CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 77-170

Name	Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg
Sponsor:	TEVA Pharmaceuticals USA
Approval Date:	February 25, 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-170

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-170

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-170

TEVA Pharmaceuticals USA
Attention: Patricia Jaworski
Senior Director, Regulatory Affairs
2 University Plaza, Suite 220
Hackensack, NJ 07601

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated June 1, 2004, 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.

Reference is also made to your amendments dated May 16, July 14, September 7, and November 18, 2005; September 4, December 13, and December 20, 2007 (2 submissions); and January 22, 2008.

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 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 and, therefore, therapeutically equivalent to the reference listed drug (RLD), Zyrtec-D Extended-Release Tablets, 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 0.1N HCl using USP Apparatus I (Basket) at 100 rpm. The test product should meet the following specifications:

Cetirizine HCl: Not less than 75% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Pseudoephedrine HCl:	*1 hr*	*30 – 50%*
	2 hr	*50 – 70%*
	4 hr	*70 – 90%*
	8 hr	*NLT 80%*

The "interim" dissolution tests and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement – Changes Being Effected when there are no revisions to the "interim" specifications or when 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 and expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

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

Your ANDA contains paragraph IV certifications to each of the patents under section 505(j)(2)(A)(vii)(IV) of the Act stating that the 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 is brought against TEVA Pharmaceuticals USA (TEVA) for infringement of one or more of the patents that were the subjects of the paragraph IV certifications. You have notified the agency that TEVA complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement was brought against TEVA 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).

FDA has determined that TEVA was the first applicant to submit a substantially complete ANDA for Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg, that contained a paragraph IV certification and therefore was eligible for 180-day generic-drug exclusivity under section 505(j)(5)(B)(iv) of the Act. However, due to the following set of circumstances, your eligibility for 180-day exclusivity was forfeited under section 505(j)(5)(D)(i)(IV).

Your ANDA was received by the agency on June 2, 2004. The ANDA filing date plus 30 months was December 2, 2006. This ANDA was not granted tentative approval within the 30-month period described in section 505(j)(5)(D)(i)(IV). We also have determined that the requirements for approval of this ANDA were not changed or reviewed after your ANDA was filed, nor was a related citizen petition submitted that would extend the 30-month period as described in section 505(q)(1)(G) of the Act. We therefore conclude that the 180-day exclusivity period described in section 505(j)(5)(B)(iv) of the Act for Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg, was forfeited by TEVA.

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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of

Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

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/

Gary Buehler

2/25/2008 04:33:38 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-170

LABELING

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride

Extended Release Tablets

5 mg / 120 mg

TO OPEN USE SCISSORS

DISTRIBUTED BY PERRIGO
ALLEGAN, MI 49010 USA

MADE IN INDIA

LOT EXP.

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride

Extended Release Tablets

5 mg / 120 mg

TO OPEN USE SCISSORS

DISTRIBUTED BY PERRIGO
ALLEGAN, MI 49010 USA

MADE IN INDIA

LOT EXP.

17600 00 X1

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride

Extended Release Tablets

5 mg / 120 mg

TO OPEN USE SCISSORS

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Extended Release Tablets

5 mg / 120 mg

TO OPEN USE SCISSORS

DISTRIBUTED BY PERRIGO
ALLEGAN, MI 49010 USA

MADE IN INDIA

LOT EXP.

EFB1021
FA17653C1

Original Prescription Strength

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets 5 mg/120 mg Antihistamine/Nasal Decongestant

Indoor & Outdoor Allergies

ALLERGY & CONGESTION

12 Hour
Relief of:

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

12 EXTENDED RELEASE TABLETS

DO NOT USE IF BLISTER UNIT IS BROKEN OR TORN

CODE AREA

: 17653 FA C1

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets 5 mg/120 mg Antihistamine/Nasal Decongestant
ALLERGY & CONGESTION

Questions? If you have questions or a medical nature, please contact your pharmacist, doctor or health care professional.

Made in India

DISTRIBUTED BY
PERRIGO
ALLEGAN, MI 49010

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
  - sneezing
  - itchy, watery eyes
  - itching of the nose or throat
  - nasal congestion
- reduces swelling of nasal passages
- temporarily relieves sinus congestion and pressure
- temporarily restores freer breathing through the nose

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

Stop use and ask a doctor if

- an allergic reaction to this product occurs. Seek medical help right away.

Drug Facts (continued)

- 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 tablets; 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

Other information

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

Inactive ingredients

colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, talc, yellow iron oxide

FORMAT: STANDARD

TYPE SIZES:

TITLE: 9 pt Helvetica Bold Cond. Oblique
TITLE (continued): 8 pt Helvetica Bold Cond. Oblique
(continued) 8 pt Helvetica Cond. Medium
HEADINGS: 8 pt Helvetica Bold Cond. Oblique
SUBHEADINGS: 6 pt Helvetica Bold Cond.
TEXT: 6 pt Helvetica Medium Cond.

LEADING: minimum 6.3 pt
BULLETS: 5 pt Square with 2 M'S spacing between statements
HEAVY LINES: 1.5 pt
HAIRLINES: 0.5 pt

12-20-07

EFB1021
FA17662C1

Original Prescription Strength

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets 5 mg/120 mg Antihistamine/Nasal Decongestant

Indoor & Outdoor Allergies

ALLERGY & CONGESTION

12 Hour
Relief of:

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

24 EXTENDED RELEASE TABLETS

DO NOT USE IF BLISTER UNIT IS BROKEN OR TORN

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets 5 mg/120 mg Antihistamine/Nasal Decongestant
ALLERGY & CONGESTION

CODE AREA

: 17662 FA C1

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
  - sneezing
  - itchy, watery eyes
  - itching of the nose or throat
  - nasal congestion
- reduces swelling of nasal passages
- temporarily relieves sinus congestion and pressure
- temporarily restores freer breathing through the nose

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

Stop use and ask a doctor if

- an allergic reaction to this product occurs. Seek medical help right away.

Drug Facts (continued)

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

Other information

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

Inactive ingredients

colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, talc, yellow iron oxide

Questions? If you have questions of a medical nature, please contact your pharmacist, doctor or health care professional.

Made in India

DISTRIBUTED BY
PERRIGO
ALLEGAN, MI 49010

0 00000 00000 0

FORMAT: STANDARD

TYPE SIZES:

TITLE: 9 pt Helvetica Bold Cond. Oblique
TITLE (continued)**: 8 pt Helvetica Bold Cond. Oblique**
(continued) **8 pt Helvetica Cond. Medium**
HEADINGS: 8 pt Helvetica Bold Cond. Oblique
SUBHEADINGS: 6 pt Helvetica Bold Cond.
TEXT: 6 pt Helvetica Medium Cond.

LEADING: minimum 6.3 pt
BULLETS: 5 pt Square with 2 M'S spacing between statements
HEAVY LINES: 1.5 pt
HAIRLINES: 0.5 pt

12-20-07

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-170

LABELING REVIEW

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

ANDA Number: 77-170

Dates of Submission: December 20, 2007 and December 13, 2007

Applicant's Name: Ivax Pharmaceuticals Inc. (b) (4)

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

BASIS OF APPROVAL:

APPROVAL SUMMARY

CARTON: (12 and 24 tablets)

Satisfactory in FPL as of December 20, 2007 e- submission.

BLISTERS: (2 x 6 and 4 x 6)

Satisfactory in FPL as of December 20, 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 THE RECORD:

1. PATENTS/EXCLUSIVITIES for NDA 21-150

   See above table.

2. MANUFACTURING FACILITY

   (b) (4)

   INDIA

   (Vol A1.2, p. 2 333)

3. SCORING:
   NDA - unscored
   ANDA - unscored

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

5. DISPENSING RECOMMENDATIONS:
   NDA - Dispense in tight containers (USP).
   ANDA - Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

6. 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 pages 2363-69 and 2526 (Volume A1.1 p. 1 022).

7. PACKAGING CONFIGURATIONS:

   NDA- packages of 24 blisters

   ANDA- packages of 12 and 24 blisters

8. CONTAINER/CLOSURE SYSTEM:

Blister Size	Film Material	Lidding Foil Base Foil
6's The blisters are child resistant	(b) (4) film	(b) (4)

9. 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, uncoated, unscored, bi-layered tablets; one layer light yellow debossed "X" and "5029" and the second layer white to off-white debossed 5/120.

Date of Review: December 26, 2007

Dates of Submission: December 20, 2007 and December 13, 2007

Primary Reviewer: Postelle Birch-Smith Team Leader: John Grace

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cc: ANDA: 77-170
Review

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
12/27/2007 12:46:55 PM
LABELING REVIEWER

John Grace
12/27/2007 12:59:53 PM
LABELING REVIEWER

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

ANDA Number:	77-170	Date of Submission:	July 14, 2005
Applicant's Name:	Ivax Pharmaceuticals Inc.		
Established Name:	Cetirizine Hydrochloride and Pseudoephedrine HCl Extended ReleaseTablets, 5 mg/120 mg		

BASIS OF TENTATIVE APPROVAL:

TENTATIVE APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No If no, list why: Tentative Approval

Container Labels:
Satisfactory in draft as of June 1, 2004 submission. (Vol. 1.1)

Professional Package Insert Labeling:
Satisfactory in draft as of June 14, 2005 submission.
(Network path: \\Cdsesub1\n77170\N_000\2005-07-14\labeling\proposed.pdf)

BASIS OF TENTATIVE APPROVAL:

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 with innovator labels in jacket.

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

Exclusivity Data

There is no unexpired exclusivity.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	

Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. **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

Exclusivity Data

There is no unexpired exclusivity.

2. MANUFACTURING FACILITY

(b) (4)

INDIA

(Vol A1.2, p. 2 333)

3. SCORING:
NDA - unscored
ANDA - unscored

4. 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]

5. DISPENSING RECOMMENDATIONS:
NDA - Dispense in tight containers (USP).
ANDA - Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

6. 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 pages 2363-69 and 2526 (Volume A1.1 p. 1 022).

7. PACKAGING CONFIGURATIONS:

NDA- bottles of 100

ANDA- The applicant proposes to market its product in (b) (4)

8. CONTAINER/CLOSURE SYSTEM:

(b) (4)

(b) (4)

(b) (4)

(Vol. p. 3 173)

9. 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, uncoated, unscored, bi-layered tablets; one layer light yellow debossed "X" and "5029" and the second layer white to off-white debossed 5/120.

Date of Review: August 22, 2005

Date of Submission: July 15, 2005

Primary Reviewer: Postelle Birch Date: 8/22/05

Team Leader: John Grace Date: 8/29/2005

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cc: ANDA: 77-170
DUP/DIVISION FILE
HFD-613/PBirch/JGrace (no cc)
V:\FIRMSAM\IVAXPharm\LTRS&REV\77-170tap.label.DOC
Review

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

ANDA Number:	77-170	Date of Submission:	June 1, 2004
Applicant's Name:	Ivax Pharmaceuticals Inc.		
Established Name:	Cetirizine Hydrochloride and Pseudoephedrine HCl Extended ReleaseTablets, 5 mg/120 mg		

Labeling Deficiencies:

1. CONTAINER ((b) (4) tablets)

Satisfactory in draft.

2. INSERT

a. Insert "lactose monohydrate" as one of the inactive ingredients in the DESCRIPTION section.

b. See pages 2, 8, 10 and 13 for other request labeling revisions.

Please revise your labels and labeling, as instructed above and submit electronically in FPL.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the guidance for industry regarding electronic submissions (Providing Regulatory Submissions in Electronic Format - ANDAs, issued 6/2002) available at the following website:

http://www.fda.gov/cder/guidance/5004fnl.htm.

Although the guidance specifies labeling to be submitted in PDF format, we request that labeling also be submitted in MS Word format to assist our review.

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 your last submission with all differences annotated and explained.

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

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels:
Professional Package Insert Labeling:
Revisions needed post-approval:

BASIS OF APPROVAL:

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 with innovator labels in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			

Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. **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

Exclusivity Data

There is no unexpired exclusivity.

2. MANUFACTURING FACILITY

(b) (4)

INDIA

(Vol A1.2, p. 2 333)

3. SCORING:
NDA - unscored
ANDA - unscored

4. 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]

5. DISPENSING RECOMMENDATIONS:
NDA - Dispense in tight containers (USP).
ANDA - Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

6. 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 pages 2363-69 and 2526 (Volume A1.1 p. 1 022).

7. PACKAGING CONFIGURATIONS:

NDA- bottles of 100

ANDA- The applicant proposes to market its product in [redacted] (b) (4)

8. CONTAINER/CLOSURE SYSTEM:

[redacted] (b) (4)

(D) (4)

(Vol. p. 3 173)

9. 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, uncoated, unscored, bi-layered tablets; one layer light yellow debossed "X" and "5029" and the second layer white to off-white debossed 5/120.

Date of Review: March 28, 2005

Date of Submission: June 1, 2004

Primary Reviewer: Postelle Birch Date: 3/28/05

Team Leader: John Grace Date: 4-27-2005

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cc: ANDA:
DUP/DIVISION FILE
HFD-613/PBirch/JGrace (no cc)
V:\FIRMSAM\IVAXPharm\LTRS&REV\77-170na1.label.DOC
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-170

CHEMISTRY REVIEW(S)

ANDA # 77-170

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

IVAX Pharmaceuticals, Inc.

Gil-Jong Kang
Office of Generic Drugs
Division of Chemistry III
Team 4

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 77-170

2. REVIEW #: 3

3. REVIEW DATE: 12-21-2007, 11-JAN-2008, 07-FEB-2008 (telephone amendment)

4. REVIEWER: Gil-Jong Kang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	June 1, 2004
Deficiency letter based on review #1	November 24, 2004
Minor Amendment	July 31, 2006
Deficiency letter based on review #2	February 27, 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	September 4, 2007
Patent amendment	September 6, 2007
Amendment(Unsolicited)	December 13, 2007
Additional document to 13-DEC-2007 amendment	December 19, 2007
Amendment (Telephone)	December 20, 2007
Additional document to 13-DEC-2007 amendment	December 20, 2007
Amendment (Telephone)	January 22, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	IVAX Pharmaceuticals, Inc.
Address:	Two University Plaza Suite 220 Hackensack, NJ 07601
Representative:	Patricia Jaworski
Telephone:	215-293-6150
Fax:	201-489-1403

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
RLD Company:	Pfizer, NDA # 21-150
Patent Certification:	Paragraph III and IV
Exclusivity:	Yes, see review #1

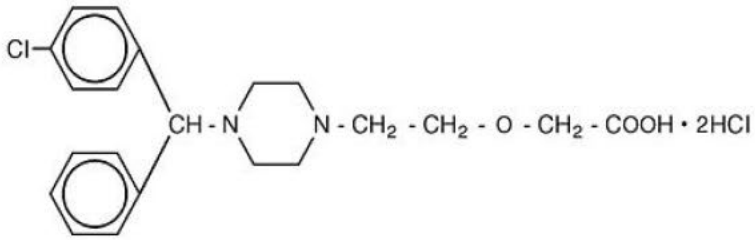
10. PHARMACOLOGICAL CATEGORY: Antihistamine / Decongestant
11. DOSAGE FORM: ER Tablets
12. STRENGTH/POTENCY: 5 mg / 120 mg
(MDD 10 mg for Cetirizine HCl and 240 mg for Pseudo HCl)

13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: ___ Rx _X__OTC

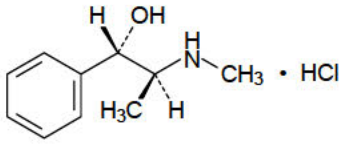
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**
_____SPOTS product – Form Completed
__X___Not a SPOTS product

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

Cetirizine Hydrochloride
(RS)-2-[2-[4-[4-chlorophenyl) phenyl methyl] piperazin-1-yl] ethoxy] acetic acid dihydrochloride



Pseudoephedrine Hydrochloride
(+) (1S-2S)-2-Methylamino-1-Phenyl-Propan-1-ol-Hydrochloride



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	12-19-07	Reviewed by G. Kang
	II			3	Adequate	1-10-07	Reviewed by R. Iser
	III			4	N/A		
	III			4	N/A		(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		
	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	31-DEC-2007	S. Ferguson
Methods Validation	N/A		
Labeling	Acceptable	27-DEC-2007	P. Birch-Smith
Bioequivalence	Bio – Acceptable Diss – Acceptable	28-Nov-2005 28-Nov-2005	P. Nwakama
EA	Satisfactory	11-17-2004	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.
___ Yes __X__ No If no, explain reason(s) below: MINOR

The Chemistry Review for ANDA 77-170

The Executive Summary

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

Firm: IVAX Pharmaceuticals, Inc.

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable with satisfactory telephone amendment dated 22-JAN-2008.

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 5 mg / 120 mg is a non-sterile product, non-USP product. The product is an un-scored, bi-layer tablet with (b) (4) (b) (4), similar to that of RLD.

Manufacturing process includes (b) (4)

Tablet description is:

Round, uncoated, bilayered tablet with light yellow colored one layer and white to off-white second layer with ⧖ 5029 debossed on one side and '5/120' debossed on the other side

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

The inactive ingredients for the drug product are: Colloidal Silicon Dioxide, NF; (b) (4) Hypromellose, (b) (4); Hydroxypropyl Cellulose, (b) (4), NF; Lactose Monohydrate (b) (4), NF; (b) (4) Magnesium Stearate, NF; Microcrystalline Cellulose, NF; Talc, NF; Iron Oxide, Yellow, NF. The proposed components are similar to the RLD product,

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

Pseudoephedrine Hydrochloride drug substance is provided by (b) (4) The firm's specifications are based on the manufacturer's and USP/EP monograph specifications. The material is noted as very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform.

Batch Sizes:
The ANDA batch (G44147) 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, with packaging in (b) (4) (b) (4)

The proposed expiration dating for the product is (b) (4) 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 section becomes approvable with satisfactory telephone amendment dated 22-JAN-2008.
Bio section is acceptable.
Labeling section is approvable.
The EES is acceptable.

Following this page, 19 Pages Withheld in Full as (b)(4)

Response: Complete accelerated stability data are provided with telephone amendment dated 22-JAN-2008 and they are within the proposed specifications (Exhibit 4).
Conclusion: acceptable

30. MICROBIOLOGY: **N/A**

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

32. LABELING: - **Acceptable, 12/27/2007**

33. ESTABLISHMENT INSPECTION: - **Acceptable, 12/31/2008**

34. BIOEQUIVALENCE: - **Bio Study – Acceptable, 11/28/2005**

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

cc: ANDA 77-170
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/G. Kang- Review Chemist/2/7/08
HFD-630/D. Gill – Team Leader/2/07/08
HFD-617/L. Matheny – Project Manager/2/08/08

F/T by: LM 2/26/08

V:\FIRMSAM\IVAXPharm\LTRS&REV\77170R03.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/

Gil Jong Kang
2/26/2008 12:48:47 PM
CHEMIST

Devinder Gill
2/26/2008 01:05:24 PM
CHEMIST

Leigh Matheny
2/26/2008 02:25:09 PM
CSO

ANDA # 77-170

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

IVAX Pharmaceuticals, Inc.

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

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 77-170

2. REVIEW #: 2

3. REVIEW DATE: 1-10-2007

4. REVIEWER: Robert Iser

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	1-June-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	July 31, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	IVAX Pharmaceuticals, Inc.
Address:	2 University Plaza Suite 220 Hackensack, NJ 07601
Representative:	Patricia Jaworski
Telephone:	215-293-6150
Fax:	201-489-1403

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
RLD Company:	Pfizer, NDA # 21-150
Patent Certification:	Paragraph III and IV
Exclusivity:	Yes, see review #1

10. PHARMACOLOGICAL CATEGORY: Antihistamine / Decongestant

11. DOSAGE FORM: ER Tablets

12. STRENGTH/POTENCY: 5 mg / 120 mg

(MDD 10 mg for Cetirizine HCl and 240 mg for Pseudo HCl)

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:

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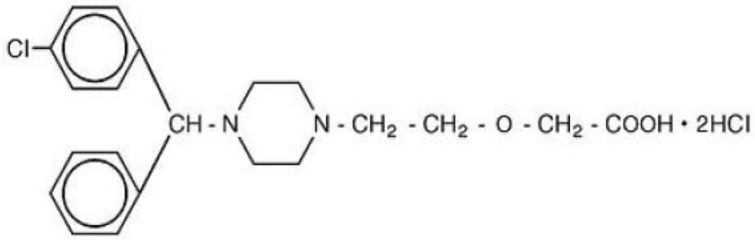
(RS)-2-[2-[4-[4-chlorophenyl) phenyl methyl] piperazin-1-yl] ethoxy] acetic acid dihydrochloride



Pseudoephedrine Hydrochloride
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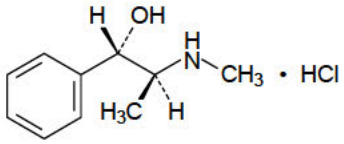

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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(b) (4)	II	(b) (4)		1	Adequate	8-2-06	Reviewed by R. Iser
	II			1	Adequate	1-10-07	Reviewed by R. Iser
	III			4	N/A		
	III			4	N/A		(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		
	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		

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3 – Reviewed previously and no revision since last review
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6 – DMF not available
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[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
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EES	Acceptable	23-Nov-2004	
Methods Validation	N/A		
Labeling	Tent. Approval	22-Aug-2005	P. Birch-Smith
Bioequivalence	Bio – Acceptable Diss – Not Acceptable	28-Nov-2005 28-Nov-2005	P. Nwakama
EA	Satisfactory	11-17-2004	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 77-170

The Executive Summary

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

Firm: IVAX Pharmaceuticals, Inc.

I. Recommendations

A. Recommendation and Conclusion on Approvability

NOT Approvable. MINOR will be issued. (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 5 mg / 120 mg is a non-sterile product, non-USP product. The product is an un-scored, bi-layer tablet with (b) (4) similar to that of RLD.

Manufacturing process include (b) (4)

Tablet description is:

Round, uncoated, bilayered tablet with light yellow colored one layer and white to off-white second layer with ⧖ 5029 debossed on one side and '5/120' debossed on the other side

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

The inactive ingredients for the drug product are: Colloidal Silicon Dioxide, NF; (b) (4) Hypromellose, (b) (4) USP; Hydroxypropyl Cellulose, (b) (4), NF; Lactose Monohydrate (b) (4) NF; (b) (4); Magnesium Stearate, NF; Microcrystalline Cellulose, NF; Talc, NF; Iron Oxide, Yellow, NF. The proposed components are similar to the RLD product,

Drug Substances:
Cetirizine Hydrochloride drug substance is provided by (b) (4). The firm's specifications are based on the manufacturer's and EP monograph specifications. The material is a (b) (4) which is water soluble.

Pseudoephedrine Hydrochloride drug substance is provided by (b) (4). The firm's specifications are based on the manufacturer's and USP/EP monograph specifications. The material is noted as very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform.

Batch Sizes:
The ANDA batch (G44147) 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, with packaging in (b) (4) (b) (4)

The proposed expiration dating for the product is (b) (4) 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 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 bio data review is acceptable and the dissolution review is not acceptable pending acknowledgement of FDA recommended specifications. The labeling review is tentatively approvable. The EES is acceptable.

Following this page, 26 Pages Withheld in Full as (b)(4)

30. MICROBIOLOGY: **N/A**

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

32. LABELING: - **Tentative Approval, 8/22/2005**

33. ESTABLISHMENT INSPECTION: - **Acceptable, 11/23/2004**

34. BIOEQUIVALENCE: - **Bio Study – Acceptable, 11/28/2005**
Dissolution – Not Acceptable, 11/28/2005

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

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-170 APPLICANT: IVAX Pharmaceuticals, Inc.

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

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4.

5.

(b) (4)

6.

7.

8.

9.

10

11 (b) (4)

12

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

1. OGD is changing its CMC review process through our question based review (QbR) initiative, which is described in more detail on the OGD website:http://www.fda.gov/cder/ogd/QbR.htm.

   OGD's QbR initiative was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD), a submission format adopted by multiple regulatory bodies including the FDA. Generic firms are strongly recommended to submit their ANDAs in the CTD format (either eCTD or paper) to facilitate the implementation of the QbR and to avoid undue delays in the review of their applications.

   Because of the increasing number of ANDA submissions OGD receives each year, the Quality Overall Summary (QOS) part of the CTD format is extremely important to making our new review process more efficient. Beginning in January 2007, all ANDA applicants are recommended to provide an electronic copy of a QOS that addresses OGD's QbR questions. The QbR-Quality Overall Summary Outline posted on our webpage http://www.fda.gov/cder/ogd/ contains all the questions to prepare the QOS.

The QOS should be submitted in both MS Word and pdf format along with the paper or electronic submission. The QOS should be provided even if the remainder of the application is not in CTD format. OGD has prepared QOS models that can be found on the OGD web site. We ask you to use these as a guide for your submissions.

Sincerely yours,

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

cc: ANDA 77-170
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630 / R. Iser- Review Chemist /1-10-07
HFD-630 / D. Gill - Team Leader /1/11/07
HFD-617 / L. Matheny - Project Manager /2/5/07

F/T by: LM 2/5/07

V:\FIRMSAM\IVAXPharm\LTRS&REV\77170R02.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
2/23/2007 03:44:33 PM
CHEMIST
minor

Leigh Matheny
2/26/2007 02:48:17 PM
CSO

Devinder Gill
2/27/2007 01:32:44 PM
CHEMIST

ANDA # 77-170

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

IVAX Pharmaceuticals, Inc.

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

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 77-170

2. REVIEW #: 1

3. REVIEW DATE: 11-17-04; revised 11-23-04

4. REVIEWER: Robert Iser

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	1-June-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	1-June-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	IVAX Pharmaceuticals, Inc.
Address:	140 Legrand Avenue Northvale, NJ 07647
Representative:	Patricia Jaworski
Telephone:	(201) 767-1700 ext 323 or 348
Fax:	(201) 767-3804

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
RLD Company:	Pfizer, NDA # 21-150
Patent Certification:	Paragraph III and IV, Page 14
Exclusivity:	Page 15

10. PHARMACOLOGICAL CATEGORY: Antihistamine / Decongestant

11. DOSAGE FORM: ER Tablets

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):

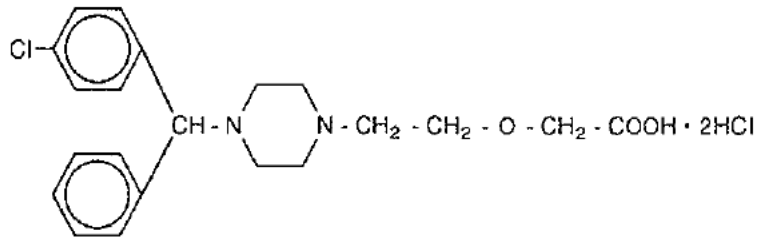
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

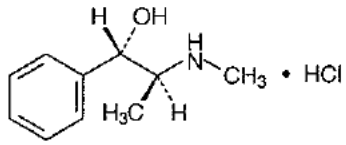
Cetirizine Hydrochloride

(RS)-2-[2-[4-[4-chlorophenyl) phenyl methyl] piperazin-1-yl] ethoxy] acetic acid dihydrochloride



Pseudoephedrine Hydrochloride

(+) (1S-2S)-2-Methylamino-1-Phenyl-Propan-1-ol-Hydrochloride



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	11-15-04	Reviewed by R. Iser
	II			1	Inadequate	11-23-04	Reviewed by R. Iser
	III			4	N/A		
	III			4	N/A		(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		
	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)
	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	Pending		
EA	Satisfactory	11-17-2004	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 77-170

The Executive Summary

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

I. Recommendations

A. Recommendation and Conclusion on Approvability

NOT Approvable. MINOR will be issued. (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 5 mg / 120 mg is a non-sterile product, non-USP product.

The inactive ingredients for the drug product are: Colloidal Silicon Dioxide, NF; (b) (4) Hypromellose, (b) (4) USP; Hydroxypropyl Cellulose, (b) (4) (b) (4) NF; Lactose Monohydrate (b) (4) NF; (b) (4) Magnesium Stearate, NF; Microcrystalline Cellulose, NF; Talc, NF; Iron Oxide, Yellow, NF

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 (G44147) 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, with

packaging in [redacted] (b) (4)
(b) (4)

The proposed expiration dating for the product is [redacted] (b) (4) 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 Composition, Synthesis, Raw Material Controls, Other Firms, Manufacturing and Processing, Container Closure System, Laboratory Controls, and Stability. All deficiencies are included in # 36.

The status of the bio data review and labeling review are still pending. The EES is 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.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-630/R.Iser, M.S.-Review Chemist/11-17-04; revised 11-23-04/ 11/24/04
HFD-630/D.Gill, Ph.D.-Team Leader/
HFD-617/S.Park, Pharm.D.-Project Manger/

V:FIRMSAM\IVAXPharm\LTRS&REV\77170.RV1.doc

C. CC Block

Cc:
ANDA 77-170
Division File
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All provided stability data meets all the proposed specifications. *The specifications for* (b) (4) (b) (4) *are included in deficiencies in section #28.*

Stability Deficiencies:

- (b) (4)
-

30. MICROBIOLOGY: **N/A**

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

32. LABELING: - **Pending**

33. ESTABLISHMENT INSPECTION: - **Pending**

34. BIOEQUIVALENCE: - **Pending**

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: **Satisfactory**

Included on pages 6 554 - 557. Exclusion from requirement for environmental assessment statement is provided and is satisfactory.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-170 APPLICANT: IVAX Pharmaceuticals, Inc.

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

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The Drug Master File (b) (4) is currently inadequate. The DMF holder, (b) (4) has been notified. Please do not respond to this letter until the DMF holder has notified you that they have responded to the deficiencies.

2. (b) (4)

3.

4.

5.

6.

7.

Following this page, 4 Pages Withheld in Full as (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 reviewed by the Division of Bioequivalence. Also, the dissolution data for release and stability will be evaluated based on the criteria set by the Division of Bioequivalence.

Sincerely yours,

DSG.M

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

cc: ANDA 77-170
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630 / R. Iser- Review Chemist /11-17-04; revised 11-23-04 11/24
HFD-630 / D. Gill - Team Leader /11/23/04 D.G.M 11-24-04
HFD-617 / S. Park - Project Manager /11/23/04 11/24/04

F/T by: EW 11/24/04

V:\FIRMSAM\IVAXPharm\LTRS&REV\77170.RV1.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-170

BIOEQUIVALENCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77 - 170
Drug Product Name	Cetirizine HCl and Pseudoephedrine HCl ER Tablets
Strength	5 mg / 120 mg
Applicant Name	Ivax Pharmaceuticals, Inc.
Address	140 Legend Ave, Northvale, New Jersey 07647
Submission Date(s)	September 7, 2005
Amendment Date(s)	N/A
Reviewer	Patrick Nwakama
First Generic	Yes
File Location	V:\firmsam\Ivax\ltrs&rev\77170a0905

I. Executive Summary

This submission is a study amendment. The firm had previously (6/1/04) submitted two acceptable BE (fasting and fed) studies. However, the firm's dissolution testing was incomplete. The firm did not conduct comparative dissolution testing in various dissolution media (pH 1.2, 4.5, and 6.8). Rather, the firm conducted dissolution testing in water only. In addition to the FDA recommended method (Basket 100 rpm in 500 mL of 0.1 N HCl), the firm was requested to submit dissolution data using Apparatus I at 100 rpm or apparatus II at 50 rpm in pH 4.5 (acetate buffer), and pH 6.8 (phosphate buffer).

In this study amendment, the firm submitted results of its dissolution testing conducted as recommended above by the DBE. The firm is proposing the following dissolution method [500 mL 0.1 N HCl, Basket, 100 rpm; NLT 75% (Q) in 30 minutes for Cetirizine HCl and Pseudoephedrine HCl (1 hr: (b) (4)%, 2 hr: 50 - 70%, 4 hr: 70 - 90% and 8 hr: NLT 80%)].

The dissolution data are acceptable. The firm's proposed dissolution method (basket 100 rpm in 500 mL of 0.1 N HCl) is acceptable. The firm's proposed specification of NLT 75% (Q) in 30 minutes for Cetirizine HCl is also acceptable. However, the firm's proposed specification of (b) (4) (b) (4) % at 1 hour for Pseudoephedrine HCl is not acceptable. The firm should be advised to acknowledge its acceptance of the FDA-recommended dissolution method and specifications [Basket 100 rpm in 500 mL of 0.1 HCl; Cetirizine HCl: NLT 75% (Q) in 30 minutes and Pseudoephedrine HCl: 1 hr: 30 - **50%**, 2 hr: 50 - 70%; 4 hr: 70 - 90%; 8hr: NLT 80%].

The application is complete pending the firm's acceptance of the FDA-recommended dissolution specifications.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Cetirizine HCl and Pseudoephedrine HCl ER Tablets
Reference Product	Zyrtec - D 12 hour® Tablets
RLD Manufacturer	Pfizer Laboratories.
NDA No.	021150
RLD Approval Date	August 10, 2001
Indication	Treatment of Seasonal and Perennial Allergy Conditions.

B. PK/PD Information

See (V:\firmsam\Ivax\ltrs&rev\77170n0604)

Relevant OGD or DBE History

This is the first generic for this drug product. The DBE has reviewed two control documents (#04078, (b) (4) and #04295, Sandoz) for this product.

The following studies are recommended to establish BE of cetirizine and pseudoephedrine extended release tablets:

a. A single-dose fasting *in vivo* BE study comparing Cetirizine and Pseudoephedrine ER Tablets, 5 mg/120 mg, to the RLD, Zyrtec-D® 12-Hour (cetirizine and pseudoephedrine) ER Tablets, 5 mg/120 mg.

b. A single-dose fed *in-vivo* BE study comparing Cetirizine and Pseudoephedrine ER Tablets, 5 mg/120 mg, to Zyrtec-D® 12 Hour ER Tablets, 5 mg/120mg.

2. Please measure the parent drugs, cetirizine and pseudoephedrine, in plasma.

3. Please conduct dissolution testing using 12 dosage units each of the test and reference products using the following FDA method:

Apparatus:	USP Apparatus 1 (Basket)
Speed:	100 rpm
Medium:	0.1 N HCl at 37°C
Volume:	500 mL
Sampling Times:	cetirizine: 15, 30, 45 and 60 minutes Pseudoephedrine: 1, 2, 4, 6 and 12 hrs.

Specifications will be determined upon review of the data submitted.

In addition, for modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffers) 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. Sampling times as stated above are recommended.

Agency Guidance N/A

Drug Specific Issues None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	0
Single-dose fed	No	0
Amendment	Yes	1
In vitro dissolution	Yes	1
Waiver requests	No	0

The current submission is a study amendment. The firm had previously (6/1/04) submitted two acceptable BE (fasting and fed) studies. The dissolution testing was incomplete. A deficiency letter to the firm was sent 7/18/2005 (see original review on V:\firmsam\Ivax\ltrs&rev\77170n0604).

DBE Deficiency Comments to the Firm (July 18, 2005):

Deficiency Comment #1:
Your in vitro dissolution testing is incomplete. As communicated to you earlier, please conduct dissolution testing using apparatus I at 100 RPM and/or apparatus II at 50 rpm in the following dissolution media: pH 4.5 (acetate buffer), and pH 6.8 (phosphate buffer) for the pseudoephedrine component. This will help in selecting the optimal dissolution method.

Firm's Response:
The firm generated new dissolution profiles using Apparatus I (Basket), at 100 rpm in pH 4.5(acetate buffer) and pH 6.8 (phosphate buffer). Sampling was performed at 1,2,3,4, and 6 hours and every two hours thereafter until 80% of the drug product was released or an asymptote was reached. The F2 factor for the cetirizine HCl component in pH 4.5 and pH 6.8 dissolution media were 77.88 and 94.45, respectively. The F2 factor for the pseudoephedrine HCl component in pH 4.5 and pH 6.8 dissolution media were 75 and 68.11, respectively. The firm proposes the following dissolution method [500 mL 0.1 N HCl, Basket, 100 rpm; NLT 75% (Q) in 30 minutes for Cetirizine HCl and Pseudoephedrine HCl (1 hr: (b) (4)%, 2 hr: 50 – 70%, 4 hr: 70 – 90% and 8 hr NLT 80%)].

DBE Comment:
The firm's response is acceptable. However, the DBE recommends the specification at 1 hour should be 30-50% for pseudoephedrine HCl.

Deficiency Comment #2:
Please also repeat the dissolution testing using the following conditions: basket 100 rpm in 500 mL of 0.1 N HCl with the sampling times of 10, 15, and 30 minutes for the cetirizine component and of 1, 2, 4, and 6 hours for the pseudoephedrine component.

Firm's Response:
The firm has conducted dissolution testing as recommended by the DBE.

DBE Comment:
The firm's response is acceptable.

Deficiency Comment #3:
Your selected QC samples for pseudoephedrine are appropriate, relative to the concentrations in the study samples for the fed and fasting studies. However, all study samples for cetirizine were below 264.25 ng/mL and 174.91 ng/mL in the fasting and fed studies, respectively. Therefore, your High QC selection for cetirizine is not appropriate. For future studies please select QC concentrations to be comparable with the expected study concentrations.

Firm's Response:
The firm acknowledges the DBE's comment that the High QC selection for cetirizine in the fed and fasting studies is not appropriate and will submit QC concentrations comparable with expected study concentrations for future studies.

DBE Comment:
The firm's response is acceptable.

D. In Vitro Dissolution

See dissolution review (V:\firmsam\IVAX\ltrs&rev\77170d0604.doc)

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
FDA-recommended specifications	Cetirizine HCl: NLT (b)(4)% (Q) in 30 minutes Pseudoephedrine: 1 hr: 30 – 50%, 2 hr: 50 – 70% and NLT 80% (Q) in 8 hours.
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	Yes
If not then why?	N/A

E. Waiver Request(s)

None

F. Dissolution Comments

The firm's proposed dissolution method is acceptable. However, the proposed specification of (b)(4)% at 1 hour time point for pseudoephedrine is not acceptable. It should be noted that the firm proposed to have a specification of NLT 80% at 8 hours, which is acceptable, even though the last time point as reported in its dissolution testing is 6 hours. Based on the submitted data, the DBE recommends the following specifications. The firm should be advised to acknowledge its acceptance of the following:

The dissolution testing should be conducted in 500 ml of 0.1N HCl using USP Apparatus I (Basket) at 100 rpm. The test product should meet the following specifications:

Cetirizine HCl:	NLT	75% (Q) in 30 minutes.
Pseudoephedrine HCl:	1 hr	30 – **50%**
	2 hr	50 – 70%
	4 hr	70 – 90%
	8 hr	NLT 80 %

G. Recommendations

1. The single-dose bioequivalence studies conducted under fasting and fed conditions by Ivax Pharmaceuticals Inc. on the test product, Cetirizine HCl and Pseudoephedrine HCl ER Tablets, 5 mg/120 mg, lot #G44147, comparing it to the reference product, Pfizer's Zyrtec – D 24 HOUR® 5 mg/120 mg tablets, lot #214N3L, are acceptable. The test product, Ivax's Cetirizine HCl and Pseudoephedrine HCl ER Tablets, 5 mg/120 mg, is bioequivalent to the reference product, Pfizer's Zyrtec – D 24 HOUR® 5 mg/120 mg tablets under fasting and fed conditions.

2. The in vitro dissolution testing is now acceptable. The firm should acknowledge its acceptance of the following:

   The dissolution testing should be conducted in 500 ml of 0.1N HCl using Basket at 100 rpm. The test product should meet the following specifications:

Cetirizine HCl:	NLT	75% (Q) in 30 minutes.
Pseudoephedrine HCl :	1 hr	30 – **50%**
	2 hr	50 – 70%
	4 hr	70 – 90%
	8 hr	NLT 80 %

The firm should be informed about the recommendations.

10/26/2005

Patrick Nwakama, Pharm.D. Branch III, Date

10/26/2005

Yih-Chain Huang, Ph.D. Branch III Date
Team Leader

10/27/05

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

Table Ia: Summary of in vitro Dissolution Data (Cetirizine HCl)

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % of Cetirizine Hydrochloride Dissolved (Range)			Study report Location
					10 min	15 min	30 min	
Dissolution study report #GM507999	Cetirizine Hydrochloride 5 mg and Pseudoephedrine Hydrochloride 120 mg ER Tablets/G44156	Cetirizine HCl 5 mg and Pseudoephedrine HCl 120 mg/tab	**Apparatus:** USP Type 1 (Basket) **Medium:** 0.1 N Hydrochloric Acid **Speed:** 100 RPM **Volume:** 500 mL **Temp of Medium:** 37 ± 0.5°C **Limit:** **For Cetirizine HCl:** NLT 75% Q i.e. equivalent to (b) (4)% of labeled amount released in 30 min. **For Pseudoephedrine HCl:** Time Interval % Release 1 (b) (4)% 2 50-70 % 4 70-90 % 8 NLT 80%	12	92	95	97 (b) (4)	(b) (4)
Dissolution study report #GM508000	ZYRTEC-D 12 Hour/214N3L	Cetirizine HCl 5 mg and Pseudoephedrine HCl 120 mg/tab		12	81	88	93 (b) (4)	

Table Ib: Summary of in vitro Dissolution Data (Pseudoephedrine HCl ER)

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % of Pseudoephedrine Hydrochloride Dissolved (Range)				Study report Location
					1 HR	2 HR	4 HR	6 HR	
Dissolution study report #GM507999	Cetirizine Hydrochloride 5 mg and Pseudoephedrine Hydrochloride 120 mg ER Tablets/G44156	Cetirizine HCl 5 mg and Pseudoephedrine HCl 120 mg/tab	**Apparatus:** USP Type I (Basket) **Medium:** 0.1 N Hydrochloric Acid **Speed:** 100 RPM **Volume:** 500 mL **Temp of Medium:** 37 ± 0.5°C **Limit:** **For Cetirizine HCl:** NLT 75% Q i.e. equivalent to (b) (4)% of labeled amount released in 30 min. **For Pseudoephedrine HCl:** Time Interval % Release 1 (b) (4)% 2 50-70 % 4 70-90 % 8 NLT 80%	12	44	60	83	94 (b) (4)	(b) (4)
Dissolution study report #GM508000	ZYRTEC-D 12 Hour/214N3L	Cetirizine HCl 5 mg and Pseudoephedrine HCl 120 mg/tab		12	42	61	86	99 (b) (4)	

Table 2a: Summary of in vitro Dissolution Data (Cetirizine HCl)

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % of Cetirizine Hydrochloride Dissolved (Range)			Study report Location
					10 min	15 min	30 min	
Dissolution study report #GM507999	Cetirizine Hydrochloride 5 mg and Pseudoephedrine Hydrochloride 120 mg ER Tablets/G44156	Cetirizine HCl 5 mg and Pseudoephedrine HCl 120 mg/tab	**Apparatus:** USP Type I (Basket) **Medium:** Acetate Buffer (pH 4.5) **Speed:** 100 RPM **Volume:** 500 mL **Temp of Medium:** 37 ± 0.5°C **Limit:** **For Cetirizine HCl:** NLT 75% Q i.e. equivalent to (b) (4)% of labeled amount released in 30 min. **For Pseudoephedrine HCl:** Time Interval % Release 1 (b) (4)% 2 50-70 % 4 70-90 % 8 NLT 80%	12	82	86	92 (b) (4)	(b) (4)
Dissolution study report #GM508000	ZYRTEC-D 12 Hour/214N3L	Cetirizine HCl 5 mg and Pseudoephedrine HCl 120 mg/tab		12	82	90	94 (b) (4)	

Table 2b: Summary of in vitro Dissolution Data (Pseudoephedrine HCl ER)

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % of Pseudoephedrine Hydrochloride Dissolved (Range)							Study report Location
					1 HR	2 HR	3 HR	4 HR	6 HR	8 HR	10 HR	
Dissolution study report #GM507909	Cetirizine Hydrochloride 5 mg and Pseudoephedrine Hydrochloride 120 mg ER Tablets/G44156	Cetirizine HCl 5 mg and Pseudoephedrine HCl 120 mg/tab	Apparatus: USP Type I (Basket) Medium: Acetate Buffer (pH 4.5) Speed: 100 RPM Volume: 500 mL Temp of Medium: 37 ± 0.5°C Limit: For Cetirizine HCl: NLT 75% Q i.e. equivalent to (b) (4)% of labeled amount released in 30 min. For Pseudoephedrine HCl: Time Interval % Release 1 (b) (4)% 2 50-70 % 4 70-90 % 8 NLT 80%	12	43	60	71	81	91	98	101 (b) (4)	(b) (4)
Dissolution study report #GM508000	ZYRTEC-D 12 Hour/214N3L	Cetirizine HCl 5 mg and Pseudoephedrine HCl 120 mg/tab		12	40	59	72	83	95	102	105 (b) (4)	

Table 3a: Summary of in vitro Dissolution Data (Cetirizine HCl)

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % of Cetirizine Hydrochloride Dissolved (Range)			Study report Location
					10 min	15 min	30 min	
Dissolution study report #GM507999	Cetirizine Hydrochloride 5 mg and Pseudoephedrine Hydrochloride 120 mg ER Tablets/G44156	Cetirizine HCl 5 mg and Pseudoephedrine HCl 120 mg/tab	**Apparatus:** USP Type 1 (Basket) **Medium:** Phosphate Buffer (pH 6.8) **Speed:** 100 RPM **Volume:** 500 mL **Temp of Medium:** 37 ± 0.5°C **Limit:** **For Cetirizine HCl:** NLT 75% Q i.e. equivalent to (b)(4)% of labeled amount released in 30 min. **For Pseudoephedrine HCl:** Time Interval % Release 1 (b)(4) % 2 50-70 % 4 70-90 % 8 NLT 80%	12	80	85	90 (b)(4)	(b)(4)
Dissolution study report #GM508000	ZYRTEC-D 12 Hour/214N3L	Cetirizine HCl 5 mg and Pseudoephedrine HCl 120 mg/tab		12	80	84	89 (b)(4)	

Table 3b: Summary of in vitro Dissolution Data (Pseudoephedrine HCl ER)

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % of Pseudoephedrine Hydrochloride Dissolved (Range)							Study report Location
					1 HR	2 HR	3 HR	4 HR	6 HR	8 HR	10 HR	
Dissolution study report #GM507999	Cetirizine Hydrochloride 5 mg and Pseudoephedrine Hydrochloride 120 mg ER Tablets/G44156	Cetirizine HCl 5 mg and Pseudoephedrine HCl 120 mg/tab	Apparatus: USP Type I (Basket) Medium: Phosphate Buffer (pH 6.8) Speed: 100 RPM Volume: 500 mL Temp of Medium: 37 ± 0.5°C Limit: For Cetirizine HCl: NLT 75% Q i.e. equivalent to (b) (4) % of labeled amount released in 30 min. For Pseudoephedrine HCl: Time Interval % Release 1 (b) (4) % 2 50-70 % 4 70-90 % 8 NLT 80%	12	41	58	79	85	87	95	97	(b) (4)
											(b) (4)	
Dissolution study report #GM508000	ZYRTEC-D 12 Hour/214N3L	Cetirizine HCl 5 mg and Pseudoephedrine HCl 120 mg/tab		12	40	57	71	80	90	98	101	
											(b) (4)	

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77170 APPLICANT: Ivax Pharmaceuticals, Inc.
DRUG PRODUCT: Cetirizine HCl and Pseudoephedrine HCl ER Tablets, 5 mg/120 mg

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

Your proposed dissolution method is acceptable. However, your proposed specification of (b) (4) % at 1 hour for pseudoephedrine is not acceptable. Based on the submitted data, the Division of Bioequivalence recommends the specification of 30-50% for pseudoephedrine at 1 hour.

Please acknowledge that you have accepted the following:

The dissolution testing should be conducted in 500 ml of 0.1N HCl using USP Apparatus I (Basket) at 100 rpm. The test product should meet the following specifications:

Cetirizine HCl: Not less than 75% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Pseudoephedrine HCl:

1 hr	*30 - 50%*
2 hr	*50 - 70%*
4 hr	*70 - 90%*
8 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 77170
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ P. Nwakama

Endorsements: (Draft and Final with Dates)
HFD-658/ P. Nwakama 10/26/2005
HFD-658/ YC Huang 10/20/2005
HFD-650/ S. Mazzella
HFD-650/ D. Conner 10/27/05

Final: 10/26/05

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BIOEQUIVALENCE – Acceptable Submission Date: September 7, 2005
[Note: The firm needs to acknowledge its acceptance of the FDA-recommended dissolution specifications.]

1. **STUDY AMENDMENT** (STA) Strength: 5 mg/120 mg
Outcome: **AC**

Outcome Decisions: AC

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 77170 SPONSOR : Ivax Pharmaceuticals Inc..

DRUG AND DOSAGE FORM: Cetirizine HCl and Pseudoephedrine HCl ER Tablets

STRENGTH(S): 5 mg/120 mg

TYPE OF STUDIES: Fasting and Fed BE Studies

CLINICAL STUDY SITE(S): Algorithme Pharma Inc., Quebec, Canada
ANALYTICAL SITE(S): (b) (4)

STUDY SUMMARY: 90% CIs within Acceptable Limits
DISSOLUTION: Acceptable

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
First Generic _Yes_	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause ____		
Other ____		

Proposed Dissolution Method and Specifications from Original Submission Acceptable? Yes __No __X__
(If no, PM should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Specifications acknowledged by firm? Yes __X__ No _____
PROJECT MANAGER: _Christina Thompson, Pharm.D.__ DATE _November 18, 2005__

PRIMARY REVIEWER: Patrick Nwakama, Pharm.D. BRANCH: III
INITIAL: PEN DATE: 11/28/05

TEAM LEADER: Yih-Chain Huang, Ph.D. BRANCH: III
INITIAL: YCH DATE: 11/28/2005

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.
INITIAL: DPC DATE: 11/30/05

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77 - 170
Drug Product Name	Cetirizine HCl and Pseudoephedrine HCl ER Tablets
Strength	5 mg / 120 mg
Applicant Name	Ivax Pharmaceuticals, Inc.
Address	140 Legend Ave, Northvale, New Jersey 07647
Submission Date(s)	June 1, 2004
Amendment Date(s)	N/A
Reviewer	Patrick Nwakama
First Generic	Yes
File Location	V:\firmsam\Ivax\ltrs&rev\77170N0604

I. Executive Summary

This is a review of in vivo bioequivalence studies only. The original dissolution testing had been reviewed separately. This submission contains two (fasting and fed) bioequivalence (BE) studies and dissolution data on Cetirizine HCl and Pseudoephedrine HCl ER Tablets 5 mg / 120 mg and the RLD (Pfizer's Zyrtec - D®) products. The BE studies are two-way, crossover studies conducted in healthy adult males (fasting: n = 27 and fed: n = 28). Statistical analyses of the plasma concentration data for Cetirizine and Pseudoephedrine demonstrate bioequivalence.

The results (point estimate, 90% CI) of the fasting BE study are **Cetirizine**: LAUCt of 1.04, 100.72 - 107.10%; LAUCi of 1.03, 99.94 -106.30% and LCmax of 1.05, 98.81 -111.66%; **Pseudoephedrine**: LAUCt of 1.00, 94.48 -106.13%; LAUCi of 1.00, 93.87 -105.49% and LCmax of 0.96, 92.21 -100.30%. The results of the fed BE study are **Cetirizine**: LAUCt of 1.00, 97.62 – 103.14%; LAUCi of 1.00, 97.73 – 103.23%; and LCmax of 1.01, 94.69 – 107.93%; **Pseudoephedrine**: LAUCt of 1.01, 97.02 – 104.47%; LAUCi of 1.01, 97.72 – 105.07%; and LCmax of 1.00, 95.98 – 103.50%.

The firm's dissolution testing is incomplete. The firm did not conduct comparative dissolution testing in different dissolution media (pH 1.2, 4.5, and 6.8). The firm conducted dissolution testing using water as dissolution medium. In addition to the FDA recommended method (basket 100 rpm in 500 mL of 0.1 HCl), the firm was requested to submit dissolution data using Apparatus I at 100 rpm or apparatus II at 50 rpm in pH 4.5 (acetate buffer), and pH 6.8 (phosphate buffer). The firm has not submitted a dissolution amendment.

Therefore, the application is incomplete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Cetirizine HCl and Pseudoephedrine HCl ER Tablets
Reference Product	Zyrtec - D 12 hour® Tablets
RLD Manufacturer	Pfizer Laboratories.
NDA No.	021150
RLD Approval Date	August 10, 2001
Indication	Treatment of Seasonal and Perennial Allergy Conditions.

B. PK/PD Information

(Sources: Electronic Drug Facts & Comparisons, 2005 PDR and Micromedex)

Bioavailability	The bioavailability of cetirizine and pseudoephedrine from the combination ER 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 Tmax was delayed by 1.8 hours and Cmax was decreased by 30%. Food had no significant effect on the PK of pseudoephedrine. Zyrtec-D 12 HOUR® Tablets may be given with or without food
Cmax	Following a single dose administration, a mean Cmax of 114 ng/mL and 309 ng/mL were observed for cetirizine and pseudo-ephedrine, respectively.
Tmax	2.2 hours and 4.4 hours for cetirizine and pseudoephedrine, respectively.
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	7.9 hours and 6.0 hours for cetirizine and pseudoephedrine, respectively.

Relevant OGD or DBE History

This is the first generic for this drug product. The DBE has reviewed two control documents (#04078, (b) (4) and #04295, Sandoz) for this product.

The following studies are recommended to establish BE of cetirizine and pseudoephedrine extended release tablets:

a. A single-dose fasting *in vivo* BE study comparing Cetirizine and Pseudoephedrine ER Tablets, 5 mg/120 mg, to the RLD, Zyrtec-D® 12-Hour (cetirizine and pseudoephedrine) ER Tablets, 5 mg/120 mg.

b. A single-dose fed *in-vivo* BE study comparing Cetirizine and Pseudoephedrine ER Tablets, 5 mg/120 mg, to Zyrtec-D® 12 Hour ER Tablets, 5 mg/120mg.

2. Please measure the parent drugs, cetirizine and pseudoephedrine, in plasma.

3. Please conduct dissolution testing using 12 dosage units each of the test and reference products using the following FDA method:

Apparatus:	USP Apparatus 1 (Basket)
Speed:	100 rpm
Medium:	0.1 N HCl at 37°C
Volume:	500 mL
Sampling Times:	cetirizine: 15, 30, 45 and 60 minutes Pseudoephedrine: 1, 2, 4, 6 and 12 hrs.

Specifications will be determined upon review of the data submitted.

In addition, for modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffers) 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. Sampling times as stated above are recommended.

Agency Guidance N/A

Drug Specific Issues 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	

D. Pre-Study Bioanalytical Method Validation

Vol 1.4, pp. 36 - 59		
	Parent	
Analyte name	Cetirizine	Pseudoephedrine
Internal Standard	(b) (4)	(b) (4)
Method description	HPLC with MS/MS Detection	HPLC with MS Detection
QC range (ng/ml)	2, 6, 80, 400 ng/mL	5, 15, 80 and 450.0 ng/mL
Standard curve range (ng/ml)	2.00 – 500.00 ng/mL	5.00 – 600.00 ng/mL
Limit of quantitation (ng/ml)	2.00 ng/mL	5.00 ng/mL
Average recovery of Drug (%)	66.1%	81.2%
Average Recovery of Int. Std (%)	79.3%	32.6%
QC Intraday precision range (%CV)	2.1 – 4.2%	2.5 – 4.5%
QC Intraday accuracy range (%)	96.0 – 100.4%	102.7 – 115.2%
QC Interday precision range (%CV)	3.9 – 7.5%	3.9 – 8.1%
QC Interday accuracy range (%)	97.6 – 103.1%	104.1 – 111.8%
Bench-top stability (hrs)	21 hours	18.7 hours
Stock stability (days)	26 days	53 days
Processed stability (hrs)	146.8 hours	94.5 hours
Freeze-thaw stability (cycles)	3 cycles	5 cycles
Long-term storage stability (days)	31 days	44 days
Dilution integrity (@ 1010.5 ng/mL & 1200.0 ng/mL for Cetirizine & Pseudoephedrine, respectively)	10-fold, 99.0%	10-fold, 103.5%
Specificity	Yes	Yes
SOPs submitted	Yes	Yes
Bioanalytical method is acceptable	Yes	Yes

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	CTN-P3-262
Study Design	Randomized, Single-Dose, two-way Crossover
No. of subjects enrolled	30
No. of subjects completing	27
No. of subjects analyzed	27
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 13 Female: 14
Test product	Cetirizine / Pseudoephedrine Tablets
Reference product	Zyrtec – D 24 HOUR® Tablets
Strength tested	5 mg / 120 mg
Dose	1 x 5 mg / 120 mg

Summary of Statistical Analysis, Fasting Bioequivalence Study		
Parameter	**Point Estimate**	**90% Confidence Interval**
Cetirizine		
AUC0-t	1.04	100.72 – 107.10
AUC∞	1.03	99.94 – 106.30
Cmax	1.05	98.81 – 111.66
Pseudoephedrine		
AUC0-t	1.00	94.48 – 106.13
AUC∞	1.00	93.87 – 105.49
Cmax	0.96	92.21 – 100.30

Reanalysis of Study Samples, Fasting Bioequivalence Study Additional information in Appendix, Table 6								
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**
Cetirizine								
Pharmacokinetic Fit	4	0	0.32	0.00	2	0	0.16	0.00
Sample Lost in Processing	1	12	0.08	0.97	1	12	0.08	0.97
Pseudoephedrine								
Pharmacokinetic Fit	5	2	0.40	0.16	4	1	0.32	0.08
Sample Lost in Processing	3	3	0.24	0.24	3	3	0.24	0.24
Above Upper Limit of Quantitation	1	0	0.08	0.00	1	0	0.08	0.00
Total	**14**	**17**	**1.12**	**1.37**	**11**	**16**	**0.88**	**1.29**

Total No. of Samples Analyzed = 1240

Did use of recalculated plasma concentration data change study outcome? No. The reviewer treated the PK fits as PK repeats and ran SAS with both the original and recalculated values. The results were similar in both PK analyses.

2. Single-dose Fed Bioequivalence Study

Study Summary, Fed Bioequivalence Study	
Study No.	CTN-P3-263
Study Design	Randomized, Single-Dose, two-way Crossover
No. of subjects enrolled	30
No. of subjects completing	28
No. of subjects analyzed	28
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	**Male:** 14 **Female:** 14
Test product	Cetirizine / Pseudoephedrine Tablets
Reference product	Zyrtec – D 24 HOUR® Tablets
Strength tested	5 mg / 120 mg
Dose	1 x 5 mg / 120 mg

Summary of Statistical Analysis, Fed Bioequivalence Study		
Parameter	**Point Estimate**	**90% Confidence Interval**
Cetirizine		
AUC0-t	1.00	97.62 – 103.14
AUC∞	1.00	97.73 – 103.23
Cmax	1.01	94.69 – 107.93
Pseudoephedrine		
AUC0-t	1.01	97.02 – 104.47
AUC∞	1.01	97.72 – 105.07
Cmax	1.00	95.98 – 103.50

Reanalysis of Study Samples, Fed Bioequivalence Study Additional information in Appendix, Table 18								
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
Cetirizine								
Inadequate Chromatography	1	0	0.08	0.0	1	0	0.08	0.0
Sample Lost in Processing	1	0	0.08	0.0	1	0	0.08	0.0
Pseudoephedrine								
Pharmacokinetic Fit	1	0	0.08	0.0	1	0	0.08	0.00
Sample Lost in Processing	0	3	0.00	0.25	0	3	0.00	0.25
Total	**3**	**3**	**0.24**	**0.25**	**3**	**3**	**0.24**	**0.25**

Total No. of Samples Analyzed = 1176

Did use of recalculated plasma concentration data change study outcome? No. The reviewer treated the PK fit as a PK repeat and ran SAS with both the original and recalculated values. The results were similar in both PK analyses.

F. Formulation

Location in appendix	Section I.B, Page 32
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	
If a tablet, is the product scored?	No
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test?	Yes
Is the formulation acceptable?	Yes
If not acceptable, why?	N/A

G. In Vitro Dissolution

See dissolution review (V:\firmsam\IVAX\ltrs&rev\77170d0604.doc)

Source of Method (USP, FDA or Firm)	Firm
Medium	Water
Volume (mL)	(b) (4) mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
FDA-recommended specifications	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Not FDA Method
Is method acceptable?	No
If not then why?	Firm requested to conduct multi-media dissolution testing.

H. Waiver Request(s)

None

I. Deficiency Comments

The firm did not conduct comparative dissolution testing in three different media (pH 1.2, 4.5, and 6.8) for pseudoephedrine HCl component. At the completion of the review of the BE studies, the DBE has not yet received the firm's dissolution amendment.

J. Recommendations

1. The single-dose bioequivalence studies conducted under fasting and fed conditions by Ivax Pharmaceuticals Inc. on the test product, Cetirizine HCl and Pseudoephedrine HCl ER Tablets, 5 mg / 120 mg, lot #G44147, comparing it to the reference product, Pfizer's Zyrtec – D 24 HOUR® 5 mg / 120 mg tablets, lot #214N3L, are acceptable. However, the application is incomplete because of the dissolution deficiency.

2. The in vitro dissolution testing is incomplete. In a separate dissolution review, the DBE has already advised the firm to conduct dissolution testing using apparatus I at 100 RPM and/or apparatus II at 50 rpm in the following dissolution media: pH 4.5 (acetate buffer), and pH 6.8 (phosphate buffer) for pseudoephedrine component. The firm was advised to repeat the dissolution testing using the following conditions: basket 100 rpm in 500 mL of 0.1 N HCl with the sampling times of 10, 15, and 30 minutes for the cetirizine component and of 1, 2, 4, and 6 hours for the component of pseudoephedrine. At the completion of BE reviews, the DBE has not yet received the firm's dissolution amendment.

The firm should be informed about the recommendations.

7/20/05

Patrick Nwakama, Pharm.D. Branch III, Date

7/20/2005

Yih-Chain Huang, Ph.D. Branch III Date
Team Leader

for Barbara M Davit 7/22/05

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	CTN-P3-262
Study Title	Randomized, 2-Way Crossover, Bioequivalence Study of Cetirizine and Pseudoephedrine ER Tablets, 5 mg/120 mg (Ivax Pharmaceuticals, Inc.) and Pfizer's Zyrtec – D 24 HOUR® 5 mg / 120 mg tablets (Pfizer) Administered as 1 x 5 mg/120 mg Tablet in Healthy Subjects under Fasting Conditions
Clinical Site	Algorithme Pharma Inc., 575 Boulevard Armand-Frappier Laval, Quebec, Canada
Principal Investigator	Eric Sicard, M.D.
Study/Dosing Dates	Period I: March 11 - 13, 2004 Period II: March 18 - 20, 2004
Analytical Site	(b) (4) (b) (4)
Analytical Director	(b) (6) B.Sc.
Analysis Dates	March 29 – April 26, 2004
Storage Period	Cetirizine – 46 days; Pseudoephedrine - 39 days (Long-term Stability: Cetirizine = 59 days and Pseudoephedrine = 44 days).

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Cetirizine and Pseudoephedrine ER	Zyrtec – D 24 HOUR®
Manufacturer	Ivax Pharmaceuticals Inc.	Pfizer
Batch/Lot No.	GAA156	214N3L
Manufacture Date	02/2004	N/A
Expiration Date	01/2006	09/2005
Strength	5 mg/120 mg	5 mg/120 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	100.2% (Cetirizine); 99.1% (Pseudoephedrine)	99.4% (Cetirizine); 98.9% (Pseudoephedrine)
Content Uniformity (mean, %CV)	97.8% (RSD = 2.3%), Cetirizine 100.2% (RSD = 0.8%), Pseudoephedrine	97.7% (RSD = 2.2%), Cetirizine 100.0% (RSD = 0.8%), Pseudoephedrine
Formulation	See Appendix Section B	
Dose Administered	1 x 5 mg/120 mg	
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 1,3,5,7,9,12,14,**15**,17,20,22,23,26,28,30 BA: 2,4,6,8,10,11,13,**16**,18,**19**,21,24,25,27,29
Blood Sampling Times	0, 0.17,0.33,0.5,0.75,1,1.33,1.67,2,2.5,3,3.5,4,5,6,7, 8,10,12,16, 24, 36 and 48 hours.
Blood Volume Collected/Sample	10 ml
Blood Sample Processing/Storage	-20°C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Overnight for ≥ 10 hours
Length of Confinement	34 hours
Safety Monitoring	Vital signs only at baseline (hour 0). No measurements specified during the study per protocol.

Comments on Study Design: Study design is acceptable.

b) Clinical Results

Table 1 Demographics of Study Subjects (n = 27)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	92.6
Mean	32	Mean	67.5	18-40	77.8	Male	44.4	Afr. Amer.	7.4
SD	10	SD	10.9	41-64	22.2	Female	55.6	Hispanic	
Range	20 – 54	Range	50.5 – 90.2	65-75				Asian	
				>75				Others	

Table 2 Dropout Information

Subject No	Subject #15	Subject #16	Subject #26
Reason	Adverse Reaction	Adverse Reaction	Personal Reasons
Period	Period I	Period I	Period I
Replacement	No	No	No

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Sore throat	1	0
Dizziness	1	3
Somnolence	1	2
Hypersensitivity	1	0
Abdominal Pain	0	2
Eructation	0	1
Loss of appetite	0	1
Respiratory problems	0	1
Dyspepsia	1	0
Fatigue	1	1
Abdominal Distension	0	1
Myalgia	0	1
Total	**6**	**13**

Table 4 Protocol Deviations

Fifty-five (55) blood sampling delays (≤ 30 min) and 1 'sample not obtained' were reported. Actual sampling times were used for pharmacokinetic analyses. The integrity of the study was not compromised.

Comments on Dropouts/Adverse Events/Protocol Deviations:
No serious adverse events or major protocol deviations occurred to alter the study outcome.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Vol. 1.11, pp. 02 - 28	Vol. 1.12, pp. 02 - 28
	Cetirizine	Pseudoephedrine
QC Conc.	6.00, 80.0, and 400.0 ng/mL	15.0. 80.0 and 450.0 ng/mL
Inter day Precision (%CV)	3.5 – 6.9%	5.2 – 7.9%
Inter day Accuracy (%)	100.6 – 102.7%	101.1 – 102.7%
Cal. Standards Conc.	2.00 – 500.00 ng/mL	5.00 – 600.00 ng/mL
Inter day Precision (%CV)	2.7 – 6.1%	3.0 – 9.7%
Inter day Accuracy (%)	97.0 – 104.7%	99.1 – 101.4%
Linearity Range (range of R^2 values)	0.9949 – 0.9994	0.9897 – 0.9999

Comments on Study Assay Quality Control: The selection of QC concentrations is appropriate, relative to the concentrations in the study samples for pseudoephedrine. However, the High QC concentration of 400 ng/mL for cetirizine is not appropriate, since all study samples for cetirizine were

below 264.25 ng/mL. For future studies, the firm should be advised to select the QC concentrations more comparable with the expected concentrations in the study samples. .

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

Comments on Chromatograms: No interfering peaks

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
(b) (4)	(b) (4)	Repeat / Reassay Samples

Table 7 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays: Study is complete.

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters, n=27

Mean plasma Cetirizine concentrations are presented in Table 11 and Figure 1:

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCI	1388.78	22.87	1362.06	27.34	1.02
AUCT	1351.82	23.30	1316.48	28.01	1.03
CMAX	177.91	19.53	171.34	24.60	1.04
KE	0.10	28.07	0.10	31.34	0.99
LAUCI	1353.63	0.02	1316.04	0.02	1.03
LAUCT	1316.07	0.02	1269.83	0.02	1.04
LCMAX	174.66	0.11	166.33	0.15	1.05
THALF	7.41	25.76	7.45	28.83	0.99
TMAX	0.82	47.67	0.86	46.91	0.96

UNIT: AUC= ng*hr/mL CMAX=ng/mL Tmax= hr
NOTE: The mean values for LAUCT, LAUCI, and LCmax are the geometric means.

Mean plasma Pseudoephedrine concentrations are presented in Table 11 and Figure 2:

	Test		Reference		
	MEAN1	CV1	MEAN2	CV2	T/R
PARAMETER					
AUCI	4398.70	25.27	4456.70	28.88	0.99
AUCT	4298.63	25.63	4333.40	29.58	0.99
CMAX	325.37	20.08	340.47	23.66	0.96
KE	0.13	17.59	0.13	21.56	0.98
LAUCI	4257.97	0.01	4283.75	0.01	0.99
LAUCT	4157.38	0.01	4156.49	0.01	1.00
LCMAX	319.14	0.06	331.95	0.07	0.96
THALF	5.42	17.28	5.42	23.19	1.00
TMAX	4.65	27.64	5.04	26.76	0.92

Table 9 Least Square Geometric Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	LOWCI12	UPPCI12
Cetirizine					
AUCI	1388.34	1359.17	1.02	98.98	105.31
AUCT	1351.42	1313.59	1.03	99.68	106.08
CMAX	177.82	171.20	1.04	98.25	109.49
LAUCI	1353.33	1313.05	1.03	99.94	106.30
LAUCT	1315.78	1266.85	1.04	100.72	107.10
LCMAX	174.57	166.20	1.05	98.81	111.66
Pseudoephedrine					
AUCI	4407.12	4460.97	0.99	92.94	104.65
AUCT	4306.94	4337.50	0.99	93.52	105.07
CMAX	326.02	341.05	0.96	91.14	100.05
LAUCI	4265.06	4285.98	1.00	93.87	105.49
LAUCT	4164.28	4158.57	1.00	94.48	106.13
LCMAX	319.73	332.47	0.96	92.21	100.30

UNIT: AUC= ng*hr/mL CMAX=ng/mL Tmax= hr

Table 10 Additional Study Information

	Cetirizine	Pseudoephedrine
Root mean square error, AUC0-t	0.066075	0.124934
Root mean square error, AUC∞	0.066348	0.125467
Root mean square error, Cmax	0.131396	0.090438
Kel and AUC∞ determined for how many subjects?	All (27 subjects)	All (27 subjects)
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
-measurable drug concentrations at 0 hr	None	None
-first measurable drug concentration as Cmax	None	None
Were the subjects dosed as more than one group?	No	No

Comments on Pharmacokinetic and Statistical Analysis:

The reviewer's calculated 90% confidence intervals for the test to reference ratios for the $LAUC_{0-t}$, $LAUC_{0-\infty}$ and LC_{max} are in agreement with the firm's reported values and are within acceptable limits of 80%-125%.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The single-dose fasting bioequivalence study is complete.

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

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
0.17	10.72	156.02	4.30	164.77	2.49
0.33	79.05	70.83	76.56	70.83	1.03
0.5	134.63	41.83	140.50	47.69	0.96
0.75	164.99	29.18	158.73	30.11	1.04
1	155.39	22.18	158.15	22.93	0.98
1.33	147.22	21.01	143.59	22.23	1.03
1.67	140.46	20.43	137.21	22.57	1.02
2	133.15	21.30	131.87	21.46	1.01
2.5	125.52	20.49	122.47	21.80	1.02
3	118.86	20.18	116.22	21.61	1.02
3.5	114.34	20.49	109.95	23.60	1.04
4	104.95	20.83	103.71	21.49	1.01
5	94.73	20.46	91.12	23.80	1.04
6	79.29	22.03	79.04	24.35	1.00
7	68.58	21.29	68.06	25.77	1.01
8	62.10	20.95	60.94	25.82	1.02
10	47.53	24.70	46.37	29.68	1.02
12	36.26	27.67	35.28	29.17	1.03
16	22.13	34.02	21.68	38.53	1.02
24	10.80	45.96	10.36	47.92	1.04
36	3.49	77.07	3.27	87.79	1.07
48	0.84	168.22	0.77	199.14	1.09

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

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
0.17	0.61	365.33	0.20	519.62	3.05
0.33	15.90	105.03	11.04	77.52	1.44
0.5	43.87	55.01	37.49	60.31	1.17
0.75	97.08	34.55	80.91	39.25	1.20
1	131.45	28.76	113.46	32.15	1.16
1.33	165.36	21.04	154.04	26.62	1.07
1.67	186.32	23.39	182.65	26.84	1.02
2	219.87	24.11	211.48	26.77	1.04
2.5	241.08	24.35	234.79	25.14	1.03
3	258.43	22.64	265.31	23.19	0.97
3.5	290.90	20.84	282.61	28.37	1.03
4	302.01	21.07	282.53	20.83	1.07
5	307.99	22.15	301.47	22.62	1.02
6	296.05	19.71	314.64	23.95	0.94
7	276.61	23.45	272.17	24.64	1.02
8	263.16	21.97	272.76	28.82	0.96
10	220.65	25.98	229.08	26.45	0.96
12	181.96	29.70	189.31	32.25	0.96
16	112.98	35.95	115.07	44.20	0.98
24	40.57	50.73	39.90	69.75	1.02
36	8.88	79.14	9.50	114.33	0.94
48	0.57	361.60	1.08	342.27	0.52

Figure 1 Mean Plasma Cetirizine Concentrations, Single-Dose Fasting Bioequivalence Study

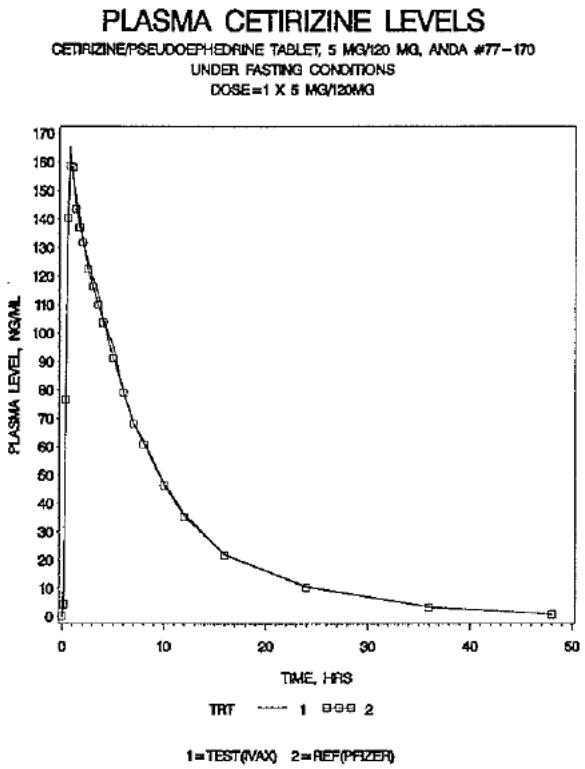
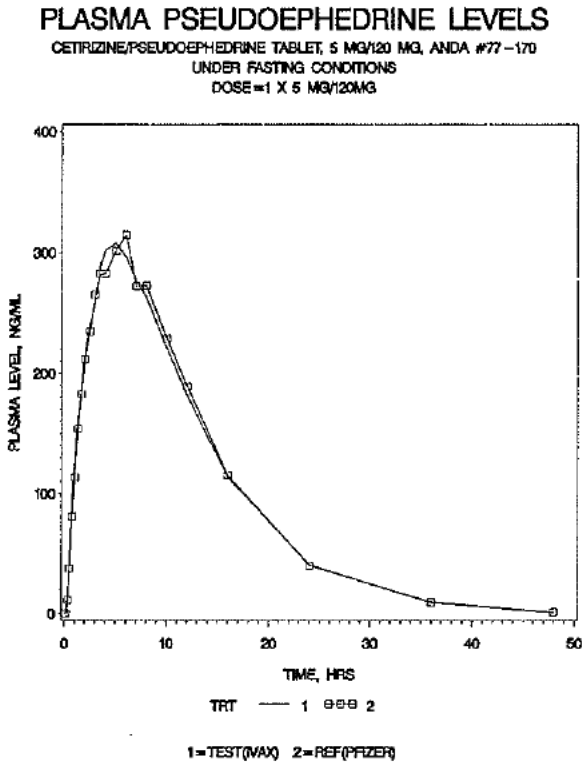


Figure 2 Mean Plasma Pseudoephedrine Concentrations, Single-Dose Fasting Bioequivalence Study



2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	CTN-P3-263
Study Title	Randomized, 2-Way Crossover, Bioequivalence Study of Cetirizine and Pseudoephedrine ER Tablets, 5 mg/120 mg (Ivax Pharmaceuticals, Inc.) and Pfizer's Zyrtec – D 24 HOUR® 5 mg / 120 mg tablets (Pfizer) Administered as 1 x 5 mg/120 mg Tablet in Healthy Subjects under Fed Conditions
Clinical Site	Algorithme Pharma Inc., 575 Boulevard Armand-Frappier Laval, Quebec, Canada
Principal Investigator	Eric Sicard, M.D.
Study/Dosing Dates	Period I: March 11 - 13, 2004 Period II: March 18 - 20, 2004
Analytical Site	(b) (4)
Analytical Director	(b) (6) B.Sc.
Analysis Dates	March 30 – April 15, 2004
Storage Period	Cetirizine – 41 days; Pseudoephedrine - 35 days (Long-term Stability: Cetirizine = 59 days and Pseudoephedrine = 44 days)

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Cetirizine and Pseudoephedrine ER	Zyrtec – D 24 HOUR®
Manufacturer	Ivax Pharmaceuticals Inc.	Pfizer
Batch/Lot No.	GAA156	214N3L
Manufacture Date	02/2004	N/A
Expiration Date	01/2006	09/2005
Strength	5 mg / 120 mg	5 mg / 120 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	100.2% (Cetirizine); 99.1% (Pseudoephedrine)	99.4% (Cetirizine); 98.9% (Pseudoephedrine)
Content Uniformity (mean, %CV)	97.8% (RSD = 2.3%), Cetirizine 100.2% (RSD = 0.8%), Pseudoephedrine	97.7% (RSD = 2.2%), Cetirizine 100.0% (RSD = 0.8%), Pseudoephedrine
Formulation	See Appendix Section B	
Dose Administered	1 x 5 mg/120 mg	
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 2,3,5,7,9,11,13,16,17,20,22,24,26,27,**30** BA: 1,4,6,8,10,12,14,15,18,19,21,23,25,28,**29**
Blood Sampling Times	0, 0.25,0.5,1,1.33,1.67,2,2.5,3,3.5,4,5,6,7, 8,10,12,16, 24, 36 and 48 h
Blood Volume Collected/Sample	10 ml
Blood Sample Processing/Storage	- 20°C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See **Table 13**
Length of Fasting before Meal	Overnight for ≥ 10 hours
Length of Confinement	34 hours
Safety Monitoring	Vital signs only at baseline (hour 0). No measurements specified during the study per protocol.
Standard FDA Meal Used?	Yes

Comments on Study Design: Study design is acceptable.

b) Clinical Results

Table 13 Demographics of Study Subjects (n = 28)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	100
Mean	33	Mean	70.1	18-40	82.1	Male	50.0	Afr. Amer.	
SD	11	SD	11.1	41-64	17.9	Female	50.0	Hispanic	
Range	20 – 52	Range	48.7 - 92.2	65-75				Asian	
				>75				Others	

Table 14 Dropout Information

None (28 of 30 subjects were analyzed per protocol)

Table 15 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Ear Stock	1	1
Dizziness	2	0
Somnolence	3	2
Headache	2	3
LFT Elevations	2	2
Menorrhagia	1	0
Abdominal Pain	1	0
Flushing	1	1
Fatigue	0	1
Pharyngolaryngeal pain	1	1
Blurred Vision	1	0
Total	**15**	**11**

Table 16 Protocol Deviations

Forty (40) blood sampling delays (≤ 10 min) were reported. Actual sampling times were used for pharmacokinetic analyses. The integrity of the study was not compromised.

Comments on Dropouts/Adverse Events/Protocol Deviations:

No serious adverse events or major protocol deviations occurred to alter the study outcome.

Bioanalytical Results

Table 17 Assay Quality Control – Within Study

	Vol. 1.4, pp. 08 - 25	Vol. 1.5, pp. 02 - 27
	Cetirizine	Pseudoephedrine
QC Conc.	6.00, 80.0, and 400.0 ng/mL	15.0. 80.0 and 450.0 ng/mL
Inter day Precision (%CV)	2.9 – 5.7%	6.9 – 9.9%
Inter day Accuracy (%)	99.6 – 103.7%	101.3 – 101.6%
Cal. Standards Conc.	2.00 – 500.00 ng/mL	5.00 – 600.00 ng/mL
Inter day Precision (%CV)	2.7 – 6.3%	3.3 – 8.4%
Inter day Accuracy (%)	97.1 – 103.6%	97.1 – 103.6%
Linearity Range (range of R^2 values)	0.9935 – 0.9995	0.9880 – 0.9997

Comments on Study Assay Quality Control: The selection of QC concentrations is appropriate, relative to the concentrations in the study samples for pseudoephedrine. However, the High QC concentration of 400 ng/mL for cetirizine is not appropriate, since all study samples for cetirizine were below 174.91 ng/mL. For future studies, the firm should be advised to select the QC concentrations more comparable with the expected concentrations in the study samples.

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

Comments on Chromatograms: No interfering peaks.

Table 18 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
(b) (4)	(b) (4)	Repeat / Reassay Samples

Table 19 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays: Study is complete.

c) Pharmacokinetic Results

Table 20 Arithmetic Mean Pharmacokinetic Parameters, N = 28

Mean plasma Cetirizine and Pseudoephedrine concentrations are presented in Table 23 and Table 24

CETIRIZINE

	Test		Reference		
	MEAN1	CV1	MEAN2	CV2	T/R
PARAMETER					
AUCI	1232.69	18.35	1230.67	20.02	1.00
AUCT	1196.08	18.72	1195.11	20.39	1.00
CMAX	116.75	14.38	116.42	20.40	1.00
KE	0.10	21.61	0.10	21.51	0.98
LAUCI	1211.93	0.02	1206.58	0.02	1.00
LAUCT	1174.80	0.02	1170.77	0.02	1.00
LCMAX	115.51	0.13	114.26	0.17	1.01
THALF	7.26	22.23	7.14	21.86	1.02
TMAX	2.68	52.63	2.95	50.76	0.91

PSEUDOEPHEDRINE

	Test		Reference		
	MEAN1	CV1	MEAN2	CV2	T/R
PARAMETER					
AUCI	4244.78	25.21	4189.87	25.98	1.01
AUCT	4138.90	25.46	4110.86	26.02	1.01
CMAX	368.54	18.75	370.52	19.30	0.99
KE	0.15	27.51	0.15	22.18	0.98
LAUCI	4117.00	0.01	4063.08	0.01	1.01
LAUCT	4012.63	0.01	3985.73	0.01	1.01
LCMAX	362.64	0.05	363.86	0.05	1.00
THALF	5.13	30.74	4.89	23.41	1.05
TMAX	4.82	28.95	4.96	23.41	0.97

UNIT: AUC = ng/mL CMAX = ng/mL TMAX = hr
NOTE: The mean values for LAUCT, LAUCI, and LCmax are the geometric means

Table 21 Least Square Geometric Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	LOWCI12	UPPCI12
Cetirizine					
AUCI	1232.69	1230.67	1.00	97.20	103.13
AUCT	1196.08	1195.11	1.00	97.16	103.00
CMAX	116.75	116.42	1.00	93.33	107.23
LAUCI	1211.93	1206.58	1.00	97.73	103.23
LAUCT	1174.80	1170.77	1.00	97.62	103.14
LCMAX	115.51	114.26	1.01	94.69	107.93
Pseudoephedrine					
AUCI	4244.78	4189.87	1.01	97.69	104.93
AUCT	4138.90	4110.86	1.01	96.96	104.40
CMAX	368.54	370.52	0.99	95.92	103.02
LAUCI	4117.00	4063.08	1.01	97.72	105.07
LAUCT	4012.63	3985.73	1.01	97.02	104.47
LCMAX	362.64	363.86	1.00	95.98	103.50

UNIT: AUC = ng/mL CMAX = ng/mL TMAX = hr

Table 22 Additional Study Information

	Cetirizine	Pseudoephedrine
Root mean square error, AUC0-t	0.060305	0.081190
Root mean square error, AUC∞	0.060126	0.079527
Root mean square error, Cmax	0.143571	0.082733
Kel and AUC∞ determined for how many subjects?	All (28 subjects)	All (28 subjects)
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
-measurable drug concentrations at 0 hr	None	None
-first measurable drug concentration as Cmax	None	None
Were the subjects dosed as more than one group?	No	No

Comments on Pharmacokinetic and Statistical Analysis:

The reviewer calculated 90% confidence intervals for the test to reference ratios for the $LAUC_{0-t}$ $LAUC_{0-\infty}$ and LC_{max} are in agreement with the firm's reported values and are within acceptable limits of 80%-125%.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The single-dose fed bioequivalence study is complete.

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

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
0.25	13.97	119.72	10.20	190.21	1.37
0.5	44.28	90.97	38.53	120.11	1.15
1	75.39	59.72	67.65	68.89	1.11
1.33	83.56	46.23	78.07	56.21	1.07
1.67	88.42	39.18	84.61	43.92	1.04
2	89.51	32.89	87.92	36.83	1.02
2.5	92.45	26.18	90.09	28.73	1.03
3	95.94	20.59	97.57	26.32	0.98
3.5	98.52	13.90	98.11	15.67	1.00
4	98.23	14.95	97.81	15.50	1.00
5	92.90	19.13	92.48	17.20	1.00
6	80.19	23.04	82.68	21.24	0.97
7	71.23	23.56	73.63	21.94	0.97
8	63.56	24.02	64.92	21.71	0.98
10	48.63	24.16	50.18	24.20	0.97
12	37.88	26.81	38.45	25.56	0.99
16	23.69	29.49	23.43	30.05	1.01
24	10.97	37.75	11.20	39.79	0.98
36	3.48	75.13	3.51	71.02	0.99
48	0.85	153.19	0.62	202.02	1.36

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

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
0.25	5.96	124.07	2.65	204.27	2.25
0.5	34.18	76.09	22.47	114.91	1.52
1	102.99	61.77	75.10	70.71	1.37
1.33	142.04	50.07	116.20	63.45	1.22
1.67	171.02	47.32	144.51	47.33	1.18
2	200.49	39.48	181.78	44.31	1.10
2.5	243.37	35.80	219.69	34.37	1.11
3	282.11	29.95	276.80	28.65	1.02
3.5	312.48	25.15	300.67	25.21	1.04
4	328.09	22.74	331.25	20.59	0.99
5	346.62	19.60	350.46	20.99	0.99
6	334.83	19.51	345.81	21.62	0.97
7	293.50	19.53	307.01	25.87	0.96
8	279.36	24.30	287.06	27.08	0.97
10	232.53	28.01	232.98	33.39	1.00
12	170.19	32.74	171.67	36.52	0.99
16	93.22	42.07	93.87	39.37	0.99
24	29.63	57.77	27.12	50.64	1.09
36	6.78	153.77	6.17	129.60	1.10
48	0.58	529.15	0.60	391.36	0.96

Figure 3 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

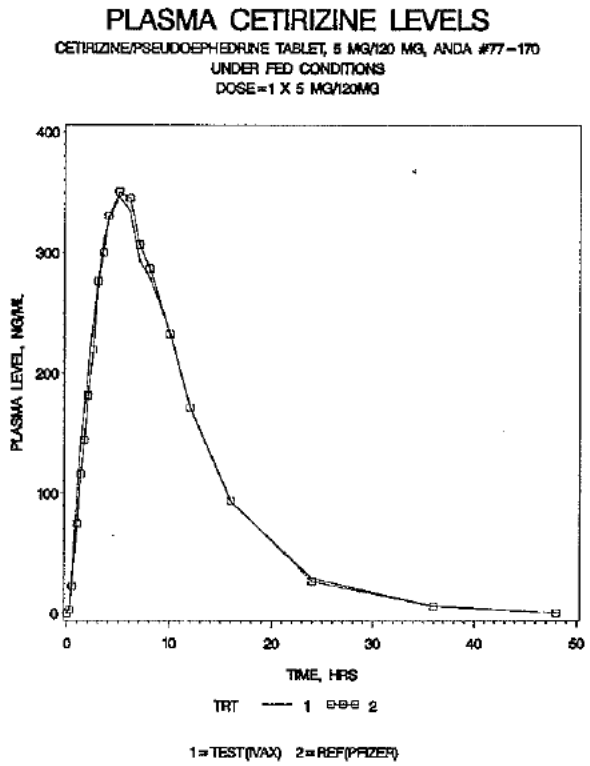
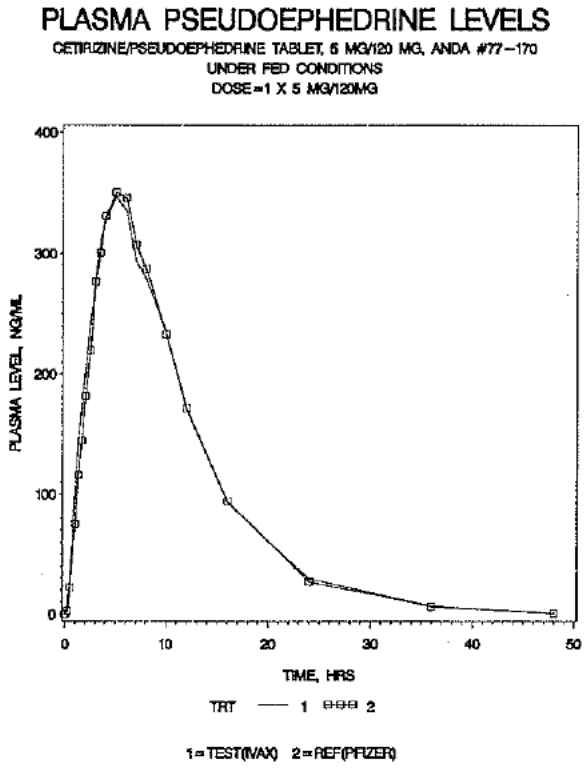


Figure 4 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



B. Formulation Data

Quantitative Composition: Cetirizine HCl / Pseudoephedrine HCl Tablets.

Component	[redacted]	Bi-layer Tablet
		mg / tablet (% w/w)
Cetirizine Hydrochloride		5.00 (0.994%)
Pseudoephedrine HCl		120.00 (23.857%)
Colloidal Silicon Dioxide		[redacted]
[redacted] Hypromellose, [redacted]		
[redacted]		
Hydroxypropyl Cellulose, [redacted]		
Lactose Monohydrate*		
Magnesium Stearate		
Microcrystalline Cellulose		
Talc		
Iron Oxide Yellow		
Total Weight		**503.00 mg (100%)**

* [redacted]

Firm lists the % of microcrystalline cellulose in the final tablet as [redacted] *Chemistry has requested the firm to resubmit a corrected page.*

All inactive ingredients used in the tablet formulation, are within the listed levels for oral route of administration products in the Inactive Ingredients Guide (IIG).

C. Dissolution Data

Source of Method (USP, FDA or Firm)	Firm
Medium	Water
Volume (mL)	[redacted] mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
Specifications	N/A

The dissolution data are incomplete.
See dissolution review (V:\firmsam\IVAX\ltrs&rev\77170d0604.doc)

Figure 3 Dissolution Profiles

None

D. Consult Reviews

None

E. SAS Output

Study	SAS Data	SAS Program	SAS Output
Cetirizine			
Fasting Study	77170CetirizFast.xls	77170Cetiriz_fast.txt	77170Cetirizfast_output.txt
Fed Study	77170CetirizFED.xls	77170Cetiriz_fed.txt	77170CetirizFed_output.txt
Pseudoephedrine			
Fasting Study	77170PseudoFAST.xls	77170Pseudo_fast.txt	77170Pseudofast_output.txt
Fed Study	77170PseudoFed.xls	77170Pseudo_Fed.txt	77170PseudoFed_output.txt

F. Additional Attachments

None

BIOEQUIVALENCE DEFICIENCY COMMENTS

ANDA: 77170 APPLICANT: Ivax Pharmaceuticals, Inc.

DRUG PRODUCT: Cetirizine HCl and Pseudoephedrine HCl ER Tablets, 5 mg / 120 mg

The Division of Bioequivalence has completed its review. The following deficiencies have been identified:

2. Your in vitro dissolution testing is incomplete. As communicated to you earlier, please conduct dissolution testing using apparatus I at 100 RPM and/or apparatus II at 50 rpm in the following dissolution media: pH 4.5 (acetate buffer), and pH 6.8 (phosphate buffer) for the pseudoephedrine component. This will help in selecting the optimal dissolution method.

2. Please also repeat the dissolution testing using the following conditions: basket 100 rpm in 500 mL of 0.1 N HCl with the sampling times of 10, 15, and 30 minutes for the cetirizine component and of 1, 2, 4, and 6 hours for the pseudoephedrine component.

Please note the following for future applications:

1. Your selected QC samples for pseudoephedrine are appropriate, relative to the concentrations in the study samples for the fed and fasting studies. However, all study samples for cetirizine were below 264.25 ng/mL and 174.91 ng/mL in the fasting and fed studies, respectively. Therefore, your High QC selection for cetirizine is not appropriate. For future studies please select QC concentrations to be comparable with the expected study concentrations.

Sincerely yours,

Barbara M. Davit

for

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

CC: ANDA 77170
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ P. Nwakama

Endorsements: (Draft and Final with Dates)
HFD-658/ P. Nwakama 7/20/05
HFD-658/ YC Huang 7/20/2005
HFD-650/ S. Mazzella
HFD-650/ D. Conner 7/22/05

Final: 7/20/05

V:\firmsam\Ivax\ltrs&rev\77170N0604

BIOEQUIVALENCE – Incomplete Submission Date: June 1, 2004
[Note: Firm has not submitted the dissolution amendment.]

1. **FASTING STUDY** (STF) Strength: 5 mg / 120 mg
Clinical: Algorithme Pharma Inc., 575 Blvd Armand-Frappier Laval, Quebec, Canada Outcome: IC
Analytical: (b) (4)

2. **FOOD STUDY** (STP) Strength: 5 mg / 120 mg
Clinical: Algorithme Pharma Inc., 575 Blvd Armand-Frappier Laval, Quebec, Canada Outcome: IC
Analytical: (b) (4)

Outcome Decisions: IC

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	77-170
Drug Product Name	Cetirizine HCl and Pseudoephedrine Extended Release Tablets
Strength	5 mg/120 mg
Applicant Name	IVAX
Submission Date(s)	06/01/04
First Generic	No
Reviewer	Z.Z. Wahba
File Location	**V:\firmsam\IVAX\ltrs&rev\77170d0604.doc**
Clinical Site	LDS Laboratories diagnostiques Inc. 175 Chemin Stillview, bureau #155 Pointe-Claire, Quebec, Canada H9R 4S3
Analytical Site	(b) (4)

EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product. The firm did not conduct comparative dissolution testing in different dissolution media (pH 1.2, 4.5, and 6.8). The firm conducted dissolution testing using water as dissolution medium. The firm will be asked to conduct additional dissolution testing including the FDA recommended method (basket 100 rpm in 500 mL of 0.1 HCl). In addition, because this is a modified release product, the firm will be asked to submit dissolution data using Apparatus I at 100 rpm or apparatus II at 50 rpm in pH 4.5 (acetate buffer), and pH 6.8 (phosphate buffer).

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

RLD METHOD

Medium	0.1 N HCl
Volume	500 mL
Temperature	37°C
Apparatus	USP 1 (basket)
Rotational Speed	100 rpm
Specifications	Cetirizine HCl: NLT 80% (Q) is released in 30 min. Pseudoephedrine HCl: 30%-50% dissolved in 1 hr, 50%-70% dissolved in 2 hrs, and NLT 80% (Q) dissolved in 6 hrs.

Source of Method: OCPB review (submission dates 01/18/2000, 04/07/2000, 08/04/2000, 09/29/2000, 11/29/2000, and 12/12/2000, reviewed by Monique Wakelkamp-Barnes, M.D., Ph.D.)

Table 1. Summary of In Vitro Dissolution Data

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)				Study Report Location
					10 min	15 min	30 min	--	
Not Provided N.P.	Test/ Cetirizine component lot #G44147	5 Mg/Tab	Firm's Dissolution Testing: USP Apparatus: 2 (Paddle) with sinkers Speed of Rotation: 50 rpm Medium: Water Volume: (b) (4) mL Temperature: 37°C Firm's proposed specifications: Cetirizine HCl: NLT 75% (Q) i.e. equivalent to (b) (4)% of the labeld amount is released in 30 min. Pseudoephedrine HCl: 1hr (b) (4)% 2 hrs 50-70% 4 hrs 70-90% 8 hrs NLT 80%	12	88 (b) (4) (b) (4)	94 (b) (4) (b) (4)	96 (b) (4) (b) (4)	-	V C1.1 p. 319
N.P.	Ref/ Cetirizine component lot #214N3L	5 Mg/Tab		12	92 (b) (4) (b) (4)	95 (b) (4) (b) (4)	98 (b) (4) (b) (4)	-	
					1 hr	2 hrs	4 hrs	8 hrs	
N.P.	Test/ Pseudoephedrine component lot #G44147	120 Mg/Tab		12	45 (b) (4) (b) (4)	63 (b) (4) (b) (4)	84 (b) (4) (b) (4)	100 (b) (4) (b) (4)	V C1.1 p. 320
N.P.	Ref/ Pseudoephedrine component lot #214N3L	120 Mg/Tab		12	40 (b) (4) (b) (4)	59 (b) (4) (b) (4)	81 (b) (4) (b) (4)	98 (b) (4) (b) (4)	

Table 2. 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

DEFICIENCY COMMENTS:

1. The firm did not conduct comparative dissolution testing in three different media (pH 1.2, 4.5, and 6.8) for pseudoephedrine HCl component.

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data summary, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.

RECOMMENDATIONS:

1. The in vitro dissolution testing conducted by IVAX on its test product, Cetirizine HCl and Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg, comparing it to Pfizer's Zyrtec-D Extended-Release Tablets, 5 mg/120 mg, is incomplete.

2. The firm should conduct dissolution testing using apparatus I at 100 RPM and/or apparatus II at 50 RPM in the following dissolution media: pH 4.5 (acetate buffer), and pH 6.8 (phosphate buffer) for pseudoephedrine component.

3. The firm should also be advised to repeat the dissolution testing using the following conditions: basket 100 rpm in 500 mL of 0.1 N HCl with the sampling times of 10, 15, and 30 minutes for the cetirizine component and of 1, 2, 4, and 6 hours for the component of pseudoephedrine.

Zakaria Z. Wahba, Ph.D. Zakaria Z. Wahba Date: 3/16/05
Review Branch III

RD INITIALED YCHuang
FT INITIALED YCHuang Date: 3/16/2005

Concur: Barbara M. Davit Date: 3/17/05
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-170 APPLICANT: IVAX

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

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

1. Your dissolution method, data and specifications are incomplete. Please conduct dissolution testing using the following conditions: basket 100 rpm in 500 mL of 0.1 N HCl with the sampling time points of 10, 15, and 30 minutes for the cetirizine component and of 1, 2, 4, and 6 hours for the pseudoephedrine component.

2. In addition, because this is a modified release product, please submit in the application dissolution profiles generated using USP Apparatus I at 100 rpm or Apparatus II at 50 rpm in pH 4.5 (acetate buffer) and pH 6.8 (phosphate buffer). Agitation speeds may have to be increased if appropriate. Adequate sampling should be performed, for example, at 1, 2, 3, 4, and 6 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. Please estimate F2 values within and between test and reference products and provide the results of F2 values with the dissolution data. The specifications for your product will be determined after the data submitted in your ANDA is reviewed. Although the dissolution method and specifications for your product will be determined after the data submitted in your ANDA is reviewed, you are encouraged to propose an optimal dissolution method and specifications. The dissolution testing should be conducted on tablets from the same lot that was used for the in vivo bioequivalence studies.

3. In order to improve the review process, the Division of Bioequivalence requests that you provide in-vivo study data, dissolution data, and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format.

We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could also provide this information for any other applications pending in the Division and in applications to be submitted in the future.

Sincerely yours,

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

ANDA 77-170 (IVAX' Cetirizine HCl & Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg)

CC: ANDA 77-170
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer
HFD-658/ Team Leader

Endorsements:
HFD-658/ Z. Wahba ZW 3/16/05
HFD-658/ YC Huang YH 3/16/2005
HFD-650/ D. Conner BZQ 3/16/05

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DISSOLUTION- INCOMPLETE Submission date: 06/01/2004

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

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

Outcome Decisions: IC– Incomplete

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-170

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-170 **FIRM NAME:** IVAX PHARMACUETICALS INC.

RELATED APPLICATION(S): NA

First Generic Product Received? YES

DRUG NAME: CETIRIZINE HYDROCHLORIDE AND PSEUDOPHEDRINE HYDROCHLORIDE

DOSAGE FORM: EXTENDED-RELEASE TABLETS, 5 MG/120 MG

Bio Assignments:	☐ Micro Review
☒ BPH	
☐ BCE	
☐ BST	

Random Queue: 4

Chem Team Leader: Gill, Dave PM: Sarah Kim Labeling Reviewer: Debbie Catterson

Letter Date: JUNE 01, 2004 **Received Date:** JUNE 02, 2004	
Comments: EC- 1 **YES** **On Cards:** YES **Therapeutic Code:** 9000000 ANTIHISTAMINE	
Archival Format: PAPER **Sections** I **(356H Sections per EDR Email)** **Review copy:** YES E-Media Disposition: YES SENT TO EDR Not applicable to electronic sections Field Copy Certification (Original Signature) YES	
Methods Validation Package (3 copies PAPER archive) **YES** (Required for Non-USP drugs)	
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

Reviewing CSO/CST [signature] **Date** 7-14-04	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: [signature]	**Date:** 15 July 2004
ADDITIONAL COMMENTS REGARDING THE ANDA:	
Top 200 Drug Product:	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES	☑
Sec. II	**Basis for Submission** **NDA# : 21-150** Ref Listed Drug: ZYRTEC- D Firm: PFIZER ANDA suitability petition required? NO If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☑
Sec. III	**Patent Certification** – P IV – '329 – P IV – '009 – P III – '358 1. Paragraph: IV 2. Expiration of Patent: 7-13-2019 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** YES	☑
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use 2. Active ingredients 3. Route of administration 4. Dosage Form 5. Strength	☑
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) How Supplied 1. 4 copies of draft (each strength and container) or 12 copies of FPL 2. 1 RLD label and 1 RLD container label 3. 1 side by side labeling comparison with all differences annotated and explained 4. Was a proprietary name request submitted? (If yes, send email to Labeling Rvwr indicating such.)	☑ (b) (4)
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES **2. Request for Waiver of In-Vivo Study(ies): NO** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) **4. Lot Numbers of Products used in BE Study(ies):** **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below) 1st generic Review	☐
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 5 MG/120 MG a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: YES – Lot # G44147	☐

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. <u>Solutions</u> (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. <u>Suspensions</u> (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation – Acceptable as per II G 2. Inactive ingredients as appropriate	☑

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers b. Type II DMF authorization letters or synthesis c. COA(s) specifications and test results from drug substance mfgr(s) d. Applicant certificate of analysis e. Testing specifications and data from drug product manufacturer(s) f. Spectra and chromatograms for reference standards and test samples g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified b. Testing specifications (including identification and characterization) c. Suppliers' COA (specifications and test results) d. Applicant certificate of analysis	☑
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) 2. CGMP Certification: YES 3. CFN numbers	☑
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address 2. Functions 3. CGMP Certification/GLP 4. CFN numbers	☑
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) 3.If sterile product: Aseptic fill / Terminal sterilization 4.Filter validation (if aseptic fill) 5. Reprocessing Statement	☑
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation 2. In-process Controls - Specifications and data Lot G 44147 (b) (4)	☑
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) 2. Components Specification and Test Data (Type III DMF References) 3. Packaging Configuration and Sizes 4. Container/Closure Testing 5. Source of supply and suppliers address (b) (4) (b) (4) (b) (4)	☑

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data 2. Certificate of Analysis for Finished Dosage Form	☑
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted 2. Post Approval Commitments 3. Expiration Dating Period 4. Stability Data Submitted a. 3 month accelerated stability data b. Batch numbers on stability records the same as the test batch	☑
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance 2. Finished Dosage Form 3. Same lot numbers	☑
Sec. XVII	**Environmental Impact Analysis Statement**	☑
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other:** 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature)	☑

1. Call Firm: 1st generic review states that dissolution data should be provided using multiple media and conditions.

ANDA 77-170 Final Check List for Branch Chief

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.

✓ 3) Check for gross errors in letter.

✓ 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 5) Check address and contact person on letter vs. 356h.

✓ 6) Check for any t-cons and verify date and correspondence date.

✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 8) Check for any comments or problems raised by reviewer on Check List.

✓ 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD. ZyrtecD 12hour

✓ 12) Check for MOU patents

✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.

✓ 14) Review Basis for Submission. ZyrtecD 12hour 21150

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer. PIII → '358 PIV → '339, 8009

✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

___ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 18) Pull USP information. (USP ___yes ✓ no)

✓ 19) Final Grammar review on letter.

✓ 20) Verify information in OGD Patent Tracking System.

✓ 21) EES slip.

✓ 22) Document in record book.

Signature Martin A. Gilman date 15 July 2004

M E M O R A N D U M

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

FROM: Cecelia M. Parise
Regulatory Policy Advisor to the Director
Office of Generic Drugs (HFD-600)

THROUGH: Gary Buehler
Director
Office of Generic Drugs (HFD-600)

SUBJECT: Forfeiture of 180-Day Exclusivity for Teva's (formerly Ivax) Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release Tablets, 5 mg/120 mg

TO: ANDA 77-170

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) describes, among other things, certain events which can result in the forfeiture of a first applicant's 180-day generic drug exclusivity as described in section 505(j)(5)(B)(iv).

The forfeiture provisions of the MMA now appear at section 505(j)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act). Included among these is section 505(j)(5)(D)(i)(IV), which states the following:

> FAILURE TO OBTAIN TENTATIVE APPROVAL.--The first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

A "first applicant" is eligible for 180-day exclusivity by virtue of filing a substantially complete ANDA with a paragraph IV certification on the first day on which such an ANDA is received. Section 505(j)(5)(B)(iv)(II)(bb). If only one such ANDA is filed on the first day, there is only one first applicant; if two or more such ANDAs are filed on the first day, first applicant status is shared.

"Tentative approval" means, generally, that an ANDA otherwise meets the requirements for approval under the Act, but cannot be fully approved for marketing because of patent or exclusivity protections. Section 505(j)(5)(B)(iv)(II)(dd). The "failure to obtain tentative approval" forfeiture provision establishes a bright line standard: If within 30 months an ANDA has been determined by the agency to meet the statutory standards for approval and it is only

patent and/or exclusivity protection that prevents full approval, then an applicant maintains eligibility for 180-day exclusivity. If this standard is not met in 30 months, eligibility for 180 day exclusivity is forfeited. It should be noted that the 30-month timeframe generally is without regard to the length of time the ANDA was under review by the Agency. One exception to this general rule, described in section 505(j)(5)(D)(i)(IV), states that forfeiture will not occur if "the failure [to obtain a tentative approval] is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed." A second exception is found in new section 505(q)(1)(G) of the Act, enacted as part of the Food and Drug Administration Amendments Act of 2007 (Pub. Law 110-85). This provides that

> If the filing of an application resulted in first-applicant status under subsection (j)(5)(D)(i)(IV) and approval of the application was delayed because of a petition, the 30-month period under such subsection is deemed to be extended by a period of time equal to the period beginning on the date on which the Secretary received the petition and ending on the date of final agency action on the petition (inclusive of such beginning and ending dates), without regard to whether the Secretary grants, in whole or in part, or denies, in whole or in part, the petition.

Thus, pursuant to this provision, the 30-month period will be extended for the prescribed period during the review of a related petition subject to section 505(q).

The terms of section 505(q)(1)(G) also clarify the scope of section 505(j)(5)(D)(i)(IV). A number of comments have suggested that this section applies only when an ANDA is eligible for a tentative approval, not when an ANDA would be eligible for a final approval because there is no patent, 30-month stay or exclusivity blocking approval. Although a narrow interpretation of the scope finds support in the text of section 505(j)(5)(D)(i)(IV), the terms of section 505(q)(1)(G) clearly describe a broader scope. Section 505(q)(1)(G) expressly states that if "approval" of the first applicant's application was delayed because of a petition, the 30-month period will be extended. Thus, Congress contemplated that section 505(j)(5)(D)(i)(IV) establishes a 30-month period within which an ANDA generally must obtain either tentative approval or final approval. This interpretation squares both with the statutory language and with not permitting the 180-day exclusivity for a first applicant whose ANDA is technically deficient to delay approval of subsequent applications. Therefore, FDA interprets section 505(j)(5)(D)(i)(IV) as requiring that, unless the period is extended for one of the reasons described in the Act, a first applicant that fails to obtain either tentative approval or approval for its ANDA within 30 months will forfeit eligibility for 180-day exclusivity.

The following is a timeline of ANDA 77-170:

6/2/2004: ANDA submitted containing 5 mg/120 mg extended-release tablets. Paragraph III (PIII) certification provided to the '358 patent and Paragraph IV (PIV) certifications submitted to the '329 and '009 patents.
6/29/2004: DBE first generic checklist completed finding BE studies acceptable for filing
7/16/2004: PIV filing letter issued to Ivax stating ANDA was acceptable for filing on 6/2/2004
7/19/2004: Authorization provided to use (b) (4) for notice purposes
11/24/2004: Chemistry review 1 completed; deficiencies faxed to firm the same day
3/16/2005: DBE dissolution review completed; deficiencies faxed to firm on 3/18/2005
4/27/2005: Labeling review 1 completed; deficiencies faxed to firm on 4/29/2005
7/22/2005: DBE Fasting and Fed studies reviews completed; deficiencies faxed to firm 7/28/2005
7/15/2005: Firm responded to labeling deficiencies
8/29/2005: Labeling found acceptable
9/8/2005: BE amendment submitted
10/27/2005: BE review completed with studies found acceptable; comments to firm on 11/3/2005
11/21/2005: Firm acknowledges BE comments
5/8/2006: Dunner letter sent to firm regarding chemistry deficiencies faxed 11/24/2004
5/24/2006: Intent to amend letter received from the firm.
6/7/2006: XP containing PIII to the '358 and PIVs to the '009, '329 and '867 patents
8/1/2006: Response to the chemistry deficiencies that issued 11/24/2004
11/30/2006: Return receipts provided documenting notice to the following entities:
- Notice sent to UCB in Brussels, BE via (b) (4) on 7/19/2004
- Notice sent to Pfizer in NY, NY via US cert on 7/19/2004
- Notice sent to Pfizer in NY, NY, UCB in Brussels, BE and UCB in Fribourg, Switzerland via (b) (4) on 6/6/2006 for the '867 patent

12/2/2006: [6/2/2004 plus 30 months]

Teva's ANDA 77-170 was received on June 2, 2004, and has not been tentatively approved as of December 19, 2007. The ANDA filing date plus 30 months was December 2, 2006; therefore, Teva's ANDA was not tentatively approved within 30 months. Teva does not claim, and the Agency does not find, that the requirements for approval changed or were reviewed, nor was a related citizen petition submitted that is subject to section 505(q). We therefore conclude that the 180-day exclusivity period described in section 505(j)(5)(B)(iv) of the Act was forfeited by Teva.

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

/s/

Patricia L. Downs
12/26/2007 10:11:26 AM
SECRETARY

Cecelia Parise
12/26/2007 10:15:42 AM
CSO

Robert L. West
12/26/2007 10:25:52 AM
PHARMACIST
for Gary Buehler

MINOR AMENDMENT

ANDA 77-170

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: IVAX Pharmaceuticals, Inc. TEL: 215-293-6150

ATTN: Patricia Jaworski, Director, Regulatory Affairs FAX: 201-489-1403

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

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated June 1, 2004, 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/120mg.

Reference is also made to your amendment dated July 31, 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: 77-170 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride 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)

8.

9.

10

11

12

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

1. OGD is changing its CMC review process through our question based review (QbR) initiative, which is described in more detail on the OGD website:http://www.fda.gov/cder/ogd/QbR.htm.

   OGD's QbR initiative was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD), a submission format adopted by multiple regulatory bodies including the FDA. Generic firms are strongly recommended to submit their ANDAs in the CTD format (either eCTD or paper) to facilitate the implementation of the QbR and to avoid undue delays in the **review** of their applications.

   Because of the increasing number of ANDA submissions OGD receives each year, the Quality Overall Summary (QOS) part of the CTD format is extremely important to making our new review process more efficient. Beginning in January 2007, all ANDA applicants are recommended to provide an electronic copy of a QOS that addresses OGD's QbR questions. The QbR-Quality Overall Summary Outline posted on our webpage http://www.fda.gov/cder/ogd/ contains all the questions to prepare the QOS.

   The QOS should be submitted in both MS Word and pdf format along with the paper or electronic submission. The QOS should be provided even if the remainder of the application is not in CTD format. OGD has prepared QOS models that can be found on the OGD web site. We ask you to use these as a guide for your submissions.

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/

Devinder Gill
2/27/2007 01:34:58 PM
for Vilayat Sayeed, Ph.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

77170
A5.1

Food and Drug Administration
Rockville MD 20857

ANDAs (See Attached List)

CERTIFIED MAIL-RETURN RECEIPT REQUESTED

IVAX Pharmaceuticals, Inc.
Attention: Patricia Jaworski
125 Wells Avenue
Congers, NY 10920

MAY -8 2006

Dear Madam:

This letter is in reference to your Abbreviated New Drug Application (ANDA), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for (See Attached List).

We refer you to our "Not Approvable" letter dated (See Attached List), which detailed the deficiencies identified during our review of your ANDA. The Agency may consider an ANDA applicant's failure to respond to a "Not Approvable" letter within 180 days to be a request by the applicant to withdraw the ANDA under 314.120(b). Your amendments to the applications are overdue. You must amend your applications within 10 days of receipt of this letter. Otherwise, an action to withdraw these applications will be initiated per 21 CFR 314.99.

If you do not wish to pursue approval of this application at this time, you should request withdrawal in accord with 21 CFR 314.65. A decision to withdraw these applications would be without prejudice to refiling.

If you have further questions you may contact Saundra T. Middleton, Project Manager, Regulatory Support Branch, at (301) 827-0498.

Please send all correspondence to the following address:

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Sincerely yours,

Saundra T. Middleton

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

cc: ANDA (see attached list)
DUP/Division File
HFD-610/PRickman

Endorsement:

HFD-615/SMiddleton, CSO, S. Middleton date 5/8/06
Word File
V:\FIRMSAM\IVAX\LTRS&REV (SEE ATTACHED LIST)
F/T by StM 5/8/06
10 DAY LETTER!

BIOEQUIVALENCY AMENDMENT

NOV 0 3 2005

ANDA 77-170

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: Ivax Pharmaceuticals, Inc.

TEL: 845-267-2444

ATTN: Patricia Jaworski

FAX: 845-268-0117

FROM: Steven Mazzella

PROJECT MANAGER: (301) 827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on September 7, 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:

NOV 0 3 2005

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77170 APPLICANT: Ivax Pharmaceuticals, Inc.
DRUG PRODUCT: Cetirizine HCl and Pseudoephedrine HCl ER Tablets, 5 mg/120 mg

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

Your proposed dissolution method is acceptable. However, your proposed specification of (b) (4) % at 1 hour for pseudoephedrine is not acceptable. Based on the submitted data, the Division of Bioequivalence recommends the specification of 30-50% for pseudoephedrine at 1 hour.

Please acknowledge that you have accepted the following:

The dissolution testing should be conducted in 500 ml of 0.1N HCl using USP Apparatus I (Basket) at 100 rpm. The test product should meet the following specifications:

Cetirizine HCl: Not less than 75% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Pseudoephedrine HCl:

1 hr	*30 - 50%*
2 hr	*50 - 70%*
4 hr	*70 - 90%*
8 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

BIOEQUIVALENCY AMENDMENT

ANDA 77-170

JUL 28 2005

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: Ivax Pharmaceuticals, Inc.

TEL: 201-767-1700 X323

ATTN: Patricia Jaworski

FAX: 201-767-3804

FROM: Steven Mazzella

PROJECT MANAGER: (301) 827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on June 1, 2004, 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:

hm

JUL 28 2005

BIOEQUIVALENCE DEFICIENCY COMMENTS

ANDA: 77170 APPLICANT: Ivax Pharmaceuticals, Inc.

DRUG PRODUCT: Cetirizine HCl and Pseudoephedrine HCl ER Tablets, 5 mg / 120 mg

The Division of Bioequivalence has completed its review. The following deficiencies have been identified:

2. Your in vitro dissolution testing is incomplete. As communicated to you earlier, please conduct dissolution testing using apparatus I at 100 RPM and/or apparatus II at 50 rpm in the following dissolution media: pH 4.5 (acetate buffer), and pH 6.8 (phosphate buffer) for the pseudoephedrine component. This will help in selecting the optimal dissolution method.

2. Please also repeat the dissolution testing using the following conditions: basket 100 rpm in 500 mL of 0.1 N HCl with the sampling times of 10, 15, and 30 minutes for the cetirizine component and of 1, 2, 4, and 6 hours for the pseudoephedrine component.

Please note the following for future applications:

1. Your selected QC samples for pseudoephedrine are appropriate, relative to the concentrations in the study samples for the fed and fasting studies. However, all study samples for cetirizine were below 264.25 ng/mL and 174.91 ng/mL in the fasting and fed studies, respectively. Therefore, your High QC selection for cetirizine is not appropriate. For future studies please select QC concentrations to be comparable with the expected study concentrations.

Sincerely yours,

Barbara M Davit

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

BIOEQUIVALENCY AMENDMENT

ANDA 77-170

MAR 18 2005

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: Ivax Pharmaceuticals Inc. TEL: 201-767-1700

ATTN: Patricia Jaworski FAX: 201-767-3804

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on June 1, 2004, 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 10 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 DEFICIENCIES MAR 18 2005

ANDA: 77-170 APPLICANT: IVAX

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

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

1. Your dissolution method, data and specifications are incomplete. Please conduct dissolution testing using the following conditions: basket 100 rpm in 500 mL of 0.1 N HCl with the sampling time points of 10, 15, and 30 minutes for the cetirizine component and of 1, 2, 4, and 6 hours for the pseudoephedrine component.

2. In addition, because this is a modified release product, please submit in the application dissolution profiles generated using USP Apparatus I at 100 rpm or Apparatus II at 50 rpm in pH 4.5 (acetate buffer) and pH 6.8 (phosphate buffer). Agitation speeds may have to be increased if appropriate. Adequate sampling should be performed, for example, at 1, 2, 3, 4, and 6 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. Please estimate F2 values within and between test and reference products and provide the results of F2 values with the dissolution data. The specifications for your product will be determined after the data submitted in your ANDA is reviewed. Although the dissolution method and specifications for your product will be determined after the data submitted in your ANDA is reviewed, you are encouraged to propose an optimal dissolution method and specifications. The dissolution testing should be conducted on tablets from the same lot that was used for the in vivo bioequivalence studies.

3. In order to improve the review process, the Division of Bioequivalence requests that you provide in-vivo study data, dissolution data, and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format.

We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could also provide this information for any other applications pending in the Division and in applications to be submitted in the future.

Sincerely yours,

for Barbara M. Davit

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

ANDA 77-170 (IVAX' Cetirizine HCl & Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg)

Table 1. Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (units/mL)	T_{max} (hr)	AUC_{0-t} (units)	AUC_{∞} (units)	T½ (hr)	K_{el} (hr^{-1})	
Study #	Fasting study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M ± S.D. M ± S.D.	Mn or Md No SD	M ± S.D. M ± S.D.	M ± S.D. M ± S.D.	Mean No SD	Mean No SD	Vol. # p. #
Study #	Fed study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean y (range)	M ± S.D. M ± S.D.	Mn or Md No SD	M ± S.D. M ± S.D.	M ± S.D. M ± S.D.	Mean No SD	Mean No SD	Vol. # p. #

Table 2. Statistical Summary of the Comparative Bioavailability Data

Drug Dose (# x mg) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	Test	Reference	Ratio	90% C.I.
AUC_{0-t}				
AUC_{∞}				
C_{max}				
Fed Bioequivalence Study				
Parameter	Test	Reference	100*Ratio	90% C.I.
AUC_{0-t}				
AUC_{∞}				
C_{max}				

Table 3. Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Provide the volume(s) and page(s)
Analyte	Provide the name(s) of the analyte(s)
Internal standard (IS)	Identify the internal standard used
Method description	Brief description of extraction method; analytical method
Limit of quantitation	LOQ, units
Average recovery of drug (%)	%
Average recovery of IS (%)	%
Standard curve concentrations (units/mL)	Standard curve range and appropriate concentration units
QC concentrations (units/mL)	List all the concentrations used
QC Intraday precision range (%)	Range or per QC
QC Intraday accuracy range (%)	Range or per QC
QC Interday precision range (%)	Range or per QC
QC Interday accuracy range (%)	Range or per QC
Bench-top stability (hrs)	hours @ room temperature
Stock stability (days)	days @ 4°C
Processed stability (hrs)	hours @ room temperature; hours @ 4°C
Freeze-thaw stability (cycles)	# cycles
Long-term storage stability (days)	17 days @ -20°C (or other)
Dilution integrity	Concentration diluted X-fold
Selectivity	No interfering peaks noted in blank plasma samples

Table 4. Summary of In Vitro Dissolution Studies

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)				Study Report Location
					min	min	min	min	
Diss. study report #	Test prod name/ #	mg Tab./Cap./Susp.	Dissolution: Apparatus Speed of Rotation: rpm Medium: Volume: mL Temperature: °C	12					
Diss. study report #	Ref prod name/ #	mg Tab./Cap/Susp.		12					

Table 5. Formulation Data

Ingredient	Amount (mg) / Tablet		Amount (%) Tablet	
	Lower strength	Higher strength	Lower strength	Higher strength
Cores				
Coating				
Total			100.00	100.0

Table 6. Demographic Profile of Subjects Completing the Bioequivalence Study

Study No.		
	Treatment Groups	
	Test Product N =	Reference Product N =
Age (years)		
Mean ± SD	50 ± 15	
Range	20-85	
Groups		
< 18	N(%)	N(%)
18 – 40	N(%)	N(%)
40 – 64	N(%)	N(%)
65 – 75	N(%)	N(%)
> 75	N(%)	N(%)
Sex		
Female	N(%)	N(%)
Male	N(%)	N(%)
Race		
Asian	N(%)	N(%)
Black	N(%)	N(%)
Caucasian	N(%)	N(%)
Hispanic	N(%)	N(%)
Other	N(%)	N(%)
Other Factors		

Table 7. Incidence of Adverse Events in Individual Studies

Body System/Adverse Event	Reported Incidence by Treatment Groups					
	Fasted Bioequivalence Study Study No.		Fed Bioequivalence Study Study No.		Other Bioequivalence Study Study No.	
	Test	Reference	Test	Reference	Test	Reference
Body as a whole						
Dizziness	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Etc.	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cardiovascular						
Hypotension						
Etc.						
Gastrointestinal						
Constipation						
Etc.						
Other organ sys.						
Total	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Table 8. Reanalysis of Study Samples

Study No. Additional information in Volume(s), Page(s)								
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]								
Reason A (e.g. below LOQ)								
Reason B								
Reason C								
Etc.								
Total								

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

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-170 APPLICANT: IVAX Pharmaceuticals, Inc.

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

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The Drug Master File (b) (4) is currently inadequate. The DMF holder, (b) (4) has been notified. Please do not respond to this letter until the DMF holder has notified you that they have responded to the deficiencies.

2. (b) (4)

3.

4.

5.

6.

7.

Following this page, 4 Pages Withheld in Full as (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 reviewed by the Division of Bioequivalence. Also, the dissolution data for release and stability will be evaluated based on the criteria set by the Division of Bioequivalence.

Sincerely yours,

DSGill

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

Telecon Record

Date: 7/14/04

ANDA: 77-170

Firm: IVAX

Drug: Cetirizine Hydrochloride and Psuedoephedrine HydrochlorideExtended-release Tablets, 5mg/120mg

FDA Participants: Paras Patel

Industry Participants: Patricia Jaworski

Phone: 201-767-1700 x 323

Agenda:

1. Paras requested the following:

   - Provide dissolution in different media and conditions as per comments from Division of Bioequivalence. Contact the Division of Bioequivalence for guidance.

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 77-170 **FIRM NAME** **IVAX Pharmaceuticals Inc.**

DRUG NAME Cetirizine HCl and Pseudoephedrine HCl

DOSAGE FORM **ER Tablets, 5 mg/120 mg**
SUBJ: Request for examination of: Bioequivalence Study

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:
Farahnaz Nouravarsani
Farah Nouravarsani Date: 6/25/2004
Reviewer

Yih-Chain Huang Date: 6/29/2004
Team Leader

— Please see comments on dissolution data.
— The firm should be advised to submit dissolution data using multiple media.

Fasting Study:

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			
Assay Methodology	☒	☐			
Procedure SOP	☒	☐			
Methods Validation	☒	☐			
Study Results Ln/Lin	☒	☐			
Adverse Events	☒	☐			
IRB Approval	☒	☐			
Dissolution Data	☒	☐			Dissolution data using multiple media and conditions were not submitted. Data were submitted only for water.
Pre-screening of Patients	☒	☐			
Chromatograms	☒	☐			
Consent Forms	☒	☐			
Composition	☒	☐			
Summary of Study	☒	☐			
Individual Data & Graphs, Linear & Ln	☒	☐			
PK/PD Data Disk Submitted)	☒	☐			
Randomization Schedule	☒	☐			
Protocol Deviations	☒	☐			
Clinical Site	☒	☐			
Analytical Site	☒	☐			

Study Investigators	☒	☐			
Medical Records	☒	☐			
Clinical Raw Data	☒	☐			
Test Article Inventory	☒	☐			
BIO Batch Size	☒	☐			
Assay of Active Content Drug	☒	☐			
Content Uniformity	☒	☐			
Date of Manufacture	☒	☐			
Exp. Date of RLD	☒	☐			
BioStudy Lot Numbers	☒	☐			
Statistics	☒	☐			
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			
Waiver requests for other strengths / supporting data	☐	☒			

Additional Comments regarding the ANDA:
None.

Fed Study:

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			
Assay Methodology	☒	☐			
Procedure SOP	☒	☐			
Methods Validation	☒	☐			
Study Results Ln/Lin	☒	☐			
Adverse Events	☒	☐			
IRB Approval	☒	☐			
Dissolution Data	☒	☐			Dissolution data using multiple media and conditions were not submitted. Data were submitted only for water.
Pre-screening of Patients	☒	☐			
Chromatograms	☒	☐			
Consent Forms	☒	☐			
Composition	☒	☐			
Summary of Study	☒	☐			
Individual Data & Graphs, Linear & Ln	☒	☐			
PK/PD Data Disk Submitted)	☒	☐			
Randomization Schedule	☒	☐			
Protocol Deviations	☒	☐			
Clinical Site	☒	☐			
Analytical Site	☒	☐			

Study Investigators	☒	☐			
Medical Records	☒	☐			
Clinical Raw Data	☒	☐			
Test Article Inventory	☒	☐			
BIO Batch Size	☒	☐			
Assay of Active Content Drug	☒	☐			
Content Uniformity	☒	☐			
Date of Manufacture	☒	☐			
Exp. Date of RLD	☒	☐			
BioStudy Lot Numbers	☒	☐			
Statistics	☒	☐			
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			
Waiver requests for other strengths / supporting data	☐	☒			

Additional Comments regarding the ANDA:
None.

M E M O R A N D U M

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

DATE : June 16, 2004

TO : Director
Division of Bioequivalence (HFD-650)

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

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 77-170 for Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release Tablets, 5mg/120mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

IVAX Pharmaceuticals Inc. has submitted ANDA 77-170 for Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release Tablets, 5mg/120mg. The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by IVAX Pharmaceuticals Inc. on June 1, 2004 for its Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

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