

Round, film-coated yellow bilayer tablets, debossed SZ 912 on one side and plain on the reverse side

---

Date of Review: October 17, 2006

Date of Submission: November 15, 2005

Primary Reviewer: Postelle Birch

Team Leader: John Grace

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cc: ANDA: 77-991
DUP/DIVISION FILE

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/s/

Postelle Birch
10/20/2006 12:53:33 PM
MEDICAL OFFICER

John Grace
10/22/2006 12:18:50 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077991

CHEMISTRY REVIEWS

ANDA # 77-991

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg / 120 mg

Sandoz, Inc.

Guoping Sun, Ph.D.

Office of Generic Drugs
Division of Chemistry III
Team 4

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 77-991

2. REVIEW #: 5

3. REVIEW DATE: 2-13-2008/revised on 2-26-08/3-3-08

4. REVIEWER: Guoping Sun, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Submission(s)	Document Date
Original	11-15-2005
Minor Amendment	10-10-2006
Minor Amendment	08-09-2007
Minor Amendment (*Response to deficiency letter*)	12-27-2007
[redacted] (b) (4)	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment (*Response to deficiency letter*)	01-31-2008
Telephone Amendment (*Addition of stability test for* [redacted] (b) (4))	02-29-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	***Sandoz Inc.***
Address:	2555 West Midway Blvd Broomfield, CO 80038
Representative:	Beth Brannan
Telephone:	303-438-4237
Fax:	303-438-4600

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug: ZYRTEC –D 12 HOUR Extended Release Tablets

RLD Company: Pfizer, NDA # 21150

Patent Certification: Paragraph III and IV, See review #1

Exclusivity: No, See review #1

10. PHARMACOLOGICAL CATEGORY: Antihistamine

11. DOSAGE FORM: Tablets

(MDD $_{\text{cetirizine HCl}}$ = 10 mg/day)

(MDD $_{\text{pseudoephedrine HCl}}$ = 240 mg/day)

12. STRENGTH/POTENCY: 5 mg / 120 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: ____ Rx __X__ OTC

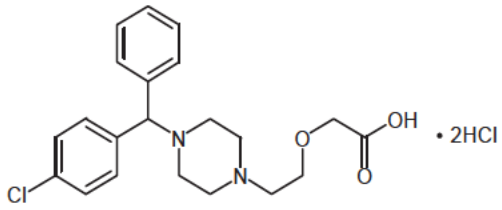
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

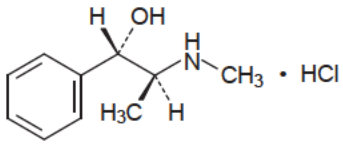
(1). Cetirizine Hydrochloride

- (±)- [2-[4-[4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride
- $C_{21}H_{27}Cl_3N_2O_3$ MW = 461.8



(2). Pseudoephedrine Hydrochloride

- (+) (1S-2S)-2-Methylamino-1-Phenyl-1-Propanol-Hydrochloride
- $C_{10}H_{16}ClNO$ MW = 201.7



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEWED	COMMENTS
(b) (4)	II		(b) (4)	3	*Adequate*	02-06-2008	Reviewed by N.Takiar
	II			1	*Adequate*	2-26-2008	Reviewed by G.Sun
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	*Acceptable*	11-16-2007	S.Adams
Methods Validation	N/A		
Labeling	*Acceptable*	1/8/2008	Postelle Birch
Bioequivalence	Dissolution- *Satisfactory* BE/BA - *Satisfactory*	9-15-06	Parthapratim Chandaroy
EA	Satisfactory	3/29/06	R. Iser
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.

__X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 77-991

The Executive Summary

Product: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets, 5 mg / 120 mg

Firm: Sandoz Inc.

I. Recommendations

A. Recommendation and Conclusion on Approvability

This ANDA is *Approvable.*

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

The proposed drug product, Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets is non-sterile, non-USP product. The drug product contains 5 mg of Cetirizine HCl in the immediate release layer and 120 mg in the extended release layer (mimics RLD).

The tablet is a 13/32 inch convex, [redacted] (b) (4), round, bi-layer tablet [redacted] (b) (4), debossed with SZ over 912 on one side and plain on the reverse side, film coated yellow. Note: Neither the RLD nor the proposed tablets are scored.

The inactive ingredients for the drug product are: Colloidal Silicon Dioxide NF; Croscarmellose Sodium NF; Hypromellose USP; Lactose Monohydrate NF; Povidone USP; Magnesium Stearate, NF; Microcrystalline Cellulose NF; D&C Yellow [redacted] (b) (4) Aluminum Lake [redacted] (b) (4) and [redacted] (b) (4)

Dissolution method:

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable (at the L1 level) by DBE.

	RLD method	FDA recommended method	Sandoz's method
Medium	0.1N HCl	0.1N HCl	0.1N HCl
Volume	500 mL	500 mL	500 mL
Temperature	37°C	37°C	37°C
Apparatus	1 (Basket)	1 (Basket)	1 (Basket)
Rotational Speed	100 rpm	100 rpm	100 rpm
Specification	Cetirizine: NLT 80% (Q) at 30 min Pseudoephedrine: 1 hr: 30-50% 2 hr: 50-70% 6 hr: NLT 80%	Cetirizine: NLT 80% (Q) at 30 min Pseudoephedrine: 1 hr: 30-50% 2 hr: 50-70% 6 hr: NLT 80%	Cetirizine: NLT 80% (Q) at 30 min Pseudoephedrine: 1 hr: 30-50% 2 hr: 50-70% 6 hr: NLT 80%

Packaging configurations:
NDA: Bottles of 100
ANDA: The applicant proposes to market its product in bottles of 30, (b) (4)

Container/closure system:

Size	Container	Closure
30 Count	120 cc, Round White, Opaque, HDPE	38 mm, Plastic CRC, w/ (b) (4) inner seal
(b) (4)		

CRC = child resistant closure

STORAGE CONDITIONS:
NDA: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]
ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Rom Temperature]

Batch Sizes: The ANDA batch (D05027) was produced at (b) (4) tablets. The proposed commercial batch size is (b) (4) tablets.

Drug Substance:
Cetirizine Hydrochloride drug substance is provided by (b) (4). The firm's specifications are based on the manufacturer's and EP monograph specifications. Note: On the drug product label Cetirizine HCl is described as white, crystalline powder that is water soluble.

Pseudoephedrine Hydrochloride drug substance is provided by (b) (4). The firm's specifications are based on the manufacturer's and USP monograph specifications. Note: On the drug label Pseudoephedrine HCl is described as fine white to off-white crystals or powder, having faint characteristic odor that is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform.

B. Description of How the Drug Product is intended to be used
The drug product will be marketed as a relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis in adults and children (12 years of age or older), with a proposed tablet strength of 5 mg of Cetirizine HCl and 120 mg Pseudoephedrine HCl, and packaging in 30, (b) (4)

The proposed expiration dating for the product is 24 months; based on three month accelerated data and the recommended storage conditions are 20-25 °C (68-77 °F) [see USP Controlled Room Temperature]. The RLD storage is listed as 20-25 °C (68-77 °F) excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation
CMC portion of the ANDA is ***acceptable***. The labeling section was found to be ***acceptable*** by Postelle Birch on 1-7-08. Bio study and dissolution review are ***acceptable*** by Parthapratim Chandaroy on 9-15-06. This ANDA is ***approvable***.

Following this page, 19 pages withheld in full (b)(4)

** Data with previous method revision (before sample prep modification)
$Data were obtained from 24 month room temperature stability testing.

30. MICROBIOLOGY: **N/A**

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS: **N/A**

32. LABELING: ***Acceptable on 1-8-08***

The labeling section was found to be **acceptable** by Postelle Birch on 1/7/2008 after reviewing the new information about OTC switch.

33. ESTABLISHMENT INSPECTION: ***Acceptable on 11-16-2007***

34. BIOEQUIVALENCE: ***Acceptable on 9-15-06***

Bio study and dissolution review are ***acceptable*** by Parthapratim Chandaroy on 9-15-06.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory per review #1

cc: ANDA 77-991
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/Guoping Sun, Ph.D.-Review Chemist/2-13-08/2-26-08/3-3-08
HFD-630/Shing Hou Liu, Ph.D.-Team Leader/
HFD-617/L. Matheny-Project Manager/

F/T by:

V:\FIRMSNZ\Sandoz\LTRS&REV\77991.R05.doc

TYPE OF LETTER: ***Approvable***

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

/s/

Guoping Sun
3/5/2008 12:39:40 PM
CHEMIST

Shing Hou Liu
3/5/2008 12:51:22 PM
CHEMIST

Leigh Matheny
3/5/2008 02:33:49 PM
CSO

ANDA # 77-991

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg / 120 mg

Sandoz, Inc.

Guoping Sun, Ph.D.

Office of Generic Drugs
Division of Chemistry III
Team 4

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 77-991

2. REVIEW #: 4

3. REVIEW DATE: 1-15-08/revised on 1-23-08

4. REVIEWER: Guoping Sun, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Submission(s)	Document Date
Original	11-15-2005
Minor Amendment	10-10-2006
Minor Amendment	08-09-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment (*Response to deficiency letter*)	12-27-2007
(b) (4)	(b) (4)

7. NAME & ADDRESS OF APPLICANT:

Name:	***Sandoz Inc.***
Address:	2555 West Midway Blvd Broomfield, CO 80038
Representative:	Beth Brannan
Telephone:	303-438-4237
Fax:	303-438-4600

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	N/A
b) Non-Proprietary Name (USAN):	Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug:	ZYRTEC –D 12 HOUR Extended Release Tablets
RLD Company:	Pfizer, NDA # 21150
Patent Certification:	Paragraph III and IV, See review #1
Exclusivity:	No, See review #1

10. PHARMACOLOGICAL CATEGORY: Antihistamine

11. DOSAGE FORM: Tablets
(MDD $_{\text{cetirizine HCl}}$ = 10 mg/day)
(MDD $_{\text{pseudoephedrine HCl}}$ = 240 mg/day)

12. STRENGTH/POTENCY: 5 mg / 120 mg

13. ROUTE OF ADMINISTRATION: Oral

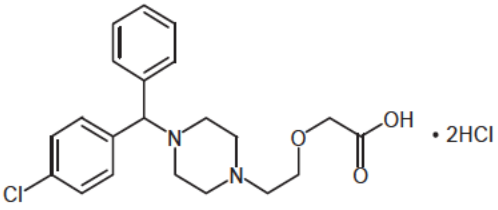
14. Rx/OTC DISPENSED: _____ Rx __X__ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

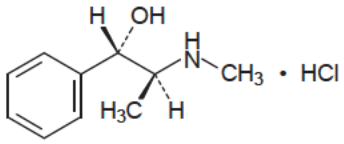
_____SPOTS product – Form Completed
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Cetirizine Hydrochloride
(±)- [2-[4-[4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride
$C_{21}H_{27}Cl_3N_2O_3$ MW = 461.8



Pseudoephedrine Hydrochloride
(+) (1S-2S)-2-Methylamino-1-Phenyl-1-Propanol-Hydrochloride
$C_{10}H_{16}ClNO$ MW = 201.7



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEWED	COMMENTS
(b) (4)	II		(b) (4)	3	*Inadequate*	12-21-07	Reviewed by D M. Darj
	II			3	Adequate	7-1-2005	Reviewed by B. Lim
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	*Acceptable*	11-16-2007	S.Adams
Methods Validation	N/A		
Labeling	*Acceptable*	1/7/2008	Postelle Birch
Bioequivalence	Dissolution- *Satisfactory* BE/BA - *Satisfactory*	9-15-06	Parthapratim Chandaroy
EA	Satisfactory	3/29/06	R. Iser
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.

__X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 77-991

The Executive Summary

Product: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets, 5 mg / 120 mg

Firm: Sandoz Inc.

I. Recommendations

A. Recommendation and Conclusion on Approvability

NOT Approvable. Minor amendment (Review #4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

The proposed drug product, Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets is non-sterile, non-USP product. The drug product contains 5 mg of Cetirizine HCl in the immediate release layer and 120 mg in the extended release layer (mimics RLD).

The tablet is a 13/32 inch convex, [redacted] (b) (4) round, bi-layer tablet [redacted] (b) (4), debossed with SZ over 912 on one side and plain on the reverse side, film coated yellow. Note: Neither the RLD nor the proposed tablets are scored.

The inactive ingredients for the drug product are: Colloidal Silicon Dioxide NF; Croscarmellose Sodium NF; Hypromellose USP; Lactose Monohydrate NF; Povidone USP; Magnesium Stearate, NF; Microcrystalline Cellulose NF; D&C Yellow [redacted] (b) (4) Aluminum Lake [redacted] (b) (4); and [redacted] (b) (4)

Dissolution method:

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable (at the L1 level) by DBE.

	RLD method	FDA recommended method	Sandoz's method
Medium	0.1N HCl	0.1N HCl	0.1N HCl
Volume	500 mL	500 mL	500 mL
Temperature	37°C	37°C	37°C
Apparatus	1 (Basket)	1 (Basket)	1 (Basket)
Rotational Speed	100 rpm	100 rpm	100 rpm
Specification	Cetirizine: NLT 80% (Q) at 30 min Pseudoephedrine: 1 hr: 30-50% 2 hr: 50-70% 6 hr: NLT 80%	Cetirizine: NLT 80% (Q) at 30 min Pseudoephedrine: 1 hr: 30-50% 2 hr: 50-70% 6 hr: NLT 80%	Cetirizine: NLT 80% (Q) at 30 min Pseudoephedrine: 1 hr: 30-50% 2 hr: 50-70% 6 hr: NLT 80%

Packaging configurations:
NDA: Bottles of 100
ANDA: The applicant proposes to market its product in bottles of 30, (b) (4)

Container/closure system:

Size	Container	Closure
30 Count	120 cc, Round White, Opaque, HDPE	38 mm, Plastic CRC, w/ (b) (4) inner seal
(b) (4)		

CRC = child resistant closure

STORAGE CONDITIONS:
NDA: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]
ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Rom Temperature]

Batch Sizes: The ANDA batch (D05027) was produced at (b) (4) tablets. The proposed commercial batch size is (b) (4) tablets.

Drug Substance:
Cetirizine Hydrochloride drug substance is provided by (b) (4). The firm's specifications are based on the manufacturer's and EP monograph specifications. Note: On the drug product label Cetirizine HCl is described as white, crystalline powder that is water soluble.

Pseudoephedrine Hydrochloride drug substance is provided by (b) (4). The firm's specifications are based on the manufacturer's and USP monograph specifications. Note: On the drug label Pseudoephedrine HCl is described as fine white to off-white crystals or powder, having faint characteristic odor that is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform.

B. Description of How the Drug Product is intended to be used
The drug product will be marketed as a relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis in adults and children (12 years of age or older), with a proposed tablet strength of 5 mg of Cetirizine HCl and 120 mg Pseudoephedrine HCl, and packaging in 30, (b) (4),

The proposed expiration dating for the product is 24 months; based on three month accelerated data and the recommended storage conditions are 20-25 °C (68-77 °F) [see USP Controlled Room Temperature]. The RLD storage is listed as 20-25 °C (68-77 °F) excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation
CMC portion of the ANDA remains ***unsatisfactory*** due to CMC minor deficiencies.
The labeling section was found to be ***acceptable*** by Postelle Birch on 1-7-08.
Bio study and dissolution review are ***acceptable*** by Parthapratim Chandaroy on 9-15-06.

Following this page, 17 pages withheld in full (b)(4)

Revised specifications are in ***BOLD/ITALIC***.
* Not specified at time of testing.
** Data with previous method revision (before sample prep modification)

Comment:
See part I for deficiencies associated with stability testing of drug product.

30. MICROBIOLOGY: **N/A**

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS: **N/A**

32. LABELING: ***Acceptable on 1-7-08***
The labeling section was found to be **acceptable** by Postelle Birch on 1/7/2008 after reviewing the new information about OTC switch.

33. ESTABLISHMENT INSPECTION: ***Acceptable on 11-16-2007***

34. BIOEQUIVALENCE: ***Acceptable on 9-15-06***
Bio study and dissolution review are ***acceptable*** by Parthapratim Chandaroy on 9-15-06.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory per review #1

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-991
APPLICANT: Sandoz, Inc.
DRUG PRODUCT: Cetirizine Hydrochloride and Pseudoephedrine Extended-Release Tablets, 5 mg/120 mg

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4.

5. [redacted] (b) (4)

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-991
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/Guoping Sun, Ph.D.-Review Chemist/1-15-08/1-23-08
HFD-630/Dave Gill, Ph.D.-Team Leader/1/24/08
HFD-617/L. Matheny-Project Manager/1/25/08

F/T by: LM 1/25/08

V:\FIRMSNZ\Sandoz\LTRS&REV\77991.R04.doc

TYPE OF LETTER: ***NOT APPROVABLE – Minor Deficiency***

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

/s/

Guoping Sun
1/30/2008 02:43:49 PM
CHEMIST

Leigh Matheny
1/30/2008 03:11:32 PM
CSO

Devinder Gill
1/30/2008 04:22:01 PM
CHEMIST

ANDA # 77-991

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg / 120 mg

Sandoz, Inc.

Guoping Sun, Ph.D.

Office of Generic Drugs
Division of Chemistry III
Team 4

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 77-991

2. REVIEW #: 3

3. REVIEW DATE: 12-12-07/revised on 12-19-07

4. REVIEWER: Guoping Sun, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Submission(s)	Document Date
Original	11-15-2005
Minor Amendment	10-10-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	08-09-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	***Sandoz Inc.***
Address:	2555 West Midway Blvd Broomfield, CO 80038
Representative:	Beth Brannan
Telephone:	303-438-4237
Fax:	303-438-4600

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug: ZYRTEC –D 12 HOUR Extended Release Tablets

RLD Company: Pfizer, NDA # 21150

Patent Certification: Paragraph III and IV, See review #1

Exclusivity: No, See review #1

10. PHARMACOLOGICAL CATEGORY: Antihistamine

11. DOSAGE FORM: Tablets
(MDD $_{\text{cetirizine HCl}}$ = 10 mg/day)
(MDD $_{\text{pseudoephedrine HCl}}$ = 240 mg/day)

12. STRENGTH/POTENCY: 5 mg / 120 mg

13. ROUTE OF ADMINISTRATION: Oral

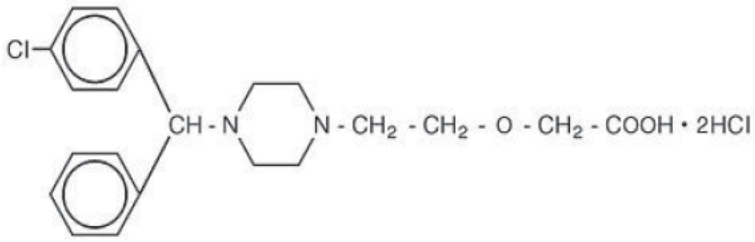
14. Rx/OTC DISPENSED: ____ Rx __X__ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

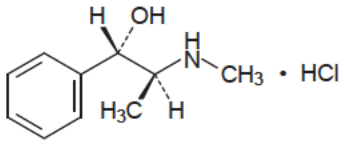
_____SPOTS product – Form Completed
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Cetirizine Hydrochloride
(±)- [2-[4-[4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride
$C_{21}H_{27}Cl_3N_2O_3$ MW = 461.8



Pseudoephedrine Hydrochloride
(+) (1S-2S)-2-Methylamino-1-Phenyl-1-Propanol-Hydrochloride
$C_{10}H_{16}ClNO$ MW = 201.7



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEWED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	11-23-2007	Reviewed by R.Shahnaz
	II			3	Adequate	7-1-2005	Reviewed by B. Lim
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	*Acceptable*	11-16-2007	S.Adams
Methods Validation	N/A		
Labeling	*Acceptable**	1/11/2007	Postelle Birch
Bioequivalence	Dissolution- *Satisfactory* BE/BA - *Satisfactory*	9-15-06	Parthapratim Chandaroy
EA	Satisfactory	3/29/06	R. Iser
Radiopharmaceutical	N/A		

*New information about OTC labeling need to be reviewed.

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.

__X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 77-991

The Executive Summary

Product: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets, 5 mg / 120 mg

Firm: Sandoz Inc.

I. Recommendations

A. Recommendation and Conclusion on Approvability

NOT Approvable. Minor amendment (Review #3)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

The proposed drug product, Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets is non-sterile, non-USP product. The drug product contains 5 mg of Cetirizine HCl in the immediate release layer and 120 mg in the extended release layer (mimics RLD).

The tablet is a 13/32 inch convex, (b) (4), round, bi-layer tablet (b) (4), debossed with SZ over 912 on one side and plain on the reverse side, film coated yellow. Note: Neither the RLD nor the proposed tablets are scored.

The inactive ingredients for the drug product are: Colloidal Silicon Dioxide NF; Croscarmellose Sodium NF; Hypromellose USP; Lactose Monohydrate NF; Povidone USP; Magnesium Stearate, NF; Microcrystalline Cellulose NF; D&C Yellow (b) (4) Aluminum Lake (b) (4) and (b) (4)

Dissolution method:

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable (at the L1 level) by DBE.

	RLD method	FDA recommended method	Sandoz's method
Medium	0.1N HCl	0.1N HCl	0.1N HCl
Volume	500 mL	500 mL	500 mL
Temperature	37°C	37°C	37°C
Apparatus	1 (Basket)	1 (Basket)	1 (Basket)
Rotational Speed	100 rpm	100 rpm	100 rpm
Specification	Cetirizine: NLT 80% (Q) at 30 min Pseudoephedrine: 1 hr: 30-50% 2 hr: 50-70% 6 hr: NLT 80%	Cetirizine: NLT 80% (Q) at 30 min Pseudoephedrine: 1 hr: 30-50% 2 hr: 50-70% 6 hr: NLT 80%	Cetirizine: NLT 80% (Q) at 30 min Pseudoephedrine: 1 hr: 30-50% 2 hr: 50-70% 6 hr: NLT 80%

Packaging configurations:
NDA: Bottles of 100
ANDA: The applicant proposes to market its product in bottles of 30, [redacted] (b) (4)

Container/closure system:

Size	Container	Closure
30 Count	120 cc, Round White, Opaque, HDPE	38 mm, Plastic CRC, w/ [redacted] (b) (4) inner seal
[redacted]		

STORAGE CONDITIONS:
NDA: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]
ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Rom Temperature]

Batch Sizes: The ANDA batch (D05027) was produced at [redacted] (b) (4) tablets. The proposed commercial batch size is [redacted] (b) (4) tablets.

Drug Substance:
Cetirizine Hydrochloride drug substance is provided by [redacted] (b) (4). The firm's specifications are based on the manufacturer's and EP monograph specifications. Note: On the drug product label Cetirizine HCl is described as white, crystalline powder that is water soluble.

Pseudoephedrine Hydrochloride drug substance is provided by [redacted] (b) (4) The firm's specifications are based on the manufacturer's and USP monograph specifications. Note: On the drug label Pseudoephedrine HCl is described as fine white to off-white crystals or powder, having faint characteristic odor that is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform.

B. Description of How the Drug Product is intended to be used
The drug product will be marketed as a relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis in adults and children (12 years of age or older), with a proposed tablet strength of 5 mg of Cetirizine HCl and 120 mg Pseudoephedrine HCl, and packaging in 30, [redacted] (b) (4)

The proposed expiration dating for the product is 24 months; based on three month accelerated data and the recommended storage conditions are 20-25 °C (68-77 °F) [see USP Controlled Room Temperature]. The RLD storage is listed as 20-25 °C (68-77 °F) excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation
CMC portion of the ANDA remains ***unsatisfactory*** due to telephone deficiencies (rev. #3).
The labeling section was found to be ***acceptable*** by Postelle Birch on 1/11/2007. However, new information about OTC labeling need to be reviewed.
Bio study and dissolution review are ***acceptable*** by Parthapratim Chandaroy on 9-15-06.

Following this page, 27 pages withheld in full (b)(4)

Stability Specifications and Results: **Not Satisfactory**

(b) (4)

[redacted]

30. MICROBIOLOGY: **N/A**

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS: **N/A**

32. LABELING: - ***Acceptable on 1-11-07***

The labeling section was found to be ***acceptable*** by Postelle Birch on 1/11/2007.
Note to Labeling reviewer: New information about OTC labeling needs to be reviewed.

33. ESTABLISHMENT INSPECTION: - **Pending**

34. BIOEQUIVALENCE: - ***Acceptable on 9-15-06***

Bio study and dissolution review are ***acceptable*** by Parthapratim Chandaroy on 9-15-06.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Satisfactory per review #1

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-991
APPLICANT: Sandoz, Inc.
DRUG PRODUCT: Cetirizine Hydrochloride and Pseudoephedrine Extended-Release Tablets, 5 mg/120 mg

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4.

5.

6.

7. [redacted] (b) (4)

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-991
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/Guoping Sun, Ph.D.-Review Chemist/12-12-07/12-19-07
HFD-630/Dave Gill, Ph.D.-Team Leader/12/20/07
HFD-617/L. Matheny-Project Manager/12/20/07

F/T by: LM 12/20/07

V:\FIRMSNZ\Sandoz\LTRS&REV\77991.R03.doc

TYPE OF LETTER: ***NOT APPROVABLE – Minor Deficiency***

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

/s/

Guoping Sun
12/21/2007 03:16:18 PM
CHEMIST

Leigh Matheny
12/21/2007 03:50:03 PM
CSO

Gil Jong Kang
12/21/2007 03:54:13 PM
CHEMIST
acting team leader

ANDA # 77-991

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg / 120 mg

Sandoz, Inc.

Robert Iser
Office of Generic Drugs
Division of Chemistry III
Team 4

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 77-991

2. REVIEW #: 2

3. REVIEW DATE: 3-16-07; revised 3-21-07

4. REVIEWER: Robert Iser

5. PREVIOUS DOCUMENTS:

Previous Submission(s)	Document Date
Original	15-November-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	10-October-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Inc.
Address:	2555 West Midway Blvd Broomfield, CO 80038
Representative:	Beth Brannan
Telephone:	303-438-4237
Fax:	303-438-4600

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	N/A
b) Non-Proprietary Name (USAN):	Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug:	ZYRTEC –D 12 HOUR Extended Release Tablets
RLD Company:	Pfizer, NDA # 21150
Patent Certification:	Paragraph III and IV, See review #1
Exclusivity:	No, See review #1

10. PHARMACOLOGICAL CATEGORY: Antihistamine

11. DOSAGE FORM: Tablets
(MDD $_{\text{cetirizine HCl}}$ = 10 mg/day)
(MDD $_{\text{pseudoephedrine HCl}}$ = 240 mg/day)

12. STRENGTH/POTENCY: 5 mg / 120 mg

13. ROUTE OF ADMINISTRATION: Oral

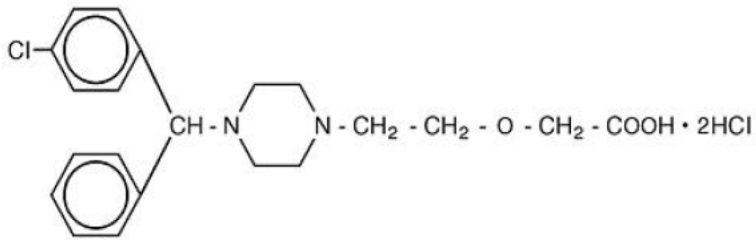
14. Rx/OTC DISPENSED: _X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

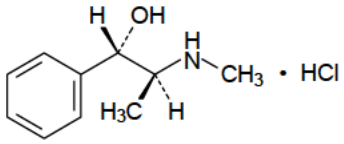
_____SPOTS product – Form Completed
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Cetirizine Hydrochloride
(±)- [2-[4-[4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride
$C_{21}H_{27}Cl_3N_2O_3$ MW = 461.8



Pseudoephedrine Hydrochloride
(+) (1S-2S)-2-Methylamino-1-Phenyl-1-Propanol-Hydrochloride
$C_{10}H_{16}ClNO$ MW = 201.7



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	12-19-2005	Reviewed by G. Sun
	II			3	Adequate	7-1-2005	Reviewed by B. Lim
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

(b) (4)		(b) (4)				
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: **N/A**

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		P. Birch
Bioequivalence	Dissolution-Not Satisfactory BE/BA - Pending	4/4/06	D. Ngo
EA	Satisfactory	3/29/06	R. Iser
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.

_X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 77-991

The Executive Summary

Product: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets, 5 mg / 120 mg
Firm: Sandoz Inc.

I. Recommendations

A. Recommendation and Conclusion on Approvability
NOT Approvable. Minor amendment (Review #2)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:
The proposed drug product, Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets is non-sterile, non-USP product. The drug product contains 5 mg of Cetirizine HCl in the immediate release layer and 120 mg in the extended release layer (mimics RLD).

The tablet is a 13/32 inch convex, (b) (4) round, bi-layer tablet (b) (4), debossed with SZ over 912 on one side and plain on the reverse side, film coated yellow. Note: Neither the RLD nor the proposed tablets are scored.

The inactive ingredients for the drug product are: Colloidal Silicon Dioxide NF; Croscarmellose Sodium NF; Hypromellose USP; Lactose Monohydrate NF; Povidone USP; Magnesium Stearate, NF; Microcrystalline Cellulose NF; D&C Yellow (b) (4) Aluminum Lake (b) (4) and (b) (4)

Drug Substance:
Cetirizine Hydrochloride drug substance is provided by (b) (4). The firm's specifications are based on the manufacturer's and EP monograph specifications. Note: On the drug product label Cetirizine HCl is described as white, crystalline powder that is water soluble.

Pseudoephedrine Hydrochloride drug substance is provided by (b) (4). The firm's specifications are based on the manufacturer's and USP monograph specifications. Note: On the drug label Pseudoephedrine HCl is described as fine white to off-white crystals or powder, having faint characteristic odor that is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform.

Batch Sizes: The ANDA batch (D05027) was produced at (b) (4) tablets. The proposed commercial batch size is (b) (4) tablets.

B. Description of How the Drug Product is intended to be used

The drug product will be marketed as a relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis in adults and children (12 years of age or older), with a proposed tablet strength of 5 mg of Cetirizine HCl and 120 mg Pseudoephedrine HCl, and packaging in 30, (b) (4) (b) (4)

The proposed expiration dating for the product is 24 months; based on three month accelerated data and the recommended storage conditions are 20-25 °C (68-77 °F) [see USP Controlled Room Temperature]. The RLD storage is listed as 20-25 °C (68-77 °F) excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of Not-Approvability is based on deficiencies are included in # 36. Based on the deficiencies described in #36, the drug product cannot be classified as safe and effective in this (second) review cycle. The firm will be informed regarding the classification of these deficiencies as a minor amendment.

The status of the EES, bio study, and labeling reviews are pending; and dissolution review is not acceptable

Following this page, 30 pages withheld in full (b)(4)

(b) (4)

[redacted]

30. MICROBIOLOGY: **N/A**

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS: **N/A**

32. LABELING: - **Pending**

Note to labeling reviewer: (b) (4) labeling was provided and relevant changes will be provided when requested by OGD.

33. ESTABLISHMENT INSPECTION: - **Pending**

34. BIOEQUIVALENCE: - **Dissolution - Not Acceptable**
BE/BA - Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory per review #1

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-991 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Cetirizine Hydrochloride and Pseudoephedrine Extended-Release Tablets, 5 mg/120 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4.

Following this page, 2 pages withheld in full (b)(4)

2. Please provide all current stability data on stability summary sheets that reflect all current specifications.

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-991
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630 / R. Iser- Review Chemist /3-16-07; revised 3-21-07/
HFD-630 / D. Gill – Team Leader /3-21-07
HFD-617 / L. Matheny – Project Manager /3/23/07

F/T by: EW 3/23/07

V:\FIRMSNZ\Sandoz\LTRS&REV\77991R02.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

Robert Iser
3/26/2007 09:31:55 AM
CHEMIST
minor

Leigh Matheny
3/26/2007 11:13:01 AM
CSO

Devinder Gill
3/27/2007 01:52:37 PM
CHEMIST

ANDA # 77-991

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg / 120 mg

Sandoz Inc.

Robert Iser
Office of Generic Drugs
Division of Chemistry III
Team 4

Table of Contents

Chemistry Review Data Sheet

1. **ANDA #:** 77-991

2. **REVIEW #:** 1

3. **REVIEW DATE:** 3-29-06, revised 4-5-2006

4. **REVIEWER:** Robert Iser

5. **PREVIOUS DOCUMENTS: N/A**

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original	15-November-2005

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Sandoz Inc.
Address:	2555 West Midway Blvd Broomfield, CO 80038
Representative:	Beth Brannan
Telephone:	303-438-4237
Fax:	303-438-4600

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name:	N/A
b) Non-Proprietary Name (USAN):	Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

9. **LEGAL BASIS FOR SUBMISSION:**

Reference Listed Drug:	ZYRTEC –D 12 HOUR Extended Release Tablets
RLD Company:	Pfizer, NDA # 21150
Patent Certification:	Paragraph III and IV, Section 3
Exclusivity:	No, Section 3

10. **PHARMACOLOGICAL CATEGORY:** Antihistamine
11. **DOSAGE FORM:** Tablets
(MDD $_{\text{cetirizine HCl}}$ = 10 mg/day)
(MDD $_{\text{pseudoephedrine HCl}}$ = 240 mg/day)

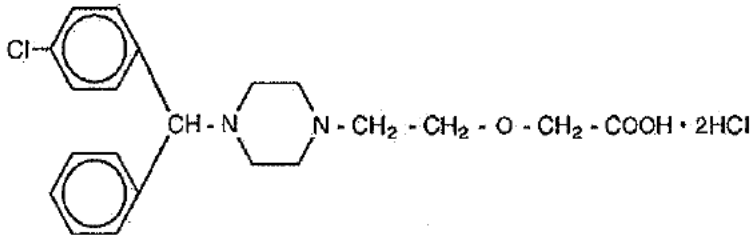
12. **STRENGTH/POTENCY:** 5 mg / 120 mg
13. **ROUTE OF ADMINISTRATION:** Oral
14. **Rx/OTC DISPENSED:** _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

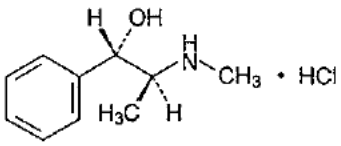
_____SPOTS product – Form Completed
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Cetirizine Hydrochloride
(±)- [2-[4-[4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride
$C_{21}H_{27}Cl_3N_2O_3$ MW = 461.8



Pseudoephedrine Hydrochloride
(+) (1S-2S)-2-Methylamino-1-Phenyl-1-Propanol-Hydrochloride
$C_{10}H_{16}ClNO$ MW = 201.7



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	12-19-2005	Reviewed by G. Sun
	II			3	Adequate	7-1-2005	Reviewed by B. Lim
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

(b) (4)	III	(b) (4)	4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: **N/A**

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Dissolution-Pending BE/BA - Pending		
EA	Satisfactory	3/29/06	R. Iser
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.

__X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 77-991

The Executive Summary

Product: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets, 5 mg / 120 mg
Firm: Sandoz Inc.

I. Recommendations

A. Recommendation and Conclusion on Approvability

NOT Approvable. Minor amendment (Review #1)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:
The proposed drug product, Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets is non-sterile, non-USP product. The drug product contains 5 mg of Cetirizine HCl in the immediate release layer and 120 mg in the extended release layer (mimics RLD).

The tablet is a 13/32 inch convex, (b) (4) (b) (4) round, bi-layer tablet (b) (4) debossed with SZ over 912 on one side and plain on the reverse side, film coated yellow. Note: Neither the RLD nor the proposed tablets are scored.

The inactive ingredients for the drug product are: Colloidal Silicon Dioxide NF; Croscarmellose Sodium NF; Hypromellose USP; Lactose Monohydrate NF; Povidone USP; Magnesium Stearate, NF; Microcrystalline Cellulose NF; D&C Yellow (b) (4) Aluminum Lake (b) (4) (b) (4) and (b) (4)

Drug Product has a MDD of 10 mg daily for Cetirizine HCl and MDD of 240 mg daily for Pseudoephedrine HCl. Drug Substance impurity identification thresholds are 0.10% and qualification thresholds are 0.15% by ICH Q3A for both actives; and Drug Product degradation product identification threshold is (b) (4) and qualification threshold is 0.5% by ICH Q3B for Cetirizine HCl and for Pseudoephedrine HCl both identification and qualification thresholds are 0.2% by ICH Q3B.

Drug Substance:
Cetirizine Hydrochloride drug substance is provided by (b) (4) The firm's specifications are based on the manufacturer's and EP monograph specifications.

Pseudoephedrine Hydrochloride drug substance is provided by (b) (4) The firm's specifications are based on the manufacturer's and USP monograph specifications.

Batch Sizes:
The ANDA batch (D05027) was produced at (b) (4) tablets. The proposed commercial batch size is (b) (4) tablets.

B. Description of How the Drug Product is intended to be used

The drug product will be marketed as a relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis in adults and children (12 years of age or older), with a proposed tablet strength of 5 mg of Cetirizine HCl and 120 mg Pseudoephedrine HCl, and packaging in 30, (b) (4)

The proposed expiration dating for the product is 24 months; based on three month accelerated data and the recommended storage conditions are 20-25 °C (68-77 °F) [see USP Controlled Room Temperature]. The RLD storage is listed as 20-25 °C (68-77 °F) excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of Not-Approvability is based on a significant number of deficiencies. This CMC review has identified deficiencies related to Raw Material Controls, Manufacturing and Processing, Laboratory Controls, and Stability. All deficiencies are included in # 36.

The status of the EES, bio study, dissolution, and labeling reviews are pending.

Based on the deficiencies described in #36, the drug product cannot be classified as safe and effective in this (first) review cycle. The firm will be informed regarding the classification of these deficiencies as a minor amendment.

Following this page, 26 pages withheld in full (b)(4)

Firm provides acknowledge that all firms referenced must be in cGMP compliance at time of approval and that DMF holders may be inspected by DMPQ (page 1544).

Pending EER:
(b) (4) (DMF Holder for (b) (4)
Sandoz (Manufacturer and Tester of Drug Product)

Accentable EER:
(b) (4) (DMF holder for (b) (4)

34. BIOEQUIVALENCE: - **Dissolution - Pending**
BE/BA - Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory - Included on page 1539. Exclusion from requirement for environmental assessment statement is provided and is satisfactory.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-991 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Cetirizine Hydrochloride Tablets and Pseudoephedrine Extended-Release Tablets, 5 mg/120 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4.

5.

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

(b) (4)

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

1. The labeling and bioequivalence portions of your application are pending. Deficiencies, if any, will be conveyed to you under separate covers.

2. Please note that the dissolution specifications are approved by the Division of Bioequivalence. Also, the dissolution data for release and stability will be evaluated based on the criteria recommended by the Division of Bioequivalence. If the Division of Bioequivalence recommends a change to your proposed dissolution methods or acceptance criteria, please provide stability sample data using the recommended dissolution methods and /or criteria that justifies your proposed expiration date.

3. Please provide all current stability data.

Sincerely yours,

DS Gill

for Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-991
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630 / R. Iser- Review Chemist /3-29-06; revised 4-5-06/ 4/7/06
HFD-630 / D. Gill - Team Leader /4-6-06 DSG.M 4-11-06
HFD-617 / L. Matheny - Project Manager /4/7/06 LMatheny 4/11/06

F/T by: EW 4/7/06

V:\FIRMSNZ\Sandoz\LTRS&REV\77991.RV1.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077991

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-991
Drug Product Name	Cetirizine Hydrochloride/Pseudoephedrine Hydrochloride Extended-Release Tablets
Strength	5 mg/120 mg
Applicant Name	Sandoz, Inc.
Address	2555 W. Midway Blvd., Broomfield, CO 80038-0446
Contact Information	Beth Brannan, Director, Regulatory Affairs, Phone: 303-438-4237 Fax: 303-438-4600
Submission Date(s)	November 15, 2005
Amendment Date(s)	February 14, 2006, May 26, 2006 (Dissolution acknowledgement)
Reviewer	Parthapratim Chandaroy, Ph.D.
First Generic	No
File Location	v:\firmsnz\Sandoz\ltrs&rev\77991N1105.doc

I. Executive Summary

The firm submitted fasting and fed bioequivalence (BE) studies comparing its test product, Cetirizine HCl/Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg to the reference listed drug (RLD), Pfizer's Zyrtec-D 12 Hour® (Cetirizine HCl/Pseudoephedrine HCl) Extended-Release Tablets, 5 mg/120 mg. The firm also submitted comparative *in vitro* dissolution data for the 5 mg/120 mg strength of the test and reference products.

The study design for each of the BE studies is a two-way, crossover in normal healthy subjects (n=40 for fasting and n= 37 for fed). Statistical analyses of the plasma concentration data for both cetirizine and pseudoephedrine demonstrate bioequivalence for both the studies.

For the fasting BE study, cetirizine results (point estimate, 90% CI) are: $\ln AUC_{0-t}$ of 1.05, 102.2-107.9; $\ln AUC_{0-\infty}$ of 1.05, 102.3-108.1 and $\ln C_{max}$ of 1.03, 98.8-107.5. For the fed BE study, cetirizine results (point estimate, 90% CI) are: $\ln AUC_{0-t}$ of 1.02, 98.9-104.4; $\ln AUC_{0-\infty}$ of 1.01, 98.7-104.3; and $\ln C_{max}$ of 1.02, 97.7-106.9.

For the fasting BE study, pseudoephedrine results (point estimate, 90% CI) are: $\ln AUC_{0-t}$ of 1.04, 100.5-106.9; $\ln AUC_{0-\infty}$ of 1.04, 100.6-107.1; and $\ln C_{max}$ of 1.02, 99.4-104.9. For the fed BE study, pseudoephedrine results (point estimate, 90% CI) are: $\ln AUC_{0-t}$ of 98.8, 94.4-103.5; $\ln AUC_{0-\infty}$ of 1.01, 97.7-105.1; and $\ln C_{max}$ of 1.04, 99.8-108.2.

There is no USP method for this product, but there is an FDA-recommended method: 500 mL of 0.1 N HCl using USP apparatus I (basket) at 100 rpm. The firm's dissolution testing data, obtained using the above method, was acceptable at the L1 level. In an amendment submitted on May 26, 2006, the firm accepted the FDA-recommended dissolution method and specifications. The dissolution testing study is **acceptable**. The application is **acceptable** with no deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Cetirizine HCl/Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg
Reference Product	ZYRTEC-D 12 HOUR® (Cetirizine HCl/Pseudoephedrine HCl) Extended-Release Tablets, 5 mg/120 mg
RLD Manufacturer	Pfizer
NDA No.	21-150
RLD Approval Date	August 10, 2001
Indication	For the relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis, in adults and children, 12 years of age and older.

B. PK/PD Information[1]

Bioavailability	The bioavailability of cetirizine and pseudoephedrine from the combination Extended-Release drug product is not significantly different from that achieved with separate administration of a cetirizine 5 mg tablet and a pseudoephedrine 120 mg extended release caplet. Co-administration of cetirizine and pseudoephedrine does not significantly affect the bioavailability of either component.
Food Effect	Food had no significant effect on the AUC of cetirizine, but T_{max} was delayed by 1.8 hours and C_{max} was decreased by 30%. Food had no significant effect on the pharmacokinetics of pseudoephedrine. **Zyrtec-D 12 HOUR® Tablets may be given with or without food.**
Tmax	Cetirizine: 2.2 hours; pseudoephedrine: 4.4 hours
Metabolism	Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting low first pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified. 1-7% of the pseudoephedrine dose appeared to be metabolized to norpseudoephedrine by N-demethylation after a single dose.
Excretion	A human mass balance study of cetirizine indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug.
Half-life	Cetirizine: 7.9 hours; pseudoephedrine: 6.0 hours
Relevant OGD or DBE History	The following documents were reviewed by the Division of Bioequivalence (DBE) for Cetirizine HCl/Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg: **Controlled Documents:** • #04-078 (b) (4) • #04-295 (Sandoz; submitted on March 16, 2004); **ANDA:** • #77-170 (Ivax; **first generic**; submitted on June 1, 2004) • #77-991 (Sandoz; submitted on November 15, 2005) – current application • (b) (4) • The DBE currently recommends the following for Cetirizine HCl/ Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg[2]: • A single-dose fasting *in vivo* bioequivalence study comparing Cetirizine HCl/Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg, to

[1] PDR® (Physicians' Desk Reference) 2006 entry for Zyrtec®
[2] Control document #04-295 (Sandoz) submitted on March 16, 2004

	the reference listed drug (RLD), Zyrtec-D 12 Hour® (Cetirizine HCl/Pseudoephedrine HCl) Extended-Release Tablets, 5 mg/120 mg. • A single-dose fed *in vivo* bioequivalence study comparing Cetirizine HCl/Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg, to the RLD. • Measure only the parent compounds, cetirizine and pseudoephedrine, in plasma. • Comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the following FDA method: Medium: 0.1 N HCl at 37 °C Volume: 500 mL Apparatus: USP Apparatus I (basket) Speed: 100 rpm Sampling Times: Cetirizine: 15, 30, 45, and 60 minutes and until at least 80% of the labeled content is dissolved. Pseudoephedrine: 1, 2, 4, 6, and 12 hours and until at least 80% of the labeled content is dissolved. In addition, for modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm /or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 phosphate buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, 4 and every 2 hours thereafter, until at least 80% of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve tablets.
Agency Guidance	None
Drug Specific Issues (if any)	None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	---
In vitro dissolution	Yes	1
Waiver requests	No	---
BCS Waivers	No	---
Vasoconstrictor Studies	No	---
Clinical Endpoints	No	---
Failed Studies	No	---
Amendments	No	---

D. Pre-Study Bioanalytical Method Validation

Report Location of the Validation Report Study No.	(Volume 4, Pages 311-474)*	
Analyte	CETIRIZINE	PSEUDOEPHEDRINE
Internal standard (IS)	(b) (4)	(b) (4)
Method description	Protein Precipitation	Protein Precipitation
Limit of quantitation (units)	1.00 ng/mL	1.00 ng/mL
Average recovery of analyte (%)	72.8 % to 103.1 %	98.6 % to 107.1 %
Average recovery of IS (%)	102.9 %	102.9 %
Standard curve concentrations (units)	1.00, 2.00, 5.00, 15.0, 40.0, 100, 300, 500 ng/mL	1.00, 2.00, 6.00, 20.0, 90.0, 250, 600, 1000 ng/mL
QC concentrations (units)	3.00, 200, 400 ng/mL	3.00, 450, 800 ng/mL
QC intra-day precision range (%)	0.9% - 6.7 %	0.8 - 9.1 %
QC intra-day accuracy range (%)	97.3 % to 107.0 %	95.1 % to 110.2 %
QC inter-day precision range (%)	2.0% - 4.7 %	4.1% - 5.9 %
QC inter-day accuracy range (%)	99.0 % to 104.0 %	98.0 % to 106.2 %
Bench-top stability (hrs)	5.00 hours @ room temperature and 25.50 hours at 5 ± 3°C	5.00 hours @ room temperature and 25.50 hours at 5 ± 3°C
Stock stability (days)	90 days	90 days
Processed stability at RT (hrs)	Not available	Not available
Processed stability at 5° C (hrs)	50.25 hours at 5 °C	50.25 hours at 5 °C
Freeze-thaw stability (cycles)	3 cycles	3 cycles
Long-term storage stability (days)	86 days	86 days
Dilution integrity	Concentration diluted 5-fold	Concentration diluted 5-fold
Selectivity	No interfering peaks noted in blank plasma samples	No interfering peaks noted in blank plasma samples

*These page numbers are for study 2005-983. The page numbers for study 2005-984 maybe slightly different.

Reviewer's note: The "QC inter-day precision and accuracy range (%)" for cetirizine were 2.3-5.2 and 100.0-104.5[3], respectively, instead of the values mentioned in the table above.

Comments on Pre-Study Bioanalytical Method Validation:
The pre-study bioanalytical method validation is **acceptable**.

[3] Volume C 1.5 p. 4177 – Analytical Method Validation Report

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	2005-983
Study Design	Open label, single-dose, randomized two-period, two-sequence, two-treatment, crossover study under fasting conditions.
No. of subjects enrolled	40
No. of subjects completing	40
No. of subjects analyzed	40, as per protocol
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 20 Female: 20
Test product	Cetirizine HCl/Pseudoephedrine HCl Extended-Release Tablets
Reference product	Zyrtec-D 12 Hour® (cetirizine HCl/pseudoephedrine HCl) Extended-Release Tablets
Strength tested	5 mg/ 120 mg
Dose	1 x 5 mg/ 120 mg tablet with approximately 240 mL water under fasting conditions.

Fasting Study Statistical Summary (n=40)**:**

Dose (1 x 5mg/120 mg Cetirizine HCl/ Pseudoephedrine HCl tablets) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study: Cetirizine Data				
Parameter	Test	Reference	Ratio	90% C.I.
AUCt	1827.34	1739.64	105.04	102.24 - 107.92
AUCinf	1866.39	1774.99	105.15	102.32 - 108.06
Cmax	207.43	201.30	103.05	98.79 - 107.49
Fasted Bioequivalence Study: Pseudoephedrine Data				
Parameter	Test	Reference	Ratio	90% C.I.
AUCt	4590.84	4429.14	103.65	100.49 - 106.91
AUCinf	4624.93	4455.37	103.81	100.62 - 107.09
Cmax	351.13	343.85	102.12	99.38 - 104.93

Reviewer's note: The values presented in above table were calculated by the firm (n=40)

Fasting Study Sample Reanalysis:

Study No. 2005-983 (Fasting) Additional Information in Volume 3, Pages 022-033								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	1	2	0.12	0.24	1	2	0.12	0.24
Reason A	0	1	0	0.12	0	1	0	0.12
Reason B	1	1	0.12	0.12	1	1	0.12	0.12
Analytical	55	61	6.56	7.26	55	61	6.56	7.26
Reason CC	0	21	0	2.50	0	21	0	2.50
Reason EE	21	22	2.50	2.62	21	22	2.50	2.62
Reason IE	1	1	0.12	0.12	1	1	0.12	0.12
Reason UISR	33	17	3.93	2.02	33	17	3.93	2.02
Total	56	63	6.67	7.50	56	63	6.67	7.50
Pharmacokinetic[1]	1	2	0.12	0.24	1	2	0.12	0.24
Reason A	0	1	0	0.12	0	1	0	0.12
Reason B	1	1	0.12	0.12	1	1	0.12	0.12
Analytical	55	68	6.56	8.10	55	61	6.56	7.26
Reason CC	0	21	0	2.50	0	21	0	2.50
Reason CP	0	7	0	0.83	0	0	0	0
Reason EE	21	22	2.50	2.62	21	22	2.50	2.62
Reason IE	1	1	0.12	0.12	1	1	0.12	0.12
Reason UISR	33	17	3.93	2.02	33	17	3.93	2.02
Total	56	70	6.67	8.33	56	63	6.67	7.50

Reason:
A: Outlying concentration value in respect to neighboring data
B: Outlier in the linear regression of data from the terminal linear phase
CC: Confirm low plasma concentration
CP: Confirm presence of interference
EE: Extraction error
IE: Injection error
UISR: Unacceptable internal standard response

[1]If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table.

Total number of samples assayed = **3518**

Reviewer's note: There were 21 samples (reference samples from subject #15 for both cetirizine and pseudoephedrine) for which analytical repeat analysis was conducted (code CC: confirm low plasma concentration). This was because subject #15 had all sample values BLQ for the reference treatment.

Did use of recalculated plasma concentration data change study outcome? No. There were 245 sample repeat analysis, including 6 pharmacokinetic repeats and 239 analytical repeats. The reviewer agrees with the reanalysis.

2. Single-dose Fed Bioequivalence Study

Study Summary, Fed Bioequivalence Study	
Study No.	2005-984
Study Design	Open label, single-dose, randomized two-period, two-sequence, two-treatment, crossover study under fed conditions.
No. of subjects enrolled	40
No. of subjects completing	37
No. of subjects analyzed	37, as per protocol
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 20 Female: 17
Test product	Cetirizine HCl/Pseudoephedrine HCl Extended-Release Tablets
Reference product	Zyrtec-D 12 Hour® (cetirizine HCl/pseudoephedrine HCl) Extended-Release Tablets
Strength tested	5 mg/ 120 mg
Dose	1 x 5 mg/ 120 mg tablet with approximately 240 mL water under fed conditions.

Fed Study Statistical Summary:

Dose (1 x 5mg/120 mg Cetirizine HCl/ Pseudoephedrine HCl tablets) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study: Cetirizine Data				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt	1542.45	1518.19	101.60	98.85-104.43
AUCinf	1575.15	1551.98	101.49	98.74-104.33
Cmax	143.40	140.30	102.21	97.70-106.94
Fed Bioequivalence Study: Pseudoephedrine Data				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt	4040.37	4088.37	98.83	94.37-103.50
AUCinf	4058.58	4004.96	101.34	97.71-105.10
Cmax	375.78	361.64	103.91	99.76-108.23

Reviewer's note: The values presented in above table were calculated by the firm (n=37).

Fed Study Sample Reanalysis:

Study No. 2005-984 (Fed) Additional Information in Volume 3 , Pages 016-027								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0	1	0	0.14	0	1	0	0.14
Reason A	0	1	0	0.14	0	1	0	0.14
Analytical	40	22	5.70	3.14	29	22	4.13	3.14
Reason CP	11	0	1.57	0	0	0	0	0
Reason IE	4	1	0.57	0.14	4	1	0.57	0.14
Reason UISR	24	21	3.42	3.00	24	21	3.42	3.00
Reason UISR/CP	1	0	0.14	0	1	0	0.14	0
Total	40	23	5.70	3.28	29	23	4.13	3.28
Pharmacokinetic[1]	1	4	0.14	0.57	1	4	0.14	0.57
Reason A	1	1	0.14	0.14	1	1	0.14	0.14
Reason B	0	3	0	0.43	0	3	0	0.43
Analytical	85	79	12.11	11.27	66	60	9.40	8.56
Reason CP	56	57	7.98	8.13	37	38	5.27	5.42
Reason IE	4	1	0.57	0.14	4	1	0.57	0.14
Reason UISR	24	21	3.42	3.00	24	21	3.42	3.00
Reason UISR/CP	1	0	0.14	0	1	0	0.14	0
Total	86	83	12.25	11.84	67	64	9.54	9.13

Reason:
A: Outlying concentration value in respect to neighboring data
B: Outlier in the linear regression of data from the terminal linear phase
CC: Confirm low plasma concentration
CP: Confirm presence of interference
EE: Extraction error
IE: Injection error
UISR: Unacceptable internal standard response

[1]If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table.

Total number of samples assayed = **2806**

Did use of recalculated plasma concentration data change study outcome? No. There were 232 sample repeat analysis, including 6 pharmacokinetic repeats and 226 analytical repeats. The reviewer agrees with the reanalysis.

F. Formulation

Location in appendix	Section IV.B, page 34
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored?	No
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test?	N/A
Is the formulation acceptable?	Yes
If not acceptable, why?	N/A

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA
Medium	0.1 N HCl
Volume (mL)	500 mL
USP Apparatus type	I (basket)
Rotation (rpm)	100 rpm
Firm's proposed specifications	Cetirizine: (b) (4) Pseudoephedrine: (b) (4) (b) (4)
FDA-recommended specifications	Cetirizine: NLT 80% (Q) in 30 minutes Pseudoephedrine: 1 hr: 30-50%; 2 hr: 50-70%; and 6 hr: NLT 80%
F2 metric calculated?	Cetirizine: No (rapidly dissolving) Pseudoephedrine: Yes (see below)
Is method acceptable? **If not then why?**	Yes

Reviewer's note: There is no USP method for this product, but there is an FDA-recommended method: 500 mL of 0.1 N HCl using USP apparatus I (basket) at 100 rpm. Based on the dissolution review (see attachment below), the firm's dissolution testing data, obtained using the above method, was acceptable at the L1 level. In an amendment submitted on May 26, 2006, the firm accepted the FDA-recommended dissolution method and specifications. The dissolution testing study is **acceptable.**

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F2 metric, test compared to reference	
Strength: **5 mg/ 120 mg**	F2 metric
0.1 N HCl	98.55
pH 1.2	87.20
pH 4.5	100.00
pH 6.8	91.20

As seen in the table above, the F2 metric values are between 87.2 and 100% in four different media, indicating similarity in dissolution profiles for the test and reference products.

H. Waiver Request(s)

Strengths for which waivers are requested	N/A
Regulation cited	N/A
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	Yes
Waivers granted?	N/A
If not then why?	

I. Deficiency Comment

None

J. Recommendations

1. The single-dose, fasting bioequivalence study (#2005-983) conducted by Sandoz, Inc. on its Cetirizine HCl/Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg (Lot #D05027), comparing it to Pfizer's Zyrtec-D 12 Hour® Extended-Release Tablets, 5 mg/120 mg (Lot #25554L), is **acceptable.**

2. The single-dose, non-fasting bioequivalence study (#2005-984) conducted by Sandoz, Inc. on its Cetirizine HCl/Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg (Lot #D05027), comparing it to Pfizer's Zyrtec-D 12 Hour® Extended-Release Tablets, 5 mg/120 mg (Lot #25554L), is **acceptable.**

3. The *in vitro* dissolution testing conducted by Sandoz, Inc. on its Cetirizine HCl/Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg (Lot #D05027), comparing to Pfizer's Zyrtec-D 12 Hour® Extended-Release Tablets, 5 mg/120 mg (Lot #25554L), is **acceptable.**

   The dissolution testing should be conducted in 500 mL 0.1 N HCl at 37°C using USP Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

Cetirizine HCl:	NLT 80% (Q) at 30 minutes
Pseudoephedrine HCl:	1 hr: 30-50%; 2 hr: 50-70%; and 6 hr: NLT 80%

   The firm should be informed of the above recommendations.

Parthapratim Chandaroy — 9/15/06

Parthapratim Chandaroy, Ph.D. Reviewer, Branch V — Date

Dhariwal. — 9/15/06

Kuldeep R. Dhariwal, Ph.D. Team Leader, Branch V — Date

Dale P. Conner — 9/18/06

Dale P. Conner, Pharm.D. — Date
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	2005-983
Study Title	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Cetirizine Hydrochloride/ Pseudoephedrine Hydrochloride 5mg/120 mg Extended Release Tablets Under Fasting Conditions
Clinical Site	Pharma Medica Research Inc., 1410 Warden Avenue, Toronto, Ontario, Canada M1R 5A3
Principal Investigator	Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C)
Study/Dosing Dates	Period I: July 7, 2005; Period II: July 14, 2005
Analytical Site	(b) (4)
Analytical Director (P.I.)	(b) (6)
Analysis Dates	August 04, 2005 – September 03, 2005
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	58 days[4]

Treatment ID	**A**	**B**
Test or Reference	Test	Reference
Product Name	Cetirizine HCl/ Pseudoephedrine HCl	Zyrtec-D 12 Hour® (cetirizine HCl/pseudoephedrine HCl)
Manufacturer	Sandoz, Inc.	Pfizer
Batch/Lot No.	D05027	25554L
Manufacture Date	June 12, 2005	N/A
Expiration Date	N/A	02/06
Strength	5 mg/120 mg	5 mg/120 mg
Dosage Form	Extended-Release Tablets	Extended-Release Tablets
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	C*: 100.1%; P*: 100.3%	C: 100.5%; P: 100.4%
Content Uniformity (mean, %CV)	C: 100.4%, 4.7% P: 100.8%, 0.8%	C: 99.7%, 3.1% P: 99.5%, 1.0%
Formulation	See **Table 25**	N/A
Dose Administered	1 x 5 mg/120 mg	1 x 5 mg/120 mg
Route of Administration	Oral	Oral

* C: Cetirizine HCl; P: Pseudoephedrine HCl

[4] The firm submitted long-term (freezer) storage stability data for 86 days (-20°C) on 2/14/2006 (vol. A2.1)

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 02, 04, 06, 08, 10, 12, 14, 16, 18, 19, 22, 24, 27, 28, 29, 32, 33, 35, 38, 40 BA: 01, 03, 05, 07, 09, 11, 13, 15, 17, 20, 21, 23, 25, 26, 30, 31, 34, 36, 37, 39
Blood Sampling Times	0 (x2), 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours post-dose
Blood Volume Collected/Sample	6 mL collected in Vacutainers containing K_2EDTA as anticoagulant
Blood Sample Processing/Storage	Blood samples were collected in pre-chilled Vacutainers. Within 30 minutes of collection, the plasma was separated by centrifugation at 3000 rpm (4°C) for 10 minutes, divided into two portions, and placed in labeled polypropylene tubes. The samples were stored at -20±5°C pending assay.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See **Table 1**
Length of Fasting	10 hours pre-dose until 4 hours post-dose
Length of Confinement	At least 10 hours pre-dose until 24 hours post-dose. All subjects were required to return for the 36 and 48 hour post-dose blood draw
Safety Monitoring	Vital signs (blood pressure, pulse rate, and temperature) were obtained at the end of each period. Adverse events were monitored throughout the study.

Comments on Study Design: The study design is **acceptable**.

b) Clinical Results

Table 1: Demographics of Study Subjects

Study No.	2005-983	2005-984
	Treatment Groups	Treatment Groups
	Test & Reference Products[a] N = 40	Test & Reference Products[a] N = 37
Age (years)		
Mean ± SD	38 ± 9	36 ± 10
Range	24 - 54	20 - 53
Groups		
< 18	0 (0%)	0 (0%)
18 - 40	22 (55%)	24 (65%)
41 - 64	18 (45%)	13 (35%)
65 - 75	0 (0%)	0 (0%)
> 75	0 (0%)	0 (0%)
Sex		
Female	20 (50%)	17 (46%)
Male	20 (50%)	20 (54%)
Race		
Asian	2 (5%)	6 (16%)
Black	6 (15%)	7 (19%)
Caucasian	32 (80%)	24 (65%)
Hispanic	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)
Other Factors		

[a] *Crossover design = Subjects completing the study received both treatments*

Reviewer's note: The BMI data (mean, standard deviation, range) for the two studies are: *Fasting* – 25.5, 2.0, 20.8-28.8; and *Fed*: 25.4, 3.0, 19.6-29.8

Table 2: Dropout Information

Subject No	Reason	Period	Replaced?
N/A	N/A	N/A	N/A

Table 3: Study Adverse Events

Body System/ Adverse Event	Reported Incidence by Treatment Groups			
	Fasted Bioequivalence Study Study No. 2005-983		Fed Bioequivalence Study Study No. 2005-984	
	Test (n = 40)	Reference (n = 40)	Test (n =38)	Reference (n =39)
Body as a Whole				
Asthenia	0 (0%)	0 (0%)	1 (2.6%)	0 (0%)
Headache	1 (2.5%)	1 (2.5%)	0 (0%)	1 (2.6%)
Pain abdo	0 (0%)	1 (2.5%)	0 (0%)	0 (0%)
Pain Back	0 (0%)	0 (0%)	2 (5.3%)	0 (0%)
Cardiovascular				
Hypertens	1 (2.5%)	1 (2.5%)	0 (0%)	1 (2.6%)
Tachycardia	0 (0%)	0 (0%)	0 (0%)	1 (2.6%)
Digestive System				
Stomatitis ulcer	0 (0%)	1 (2.5%)	0 (0%)	0 (0%)
Glossitis	0 (0%)	1 (2.5%)	0 (0%)	0 (0%)
Nausea	1 (2.5%)	0 (0%)	0 (0%)	0 (0%)
Diarrhea	1 (2.5%)	1 (2.5%)	0 (0%)	0 (0%)
Hemic and Lymphatic System				
Thrombocythem	1 (2.5%)	0 (0%)	0 (0%)	0 (0%)
Leukocytosis	0 (0%)	1 (2.5%)	0 (0%)	0 (0%)
WBC abnorm	0 (0%)	2 (5.0%)	0 (0%)	0 (0%)
Nervous System				
Somnolence	0 (0%)	1 (2.5%)	4(10.5%)	8 (20.5%)
Dry Mouth	0 (0%)	1 (2.5%)	0 (0%)	0 (0%)
Dizziness	1 (2.5%)	1 (2.5%)	0 (0%)	0 (0%)
Metabolic and Nutritional Disorders				
Creatinine Inc	0 (0%)	0 (0%)	1 (2.6%)	0 (0%)
Hyperglycem	0 (0%)	0 (0%)	1 (2.6%)	0 (0%)
Hyperkalem	1 (2.5%)	0 (0%)	0 (0%)	1 (2.6%)
SGOT Inc	0 (0%)	0 (0%)	0 (0%)	1 (2.6%)
SGPT Inc	0 (0%)	0 (0%)	0 (0%)	1 (2.6%)
Urogenital System				
Urin Abnorm	1 (2.5%)	1 (2.5%)	0 (0%)	0 (0%)
Hematuria	1 (2.5%)	0 (0%)	0 (0%)	0 (0%)
Total	9 (22.5%)	13 (32.5%)	9 (23.7%)	14 (35.9%)

Reviewer's note: The number of total adverse events provided in the above table should be: *Fasting Study*: Test: 10 (2 urine abnormality AE, instead of 1); reference: 16 (2 diarrhea AE, instead of 1; 4 WBC abnormality AE, instead of 2).

Table 4: Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling time deviations (samples drawn late)	Many	many

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There were a total of 26 post-dose adverse events reported by 10 subjects (10: test; 16: reference). All events were "mild" in severity. Fifteen of the adverse events (elevated level of blood particles and protein in urine, elevated level of potassium and blood particles in blood, hypertension, open sore on tongue, and cold sore on lower lip) were "unrelated" or "unlikely" related to the study treatments. The remaining 11 adverse events (headache, dizziness, nausea, diarrhea, stomach cramps, somnolence, and dry mouth) were "possibly" related to the study treatments.
- There were several blood draw deviations in the study with a maximum deviation of 93 minutes, at the 36 hour post-dose time point. All the time-points were corrected for any deviation before pharmacokinetic analysis.
- **The adverse events and protocol deviations did not compromise the integrity of the study.**

c) Bioanalytical Results

Table 5: Assay Quality Control – Within Study

	Cetirizine								
QC Conc. (ng/mL)	3.00			200		400			
Inter day Precision (%CV)	3.1			2.1		2.4			
Inter day Accuracy (%)	98.7			103.5		100.8			
Cal. Standards Conc. (ng/mL)	1.00	2.00	5.00	15.0	40.0	100	300	500	
Inter day Precision (%CV)	3.8	2.0	2.4	2.6	2.1	0.9	1.1	0.4	
Inter day Accuracy (%)	105.0	99.0	96.2	100.7	100.0	98.5	101.0	99.6	
Linearity Range (range of r^2 values)	0.9998-1.0000								

	Pseudoephedrine								
QC Conc. (ng/mL)	3.00			450		800			
Inter day Precision (%CV)	6.9			6.1		7.5			
Inter day Accuracy (%)	104.0			105.8		103.1			
Cal. Standards Conc. (ng/mL)	1.00	2.00	6.00	20.0	90.0	250	600	1000	
Inter day Precision (%CV)	4.5	5.5	3.5	4.7	3.3	2.3	1.8	0.5	
Inter day Accuracy (%)	107.0	99.5	97.5	97.0	98.3	99.6	101.2	99.6	
Linearity Range (range of r^2 values)	0.9993-1.0000								

Comments on Study Assay Quality Control: None.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: None.

Table 6: SOPs dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
LAB105.03	June 16, 2003	Replicate and Repeat Sample Analysis Procedure And Acceptance Criteria

Table 7: Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

- There were a total of 3518 study samples analyzed. 245 samples (cetirizine -Test: 56, Reference: 63; pseudoephedrine -Test: 56, Reference: 70) were reanalyzed, representing 6.96% of the total study assays, including six pharmacokinetic repeats (same 3 time points for both cetirizine and pseudoephedrine).
- The analytical method and data are **acceptable**.

d) Pharmacokinetic Results

Table 8: Arithmetic Mean Pharmacokinetic Parameters (n=40)

Mean plasma concentrations are presented in **Tables 11-12** and **Figures 1-2**.

Cetirizine:

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	ng/mL x hr	1872.85	23.41	1771.17	21.36	1.06
AUC_{∞}	ng/mL x hr	1916.52	24.51	1810.27	22.27	1.06
C_{max}	ng/mL	210.93	18.64	200.23	24.85	1.05
T_{max}	hr	0.98	43.87	0.79	42.10	1.23
K_e	hr^{-1}	0.09	16.53	0.09	16.33	1.00
$T_{1/2}$	hr	8.14	18.06	8.14	17.18	1.00

Pseudoephedrine:

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	ng/mL x hr	4728.32	24.85	4622.30	26.91	1.02
AUC_{∞}	ng/mL x hr	4767.88	25.38	4652.34	27.16	1.02
C_{max}	ng/mL	357.58	18.89	342.63	24.83	1.04
T_{max}	hr	4.92	23.40	4.72	24.67	1.04
K_e	hr^{-1}	0.13	18.96	0.13	16.91	0.99
$T_{1/2}$	hr	5.70	20.87	5.61	17.02	1.02

Table 9: Geometric Means and 90% Confidence Intervals (n=40)

Cetirizine:

Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	1827.34	1739.64	1.05	102.21-107.95
AUC_{∞}	1866.39	1774.99	1.05	102.28-108.10
C_{max}	207.43	201.30	1.03	98.74-107.55

Pseudoephedrine:

Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	4590.84	4429.14	1.04	100.45-106.95
AUC_{∞}	4624.93	4455.37	1.04	100.58-107.14
C_{max}	351.13	343.85	1.02	99.34-104.97

Reviewer's note: The values in the above Table 9 were calculated by the reviewer (see comments in the "Comments on Pharmacokinetic and Statistical Analysis" section).

Table 10: Additional Study Information

	cetirizine	pseudoephedrine
Root mean square error, $lnAUC_{0-t}$	0.070622	0.080967
Root mean square error, $lnAUC_{0-\infty}$	0.071454	0.081582
Root mean square error, lnC_{max}	0.110413	0.071172
K_{el} and $AUC_{0-\infty}$ determined for how many subjects?	40 (test); 39 (reference)	40 (test); 39 (reference)
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
-measurable drug concentrations at 0 hr	None	#2: reference
-first measurable drug concentration as C_{max}	#31: test; #27: reference	None
Were the subjects dosed as more than one group?	No	No

Comments on Pharmacokinetic and Statistical Analysis:

- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.
- The 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{0-\infty}$, and lnC_{max} are within the acceptable limits of 80-125%.
- All concentration values obtained from the reference treatment of Subject #15 were BLQ (Below Limit of Quantitation), for both cetirizine and pseudoephedrine. The firm included data from subject #15 for the pharmacokinetic analysis, although reported confidence intervals were calculated excluding data from subject #15. The reviewer included subject #15 for the confidence interval calculations, and the 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{0-\infty}$, and lnC_{max} were still within the acceptable limits of 80-125%.
- The measurable drug concentration (1.39 ng/mL) at the 0 hour time-point for subject #2 (reference) was less than 5% of the corresponding C_{max} (311 ng/mL). Therefore, subject #2 should be included in the pharmacokinetic analysis.
- For cetirizine, there were two subjects (#27 and #31) with first measurable drug concentration as C_{max}. Both the subjects were included in determining the pharmacokinetic parameters. The firm did not acquire blood sample: (i) within the first 15 minutes, and (ii) four samples within the first hour. Therefore, the reviewer excluded both the subjects and recalculated the pharmacokinetic parameters. The 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{0-\infty}$, and lnC_{max} were still within the acceptable limits of 80-125%.
- There were six pharmacokinetic repeats. The reviewer replaced the repeated values with the original values and recalculated the pharmacokinetic parameters. The 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{0-\infty}$, and lnC_{max} were still within the acceptable limits of 80-125%.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:
The single-dose fasting study is **acceptable**.

Table 11 Mean Cetirizine Plasma Concentrations (ng/mL), Single-Dose Fasting Bioequivalence Study

Time	Test (n=40)		Reference (n=40)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	N/A
0.33	72.37	84.66	80.98	80.03	0.89
0.67	187.41	31.35	188.72	30.88	0.99
1	190.56	20.33	183.13	24.63	1.04
1.33	177.60	16.66	170.85	24.03	1.04
1.67	171.28	14.14	159.55	23.46	1.07
2	167.58	15.05	152.80	23.63	1.10
2.33	160.98	15.98	146.80	23.55	1.10
2.67	155.83	16.19	141.60	23.32	1.10
3	148.85	17.09	135.21	23.27	1.10
3.5	141.66	18.02	127.99	23.66	1.11
4	133.77	17.31	121.82	23.85	1.10
5	113.92	18.04	104.06	24.70	1.09
6	100.09	19.78	91.98	24.89	1.09
8	79.72	21.09	73.71	25.95	1.08
10	63.02	24.68	57.40	28.46	1.10
12	51.78	27.41	47.06	30.92	1.10
16	34.35	34.43	31.62	34.80	1.09
24	19.25	45.40	17.28	42.77	1.11
36	7.58	64.02	6.85	59.06	1.11
48	3.15	77.93	2.83	74.81	1.12

Table 12 Mean Pseudoephedrine Plasma Concentrations (ng/mL), Single-Dose Fasting Bioequivalence Study

Time	Test (n=40)		Reference (n=40)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.03	632.46	0.00
0.33	10.15	97.37	9.67	93.53	1.05
0.67	64.22	41.64	69.79	46.79	0.92
1	119.92	29.08	121.85	32.63	0.98
1.33	152.29	24.92	156.71	29.07	0.97
1.67	190.50	23.13	180.53	30.17	1.06
2	228.20	21.06	210.53	30.14	1.08
2.33	257.33	17.78	233.53	28.54	1.10
2.67	279.85	17.95	255.10	29.27	1.10
3	298.23	18.85	271.43	28.12	1.10
3.5	316.60	19.28	296.68	25.85	1.07
4	327.00	19.48	311.98	25.53	1.05
5	350.93	18.65	331.08	24.51	1.06
6	320.00	20.56	311.43	27.77	1.03
8	299.63	22.66	284.25	29.43	1.05
10	246.20	26.13	234.85	33.19	1.05
12	192.55	28.35	187.69	37.01	1.03
16	119.25	36.87	113.88	43.97	1.05
24	39.91	50.35	37.82	55.26	1.06
36	11.32	85.15	10.22	75.92	1.11
48	3.36	135.83	2.77	104.36	1.21

Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (n=40)

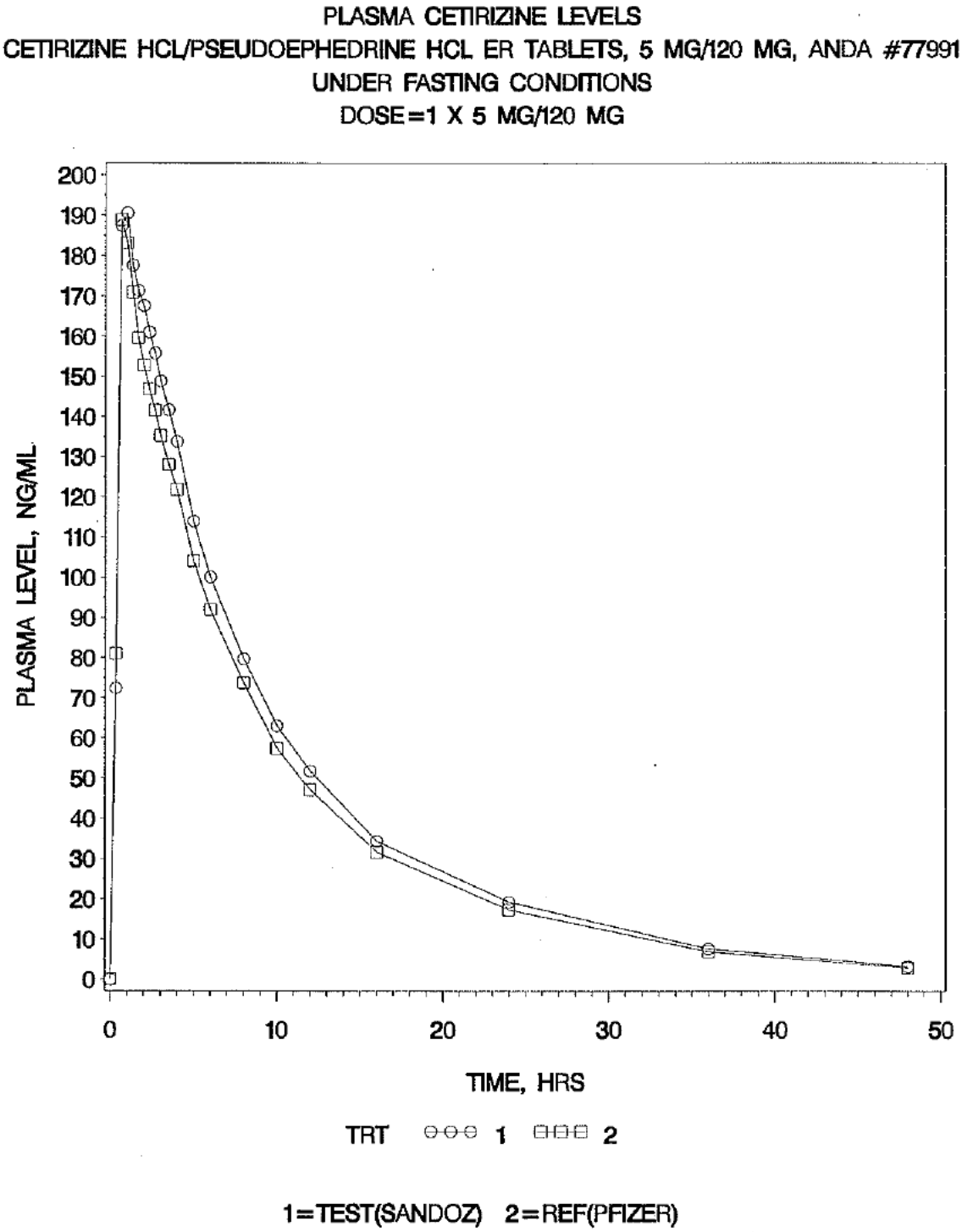
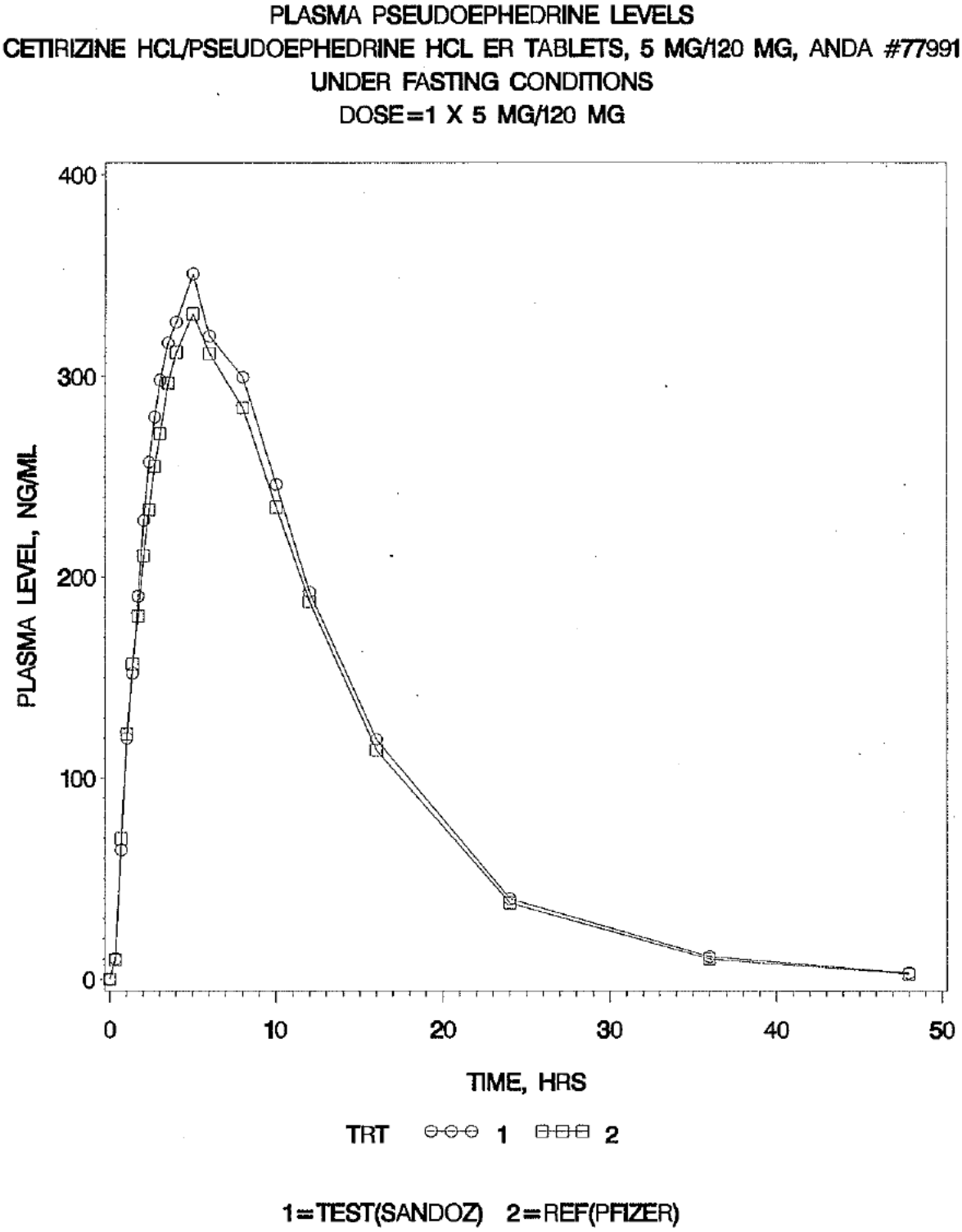


Figure 2 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (n=40)



2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	2005-984
Study Title	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Cetirizine Hydrochloride/ Pseudoephedrine Hydrochloride 5mg/120 mg Extended Release Tablets Under Fed Conditions
Clinical Site	Pharma Medica Research Inc., 1410 Warden Avenue, Toronto, Ontario, Canada M1R 5A3
Principal Investigator	Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C)
Study/Dosing Dates	Period I: June 27, 2005; Period II: July 4, 2005
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	July 29, 2005 – August 12, 2005
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	47 days[5]

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Cetirizine HCl/ Pseudoephedrine HCl	Zyrtec-D 12 Hour® (cetirizine HCl/pseudoephedrine HCl)
Manufacturer	Sandoz, Inc.	Pfizer
Batch/Lot No.	D05027	25554L
Manufacture Date	June 12, 2005	N/A
Expiration Date	N/A	02/06
Strength	5 mg/120 mg	5 mg/120 mg
Dosage Form	Extended-Release Tablets	Extended-Release Tablets
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	C*: 100.1%; P*: 100.3%	C: 100.5%; P: 100.4%
Content Uniformity (mean, %CV)	C: 100.4%, 4.7% P: 100.8%, 0.8%	C: 99.7%, 3.1% P: 99.5%, 1.0%
Formulation	See **Table 25**	N/A
Dose Administered	1 x 5 mg/120 mg	1 x 5 mg/120 mg
Route of Administration	Oral	Oral

* C: Cetirizine HCl; P: Pseudoephedrine HCl

[5] The firm submitted long-term (freezer) storage stability data for 86 days (-20°C) on 2/14/2006 (vol. A2.1)

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 02, 03, 05, 06, 09, 12, 13, 16, 17, 20, 21, 24, 25, 26, 30, 31, 33, 34, 39, 40 BA: 01, 04, 07, 08, 10, 11, 14 15, 18, 19, 22, 23, 27, 28, 29, 32, 35, 36, 37, 38
Blood Sampling Times	0 (x2), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, and 48 hours post-dose
Blood Volume Collected/Sample	Same as Fasting study
Blood Sample Processing/Storage	Same as Fasting study
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See **Table 13**
Length of Fasting before Meal	After an overnight fast for at least 10 hours, subjects were served with a high-fat, high-calorie breakfast 30 minutes before drug administration and each subject had to consume the entire breakfast before dosing. Subjects fasted for 4 hours post-dose.
Length of Confinement	Same as Fasting study
Safety Monitoring	Same as Fasting study
Standard FDA Meal Used?	Yes
If no, then meal is listed in table below	N/A

Comments on Study Design: The study design is **acceptable**.

b) Clinical Results

Table 13: Demographics of Study Subjects

Reviewer's note: The subject demographics data from both the studies (fasting and fed) were provided together by the firm (see **Table 1**).

Table 14: Dropout Information

Subject #	Reason	Period	Replaced?
12	Voluntarily withdrew from the study for personal reasons	Before II	N/A
18	Same as above	Before II	N/A
29	Same as above	Before II	N/A

Table 15: Study Adverse Events

Reviewer's note: Adverse event data from both the studies (fasting and fed) were provided together by the firm (see **Table 3**).

Table 16: Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling time deviations (many samples drawn late and 2 deviations for drawing samples early)	many	many

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There were a total of 23 post-dose adverse events reported by 15 subjects (9: test; 14: reference). All events were "mild" in severity. Six of the adverse events (elevated level of glucose/creatinine/potassium in blood, back pain, and hypertension) were "unrelated" or "unlikely" related to the study treatments. The remaining 17 adverse events (somnolence, tiredness, headache, racing heart, and elevated AST/ALT in blood) were "possibly" related to the study treatments.
- There were several blood draw deviations in the study with a maximum deviation of 48 minutes, at the 48 hour post-dose time point. All the time-points were corrected for any deviation before pharmacokinetic analysis.
- **The adverse events and protocol deviations did not compromise the integrity of the study.**

c) Bioanalytical Results

Table 17: Assay Quality Control – Within Study

	Cetirizine								
QC Conc. (ng/mL)	3.00			200		400			
Inter day Precision (%CV)	3.6			1.9		1.9			
Inter day Accuracy (%)	98.0			102.0		101.0			
Cal. Standards Conc. (ng/mL)	1.00	2.00	5.00	15.0	40.0	100	300	500	
Inter day Precision (%CV)	3.0	1.4	2.2	1.5	1.9	1.3	1.0	0.3	
Inter day Accuracy (%)	105.0	98.5	97.4	100.7	99.5	98.7	101.3	99.6	
Linearity Range (range of r^2 values)	0.9998-1.0000								

	Pseudoephedrine								
QC Conc. (ng/mL)	3.00		450		800				
Inter day Precision (%CV)	5.6		3.7		7.6				
Inter day Accuracy (%)	99.0		101.8		102.0				
Cal. Standards Conc. (ng/mL)	1.00	2.00	6.00	20.0	90.0	250	600	1000	
Inter day Precision (%CV)	6.4	4.2	4.2	3.0	3.4	3.7	3.0	1.0	
Inter day Accuracy (%)	108.0	101.0	95.5	98.0	96.6	99.2	102.5	99.3	
Linearity Range (range of r^2 values)	0.9982-1.0000								

Comments on Study Assay Quality Control: None.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: None.

Table 18: SOPs dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
LAB105.03	June 16, 2003	Replicate and Repeat Sample Analysis Procedure And Acceptance Criteria

Table 19: Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

- There were a total of 2806 study samples analyzed. 232 samples (cetirizine -Test: 40, Reference: 23; pseudoephedrine -Test: 86, Reference: 83) were reanalyzed, representing 8.27% of the total study assays, including six pharmacokinetic repeats (1: cetirizine and 5: pseudoephedrine).
- The analytical method and data are **acceptable.**

d) Pharmacokinetic Results

Table 20: Arithmetic Mean Pharmacokinetic Parameters (n=37)

Mean plasma concentrations are presented in **Tables 23-24** and **Figures 3-4**.

Cetirizine:

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	ng/mL x hr	1574.73	20.75	1553.24	22.28	1.01
AUC_{∞}	ng/mL x hr	1611.17	21.77	1590.47	23.15	1.01
C_{max}	ng/mL	146.51	21.96	142.22	17.30	1.03
T_{max}	hr	2.66	47.13	2.69	49.12	0.99
K_e	hr^{-1}	0.09	15.39	0.09	15.17	1.02
$T_{1/2}$	hr	7.95	17.39	8.12	15.72	0.98

Pseudoephedrine:

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	ng/mL x hr	4148.08	22.29	4226.13	25.27	0.98
AUC_{∞}	ng/mL x hr	4166.87	22.30	4143.27	23.86	1.01
C_{max}	ng/mL	387.00	24.42	369.62	20.89	1.05
T_{max}	hr	4.51	23.43	4.78	19.94	0.94
K_e	hr^{-1}	0.14	14.82	0.13	17.00	1.01
$T_{1/2}$	hr	5.23	13.54	5.29	15.92	0.99

Table 21: Geometric Means and 90% Confidence Intervals (n=37)

Cetirizine:

Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	1542.45	1518.19	1.02	98.85-104.43
AUC_{∞}	1575.15	1551.98	1.01	98.74-104.33
C_{max}	143.40	140.30	1.02	97.70-106.94

Pseudoephedrine:

Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	4040.37	4088.37	0.99	94.37-103.50
AUC_{∞}	4058.58	4004.96	1.01	97.62-105.20
C_{max}	375.78	361.64	1.04	99.76-108.23

Reviewer's note: The values in the above Table 21 were calculated by the reviewer (90% CI for AUC_{∞} is slightly different from the firm's calculation of 97.71-105.10).

Table 22: Additional Study Information

	cetirizine	pseudoephedrine
Root mean square error, $lnAUC_{0-t}$	0.069904	0.117509
Root mean square error, $lnAUC_{0-\infty}$	0.070056	0.089998
Root mean square error, lnC_{max}	0.114946	0.103663
K_{el} and $AUC_{0-\infty}$ determined for how many subjects?	#37 (test and reference)	#6 and #37 (reference)
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
-measurable drug concentrations at 0 hr	None	#37: reference
-first measurable drug concentration as C_{max}	#20: test; #32: reference	None
Were the subjects dosed as more than one group?	No	No

Comments on Pharmacokinetic and Statistical Analysis:

- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.
- The 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{0-\infty}$, and lnC_{max} are within the acceptable limits of 80-125%.
- The measurable pseudoephedrine concentration (99.1 ng/mL) at the 0 hour time-point for subject #37 (reference) was more than 5% of the corresponding C_{max} (315 ng/mL). Therefore, subject #37 should be excluded from the pharmacokinetic analysis for pseudoephedrine. The firm included data from subject #37 in the pharmacokinetic analysis. The reviewer removed data from subject #37 and recalculated all the pharmacokinetic parameters. The 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{0-\infty}$, and lnC_{max} were still within the acceptable limits of 80-125%.
- For cetirizine, there were two subjects (#20 and #32) with first measurable drug concentration as C_{max}. Both the subjects were included in determining the pharmacokinetic parameters. The firm did not acquire blood sample: (i) within the first 15 minutes, and (ii) four samples within the first hour. Therefore, the reviewer excluded both the subjects and recalculated the pharmacokinetic parameters. The 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{0-\infty}$, and lnC_{max} were still within the acceptable limits of 80-125%.
- There were six pharmacokinetic repeats and the firm used three of the repeat values for the pharmacokinetic calculations. The reviewer replaced the repeated values with the original values and recalculated the pharmacokinetic parameters. The 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{0-\infty}$, and lnC_{max} were still within the acceptable limits of 80-125%.

Summary and Conclusions, Single-Dose Fed Bioequivalence Study:

The single-dose fed study is **acceptable**.

Table 23: Mean Cetirizine Plasma Concentrations (ng/mL), Single-Dose Fed Bioequivalence Study

Time	Test (n=37)		Reference (n=37)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	N/A
0.5	26.01	164.32	30.22	148.73	0.86
1	61.36	93.74	67.87	80.03	0.90
1.5	95.69	60.50	96.41	47.64	0.99
2	114.45	44.11	114.99	36.03	1.00
2.5	121.29	36.04	120.46	30.37	1.01
3	123.75	26.60	122.64	25.67	1.01
3.5	122.88	22.81	122.62	21.04	1.00
4	120.30	22.16	120.29	20.15	1.00
5	107.47	19.47	108.73	21.19	0.99
6	96.64	19.41	95.45	21.95	1.01
7	87.24	22.90	84.74	21.76	1.03
8	77.89	25.21	75.78	22.68	1.03
10	61.48	31.85	59.13	25.41	1.04
12	50.12	34.84	48.60	26.45	1.03
16	32.83	34.77	31.43	31.62	1.04
24	17.94	44.62	17.34	42.19	1.03
36	6.69	57.84	6.46	51.17	1.04
48	2.64	75.65	2.72	68.14	0.97

Table 24: Mean Pseudoephedrine Plasma Concentrations (ng/mL), Single-Dose Fed Bioequivalence Study

Time	Test (n=37)		Reference (n=37)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	2.68	608.28	N/A
0.5	20.97	105.77	22.28	127.32	0.94
1	70.74	83.74	72.70	82.18	0.97
1.5	135.98	65.03	132.50	54.19	1.03
2	201.39	53.87	195.31	40.31	1.03
2.5	252.96	45.25	237.59	33.67	1.06
3	297.79	38.32	281.84	30.56	1.06
3.5	334.82	34.63	314.59	27.99	1.06
4	348.01	31.14	330.70	25.19	1.05
5	354.54	23.39	360.49	22.31	0.98
6	333.81	22.88	331.68	23.41	1.01
7	308.19	23.98	313.59	23.97	0.98
8	280.19	25.90	286.59	25.92	0.98
10	215.79	28.95	216.41	27.43	1.00
12	164.95	28.84	164.44	28.11	1.00
16	89.59	33.73	94.43	37.43	0.95
24	26.62	35.00	27.68	42.32	0.96
36	6.57	50.08	8.93	159.18	0.74
48	1.57	77.86	6.40	377.87	0.25

Figure 3: Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study (n=37)

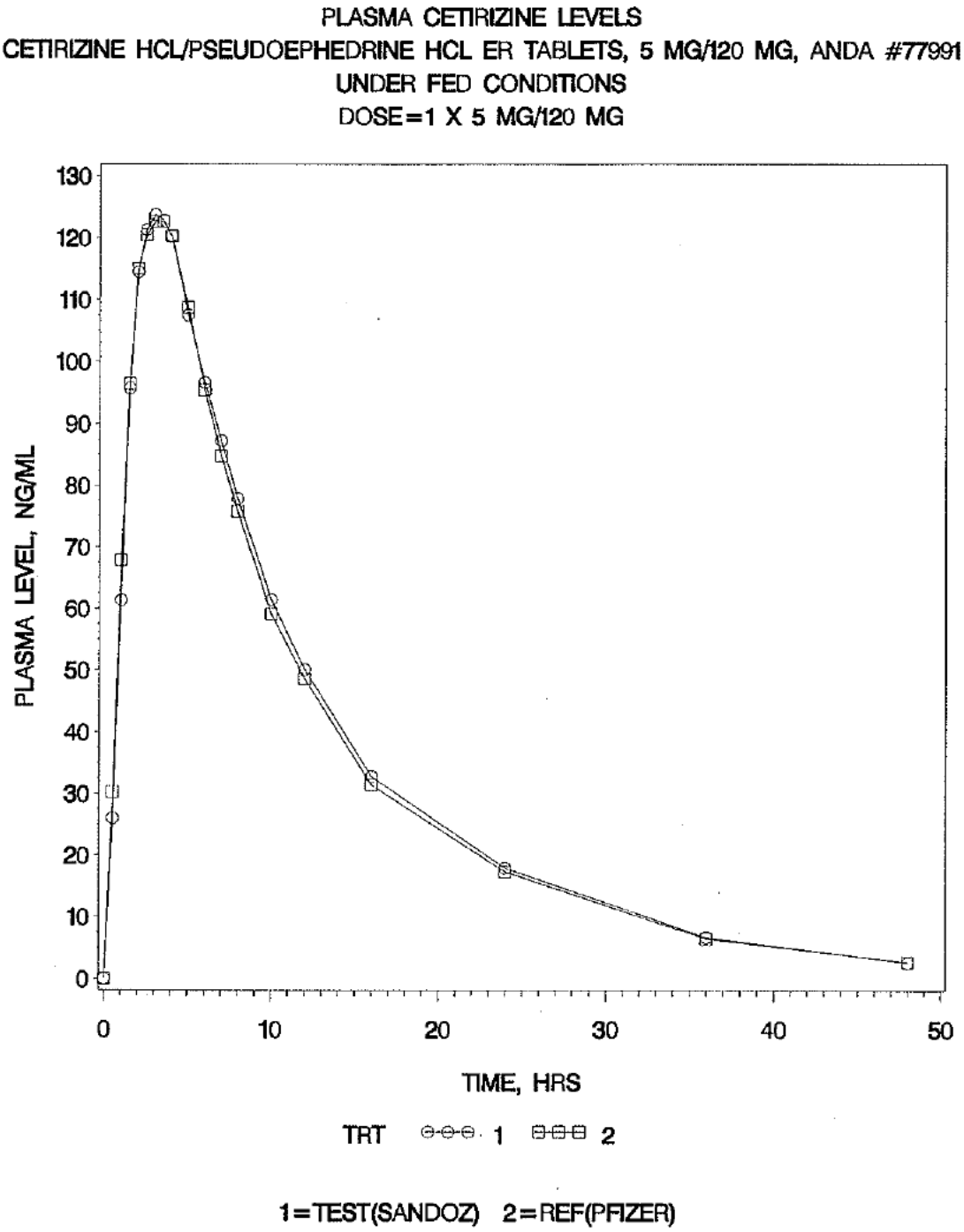
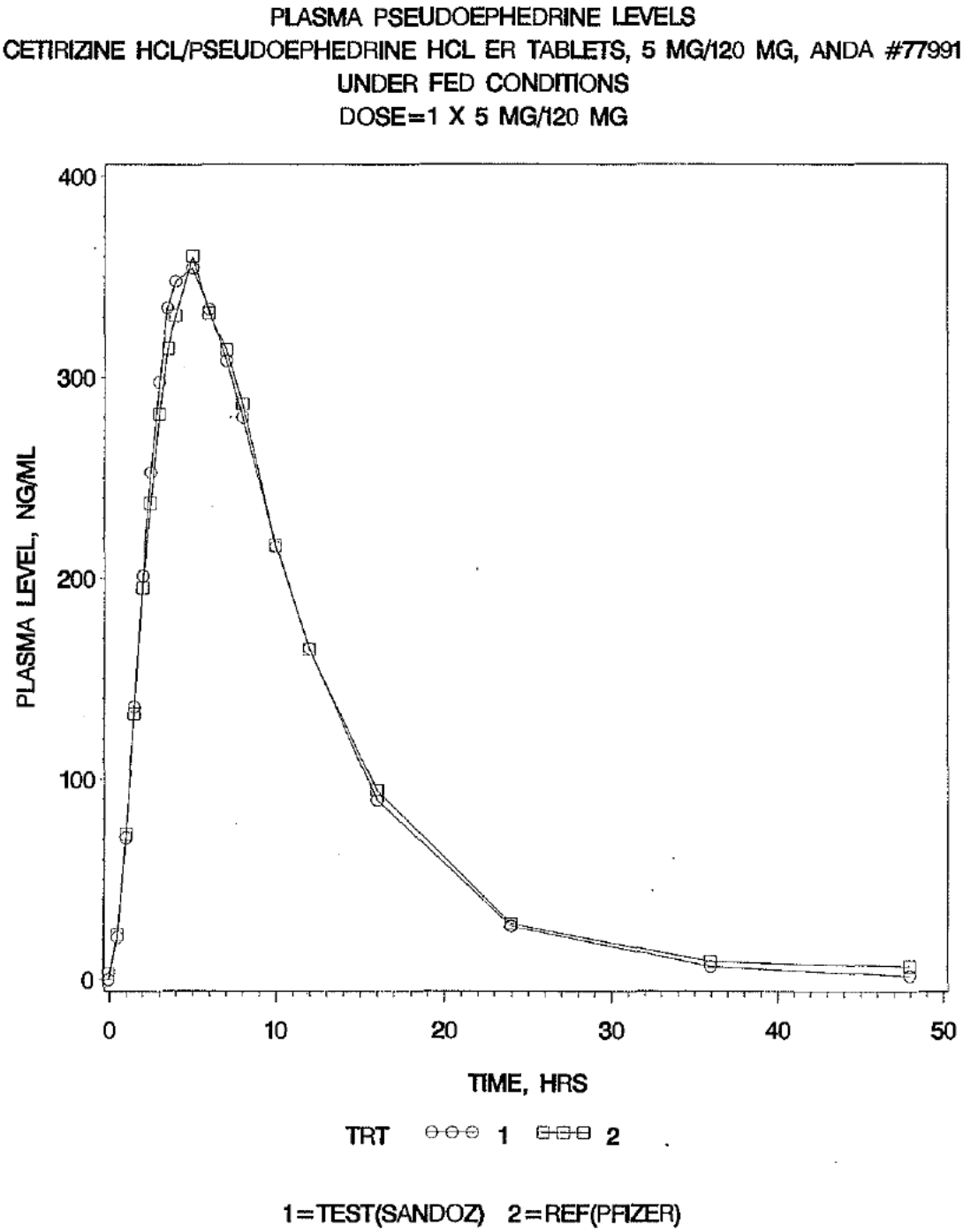


Figure 4: Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study (n=37)



B. Formulation Data

Table 25 Formulation of Cetirizine HCl/Pseudoephedrine HCl Extended-Release Tablets

(b) (4)

[redacted]

C. Dissolution Data

FDA METHOD

Medium	0.1 N HCl
Volume	500 mL
Temperature	37°C ± 0.5°C
Apparatus	I (basket)
Rotational Speed	100 rpm

[6] Chemistry review submitted on 4/7/06 (v:\firmsnz\sandoz\ltrs&rev\77991.rv1.doc)

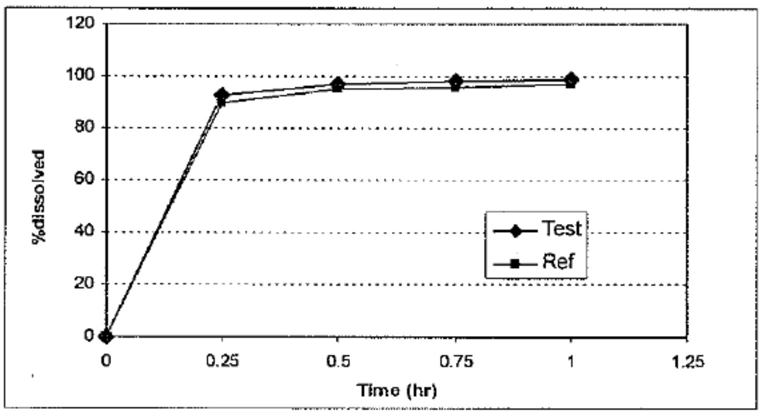
Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolution (Range)				Study Report Location
					15 min	30 min	45 min	60 min	
N/A	**Test Product** (cetirizine HCl component); Lot No. D05627	5 mg/120 mg ER tablet	500 mL of 0.1N HCl @ 37 ± 0.5°C USP Apparatus 1 (basket) at 100 RPM specification: (b) (4)	12	92% (b) (4)	97% (b) (4)	[illegible] (b) (4)	100% (b) (4)	Volume 4, Attachment 4 of ANDA
N/A	**Reference Product** Zyrtec-D 12-Hour (cetirizine HCl component); Lot No. Z1154L			12	90% (b) (4)	95% (b) (4)	96% (b) (4)	97% (b) (4)	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolution (Range)					Study Report Location
					1 hr	2 hr	4 hr	6 hr	12 hr	
N/A	**Test Product** (pseudoephedrine HCl component); Lot No. D05627	5 mg /120 mg ER tablet	500 mL of 0.1 N HCl @ 37 ± 0.5°C USP Apparatus 1 (basket) at 100 RPM specification: (b) (4)	12	41% (b) (4)	60% (b) (4)	84% (b) (4)	95% (b) (4)	103% (b) (4)	Volume 4, Attachment 4 of ANDA
N/A	**Reference Product** Zyrtec-D 12-Hour (pseudoephedrine HCl component); Lot No. Z1154L			12	40% (b) (4)	60% (b) (4)	84% (b) (4)	95% (b) (4)	102% (b) (4)	

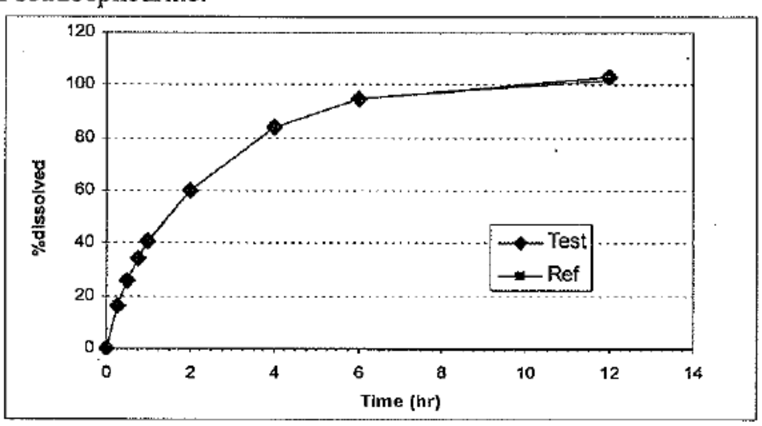
Dissolution Profile:

<u>0.1 N HCl:</u>

Cetirizine:

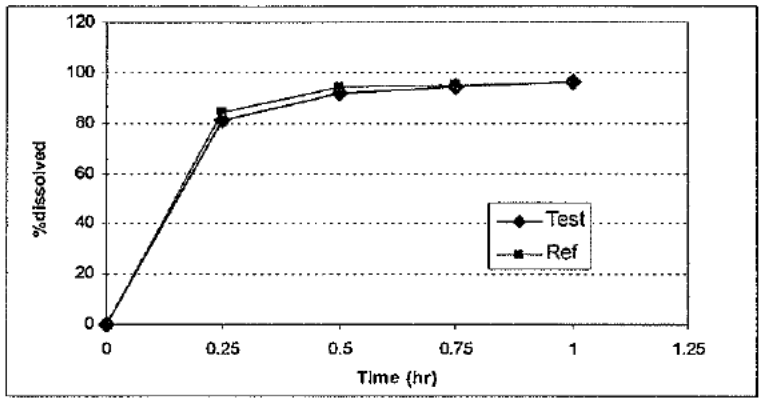


Pseudoephedrine:

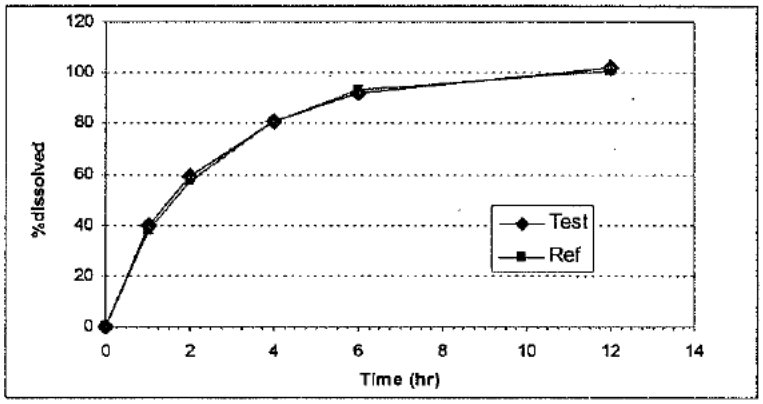


pH 1.2:

Cetirizine:

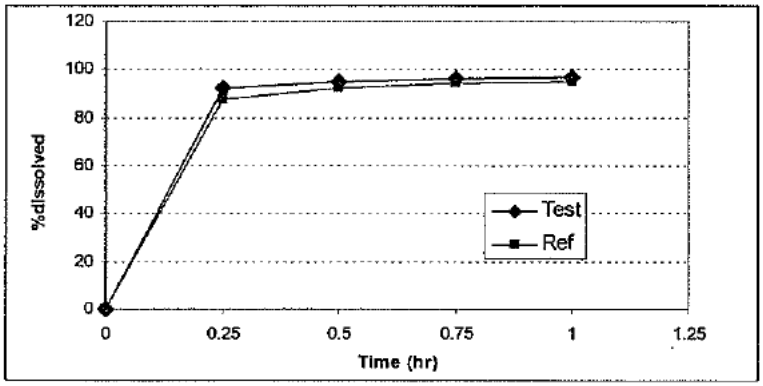


Pseudoephedrine:



pH 4.5:

Cetirizine:



D. Consult Reviews

None

E. SAS Output

Cetirizine:

	SAS DATA	SAS PROGRAM	SAS OUTPUT
Single-dose fasting BE study (Study #2005-983)	 ConcPkData.xls	 SASprogram.txt	 SASoutput.txt
Single-dose fed BE study (Study #2005-984)	 ConcPkData.xls	 SASprogram.txt	 SASoutput.txt

Pseudoephedrine:

	SAS DATA	SAS PROGRAM	SAS OUTPUT
Single-dose fasting BE study (Study #2005-983)	 ConcPkData.xls	 SASprogram.txt	 SASoutput.txt
Single-dose fed BE study (Study #2005-984)	 ConcPkData.xls	 CSASprogram.txt	 SASoutput.txt

F. Additional Attachments

None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-991 APPLICANT: Sandoz, Inc.

DRUG PRODUCT: Cetirizine Hydrochloride/Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg

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

We acknowledge that you have accepted the following dissolution method and specifications:

The dissolution testing should be conducted in 500 mL of 0.1 N HCl at 37°C, using USP Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

Cetirizine HCl:	NLT 80% (Q) at 30 minutes
Pseudoephedrine HCl:	1 hr: 30-50%; 2 hr: 50-70%; and 6 hr: NLT 80%

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

Sincerely yours,

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

CC: ANDA #77-991
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ Reviewer P. Chandaroy
HFD-650/ Project manager C. Thompson
HFD-650/ Team Leader K. R. Dhariwal

v:\firmsnz\Sandoz\ltrs&rev\77991N1105.doc

Printed in final on 09/15/06

Endorsements: (Final with Dates)
HFD-650/P. Chandaroy 9/15/06
HFD-650/K. R. Dhariwal 9/15/06
HFD-650/D. P. Conner 9/18/06

BIOEQUIVALENCE – **ACCEPTABLE** Submission Date: November 15, 2005

✓ 1. **FASTING STUDY** (STF) Strength: 5 mg/120 mg
Clinical: Pharma Medica Research Inc., **Outcome: AC**
1410 Warden Avenue, Toronto, Ontario,
Canada M1R 5A3
Analytical: (b) (4)

✓ 2. **FOOD STUDY** (STP) Strength: 5 mg/120 mg
Clinical: Same as fasting study **Outcome: AC**
Analytical: Same as fasting study

Outcome Decisions: AC - Acceptable
WinBio Comments: AC

3.1

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #	77-991 **SPONSOR:** Sandoz, Inc.
DRUG & DOSAGE FORM:	Cetirizine HCl/Pseudoephedrine HCl Extended-Release Tablets
STRENGTH(S):	5 mg/120 mg
TYPES OF STUDIES:	Fasting and Fed
CLINICAL STUDY SITE(S):	**Fasting and Fed:** Pharma Medica Research Inc., 1410 Warden Avenue, Toronto, Ontario, Canada M1R 5A3
ANALYTICAL SITE(S):	**Fasting and Fed:** (b) (4)
STUDY SUMMARY:	Fasting and fed studies are acceptable
DISSOLUTION:	The dissolution testing is acceptable.

DSI INSPECTION STATUS

Inspection needed:	No	**Inspection status:**	**Inspection results:**
First Generic	No		
New facility	No		
For cause			
Other			

Proposed Dissolution Method and Specifications from Original Submission Acceptable?

Yes _____ No x (If no, project Manager should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Specifications acknowledged by firm? Yes x No ___

AMENDMENT DATE: May 26, 2006

PROJECT MANAGER: _____ **DATE:** _____

PRIMARY REVIEWER: Parthapratim Chandaroy, Ph.D. **BRANCH:** V
INITIAL: PC DATE: 9/15/06

TEAM LEADER: Kuldeep R. Dhariwal, Ph.D. **BRANCH:** V
INITIAL: KRD DATE: 9/15/06

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: DPC DATE: 9/18/06

3.1

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	77-991
Drug Product Name	Cetirizine HCl and Pseudoephedrine HCl Extended-Release Tablets
Strength	5 mg/120 mg
Applicant Name	Sandoz Inc.
Submission Date(s)	November 15, 2005
First Generic	No
Reviewer	Diem-Kieu H. Ngo, Pharm.D.
File Location	**V:\firmsnz\Sandoz\ltrs&rev\77991D1105.doc**
Clinical Site	Pharma Medica Research Inc. 1410 Warden Avenue Toronto, Ontario, Canada M1R 5A3
Analytical Site	(b) (4)

EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable (at the L1 level). However the firm's proposed specifications are not the same as the FDA-recommended specifications. The firm should indicate if it accepts the FDA-recommended dissolution method and specifications. The dissolution testing is incomplete.

The DBE will review the fasting and fed BE studies at a later date.

RLD METHOD

Medium	0.1N HCl
Volume	500 mL
Temperature	37°C
Apparatus	1 (Basket)
Rotational Speed	100 rpm
Specification	Cetirizine: NLT 80% (Q) at 30 minutes Pseudoephedrine: 1 hr: 30-50%; 2 hr: 50-70%; and 6 hr: NLT 80%

Source of Method: DBE Review of 04-295, dated 5/4/2005 (v:\\firmsnz\Sandoz\controls\04295c0304.doc)

Table 1. Summary of In Vitro Dissolution Data using FDA-recommended method

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolution (Range)				Study Report Location
					15 min	30 min	45 min	60 min	
N/A	**Test Product** (Cetirizine HCl component) Lot No. D05027	5 mg/120 mg ER Tablet	500 mL of 0.1N HCl @ 37 ± 0.5°C USP Apparatus 1 (Basket) at 100 RPM Specification: NLT (b) (4) (Q) in (b) (4) minutes	12	90% (b) (4)	96% (b) (4)	99% (b) (4)	100% (b) (4)	Volume 4, Attachment 6 of ANDA
N/A	**Reference Product** Zyrtec-D 12-Hour (Cetirizine HCl component) Lot No. 25554L			12	90% (b) (4)	95% (b) (4)	96% (b) (4)	97% (b) (4)	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolution (Range)					Study Report Location
					1 hr	2 hr	4 hr	6 hr	12 hr	
N/A	Test Product (Pseudoephedrine HCl component) Lot No. D05027	5 mg /120 mg ER Tablet	500 mL of 0.1 N HCl @ 37 ± 0.5°C USP Apparatus 1 (Basket) at 100 RPM Specification: (b) (4)	12	41% (b) (4)	60% (b) (4)	84% (b) (4)	95% (b) (4)	103% (b) (4)	Volume 4, Attachment 6 of ANDA
N/A	Reference Product Zyrtec-D 12-Hour (Pseudoephedrine HCl component) Lot No. 25554L			12	40% (b) (4)	60% (b) (4)	84% (b) (4)	95% (b) (4)	102% (b) (4)	

Table 2. Summary of In Vitro Dissolution Data in Three Different Media

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)				Study Report Location
					15 min	30 min	45 min	60 min	
N/A	Sandoz / D05027 Cetirizine HCl Component	5 mg/ 120 mg ER Tab	Dissolution: Apparatus 1 (USP) Speed of Rotation: 100 rpm Medium: 0.1 N HCl pH 1.2 Volume: 500 mL Temperature: 37°C	12	81 (b) (4)	92 (b) (4)	94 (b) (4)	96 (b) (4)	V 1.1 p. 10-11
N/A	Zyrtec D® 12-Hour / 25554L Cetirizine HCl Component			12	84 (b) (4)	94 (b) (4)	95 (b) (4)	96 (b) (4)	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)					Study Report Location
					1 hr	2 hr	4 hr	6 hr	12 hr	
N/A	Sandoz / D05027 Pseudoephedrine HCl Component	5 mg/ 120 mg ER Tab	Dissolution: Apparatus 1 (USP) Speed of Rotation: 100 rpm Medium: 0.1 N HCl pH 1.2 Volume: 500 mL Temperature: 37°C	12	40 (b) (4)	59 (b) (4)	81 (b) (4)	92 (b) (4)	102 (b) (4)	V 1.1 p. 12-13
N/A	Zyrtec D® 12-Hour / 25554L Pseudoephedrine HCl Component			12	38 (b) (4)	57 (b) (4)	81 (b) (4)	93 (b) (4)	101 (b) (4)	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)				Study Report Location
					15 min	30 min	45 min	60 min	
N/A	Sandoz / D05027 Cetirizine HCl Component	5 mg/ 120 mg ER Tab	Dissolution: Apparatus 1 (USP) Speed of Rotation: 100 rpm Medium: Sodium Acetate Buffer, pH 4.5 Volume: 500 mL Temperature: 37°C	12	91 (b) (4)	95 (b) (4)	97 (b) (4)	98 (b) (4)	V 1.1 p. 15-16
N/A	Zyrtec D® 12-Hour / 25554L Cetirizine HCl Component			12	88 (b) (4)	92 (b) (4)	94 (b) (4)	95 (b) (4)	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)					Study Report Location
					1 hr	2 hr	4 hr	6 hr	12 hr	
N/A	Sandoz / D05027 Pseudoephedrine HCl Component	5 mg/ 120 mg ER Tab	Dissolution: Apparatus 1 (USP) Speed of Rotation: 100 rpm Medium: Sodium Acetate Buffer, pH 4.5 Volume: 500 mL Temperature: 37°C	12	42 (b) (4)	62 (b) (4)	85 (b) (4)	96 (b) (4)	10[illegible](b) (4)	V 1.1 p. 17-18
N/A	Zyrtec D® 12-Hour / 25554L Pseudoephedrine HCl Component			12	42 (b) (4)	62 (b) (4)	85 (b) (4)	96 (b) (4)	102 (b) (4)	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)				Study Report Location
					15 min	30 min	45 min	60 min	
N/A	Sandoz / D05027 Cetirizine HCl Component	5 mg/ 120 mg ER Tab.	Dissolution: Apparatus 1 (USP) Speed of Rotation: 100 rpm Medium: Potassium Phosphate Buffer, pH 6.8 Volume: 500 mL Temperature: 37°C	12	91 (b) (4)	95 (b) (4)	96 (b) (4)	97 (b) (4)	V 1.1 p. 20-21
N/A	Zyrtec D® 12-Hour / 25554L Cetirizine HCl Component			12	84 (b) (4)	90 (b) (4)	92 (b) (4)	93 (b) (4))	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)					Study Report Location
					1 hr	2 hr	4 hr	6 hr	12 hr	
N/A	Sandoz / D05027 Pseudoephedrine HCl Component	5 mg/ 120 mg ER Tab	Dissolution: Apparatus 1 (USP) Speed of Rotation: 100 rpm Medium: Potassium Phosphate Buffer, pH 6.8 Volume: 500 mL Temperature: 37°C	12	40 (b) (4)	59 (b) (4)	81 (b) (4)	92 (b) (4)	102 (b) (4)	V 1.1 p. 22-23
N/A	Zyrtec D® 12-Hour / 25554L Pseudoephedrine HCl Component			12	40 (b) (4)	59 (b) (4)	82 (b) (4)	94 (b) (4)	103 (b) (4)	

Table 3. SAS Transport Files

Are the SAS files located in the EDR? (Yes/No)	
Fasting BE Study	
Plasma Data	Yes
PK data	Yes
Fed BE Study	
Plasma Data	Yes
PK Data	Yes

COMMENTS:

1. The firm submitted dissolution testing data for its Cetirizine HCl and Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg, and Pfizer's Zyrtec-D® 12-Hour Tablets, 5 mg/120 mg, using the FDA-recommended method. The dissolution data using the FDA-recommended method indicate that the test product pass the FDA-recommended specifications (Cetirizine HCl: NLT 80% (Q) in 30 minutes; Pseudoephedrine HCl: 1 hr: 30-50%; 2 hr: 50-70%; and 6 hr: NLT 80%) at the L1 level. The firm's proposed specifications are not the same as the FDA-recommended specifications. The firm should indicate if it accepts the FDA-recommended dissolution method and specifications.

2. The firm also submitted dissolution testing data for its Cetirizine HCl and Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg, and Pfizer's Zyrtec-D® 12-Hour Tablets, 5 mg/120 mg, using three other media (0.1N HCl at pH 1.2, Acetate Buffer at pH 4.5, and Phosphate Buffer at pH 6.8). The data for these tests show that the profiles are similar for the test and reference products.

3. The firm has submitted the eight summary tables electronically.

DEFICIENCY COMMENT:

The firm should indicate if it accepts the FDA-recommended dissolution method and specifications.

RECOMMENDATIONS:

1. The *in vitro* dissolution testing conducted by Sandoz Inc. on its test product, Cetirizine HCl and Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg, comparing it to Pfizer's Zyrtec-D® 12-Hour Tablets, 5 mg/120 mg, is incomplete, pending the firm's acceptance of the FDA-recommended dissolution method and specifications.

2. The dissolution testing should be conducted in 500 mL of 0.1N HCl at 37°C using USP Apparatus 1 (Basket) at 100 rpm. The test product should meet the following dissolution specifications:

Cetirizine HCl:	NLT 80% (Q) at 30 minutes
Pseudoephedrine HCl:	1 hr: 30-50%; 2 hr: 50-70%; and 6 hr: NLT 80%

The firm should be informed of the above deficiency comment and recommendations

4/4/2006

Diem-Kieu H. Ngo, Pharm.D.
Review Branch V
Division of Bioequivalence
Office of Generic Drugs

4/4/2006

Kuldeep R. Dhariwal, Ph.D.
Review Branch V
Division of Bioequivalence
Office of Generic Drugs

4/4/06

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs

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BIOEQUIVALENCE DEFICIENCY

ANDA: 77-991 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Cetirizine HCl and Pseudoephedrine HCl
Extended-Release Tablets, 5 mg/120 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the fasting and fed bioequivalence studies will be conducted later. The following deficiency has been identified:

The DBE concurs with the use of the following dissolution method:

The dissolution testing should be conducted in 500 mL of 0.1N HCl at 37°C using USP Apparatus 1 (Basket) at 100 rpm.

The DBE recommends the following specifications:

Cetirizine HCl:	NLT 80% (Q) at 30 minutes
Pseudoephedrine HCl:	1 hr: 30-50%; 2 hr: 50-70%; and 6 hr: NLT 80%

With your response to the above deficiency, please indicate if you accept the above dissolution method and specifications.

Sincerely yours,

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

CC: ANDA # 77-991
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-658/ Reviewer D. Ngo
HFD-658/ Project Manager C. Thompson
HFD-658/Team Leader K. Dhariwal

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Printed in final on 4/4/2006

Endorsements: (Final with Dates)
HFD-658/D. Ngo DN 4/4/06
HFD-658/K. Dhariwal 4/4/06
HFD-650/D. Conner BMD 4/4/06

BIOEQUIVALENCE - INCOMPLETE Submission date: November 15, 2005

[NOTE: The *in vitro* testing is incomplete. The fasting and fed BE studies are pending review]

1. DISSOLUTION (Dissolution Data) Strength: 5 mg/120 mg
Outcome: IC

Outcome Decisions: IC – Incomplete
WinBio Comments: IC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077991

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-991 Applicant Sandoz Inc.
Drug Cetirizine Hydrochloride and Pseudoephedrine HCL Extended-Release Tablets
Strength(s) 5 mg/120 mg

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

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer** Chief, Reg. Support Branch	Date 28 FEB 2008 Initials MHS	Date 3/4/08 Initials rlw

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = NDA#21-150
Date Checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☒
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.

Comments: ANDA submitted on 11/17/2005 with PIII to the '358, PIV to the '009 and '329. ANDA ack for filing with PIV on 11/17/2005 (LO dated 1/17/2006). RR from Pfizer signed and dated 2/9/2006, RR from Whitby PHarmaceuticals signed and dated 2/9/2006. The 4/17/2006 XP states that Sandoz was not sued within 45 days. On 4/17/2007 Sandoz provided PIV to the '867. On 6/12/2007 Sandoz provided RR showing that notice was given on the '867 patent and also stated that litigation was not initiated within 45 days. On 12/3/2007 Sandoz provided their amendment stating that they were now seeking approval based upon the OTC version of Zyrtec-D. On 12/7/2007 Sandoz provided PIV to the '614. On 12/13/2007 Sandoz provided documentation of notice (b)(4) delivery notification receipts show that notice was delivered to Pfizer(NY,NY) on 12/7/2007 and UCB S.A.(Brussels, BE) on 12/10/2007. Sandoz provided PII cert to the '358 on 12/13/2007. 12/14/2007-firm provides patent certifications which identify the product as OTC. There is no blocking 180 day exclusivity for this drug product as Teva/IVAX was eligible for this exclusivity with ANDA 77-170 but forfeited this exclusivity(see AP letter for 77-170 for details). ANDA is eligible for Full Approval.

2. **Project Manager**, Leigh Ann Matheny Team 4 Review Support Branch	Date 2/27/08 Initials LM	Date 2/28/08 Initials LM

Original Rec'd date 11/15/05
Date Acceptable for Filing 11/17/05
Patent Certification (type) IV
Date Patent/Exclus.expires 2016;2019;2022
Citizens' Petition/Legal Case Yes ☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☐
Bio Review Filed in DFS: Yes ☐ No ☐
Suitability Petition/Pediatric Waiver

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 11/16/07
Date of Office Bio Review 9/15/06
Date of Labeling Approv. Sum 1/8/08
Date of Sterility Assur. App. n/a
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. **Labeling Endorsement**
Reviewer: Labeling Team Leader:

Date3/4/08
Name/InitialsPostelle Birch/P.B.

Date3/04/08
Name/InitialsJohn Grace/J.G.

Comments:
E-mail concurrence from Postelle Birch and John Grace: CONCUR

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 2/29/08
OGD Regulatory Counsel, Post-MMA Language Included ☐ InitialsDTR
Comments:Changes to AP ltr saved to V drive.

5. Div. Dir./Deputy Dir. Date3/4/08
Chemistry Div. III InitialsDSG

Comments:CMC is acceptable for approval.

6. Frank Holcombe **First Generics Only** Date3/4/08
Assoc. Dir. For Chemistry Initialsrlw/for
Comments: (First generic drug review)
N/A. TEVA Pharmaceuticals USA's ANDA 77-170 for this drug product was approved on February 25, 2008.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Zyrtec-D 12-Hour Extended-release Tablets, 5 mg/120 mg
Pfizer Inc. NDA 21-150 (OTC)

8. Peter Rickman Date3/5/08
Director, DLPS Initialsrlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐
Comments:Bioequivalence studies (fasting and non-fasting) found acceptable. Statistical analyses of the plasma concentration data for both cetirizine and pseudoephedrine demonstrate bioequivalence for both studies. In-vitro dissolution data also found acceptable. Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 9/18/06.

Final-printed labeling (FPL) found acceptable (OTC) 1/8/08.

CMC found acceptable for approval (Chemistry Review #5) 3/3/08.

OR

8. Robert L. West Date 3/5/08
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments:Acceptable EES dated 11/16/07 (Verified 3/4/08). No "OAI" Alerts noted.

Sandoz made paragraph IV certifications to the '009, '329, '867 and '614 patents, but was not sued within the 45-day period. There are no other patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDa is recommended for approval.

9. Gary Buehler Date 3/5/08
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Leigh Ann Matheny Team 4 Date3/5/08

Review Support Branch Initials LM
N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
2:28 pm Time notified of approval by phone
3:35 pm Time approval letter faxed

FDA Notification:
3/5/08 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
3/7/08 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 021150 Product 002 in the OB_OTC list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021150	002	6469009	JUL 13,2019		Y	U-295
021150	002	6489329	APR 08,2016		Y	
021150	002	7014867	JUN 10,2022		Y	
021150	002	7226614	JUN 10,2022			U-295

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as descr bed in 21 CFR 314.53(d)(5).

2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.

3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply

4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.

5. U.S. Patent Nos. RE 36481 and RE 36520 were relisted for Zocor (NDA 19-766) pursuant to the decision and related order in Ranbaxy Labs. v.Leavitt, No. 05-1838 (D.D.C. April 30, 2006). The '481 and '520 patents remained listed in Approved Drug Products with Therapeutic Equivalence Evaluations until any applicable periods of exclusivity pursuant to section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act were triggered and run. For additional information on this matter, please refer to Docket Nos. 2005P-0008 and 2005P-0046. Patents were subsequently delisted in the December 2006 Orange Book update as the exclusivity periods have triggered and run to expiration.

6. Patent number 4904769 listed on all products of NDA 20482 Precose (Acarbose) was requested to be delisted by the sponsor on 4/16/2007. This patent has remained listed because, under Section 505(j)(5)(D)(i) of the Act, a first applicant may retain eligibility for 180-day exclusivity based on a paragraph IV certification to this patent for a certain period.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through January, 2008
Patent and Generic Drug Product Data Last Updated: March 04, 2008

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/s/

Leigh Matheny

3/7/2008 03:12:35 PM

MINOR AMENDMENT

ANDA 77-991

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Sandoz, Inc. TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs FAX: 303-438-4600

FROM: Leigh Ann Bradford PROJECT MANAGER: (301) 827-5727

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 15, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cetirizine Hydrochloride and Pseudoephedrine Extended-Release Tablets, 5 mg/120 mg.

Reference is also made to your amendment dated August 9, 2007.

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

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

SPECIAL INSTRUCTIONS:

In an effort to improve document flow and availability to review staff, please submit your response in electronic PDF format, with a signed cover letter and 356h form.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-991
APPLICANT: Sandoz, Inc.
DRUG PRODUCT: Cetirizine Hydrochloride and Pseudoephedrine Extended-Release Tablets, 5 mg/120 mg

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies:

1. (b) (4)

2

3

4

5

6

7

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Gil Jong Kang
12/21/2007 03:52:37 PM
acting team leader

MINOR AMENDMENT

ANDA 77-991

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

APPLICANT: Sandoz, Inc. TEL: 303-438-4237

ATTN: Beth Brannan, Director, Regulatory Affairs FAX: 303-438-4600

FROM: Leigh Ann Matheny PROJECT MANAGER: (301) 827-5727

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 15, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg.

Reference is also made to your amendment dated October 10, 2006.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__4__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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

SPECIAL INSTRUCTIONS:

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-991 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Cetirizine Hydrochloride and Pseudoephedrine Extended-Release Tablets, 5 mg/120 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

1.

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Following this page, 1 page withheld in full (b)(4)

13 [redacted] (b) (4)

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

1. Please be informed that any changes to the drug substance specifications should be reflected in the in-house secondary standard specifications, as applicable.

2. Please provide all current stability data on stability summary sheets that reflect all current specifications.

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Devinder Gill
3/27/2007 01:51:44 PM
for Vilayat Sayeed, Ph.D.

Telephone Fax

ANDA 77-991

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301-827-7347

TO: Sandoz Inc.

TEL: 303-438-4237

ATTN: Beth Brannan

FAX: 303-438-4600

FROM: Postelle Birch-Smith

:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets, 5 mg/120 mg
.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

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

ANDA Number: 77-991

Date of Submission: November 15, 2005

Applicant's Name: Sandoz Inc.

Established Name: Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets, 5 mg/120 mg

---

Labeling Deficiencies:

1. CONTAINER (bottles of 30, [redacted] (b) (4)

Revise the [redacted] (b) (4) to read, [redacted] (b) (4)

2. INSERT

a. [redacted] (b) (4)

b. Place all section headings on a single line.

c. Revise "Cetirizine Hydrochloride and Pseudophedrine Hydrochloride" to read "Cetirizine Hydrochloride and Pseudophedrine Hydrochloride Extended Release Tablets" [redacted] (b) (4)

3. GENERAL COMMENT

Your submission did not address the 7014867 patent. Please comment.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

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

{See appended electronic signature page}

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

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

/s/

John Grace
10/22/2006 12:23:03 PM
for Wm.Peter Rickman

MINOR AMENDMENT

ANDA 77-991

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

APR 1 2 2006

APPLICANT: Sandoz Inc.

TEL: 303-438-4237

ATTN: Beth Brannan

FAX: 303-438-4600

FROM: Leigh Ann Matheny

PROJECT MANAGER: (301) 827-5727

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 15, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cetirizine Hydrochloride and Pseudoephedrine Extended-Release Tablets, 5 mg/120 mg.

Reference is also made to your amendment dated February 14, 2006.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__5__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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

SPECIAL INSTRUCTIONS:

4/11/06

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-991 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Cetirizine Hydrochloride and Pseudoephedrine Extended-Release Tablets, 5 mg/120 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

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

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

1. The labeling and bioequivalence portions of your application are pending. Deficiencies, if any, will be conveyed to you under separate covers.

2. Please note that the dissolution specifications are approved by the Division of Bioequivalence. Also, the dissolution data for release and stability will be evaluated based on the criteria recommended by the Division of Bioequivalence. If the Division of Bioequivalence recommends a change to your proposed dissolution methods or acceptance criteria, please provide stability sample data using the recommended dissolution methods and /or criteria that justifies your proposed expiration date.

3. Please provide all current stability data.

Sincerely yours,

DSG.u

for Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY AMENDMENT

ANDA 77-991

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

APR 12 2006

APPLICANT: Sandoz, Inc.

TEL: 303-438-4237

ATTN: Beth Brannan

FAX: 303-438-4600

FROM: Christina Thompson

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on November 15, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release Tablets, 5 mg/120 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 1 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

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

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCY

ANDA: 77-991 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Cetirizine HCl and Pseudoephedrine HCl
Extended-Release Tablets, 5 mg/120 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the fasting and fed bioequivalence studies will be conducted later. The following deficiency has been identified:

The DBE concurs with the use of the following dissolution method:

The dissolution testing should be conducted in 500 mL of 0.1N HCl at 37°C using USP Apparatus 1 (Basket) at 100 rpm.

The DBE recommends the following specifications:

Cetirizine HCl:	NLT 80% (Q) at 30 minutes
Pseudoephedrine HCl:	1 hr: 30-50%; 2 hr: 50-70%; and 6 hr: NLT 80%

With your response to the above deficiency, please indicate if you accept the above dissolution method and specifications.

Sincerely yours,

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