CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-989

Name: Loratadine and Pseudoephedrine Sulfate
Extended-release Tablets
10 mg/240 mg
(24 Hour formulation)

Sponsor: IMPAX Laboratories Inc.

Approval Date: March 4, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-989

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-989

APPROVAL LETTER

ANDA 75-989

MAR 4 2004

IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 14, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg (24-hour formulation)(OTC).

Reference is also made to the Tentative Approval letter from this office dated May 24, 2002, and to your amendments dated January 22, 2001; and February 14, October 1, and November 12, 2003.

The listed drug product (RLD) referenced in your application, Claritin-D® 24-Hour Extended-release Tablets of Schering Corporation (Schering), is subject to periods of patent protection. As noted in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, (the "Orange Book"), U.S. Patent 4,659,716 (the '716 patent) is scheduled to expire on October 21, 2004, U.S. Patent 4,863,931 (the '931 patent) is scheduled to expire on March 15, 2009, and U.S. Patent 5,314,697 (the '697 patent) is scheduled to expire on April 23, 2013. Your application contains paragraph IV patent certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg (24-Hour Formulation), under this ANDA will not infringe upon the claims of the '716, '931, or '697 patents. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an infringement action was brought against IMPAX Laboratories, Inc. (IMPAX) for infringement of one or more of the patents that were the subjects of the paragraph IV certifications. This action must

be brought against IMPAX prior to the expiration of forty-five (45) days from the date the notice provided by IMPAX under paragraph (2)(B)(I) was received by the patent and NDA holder(s).

You have notified the Agency that IMPAX complied with the requirements of Section 505(j)(2)(B) of the Act. As a result, in January 2001, Schering initiated a lawsuit alleging infringement of the '716 and '697 patents against you in the United States District Court for the District of New Jersey (Schering Corporation v. IMPAX Laboratories, Inc., Civil Action No.01-0009(JAG)).

The Agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application, has expired with respect to the litigation involving the '716 and '697 patents. The Agency also recognizes that no legal action regarding the '931 patent was brought against IMPAX within the statutory forty-five day period.

Furthermore, the Act provides that approval of an ANDA that contains a paragraph IV certification, and that is for a drug product for which a previous abbreviated application has been submitted which also contains a paragraph IV certification, shall be made effective not earlier than one hundred and eighty days after:

1. the date the Secretary receives notice of the first commercial marketing of the drug product under the previous application, or

2. the date of a final decision of a court holding the patent(s) which is the subject of the certification to be invalid or not infringed, whichever event occurs first {Section 505(j)(5)(B)(iv)}.

As noted in the "Orange Book", an abbreviated new drug application for this drug product was approved for Andrx Pharmaceuticals, Inc. (Andrx) on February 21, 2003. This application also contained a paragraph IV certification and was the first application received by the Agency for this drug product. Consequently, Andrx became eligible for 180 days of market exclusivity commencing on the date of first commercial marketing. According to the "Orange Book", Andrx's market exclusivity expired on November 29, 2003.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for Over-the-Counter (OTC) use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg (24-Hour Formulation) to be bioequivalent to the listed drug Claritin-D® 24-Hour Extended-release Tablets of Schering Corporation. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution tests and tolerances are:

The dissolution testing should be conducted in 900 mL of 0.1N HCl for one hour. Then the medium should be replaced with 900 mL of 0.05M phosphate buffer at pH 6.8 containing 0.01% sodium lauryl sulfate at 37°C using USP 24 apparatus 1 (basket) at 75 rpm. The test product should meet the following "interim" specifications:

For Loratadine:

NLT (b) (4) % of loratadine is dissolved in 30 minutes

For Pseudoephedrine:

Time	Percent Dissolved
1 hour	(b) (4)
2 hours	
4 hours	
8 hours	
18 hours	

The "interim" dissolution tests and tolerances should be finalized by submitting dissolution data from the first three production size batches in a supplemental application. A "Special Supplement - Changes Being Effected" (CBE-0) should be submitted when there are no revisions to be proposed to the "interim" specifications or the proposed final specifications are tighter than the "interim" specifications. In all other instances, a Prior Approval Supplement should be submitted.

Under 21 CFR 314-70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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

Sincerely yours,

Robert L. Lest / for 3/4/2004

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

cc:

ANDA 75-989
Division File
FIELD COPY
HFD-610/RWest
HFD-330/
HFD-205/
HFD-610/Orange Book Staff

Endorsements:

HFD-623/U.Atwal/ 2/27/04
HFD-623/D.Gill/ DSGill 3-1-04
HFD-617/S.Kim/ S. Pan 3/01/04
HFD-613/D.Catterson/ Lisa M. Catterson 3/2/04
HFD-613/J.Grace/ 3/2/04

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Robert Lewis 3/4/2004

F/T by:

APPROVAL

CDRH satisfactory
3/4/04.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-989

TENTATIVE APPROVAL LETTER

ANDA 75-989

MAY 24 2002

Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 14, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg (24-hour formulation).

Reference is also made to your amendments dated August 16, 2001, and February 27, 2002.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. However, because of the presence of the patents listed for the reference drug product as explained below, this application is **tentatively approved**. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product (RLD) referenced in your application, Claritin-D 24 Hour Extended-release Tablets of Schering Corp., is subject to periods of patent protection. These patents, which are listed in the agency's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations", the "Orange Book", and their expiration dates are December 19, 2002 (U.S. Patent No. 4,282,233, the '233 patent), October 21, 2004 (U.S. Patent No. 4,659,716, the '716 patent), March 15, 2009 (U.S. Patent No. 4,863,931, the '931 patent), and October 23, 2013 (U.S. Patent No. 5,314,697, the '697 patent). Your application

contains a patent certification under Section 505(j)(2)(A)(vii)(III) of the Act for the '233 patent stating that you will not market this drug product prior to the expiration of this patent. Your application also contains "Paragraph IV Certifications" under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe upon the '716,'931, or '697 patents. 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 Impax Laboratories, Inc. (Impax) for infringement of one or more of the patents that are the subject of the "paragraph IV certifications". This action must be brought against Impax prior to the expiration of forty-five (45) days from the date the notice provided by Impax under paragraph (2)(B)(I) is received. You have notified FDA that Impax has complied with the requirements of Section 505(j)(2)(B) of the Act and that litigation is currently underway in the United States District Court for the District of New Jersey involving a challenge to the '716 and '697 patents (Schering Corporation v. Impax Laboratories, Inc., Civil Action No. 01-0009 (JAG)). Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of a court decision [505(j)(5)(B)(iii)(I), (II), or (III)], or,

   c. the '233, '716 and '697 patents have all expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

You must amend your application prior to final approval. Your MINOR AMENDMENT - FINAL APPROVAL REQUESTED should notify the agency of the legal issues that may affect the effective date of final approval. This amendment and should also include:

1. a copy of a final order or judgement, a settlement agreement between the parties, a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

   b. a statement that no such changes have been made to the application since the date of tentative approval.

Any significant changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made. Should you wish to make such changes prior to final approval, they should be categorized as representing either "major" or "minor" changes in your cover letter. This amendment will be reviewed according to OGD policies in effect at the time of receipt.

In addition to, or instead of, the pre-approval amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the "Orange Book".

The amendment requesting final approval should be designated as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED in your cover letter. Before you submit the amendment, or if you have questions concerning the status of this application, please contact Ruby Wu, R.Ph., Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

Robert Lee Sist / for 5/24/2002

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

cc:

ANDA 75-989
Division File
FIELD COPY
HFD-610/RWest
HFD-330/
HFD-205/

Endorsements:

HFD-623/U.Atwal/ 4/22/02
HFD-623/D.Gill/ 4-23-02
HFD-617/R.Wu/4/22/02 4/23/02
HFD-613/D.Catterson/ 4/23/02
HFD-613/J.Grace/ 4/23/2002

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F/T by: DJ 4/22/02

TENTATIVE APPROVAL

5/24/2002

4/24/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-989

LABELING

LEGEND

STANDARD FORMAT
Helvetica Condensed
Variable horizontal scale adheres to 39 characters per inch

Drug Facts - 9 pt Helvetica Cnd. Bold Italic

Drug Facts (continued)
Drug Facts - 8 pt Helvetica Cnd. Bold Italic
(continued) - 8 pt Helvetica Cnd.

Headings - 8 pt Helvetica Cnd. Bold Italic

Sub Heads -6 pt Helvetica Cnd. Bold

Text - 6 pt Helvetica Cnd, minimum leading 6.5

Square Bullets - 3.5 pt Zaph Dingbats no compression

Border - 1 pt rule, 3/64" gap all around

Barline - 1 pt rule

Hairline - .5 pt rule

IMPAX NDC 64896-171-03

Loratadine and Pseudoephedrine Sulfate Extended Release Tablets (24-Hour Formulation)

Loratadine 10 mg/Antihistamine
Pseudoephedrine Sulfate 240 mg/Nasal Decongestant

Allergy & Congestion Non-Drowsy*

Relief of:
Nasal and Sinus Congestion
Sneezing; Runny Nose
Itchy, Watery Eyes
Itchy Throat or Nose

APPROVAL
MAR 04 2004

1000 EXTENDED RELEASE TABLETS

***When taken as directed. See Drug Facts Panel.**

Drug Facts

Active Ingredients (in each tablet) ***Purpose***
Loratadine 10 mg ..... Antihistamine
Pseudoephedrine sulfate 240 mg ..... Nasal decongestant

Uses

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

Warnings

Do not use
- if you have ever had an allergic reaction to this product or any of its ingredients
- 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
- high blood pressure
- diabetes
- trouble urinating due to an enlarged prostate gland
- liver or kidney disease. Your doctor should determine if you need a different dose.

When using this product do not take more than directed.
Taking more than directed may cause drowsiness.

Drug Facts (continued)

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

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- do not divide, crush, chew or dissolve the tablet

adults and children 12 years and over	1 tablet daily with a full glass of water; not more than 1 tablet in 24 hours.
children under 12 years of age	ask a doctor
consumers with liver or kidney disease	ask a doctor

Other Information

- safety sealed: do not use if the bottle seal imprinted with "sealed for your protection" is open or torn
- store between 20° and 25° C (68° and 77° F)
- protect from light and store in a dry place

Inactive Ingredients

colloidal silicon dioxide, hydrogenated vegetable oil, hypromellose, magnesium stearate, pharmaceutical ink, polyethylene glycol, polyethylene oxide, titanium dioxide

Lot No.:

Manufactured by IMPAX Laboratories, Inc.
Hayward, CA 94544 USA

Exp. Date:

LA-322-02 Rev. 10/2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-989

LABELING REVIEWS

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

ANDA Number:	75-989
Date of Submission:	September 14, 2000 (Original draft labeling)
Applicant's Name:	Impax Laboratories, Inc.
Established Name:	Loratadine and Pseudoephedrine Sulfate Extended Release Tablets 10 mg/240 mg (24 Hour Formulation)

Labeling Deficiencies:

1. **CONTAINER** (Bottles of (b) (4) 1000) and
2. **INSERT:**

Please refer to the attached mocked-up copy of your draft container labels and insert labeling for all of the requested labeling revisions.

Please revise your labels and labeling, as instructed above, and submit four draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.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
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Copy of firm's mocked-up container labels and insert labeling.

Following this page, 10 pages withheld in full- (b)(4) Draft labeling

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 24		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?			X
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?		X	
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.			
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: None

FOR THE RECORD:

1. MODEL LABELING
   This review was based on the labeling of CLARITIN-D® 24 HOUR (loratadine and pseudoephedrine sulfate, USP) Extended Release Tablets by Schering Corporation (NDA 20-470/S-002), revised October 1997; approved October 6, 1997; acknowledged and retained on March 30, 1998.

2. PATENT/EXCLUSIVITIES

Patent Data – NDA 20-470

No	Expiration	Use Code	Use	File
4282233	June 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis	P-III
4282233 (Ped)	December 19, 2002	U-77		P-III
4659716	April 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite	P-IV
4659716(Ped)	October 21, 2004	U-142		P-IV
4863931	September 15, 2008			P-IV
4863931(Ped)	March 15, 2009			P-IV
5314697	April 23, 2013			P-IV
5314697 (Ped)	April 23, 2013			P-IV

Exclusivity Data For NDA 20-470

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   Impax Laboratories, Inc.
   30831 Huntwood Avenue
   Hayward, CA 94544 (Vol. A1.20, Section IX.1, Page 004667)

4. CONTAINER/CLOSURE (Vol. A 1.21, Section XIII.3, Page 004903)

   (b) (4)

   1000 count: 1500 cc wide mouth round white HDPE bottle with fine ribbed white plastic cap, with (b) (4) printed liner

5. INACTIVE INGREDIENTS (Vol. A1.20, Section VII.2, Page 004512)

   Although IMPAX did list the components in the black ink used to imprint its tablets, the firm did not include this information in the DESCRIPTION section of the insert labeling. This omission is OK and is in keeping with OGD's policy which only "encourages" the inclusion of dyes that may be contained therein, but not necessarily each ingredient.

6. PRODUCT DESCRIPTION

   The tablet imprintings 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). They are described as follows: white to off white oval, biconvex, coated tablets printed "G 1711" in black on one side.

7. PACKAGING CONFIGURATIONS (Vol. A 1.21, Section XIII.3, Page 004903)

   RLD: Bottles of 100, and blister packages of 10 x 10 tablet Unit Dose-Hospital Pack.
   ANDA: Bottles of (b) (4) 1000

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP: None
   RLD: Store between 15° and 25° C (59° and 77°F).
   ANDA: Store (b) (4)

9. DISPENSING STATEMENTS COMPARISON

   USP: None
   RLD: Dispense in a tight container as defined in USP/NF. (Container label only)
   ANDA: (b) (4)

10. BIOAVAILABILITY/BIOEQUIVALENCE:
    The Division of Bioequivalence concluded on March 20, 2001 that it had completed its review of bioequivalence and had no further questions at the time. (Vol. 1.1, NC 11-01-01)

Date of Review:	**Date of Submission:**
August 7, 2001	September 14, 2000 (Original draft)
Primary Reviewer:	**Date:**
L N Golson	8/7/01
Team Leader:	**Date:**
John D Grace	8/8/2001

cc: ANDA: 75-989
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
V:\FIRMSAM\IMPAX\LTRS&REV\75989na1.l
Review

TENTATIVE APPROVAL SUMMARY

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

ANDA Number: 75-989

Date of Submission: August 16, 2001 (Amendment)

Applicant's Name: IMPAX Laboratories, Inc.

Established Name: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets 10 mg/240 mg (24 Hour Formulation)

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? **No**. – The firm submitted 4 draft copies of their labels and labeling, which is acceptable for a Tentative Approval. Final Printed Labeling will be submitted by the firm 60 days prior to full approval of this application.

CONTAINER Labels – [Bottles of (b) (4) 1000]:
Satisfactory in **draft** as of the August 16, 2001 submission.

Professional Package INSERT:
Satisfactory in **draft** as of the August 16, 2001 submission.

Revisions needed post-tentative approval: **Yes**. The following are labeling revisions that are mostly editorial in nature, and therefore can be "post-tentative approval" revisions:

1. CONTAINER ((b) (4) 1000's):

   a. Front panel: Revise "10mg/240mg*" to read "10 mg/240 mg*". [Note: Insert spaces.]

   b. Side panel:

      i. Revise "*Each tablet…" to read "*Each extended-release tablet…".

      ii. Insert "USP" after "pseudoephedrine sulfate".

   c. Side panel of 1000's label only: Revise "…240mgof…" to read "…240 mg of…".

2. INSERT:

   ADVERSE REACTIONS: Last paragraph, last sentence: Revise to read: "In many of these cases,…".

I communicated these revisions to Mark C. Shaw, of IMPAX Laboratories, Inc., by telephone and by facsimile on January 4, 2002.

Patent Data – NDA 20-470

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4282233	June 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4282233*PED	December 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4659716	April 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4659716*PED	October 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4863931	September 15, 2008	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
4863931*PED	March 15, 2009	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
5314697	April 23, 2013	n/a	Stable extended release oral dosage composition comprising loratadine and pseudoephedrine (http://www.uspto.gov/patft/index.html)	IV	None
5314697*PED	April 23, 2013	n/a	Stable extended release oral dosage composition comprising loratadine and pseudoephedrine (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 20-470

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:

Was this approval based upon a petition? No.

What is the RLD on the 356(h) form: CLARITIN-D® 24 HOUR

NDA Number: 20-470

NDA Drug Name: Loratadine and Pseudoephedrine Extended Release Tablets 10 mg/240 mg

NDA Firm: Schering Corporation

Date of Approval of NDA Insert and supplement: October 6, 1997; NDA 20-470/SLR-002

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 CHECKLIST

Applicant's 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.		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 -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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. [see FTR]		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?			x
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	
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.		x	
Scoring: Describe scoring configuration of RLD and applicant (p. #) 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 p. # 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?[see FTR]		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		

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling of CLARITIN-D® 24 HOUR (loratadine and pseudoephedrine sulfate, USP) Extended Release Tablets by Schering Corporation (NDA 20-470/S-002), revised October 1997; approved October 6, 1997; acknowledged and retained on March 30, 1998.

2. PATENT/EXCLUSIVITIES

Patent Data – NDA 20-470

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4282233	June 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4282233*PED	December 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4659716	April 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4659716*PED	October 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4863931	September 15, 2008	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
4863931*PED	March 15, 2009	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
5314697	April 23, 2013	n/a	Stable extended release oral dosage composition comprising loratadine and pseudoephedrine (http://www.uspto.gov/patft/index.html)	IV	None
5314697*PED	April 23, 2013	n/a	Stable extended release oral dosage composition comprising loratadine and pseudoephedrine (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 20-470

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

The following comments are from the previous reviewer:

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Impax Laboratories, Inc.
30831 Huntwood Avenue
Hayward, CA 94544 (Vol. A1.20, Section IX.1, Page 004667)

4. CONTAINER/CLOSURE (Vol. A 1.21, Section XIII.3, Page 004903)

(b) (4)

1000 count: 1500 cc wide mouth round white HDPE bottle with fine ribbed white plastic cap, with (b) (4) printed liner

5. INACTIVE INGREDIENTS (Vol. A1.20, Section VII.2, Page 004512)

Although IMPAX did list the components in the black ink used to imprint its tablets, the firm did not include this information in the DESCRIPTION section of the insert labeling. This omission is OK and is in keeping with OGD's policy which only "encourages" the inclusion of dyes that may be contained

therein, but not necessarily each ingredient.

6. PRODUCT DESCRIPTION

The tablet imprintings 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). They are described as follows: white to off white oval, biconvex, coated tablets printed "G 1711" in black on one side.

7. PACKAGING CONFIGURATIONS (Vol. A 1.21, Section XIII.3, Page 004903)

RLD: Bottles of 100, and blister packages of 10 x 10 tablet Unit Dose-Hospital Pack.
ANDA: Bottles of (b) (4) 1000

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None
RLD: Store between 15° and 25° C (59° and 77°F).
ANDA:Store (b) (4)

9. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: Dispense in a tight container as defined in USP/NF. (Container label only)
ANDA: (b) (4)

10. BIOAVAILABILITY/BIOEQUIVALENCE:
The Division of Bioequivalence concluded on March 20, 2001 that it had completed its review of bioequivalence andhad no further questions at the time. (Vol. 1.1, NC 11-01-01)

Date of Review: 1/04/02 Date of Submission: 8/16/01

Primary Reviewer: Debra Catterson Date:
Debra M. Catterson 1/4/02

Team Leader: John Grace Date:
John J Grace 1/7/2002

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cc: ANDA 75-989
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
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Review

APPROVAL SUMMARY

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

ANDA Number: 75-989

Date of Submission: November 12, 2003 (Amendment– FPL)

Applicant's Name: IMPAX Laboratories, Inc.

Established Name: Loratadine (10 mg) and Pseudoephedrine Sulfate (240 mg) Extended Release Tablets (24 Hour Formulation) (OTC)

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes.

CONTAINER Labels – Bottles of 1000's:
Satisfactory as of the November 12, 2003 submission. [Rev. 10/2003]

Revisions needed post-approval: None.

Patent Data – NDA 20-470

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4659716	April 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4659716*PED	October 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4863931	September 15, 2008	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
4863931*PED	March 15, 2009	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
5314697	April 23, 2013	n/a	Stable extended release oral dosage composition comprising loratadine and pseudoephedrine (http://www.uspto.gov/patft/index.html)	IV	None
5314697*PED	April 23, 2013	n/a	Stable extended release oral dosage composition comprising loratadine and pseudoephedrine (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 20-470

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:

Was this approval based upon a petition? No.

What is the RLD on the 356(h) form: CLARITIN-D® 24 HOUR

NDA Number: 20-470

NDA Drug Name: Loratadine (10mg) and Pseudoephedrine Sulfate (240 mg) Extended Release Tablets

NDA Firm: Schering Corporation

Date of Approval of NDA Insert and supplement: NDA 20-470/SLR-019: Approved June 25, 2003

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 CHECKLIST

Applicant's 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.		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 -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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. [see FTR]		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?			x
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	
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.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) 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 p. # 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?[see FTR]		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		

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for CLARITIN-D® 24 HOUR (loratadine and pseudoephedrine sulfate, USP) Extended Release Tablets by Schering Corporation; NDA 20-470/SLR-019; approved June 25, 2003.

2. PATENT/EXCLUSIVITIES

Patent Data – NDA 20-470

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4659716	April 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4659716*PED	October 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4863931	September 15, 2008	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
4863931*PED	March 15, 2009	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
5314697	April 23, 2013	n/a	Stable extended release oral dosage composition comprising loratadine and pseudoephedrine (http://www.uspto.gov/patft/index.html)	IV	None
5314697*PED	April 23, 2013	n/a	Stable extended release oral dosage composition comprising loratadine and pseudoephedrine (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 20-470

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Impax Laboratories, Inc.
30831 Huntwood Avenue
Hayward, CA 94544 (Vol. A1.20, Section IX.1, Page 004667)

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD - Store between 20°C to 25°C (68°F to 77°F). Protect from light and store in a dry place.
ANDA - Store between 20° and 25°C (68° and 77°F). Protect from light and store in a dry place.

5. INACTIVE INGREDIENTS

The listing of inactive ingredients in the Drug Facts labeling appears to be consistent with the listing of inactive ingredients found in the Components and Composition statement. (Vol. A1.20, Section VII.1, Page 004511) with one discrepancy: The Drug Facts labeling lists "pharmaceutical ink" under the inactive ingredients, and I could not find this in the original C&C statement. I spoke to Michele Anderson of Impax Labs. on Dec. 18, 2002, and she explained that "pharmaceutical ink" is listed as " (b) (4) Black Ink" in the original components and composition statement.

6. CONTAINER/CLOSURE

1000 count: 1500 cc wide mouth round white HDPE bottle with fine ribbed white plastic cap, with (b) (4) inner liner that is imprinted "Sealed For Your Protection."
(Vol. A1.21, Section XIII.3, Page 004903)

Date of Review: 11/25/03 Date of Submission: 11/12/03

Primary Reviewer: Debra Catterson Date:
Debra M. Catterson 11/25/03

Team Leader: John Grace Date:
John J Grace 11/26/2003

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cc:
ANDA 75-989
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-989

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO.: **1** ANDA: **75-989**

3. NAME AND ADDRESS OF APPLICANT:
Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION:
Claritin-D® 24 Hour of Schering Corporation

5. SUPPLEMENTS: **N/A**

6. PROPRIETARY NAME: **N/A**

7. NONPROPRIETARY NAME: Loratadine and pseudoephederine sulfate, USP

8. SUPPLEMENTS PROVIDE FOR: **N/A**

9. AMENDMENTS AND OTHER DATES:
Original Submission Date September 14, 2000
Acceptable for filing Date September 8, 2000
New Correspondence Date October 30, 2000
Acknowledgement Letter Date November 8, 2000
New Correspondence Date November 27, 2000
New Correspondence Date January 2, 2000

10. PHARMACOLOGICAL CATEGORY:
Relief of symptoms of seasonal allergic rhinitis.

11. R_x/OTC: **R_x**

12. RELATED IND/NDA/DMF(s): **See DMF checklist.**

13. DOSAGE FORM: Extended release tablet

14. POTENCY: **10 mg/240 mg**

15. CHEMICAL NAME AND STRUCTURE:

Loratadine. 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-,ethyl ester. $C_{22}H_{23}ClN_2O_2$. 382.89. 79794-75-5.
Antihistaminic.

AND

Pseudoephedrine Sulfate. Benzenemethanol, α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate.
$(C_{10}H_{15}NO)2 \bullet H2SO4$. 428.54.
Vasoconstrictor.

16. RECORDS AND REPORTS: **N/A**

17. COMMENTS: See review.
Toxicology consult is required for the component Polyethylene Oxide,NF (b)(4) used in the product Formulation.

18. CONCLUSIONS AND RECOMMENDATIONS:
Not Approvable, Minor

19. REVIEWER:
U.S. Atwal, Ph.D.

DATE COMPLETED:
February 21, 2001

DATE REVISED:
March 8, 2001
USA

Following this page, 21 pages withheld in full- (b)(4) Chemistry review #1

MAR 20 2001

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-989 APPLICANT: Impax Pharmaceuticals, Inc.

DRUG PRODUCT: Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg

The deficiencies presented below represent **MINOR** deficiencies.

A. Chemistry Deficiencies:

1. (b) (4)

2.

3.

4.

5.

(b) (4)

6.

7.

8.

9.

10.

11.

12.

13.

14. (b) (4)

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

1. Labeling portion of your application is under review. Deficiencies, if any, will be conveyed to you under separate cover.

2. Since this drug product is not covered by an official monograph in the USP, the analytical methods must be validated by an FDA field laboratory prior to the approval of the application. Samples for the methods validation will be requested by the FDA at the appropriate time.

3. All DMFs referenced in this ANDA have to be found satisfactory at the time of approval of the ANDA. Some of the DMF holders may have to be inspected by our Division of Manufacturing and Product Quality.

4. Please commit to update specifications for all the inactive compendial ingredients to meet current requirements established in the USP/NF.

5. Please provide all available room temperature stability data for the finished product.

6. A satisfactory CGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

7. Please note that dissolution specifications will be established by the Division of Bioequivalence. Please revise your release and stability dissolution specifications if you have been informed about the dissolution specifications by the Division of Bioequivalence.

Sincerely yours,

DSGill

for Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-989
ANDA DUP 75-989
DIV FILE
Field Copy

Endorsements:

HFD-623/U.S. Atwal,Ph.D./3/6/01 3/15/01
HFD-623/N.Takiar for D. Gill, Ph.D./3/9/01 N. Takiar for 3/16/01
HFD-617/R. Yu/3/9/01 RYu 3/16/01
F/T by: gp/3/12/01
V:\FIRMSAM\IMPAX\LTRS&REV\75989.RV1

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

DSGill for Dr. Patel
3-19-01

1. CHEMISTRY REVIEW NO.: **2** ANDA: **75-989**

3. NAME AND ADDRESS OF APPLICANT:
Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION:
Claritin-D® 24 Hour of Schering Corporation

5. SUPPLEMENTS: **N/A**

6. PROPRIETARY NAME: **N/A**

7. NONPROPRIETARY NAME: Loratadine and pseudoephederine sulfate, USP

8. SUPPLEMENTS PROVIDE FOR: **N/A**

9. AMENDMENTS AND OTHER DATES:
Original Submission Date September 14, 2000
Acceptable for filing Date September 8, 2000
New Correspondence Date October 30, 2000
Acknowledgement Letter Date November 8, 2000
New Correspondence Date November 27, 2000
New Correspondence Date January 2, 2000
New Correspondence Date January 12, 2001 (Patent Amendment)
Amendment Date January 22, 2001 (Bio Amendment)
New Correspondence Date March 1, 2001 (Supplemental information re Legal Action for Patent Infringement)
Minor Amendment Date July 17, 2001 (This Review)

10. PHARMACOLOGICAL CATEGORY:
Relief of symptoms of seasonal allergic rhinitis.

11. R_x/OTC: **R_x**

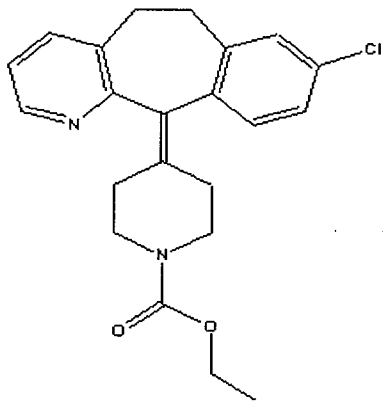
12. RELATED IND/NDA/DMF(s): **See DMF checklist.**

13. DOSAGE FORM: Extended release tablet

14. POTENCY: **10 mg/240 mg**

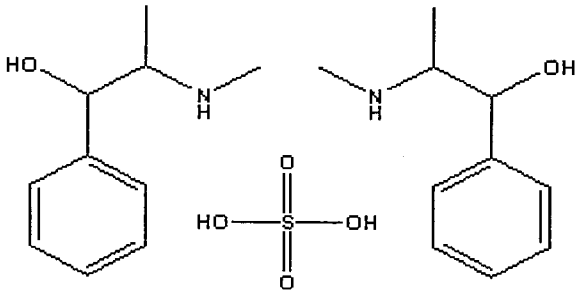
15. CHEMICAL NAME AND STRUCTURE:

Loratadine. 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-,ethyl ester. $C_{22}H_{23}ClN_2O_2$. 382.89. 79794-75-5.
Antihistaminic.



AND

Pseudoephedrine Sulfate. Benzenemethanol, α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate.
$(C_{10}H_{15}NO)2 \bullet H2SO4$. 428.54.
Vasoconstrictor.



16. RECORDS AND REPORTS: **N/A**

17. COMMENTS: See review.

18. CONCLUSIONS AND RECOMMENDATIONS:
Not Approvable, Fax.

19. REVIEWER:
U.S. Atwal, Ph.D.

DATE COMPLETED:
August 9, 2001

Following this page, 19 pages withheld in full- (b)(4) Chemistry review #2

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-989 APPLICANT: Impax Pharmaceuticals, Inc.

DRUG PRODUCT: Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg

The deficiencies presented below represent FAX deficiencies.

A. Chemistry Deficiencies:

1. (b) (4)

2.

3.

4.

5.

6. (b) (4)

7.

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

Your amendment must also include your response to the labeling comments that were sent to you on August 8, 2001.

Sincerely yours,

Paul Schwender for 8/23/01

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-989
ANDA DUP 75-989
DIV FILE
Field Copy

Endorsements:

HFD-623/U.S. Atwal,Ph.D./8/9/01 USAtwal 8/15/01
HFD-623/D. Gill, Ph.D./8/10/01 DSGill 8-15-01
HFD-617/R. Yu/8/14/01 RY 8-15-01

F/T by: DJ 8/15/01
V:\FIRMSAM\IMPAX\LTRS&REV\75989.RV2

CHEMISTRY REVIEW - NOT APPROVABLE - FAX.

1. CHEMISTRY REVIEW NO.: **3** ANDA: **75-989**

3. NAME AND ADDRESS OF APPLICANT:
Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION:
Claritin-D 24 Hour of Schering Corporation

5. SUPPLEMENTS: **N/A**

6. PROPRIETARY NAME: **N/A**

7. NONPROPRIETARY NAME: Loratadine and Pseudoephederine Sulfate, USP

8. SUPPLEMENTS PROVIDE FOR: **N/A**

9. AMENDMENTS AND OTHER DATES:
Original Submission Date September 14, 2000
Acceptable for filing Date September 8, 2000
New Correspondence Date October 30, 2000
Acknowledgement Letter Date November 8, 2000
New Correspondence Date November 27, 2000
New Correspondence Date January 2, 2000
New Correspondence Date January 12, 2001 (Patent Amendment)
Amendment Date January 22, 2001 (Bio Amendment)
New Correspondence Date March 1, 2001 (Supplemental information re Legal Action for Patent Infringement)
Minor Amendment Date July 17, 2001
Amendment Date August 13, 2001 (This Review)
Minor Amendment Date October 8, 2001 (This Review)

10. PHARMACOLOGICAL CATEGORY:
Relief of symptoms of seasonal allergic rhinitis.

11. R_x/OTC: **R_x**

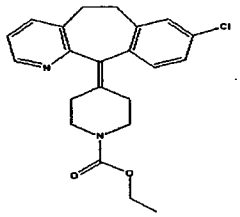
12. RELATED IND/NDA/DMF(s): **See DMF checklist.**

13. DOSAGE FORM: Extended release tablet

14. POTENCY: **10 mg/240 mg**

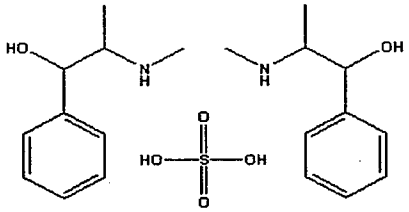
15. CHEMICAL NAME AND STRUCTURE:

Loratadine. 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-,ethyl ester. $C_{22}H_{23}ClN_2O_2$. 382.89. 79794-75-5.



AND

Pseudoephedrine Sulfate. Benzenemethanol, α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate. $(C_{10}H_{15}NO)2 \cdot H2SO4$. 428.54.
Vasoconstrictor.



16. RECORDS AND REPORTS: **N/A**

17. COMMENTS: See review.

18. CONCLUSIONS AND RECOMMENDATIONS:
Not Approvable, Fax.

19. REVIEWER:
U.S. Atwal, Ph.D.

DATE COMPLETED:
October 29, 2001

DATE REVISED:
November 19, 2001

Following this page, 13 pages withheld in full- (b)(4) Chemistry review #3

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-989 APPLICANT: Impax Pharmaceuticals, Inc.

DRUG PRODUCT: Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg

The deficiencies presented below represent FAX deficiencies.

A. Chemistry Deficiencies:

1. (b) (4)

2.

3.

4.

5.

6.

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

1. Since this drug product is not covered by an official monograph in the USP, the analytical methods validation is required. Samples for the methods validation have been requested by the FDA.

2. Labeling comments, if any, will follow under separate cover.

Sincerely yours,

Paul Shrivastava for 11/28/01

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-989
DIV FILE
Field Copy

Endorsements:

HFD-623/U.S. Atwal, Ph.D./11/19/01 N. Taleiac for Atwal 11/28/01
HFD-623/D. Gill, Ph.D./11/23/01 J. Franalis for D. Gill 11/28/01
HFD-617/R. Wu/11/28/01 R Wu 11/28/01

F/T by: gp/11/28/01
V:\FIRMSAM\IMPAX\LTRS&REV\75989.RV3

1. CHEMISTRY REVIEW NO.: 4 ANDA: **75-989**

3. NAME AND ADDRESS OF APPLICANT:
Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION:
Claritin-D® 24 Hour (Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10mg/240mg) of Schering Corporation; NDA #: 20-470.

5. SUPPLEMENTS: N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Loratadine and Pseudoephederine Sulfate, USP

8. SUPPLEMENTS PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original Submission Date September 14, 2000
Acceptable for filing Date September 8, 2000
New Correspondence Date October 30, 2000
Acknowledgement Letter Date November 8, 2000
New Correspondence Date November 27, 2000
New Correspondence Date January 2, 2000
New Correspondence Date January 12, 2001 (Patent Amendment)
Amendment Date January 22, 2001 (Bio Amendment)
New Correspondence Date March 1, 2001 (Supplemental information re Legal Action for Patent Infringement)
Minor Amendment Date July 17, 2001
Amendment Date August 13, 2001
Minor Amendment Date October 8, 2001
Amendment Date November 28, 2001 (This Review)
Tcon. Date December 17, 2001 (This Review)
Fax. Correspondence Date December 4, 2001(This Review)
Tcon. Date December 17, 2002 (This Review)
Fax. Amendment Date December 27, 2001 (This Review)

10. PHARMACOLOGICAL CATEGORY:
Relief of symptoms of seasonal allergic rhinitis.

11. R_x/OTC: R_x

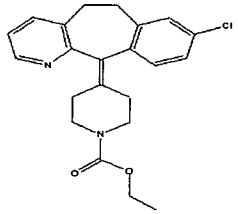
12. RELATED IND/NDA/DMF(s): See DMF checklist.

13. DOSAGE FORM: Extended release tablet

14. POTENCY: 10 mg/240 mg

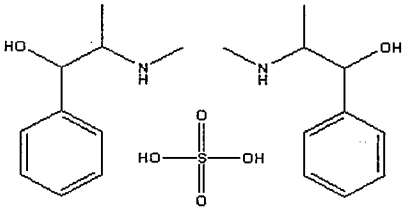
15. CHEMICAL NAME AND STRUCTURE:

Loratadine. 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-,ethyl ester. $C_{22}H_{23}ClN_2O_2$. 382.89. 79794-75-5.



AND

Pseudoephedrine Sulfate. Benzenemethanol, α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate. $(C_{10}H_{15}NO)2 \cdot H2SO4$. 428.54.
Vasoconstrictor.



16. RECORDS AND REPORTS: **N/A**

17. COMMENTS: See review.

18. CONCLUSIONS AND RECOMMENDATIONS:
Not Approvable, Minor

19. REVIEWER:
U.S. Atwal, Ph.D.

DATE COMPLETED:
January 22, 2002

DATE REVISED:
January 29, 2002

Following this page, 11 pages withheld in full- (b)(4) Chemistry review #4

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-989 APPLICANT: Impax Pharmaceuticals, Inc.

DRUG PRODUCT: Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg

The deficiency presented below represents a **MINOR** deficiency.

A. Chemistry Deficiency:

(b) (4)

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

1. Since this drug product is not covered by an official monograph in the USP, the analytical methods validation is required. Samples for the methods validation have been requested by the FDA.

2. Please provide updated controlled room temperature stability data.

Sincerely yours,

Paul Schwartz for 2/1/02

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-989
DIV FILE
Field Copy

Endorsements:

HFD-623/U.S. Atwal, Ph.D./1/29/02 1/31/02
HFD-623/J. Franolic for/D. Gill, Ph.D./1/29/02
HFD-617/R. Wu/1/30/02 RWu 2/1/02

F/T by: DJ 1/30/02
V:\FIRMSAM\IMPAX\LTRS&REV\75989.RV4

1. CHEMISTRY REVIEW NO.: 5 ANDA: **75-989**

3. NAME AND ADDRESS OF APPLICANT:
Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION:
Claritin-D® 24 Hour (Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10mg/240mg) of Schering Corporation; NDA #: 20-470.

5. SUPPLEMENTS: N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Loratadine and Pseudoephederine Sulfate, USP

8. SUPPLEMENTS PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original Submission Date September 14, 2000
Acceptable for filing Date September 8, 2000
New Correspondence Date October 30, 2000
Acknowledgement Letter Date November 8, 2000
New Correspondence Date November 27, 2000
New Correspondence Date January 2, 2000
New Correspondence Date January 12, 2001 (Patent Amendment)
Amendment Date January 22, 2001 (Bio Amendment)
New Correspondence Date March 1, 2001 (Supplemental information re Legal Action for Patent Infringement)
Minor Amendment Date July 17, 2001
Amendment Date August 13, 2001
Minor Amendment Date October 8, 2001
Amendment Date November 28, 2001
Tcon. Date December 17, 2001
Fax. Correspondence Date December 4, 2001
Tcon. Date December 17, 2002
Fax. Amendment Date December 27, 2001
Minor Amendment Date February 27, 2002 (This Review)

10. PHARMACOLOGICAL CATEGORY:
Relief of symptoms of seasonal allergic rhinitis.

11. R_x/OTC: R_x

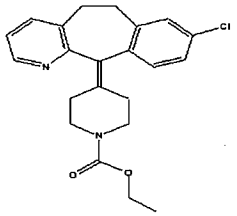
12. RELATED IND/NDA/DMF(s): See DMF checklist.

13. DOSAGE FORM: Extended Release Tablet

14. POTENCY: 10 mg/240 mg

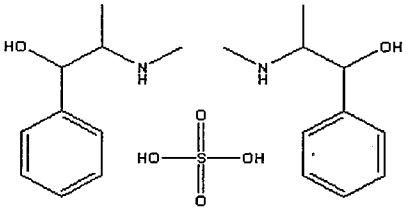
15. CHEMICAL NAME AND STRUCTURE:

Loratadine. 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-,ethyl ester. $C_{22}H_{23}ClN_2O_2$. 382.89. 79794-75-5.



AND

Pseudoephedrine Sulfate. Benzenemethanol, α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate. $(C_{10}H_{15}NO)2 \cdot H2SO4$. 428.54.
Vasoconstrictor.



16. RECORDS AND REPORTS: **N/A**

17. COMMENTS: See review.

18. CONCLUSIONS AND RECOMMENDATIONS:
Approvable (Tentative Approval)

19. REVIEWER: U.S. Atwal, Ph.D.

DATE COMPLETED: April 18, 2002

Following this page, 10 pages withheld in full- (b)(4) Chemistry review #5

cc: ANDA 75-989
DIV FILE
Field Copy

Endorsements:

HFD-623/U.S. Atwal, Ph.D./4/18/02 4/22/02
HFD-623/D. Gill, Ph.D./4/22/02 DS Gill 4-23-02
HFD-617/R. Wu/4/22/02 RWu 4/23/02

V:\FIRMSAM\IMPAX\LTRS&REV\75989.RV5
F/T by: DJ 4/22/02

ANDA 75-989 TENTATIVE APPROVAL SUMMARY

PRODUCT: Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets

FIRM: IMPAX Laboratories, Inc.

DOSAGE FORM: Extended-Release Tablet

STRENGTH: 10 mg/240 mg

cGMP STATEMENT/EIR UPDATE STATUS: Acceptable on 08-MAR-2001

BIO STUDY: Approve (Per Bio Review Dated 01/22/01, signed off 2/6/01)

VALIDATION: Satisfactory (Per NRL's report dated 03/18/02).

STABILITY: Thirteen weeks accelerated (40°C/75% RH) stability data and 104 weeks Controlled Room Temperature, CRT, (25°C±2°C/60%±5% RH) stability data for (b) (4) (b) (4) largest (1000's) package sizes are provided. The container/closure system used for the stability study is equivalent to the system proposed for commercial use. The reported data are with in established specifications. Thus, 24 month expiration date is justified.

Tests and specifications for the drug product on stability include: (b) (4) (Satisfactory).

LABELING: Tentatively Approved (per review dated 01/04/02).

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH: (b) (4) Tablets (Lot #R99044)

SIZE OF STABILITY BATCHES: Stability batch size is the same as the test/bio-batch, (b) (4) Tablets. The (b) (4) package size on stability is designated as R99044 (b) (4); the 1000's package size on stability is designated as R99044-1000.

PROPOSED PRODUCTION BATCHES: The proposed maximum batch size for production runs is the same as the ANDA batch, (b) (4) Tablets. The manufacturing process for production batches remains the same as that for the ANDA batch.

CHEMIST: ***U.S. ATWAL, Ph.D.*** **DATE:** 4/22/02

SUPERVISOR: ***D. Gill, Ph.D.*** **DATE:** 4-23-02

1. CHEMISTRY REVIEW NO.: 6 ANDA: **75-989**

3. NAME AND ADDRESS OF APPLICANT:
Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION:
Claritin-D® 24 Hour (Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10mg/240mg) of Schering Corporation; NDA #: 20-470.

5. SUPPLEMENTS: N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Loratadine and Pseudoephederine Sulfate, USP

8. SUPPLEMENTS PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original Submission Date September 14, 2000
Acceptable for filing Date September 8, 2000
New Correspondence Date October 30, 2000
Acknowledgement Letter Date November 8, 2000
New Correspondence Date November 27, 2000
New Correspondence Date January 2, 2000
New Correspondence Date January 12, 2001 (Patent Amendment)
Amendment Date January 22, 2001 (Bio Amendment)
New Correspondence Date March 1, 2001 (Supplemental information re Legal Action for Patent Infringement)
Minor Amendment Date July 17, 2001
Amendment Date August 13, 2001
Minor Amendment Date October 8, 2001
Amendment Date November 28, 2001
Tcon. Date December 17, 2001
Fax. Correspondence Date December 4, 2001
Tcon. Date December 17, 2002
Fax. Amendment Date December 27, 2001
Minor Amendment Date February 27, 2002
General Correspondence Date July 16, 2003 (this review)
Minor Amendment Date October 1, 2003 (this review)
Labeling Amendment Date November 12, 2003

10. PHARMACOLOGICAL CATEGORY:
Relief of symptoms of seasonal allergic rhinitis.

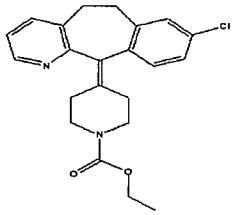
11. R_x/OTC: OTC

12. RELATED IND/NDA/DMF(s): See DMF checklist.

13. DOSAGE FORM: Extended Release Tablet

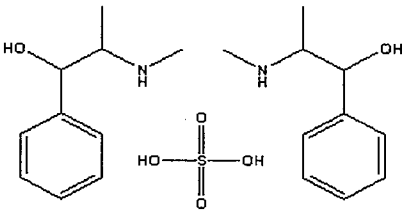
14. POTENCY: 10 mg/240 mg

15. CHEMICAL NAME AND STRUCTURE:
Loratadine. 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-,ethyl ester. $C_{22}H_{23}ClN_2O_2$. 382.89. 79794-75-5.



AND

Pseudoephedrine Sulfate. Benzenemethanol, α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate. $(C_{10}H_{15}NO)2 \cdot H2SO4$. 428.54.
Vasoconstrictor.



16. RECORDS AND REPORTS: **N/A**

17. COMMENTS:
This ANDA was tentatively approved by OGD on May 24, 2002. On the October 1, 2003 amendment, firm requests Final Approval of the application.

18. CONCLUSIONS AND RECOMMENDATIONS:
Approvable

19. REVIEWER: U.S. Atwal, Ph.D.

DATE COMPLETED: January 12, 2004

Following this page, 11 pages withheld in full- (b)(4) Chemistry review #6

cc: ANDA 75-989
DIV FILE
Field Copy

Endorsements:

HFD-623/U.S. Atwal, Ph.D./ USAtwal 2/27/04
HFD-623/D. Gill, Ph.D./ DSGill 3-1-04
HFD-617/S. Kim, PM/ S. Park 3/2/04

V:\FIRMSAM\IMPAX\LTRS&REV\75989.RV6
F/T by: SMS 2.27.04

APPROVAL ; PENDING EER 2.26.04

ANDA 75-989 APPROVAL SUMMARY

PRODUCT: Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets

FIRM: IMPAX Laboratories, Inc.

DOSAGE FORM: Extended-Release Tablet

STRENGTH: 10 mg/240 mg

cGMP STATEMENT/EIR UPDATE STATUS: PENDING 2.27.07

BIO STUDY: Acceptable 2/06/01

VALIDATION: Satisfactory (Per NRL's report dated 03/18/02).

STABILITY: Thirteen weeks accelerated (40°C/75% RH) stability data and 104 weeks Controlled Room Temperature, CRT, (25°C±2°C/60%±5% RH) stability data for (b) (4) (b) (4) largest (1000's) package sizes are provided. The container/closure system used for the stability study is equivalent to the system proposed for commercial use. The reported data are with in established specifications. Thus, 24 month expiration date is justified.

Tests and specifications for the drug product on stability include: (b) (4) (Satisfactory).

LABELING: Acceptable 11/26/03

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH: (b) (4) Tablets (Lot #R99044)

SIZE OF STABILITY BATCHES: Stability batch size is the same as the test/bio-batch, (b) (4) Tablets. The (b) (4) package size on stability is designated as R99044 (b) (4); the 1000's package size on stability is designated as R99044-1000.

PROPOSED PRODUCTION BATCHES: The proposed maximum batch size for production runs is the same as the ANDA batch, (b) (4) Tablets. The manufacturing process for production batches remains the same as that for the ANDA batch.

CHEMIST: ***U.S. ATWAL, Ph.D.*** U S Atwal ***DATE:*** 2/27/04

SUPERVISOR: ***D. Gill, Ph.D.*** DS Gill ***DATE:*** 3-1-04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-989

BIOEQUIVALENCE REVIEWS

Loratadine and pseudoephedrine sulfate
10 mg/240mg ER Tablet
ANDA No. 75989
Reviewer: Andre Jackson
V:\Firmsam\Impax\Ltrs&Rev\75989SD.900

Impax Laboratories, Inc.
Hayward, Ca.
Submission Date:
September 14, 2000

Review of Single Dose Fasting Study, Single Dose Post-Prandial Study and Dissolution Data and Summary of Multiple Dose Study

Introduction

Indication: Nasal Decongestion
RLD: Claritin-D® 24 hour

History

This study was undertaken and completed before the Guidance for Industry-Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations was published on October 27, 2000. Therefore this study contained analysis for the loratadine metabolite, descarboethoxyloratadine. There was also a multiple dose study submitted to meet the previous requirements for an extended release formulation. However, since the implementation of the Guidance for Industry-Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations by the FDA, metabolites are only preferred when parent drug levels are too low for analysis or the metabolite may be formed as a result of gut wall metabolism. Therefore the metabolite for loratadine is not required. Also multiple dose studies are no longer requested for the approval of extended-release formulations.

Consequently, only summary tables of the 90% confidence intervals will be provided in this review for the metabolite, descarboethoxyloratadine and the results from the steady-state study.

Background

Loratadine is rapidly absorbed and extensively metabolized to an active metabolite (descarboethoxy loratadine). The mean elimination half-lives, found in studies in normal adult subjects, were 8.4 hours for loratadine and 28 hours for descarboethoxy loratadine. The bioavailability of loratadine and pseudoephedrine sulfate from Claritin-D 24 hour ER tablets is similar to that achieved with separate administration of the components. Coadministration of loratadine and pseudoephedrine does not significantly affect the bioavailability of either component.

Dosage: Adults and children 12 years of age and over: one tablet daily with a full glass of water.

Single-dose Fasting Bioequivalence Study

Study Information

Study Number: 99281
Clinical Site: Gateway Medical Research, Inc.
St. Charles, Mo.
Investigator: Steven Herrmann, M.D.
Study Dates: Period I-January 30, 2000
Period II-February 13, 2000
Analytical Site: (b) (4)

Analytical Director: (b) (6) **Ph.D.**
Analysis Dates: June 6, 200-July 6, 2000
Storage Period: 158 days

Treatment ID	A	B
Test or Reference	TEST	REFERENCE
Product Name	Loratadine/Pseudoephedrine sulfate	Claritan-D® 24 hour
Manufacturer	Impax Laboratories	Schering Corporation
Batch/Lot No.	R99044	9-DCS-2015
Manufacture Date	1/04/00	N/A
Expiration Date	N/A	07/00
Strength	Loratadine 10 mg/Pseudoephedrine 240 mg	Loratadine 10 mg/Pseudoephedrine 240 mg
Dosage Form	Extended-Release Tablet	Extended-Release Tablet
Batch Size	(b) (4)	N/A
Potency Loratadine/Pseudoephedrine	101.8%/99.5%	104.5%/99.6%
Content Uniformity Loratadine/Pseudoephedrine	86.9-113.4%/92.3-101.1%	94.4-113.7%/99.0-101.7%
Formulation	See Table #1	N/A
Dose Administered	Loratadine 10 mg/Pseudoephedrine 240 mg	Loratadine 10 mg/Pseudoephedrine 240 mg
Route of Administration	Oral	Oral
Length of Fasting	Overnight	Overnight
Length of Confinement	10 hrs pre-dose until 24 hrs post-dose	10 hrs pre-dose until 24 hrs post-dose

No. of Sequences	2	**Crossover**	Y
No. of Periods	2	**Replicate Design**	N
No. of Treatments	2	**Washout Period**	14 days

Randomization Scheme	AB- 1,2,6,9,10,11,12,14,17,18,19,21,22,23,26,30,32,33,37,40 BA- 3,4,5,7,8,13,15,16,20,23,24,25,27,28,29,31,34,35,36,38,39
Blood Sampling Times	0,0.5,1,1.25,1.5,1.75,2,3,4,6,8,12,16,24,36,48,60,72,96,120 and 144 hrs post-dose
Blood Volume Collected/Sample	2x7 mL-Time 0 to 72 hrs 1x7 mL -Time 96-144 hrs
Blood Sample Processing/Storage	Frozen @ -20^{0}C

IRB Approval	Y
Informed Consent	Y
No. Enrolled	40
No. Completing	39
No. With Plasma Samples Analyzed	39
No. of Dropouts	1-#38 did not return for period II
Restrictions	Standard dietary, activity, and drug restrictions, inclusion/exclusion criteria were followed as per the protocol.
Safety Monitoring	Vital signs (blood pressure and pulse rate) were obtained at baseline and at 2,4,8 and 24 hrs post-dose.
Sex(es) Included	All males
Healthy Subjects Only	Y

Table 1. Formulation for the Loratadine 10 mg/Pseudoephedrine 240 mg ER Tablet

Ingredient	Per Tablet	Per ANDA Batch	Per Commercial Scale-Up Batch
Loratadine, (b) (4)	(b) (4)		
Pseudoephedrine sulfate, USP			
Hydroxypropyl methylcellulose, (b) (4), USP			
Hydrogenated vegetable oil, (b) (4), NF (b) (4)			
Polyethylene oxide, NF (b) (4) (b) (4)			
Colloidal silicon dioxide, NF (b) (4)			
Polyethylene glycol, NF (b) (4)			

Titanium dioxide, USP (b) (4)
Magnesium stearate, NF
(b) (4)
Total 809.42 mg (b) (4)
Batch size (# Tablets): (b) (4)

(b) (4)

Study Results

Clinical

Adverse Events No adverse events were reported

Protocol Deviations Protocol deviations were mainly late sample draws. Study integrity was not compromised by the deviations.

Analytical Method Validation
NOT TO BE RELEASED UNDER FOI

Analyte Parent
Assay Method LC\MS\MS
Matrix Plasma
Internal Standard (b) (4)

Parameter	Loratadine	Pseudoephedrine
Method	LC\MS\MS	LC\MS\MS
Sensitivity/LOQ	0.04 ng/mL	10 ng/mL
Linearity (Standard curve samples)	0.04 ng/mL-8 ng/mL	10 ng/mL-1000 ng/mL
Quality Control (QC) Samples	0.1 ng/mL 1.0 ng/mL 6.0 ng/mL	20 ng/mL 250 ng/mL 900 ng/mL
Precision of Standards (%CV)	7.7% @ 0.04 ng/mL 2.3% @ 8.0 ng/mL	6.8% @ 10 ng/mL 3.6% @ 1000 ng/mL
Precision of QC Samples (%CV)	16.7% @ 0.1 ng/mL 10.4% @ 6.0 ng/mL	6.7% @ 20 ng/mL 13.8% @ 900 ng/mL
Accuracy of Standards (%)	103% @ 0.04 ng/mL	99% @ 10 ng/mL

	102% @ 8.0 ng/mL	102% @ 1000 ng/mL
Accuracy of QC Samples (%)	107% @ 0.1 ng/mL 102% @ 6.0 ng/mL	99.5% @ 20 ng/mL 96.8% @ 900 ng/mL
Stability		
Freeze-thaw	3 cycles	3 cycles
Benchtop Sample Stability at RT	4 hrs @ RT	4 hrs @ RT
Long term at -20° C	1 month	1 month
Recovery Low Med High	 104% @ 0.1 ng/mL 109% @ 1.0 ng/mL 76% @ 6.0 ng/mL	 101% @ 20 ng/mL 102% @ 250 ng/mL 88.2% @ 900 ng/mL

Comments: The analytical data is incomplete due to the inadequate long term stability data.

Pharmacokinetic/Statistical Analysis

STATISTICAL ANALYSIS:

AUC(0-T), AUCinf, Cpeak and log transformed AUC(0-T), AUCinf and Cpeak were analyzed by Analysis of Variance (ANOVA) with effects for treatments, sequence of dosing, subjects within sequence, and study period in the statistical model.

The two one-sided hypotheses at the alpha=0.05 level of significance were tested for AUCT, AUCinf, Cpeak in original scale and after log transformation, by constructing the 90% confidence intervals for the differences between the test and the reference least squares means, and were reported relative to the reference means.

RESULTS

Table 2. Loratadine plasma levels. Values are mean ± sd.

	TEST		REFERENCE	
HOUR0	0.00	0.00	0.00	0.00
HOUR0.5	0.48	0.72	0.63	1.09
HOUR1	1.82	2.38	2.03	2.68
HOUR1.25	1.77	2.12	2.02	2.61
HOUR1.5	1.83	2.44	1.81	2.29
HOUR1.75	1.57	1.87	1.64	2.12
HOUR2	1.41	1.77	1.39	1.78
HOUR3	0.86	1.03	0.85	1.14
HOUR4	0.51	0.65	0.50	0.66

HOUR6	0.21	0.25	0.19	0.25
HOUR8	0.10	0.13	0.11	0.15
HOUR12	0.04	0.07	0.04	0.08
HOUR16	0.02	0.05	0.02	0.05
HOUR24	0.01	0.03	0.01	0.03
HOUR36	0.01	0.02	0.01	0.02
HOUR48	0.01	0.02	0.01	0.02
HOUR60	0.00	0.01	0.00	0.02
HOUR72	0.00	0.01	0.00	0.01
HOUR96	0.00	0.01	0.01	0.07
HOUR120	0.00	0.00	0.00	0.00
HOUR144	0.00	0.00	0.00	0.00

Table 3. Loratadine plasma parameters. Values are mean ± sd.

	TEST		REFERENCE		Ratio(T/R)
CPEAK, ng/mL	2.11	2.65	2.25	2.87	0.93
LCPEAK, ng/mL	0.21	1.03	0.27	1.03	0.94[1]
AUCL,[2] ng/mL x hr	6.00	7.93	6.33	8.83	0.95
LAUCL, ng/mL x hr	1.18	1.10	1.20	1.12	0.98
AUCI,[3] ng/mL x hr	5.79	7.97	4.90	8.45	1.18
LAUCI, ng/mL x hr	1.22	0.98	1.07	0.91	1.16
TMAX, hr	1.24	0.30	1.21	0.29	---
KEL, hr-1	0.32	0.18	0.39	0.18	---
THALF, hr	7.06	16.89	3.63	8.49	---

1.Ratio of geometric means
2.Area to the last quantifiable concentration
3.Area to time infinity

Table 4. 90% confidence intervals for loratadine

Parameter	Lower Limit	Upper Limit
LAUCI	91	118
LAUCL	85	112

LCPEAK	82	107

Table 5. 90% confidence intervals and T/R ratio for descarboethoxyloratadine

Parameter	Lower Limit	Upper Limit	T/R
LAUCI	92.1	106.2	98.9
LAUCL	91.3	105.8	98.3
LCPEAK	88.8	106.8	97.4

Table 6. Pseudoephedrine plasma levels. Values are mean ± sd.

	TEST		REFERENCE	
HOUR0	0.00	0.00	0.00	0.00
HOUR0.5	25.98	18.09	27.38	21.94
HOUR1	91.40	37.79	93.68	28.05
HOUR1.25	118.41	45.42	122.60	32.13
HOUR1.5	144.02	53.21	144.78	40.38
HOUR1.75	162.68	54.72	160.08	33.82
HOUR2	179.90	62.10	178.64	40.55
HOUR3	220.92	53.28	230.62	54.45
HOUR4	282.95	62.87	276.77	56.82
HOUR6	349.46	87.71	348.18	87.63
HOUR8	355.41	97.40	334.69	87.52
HOUR12	297.65	100.01	274.05	74.19
HOUR16	218.43	76.60	210.19	53.86
HOUR24	100.95	38.45	102.60	33.46
HOUR36	26.41	15.26	33.70	26.43
HOUR48	2.47	5.50	5.64	14.41
HOUR60	0.00	0.00	2.03	12.65
HOUR72	0.00	0.00	0.68	4.23
HOUR96	0.00	0.00	0.29	1.83
HOUR120	0.00	0.00	0.00	0.00
HOUR144	0.00	0.00	0.00	0.00

Table 7. Pseudoephedrine plasma parameters. Values are mean ± sd.

	TEST		REFERENCE		Ratio(T/R)
CPEAK, ng/mL	377.67	97.02	360.38	83.93	1.05

LCPEAK, ng/mL	5.90	0.25	5.86	0.22	1.04[1]
AUCL,[2] ng/mL x hr	6393.98	1810.91	6382.96	1604.13	1.00
LAUCL, ng/mL x hr	8.72	0.30	8.73	0.25	0.99
AUCI,[3] ng/mL x hr	6613.59	1806.90	6618.69	1592.69	0.99
LAUCI, ng/mL x hr	8.76	0.29	8.77	0.24	0.99
TMAX, hr	7.54	1.86	6.51	1.19	----
KEL, hr-1	0.11	0.02	0.10	0.02	-----
THALF, hr	6.58	1.28	7.28	1.98	----

1.Ratio of geometric means
2.Area to the last quantifiable concentration
3.Area to time infinity

Table 8. 90% confidence intervals for pseudoephedrine

Parameter	Lower Limit	Upper Limit
LAUCI	92	105
LAUCL	93	106
LCPEAK	98	111

Sample Repeats

1635 samples were analyzed for loratadine and pseudoephedrine. Twenty-five loratadine samples (1.5%) and 12 (0.7%) pseudoephedrine samples were re-analyzed. Samples were repeated because the sample had either a high internal standard, a low internal standard, or was below the quantifiable limit. There were no samples repeated due to **pharmacokinetic anomalies.**

ALL CALCULATIONS WERE VERIFIED BY THE REVIEWER EXCEPT THOSE FOR THE METABOLITE, DESCARBOETHOXYLORATADINE, WHICH DOES NOT REPRESENT PIVOTAL DATA FOR THIS SUBMISSION.

Single-dose Post-Prandial Bioequivalence Study

A. Study Information

Study Number: 99284
Clinical Site: Gateway Medical Research
St. Charles Mo.
Investigator: David B. Erasmus, M.D.
Study Dates: Period I-January 22, 2000
Period II-February 5, 2000
Period III-February 19, 2000
Analytical Site: (b) (4)

Analytical Director: (b) (6) **, Ph.D.**
Analysis Dates: June 9, 2000-July 6, 2000
Storage Period: 167 days

Treatment ID	A	B	C
Test or Reference	TEST FASTING	TEST FOOD	REFERENCE FOOD
Product Name	Loratadine/ Pseudoephedrine sulfate	Loratadine/ Pseudoephedrine sulfate	Claritan-D® 24 hour
Manufacturer	Impax Laboratories	Impax Laboratories	Schering Corporation
Batch/Lot No.	R99044	R99044	9-DCS-2015
Dose Administered	Loratadine 10 mg/Pseudo ephedrine 240 mg	Loratadine 10 mg/Pseudo ephedrine 240 mg	Loratadine 10 mg/Pseudo ephedrine 240 mg
Route of Administration	Oral	Oral	Oral
Length of Fasting	Overnight	Overnight	Overnight
Standardized Breakfast	N	Y	Y
Length of Confinement	10 hrs pre-dose until 24 hrs post-dose	10 hrs pre-dose until 24 hrs post-dose	10 hrs pre-dose until 24 hrs post-dose

No. of Sequences	6	**Crossover**	Y
No. of Periods	3	**Replicate Design**	N
No. of Treatments	3	**Washout Period**	14 days

Randomization Scheme	BCA-1,9,18,20,30 CAB-2,10,15,21,29 CBA-3,12,13,22,28 ACB-4,7,14,23,25 BAC-5,11,17,19,26 ABC-6,8,16,24,27
Blood Sampling Times	0,0.5,1,1.25,1.5,1.75,2,3,4,6,8,12,16,24,36,48,60,72, 96,120 and 144 hrs post-dose
Blood Volume Collected/Sample	2x7 mL-Time 0 to 72 hrs 1x7 mL -Time 96-144 hrs
Blood Sample Processing/Storage	Frozen @ -20^{0}C

IRB Approval	Y
Informed Consent	Y
No. Enrolled	30
No. Completing	30
No. With Plasma Samples Analyzed	30
No. of Dropouts	0
Restrictions	Standard dietary, activity, and drug restrictions, inclusion/exclusion criteria were followed as per the protocol.
Safety Monitoring	Vital signs (blood pressure and pulse rate) were obtained at baseline and at 2,4,8 and 24 hrs post-dose.
Sex(es) Included	All males
Healthy Subjects Only	Y

Study Results

Clinical

Adverse Events	Six adverse events were reported. Two were for subjects receiving the test under fasting conditions while the remaining events were seen with the test fed treatment. The adverse events were headache and sore throat.
Protocol Deviations	Protocol deviations were mainly late sample draws. Study integrity was not compromised by the deviations.

Analytical

Analyte Parent
Assay Method LC\MS\MS
Matrix Plasma
Internal Standard (b) (4)

Parameter	Loratadine	Pseudoephedrine
Method	LC\MS\MS	LC\MS\MS
Sensitivity/LOQ	0.04 ng/mL	10 ng/mL
Linearity (Standard curve samples)	0.04 ng/mL-8 ng/mL	10 ng/mL-1000 ng/mL
Quality Control (QC) Samples	0.1 ng/mL 1.0 ng/mL 6.0 ng/mL	20 ng/mL 250 ng/mL 900 ng/mL
Precision of Standards (%CV)	8.9% @ 0.04 ng/mL 2.9% @ 8.0 ng/mL	8.1% @ 10 ng/mL 3.1% @ 1000 ng/mL
Precision of QC Samples (%CV)	15.4% @ 0.1 ng/mL 11.3% @ 6.0 ng/mL	11.3% @ 20 ng/mL 14.3% @ 900 ng/mL
Accuracy of Standards (%)	106% @ 0.04 ng/mL 101% @ 8.0 ng/mL	97.3% @ 10 ng/mL 101% @ 1000 ng/mL
Accuracy of QC Samples (%)	104% @ 0.1 ng/mL 97.2% @ 6.0 ng/mL	99.0% @ 20 ng/mL 102% @ 900 ng/mL

Comments: The analytical method is incomplete, insufficient storage time for the long-term stability study.

Pharmacokinetic/Statistical Analysis

Same as for the fasting study

RESULTS

Table 9. Loratadine plasma levels. Values are mean ± sd.

	TEST FASTING		TEST FED		REFERENCE FED	
HOUR0	0.01	0.02	0.01	0.02	0.00	0.02
HOUR0.5	0.36	0.42	0.53	0.93	0.35	0.66
HOUR1	1.46	1.32	1.83	2.83	1.45	1.66
HOUR1.25	1.65	1.61	2.03	2.77	1.88	1.85
HOUR1.5	1.75	1.80	2.21	2.76	2.19	1.96
HOUR1.75	1.56	1.72	2.17	2.38	2.24	1.87
HOUR2	1.38	1.52	2.10	1.81	2.20	1.77

HOUR3	0.82	0.85	1.60	1.31	1.65	1.39
HOUR4	0.47	0.57	1.07	0.81	1.15	0.94
HOUR6	0.22	0.27	0.49	0.38	0.50	0.36
HOUR8	0.12	0.13	0.24	0.19	0.25	0.18
HOUR12	0.06	0.07	0.12	0.10	0.12	0.09
HOUR16	0.04	0.05	0.08	0.08	0.07	0.06
HOUR24	0.03	0.03	0.04	0.04	0.04	0.04
HOUR36	0.02	0.02	0.03	0.04	0.05	0.06
HOUR48	0.01	0.02	0.02	0.03	0.02	0.03
HOUR60	0.01	0.02	0.02	0.03	0.02	0.03
HOUR72	0.01	0.02	0.02	0.04	0.01	0.03
HOUR96	0.01	0.02	0.01	0.02	0.02	0.05
HOUR120	0.01	0.02	0.00	0.02	0.01	0.02
HOUR144	0.01	0.02	0.01	0.02	0.01	0.02

Table 10. Plasma parameters for loratadine. Values are mean ± sd.

	TEST FASTING		TEST FED		REFERENCE FED		Ratio (T_{Fed}/R_{Fed})
AUCL, ng/mL	6.74	6.75	11.39	9.56	11.77	8.37	0.97
LAUCL,[2] ng/Ml	1.48	0.99	2.17	0.75	2.21	0.76	0.96[1]
AUCI,[3] ng/Ml x hr	5.85	5.34	8.95	5.15	11.79	9.97	0.76
LAUCI, ng/mL x hr	1.42	0.85	2.04	0.57	2.18	0.78	0.86
CPEAK,[3] ng/mL x hr	1.98	1.87	2.86	2.76	2.71	2.04	1.05
LCPEAK, ng/mL x hr	0.26	0.99	0.73	0.81	0.73	0.76	1.00
TMAX, hr	1.29	0.32	1.93	0.86	2.10	1.04	---
THALF, hr	6.37	7.87	9.71	12.55	11.83	13.65	---
KEL, hr-1	0.26	0.19	0.16	0.13	0.16	0.13	---

1.Ratio of geometric means
2.Area to the last quantifiable concentration
3.Area to time infinity

Table 11. Ratios for descarboethoxyloratadine based upon log-transformed data. (Data not recalculated by the reviewer-Firm supplied data)

Parameter	Ratio
LCPEAK	1.04
LAUCL	1.05
LAUCI	1.01

Table 12. Pseudoephedrine plasma concentrations. Values are mean ± sd.

	TEST FASTING		TEST FED		REFERENCE FED	
HOUR0	0.00	0.00	1.10	4.25	0.00	0.00
HOUR0.5	25.28	29.22	13.93	19.05	6.44	10.45
HOUR1	93.86	33.62	65.34	44.93	49.71	35.70
HOUR1.25	119.63	42.26	90.56	47.40	76.41	46.76
HOUR1.5	141.34	44.77	115.07	56.00	105.47	52.98
HOUR1.75	154.95	51.43	148.95	75.84	129.46	47.98
HOUR2	181.73	52.20	174.73	81.10	148.54	38.95
HOUR3	254.83	57.87	275.80	107.41	237.22	53.89
HOUR4	304.77	54.57	335.17	113.36	300.10	60.89
HOUR6	353.23	73.79	411.90	105.58	379.70	77.69
HOUR8	366.47	88.15	425.83	130.43	392.23	89.29
HOUR12	306.90	72.87	335.83	101.48	312.00	88.25
HOUR16	235.63	67.31	223.72	77.68	228.80	63.66
HOUR24	111.54	37.57	84.87	31.35	99.50	33.83
HOUR36	31.11	15.69	20.15	10.84	25.75	13.81
HOUR48	3.14	5.93	4.31	19.77	1.88	5.05
HOUR60	0.00	0.00	1.75	7.20	0.00	0.00
HOUR72	0.00	0.00	0.39	2.12	0.65	3.58
HOUR96	0.00	0.00	0.73	3.98	0.00	0.00
HOUR120	0.00	0.00	0.00	0.00	0.93	5.09
HOUR144	0.00	0.00	0.00	0.00	0.00	0.00

Table 13. Pseudoephedrine plasma parameters. Values are mean ± sd.

	TEST FASTING		TEST FED		REFERENCE FED		Ratio (T_{Fed}/R_{Fed})
AUCL, ng/mL	6788.02	1598.58	6829.32	1886.09	6638.24	1577.40	1.03
LAUCL,[2] ng/Ml	8.79	0.25	8.79	0.29	8.77	0.26	1.02
AUCI,[3] ng/Ml x hr	7109.27	1476.84	7238.60	1824.81	6950.61	1583.97	1.04

LAUCI, ng/mL x hr	8.85	0.21	8.86	0.26	8.82	0.25	1.04
CPEAK, [3] ng/mL x hr	379.90	79.20	451.80	126.29	409.40	83.25	1.10
LCPEAK, ng/mL x hr	5.92	0.21	6.08	0.28	5.99	0.21	1.09
TMAX, hr	6.73	1.53	7.47	2.03	7.00	1.55	---
THALF ,hr	7.35	1.87	6.04	0.78	6.83	1.13	---
KEL, hr-1	0.10	0.02	0.12	0.01	0.10	0.02	---

Comment: The test fed plasma concentration curves for loratadine and pseudoephedrine exhibited a measurable concentration at time zero. However, the values were less than 5% of Cmax and in accordance with the Guidance for Industry-Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations published on October 27, 2000, the subjects were not deleted from the data set

ALL CALCULATIONS WERE VERIFIED BY THE REVIEWER EXCEPT THOSE FOR THE METABOLITE, DESCARBOETHOXYLORATADINE, WHICH DOES NOT REPRESENT PIVOTAL DATA FOR THIS SUBMISSION.

Sample Repeats

1883 samples were analyzed with 58 loratadine (3%) and 44 pseudoephedrine (2.3%) samples reanalyzed. They were mainly for subject #25 who exhibited many levels near the LOQ. Samples were repeated because the sample had either a high internal standard, a low internal standard, or was below the quantifiable limit. There were no samples repeated due to **pharmacokinetic anomalies.**

Multiple -Dose Bioequivalence Study

The 90% CI data for the multiple dose study supplied by the firm are summarized in the following tables for the loratadine, descarboethoxyloratadine and pseudoephedrine. Only summary data are presented since multiple dose studies are no longer recommended for the approval of extended release formulations based upon the Guidance for Industry-Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations published on October 27, 2000.

Table 14 . Test to reference ratio and 90% CI calculated by the firm for the mutiple dose study for loratadine.

Parameter	Ratio	Upper CI	Lower CI
LNAUC(0-24)	102	115.9	90.0
LNCPEAK	102.7	117.4	89.9

Table 15. Test to reference ratio and 90% CI calculated by the firm for the mutiple dose study for descarboethoxyloratadine.

Parameter	Ratio	Upper CI	Lower CI
LNAUC(0-24)	101.2	108.6	94.3
LNCPEAK	95.0	105.7	85.3

Table 16. Test to reference ratio and 90% CI calculated by the firm for the mutiple dose study for pseudoephedrine

Parameter	Ratio	Upper CI	Lower CI
LNAUC(0-24)	100.1	106.7	93.9
LNCPEAK	103.0	109.3	97.1

The CI's presented by the firm supports the bioequivalence of their formulation.

Dissolution Method

The dissolution method for the innovator product is :

Method: USP Apparatus II, 50 rpm, 1000 ml 0.1N hydrochloric acid in first hour and 1000 ml 0.1M phosphate buffer (pH 7.5) for additional 16 hours, 37 degrees C.

Specifications:
Loratadine: Q = (b) (4) % in 30 minutes
Pseudoephedrine:
1 hour (b) (4)
2 hours
4 hours
8 hours
16 hours

Two sets of dissolution profiles were generated. The first set was generated following the IMPAX dissolution method TLPSDR24, under the following conditions (all studies were done at wavelength=210 nm):

Apparatus	Speed	Media
USP Apparatus I (basket)	75 rpm	900 mL 0. 1 N HCl for one hour, then replace medium with 900 ml- 0.05M phosphate buffer at pH 6.8 containing 0.01% sodium lauryl sulfate (SLS)

The second set of dissolution profiles was generated under the following conditions, as suggested by the Office of Generic Drugs, Division of Bioequivalence:

Apparatus	Speed	Media
USP Apparatus 2 (paddle)	50and75 rpm	900 mL 0.1N HCl for one hour, then replace medium with 900 mL 0. 1 M phosphate buffer at pH 7.5 for 16 additional hours

The dissolution data is presented in appended Tables 17-28.

Comments:

1. The 90% CI for LAUCL, LAUCI, LCPEAK for the fasting study were within the acceptable limits of 80-125% of the reference.

2. The test/reference ratio of geometric means for LAUCL, LAUCI, LCPEAK were within 0.8-1.25 of the reference.

3. The proposed Impax dissolution method TLPSDR24 is acceptable. The firm's proposed specifications were:

NLT (b) (4) % of loratadine is dissolved in 30 min

For pseudoephedrine:

1 hour	(b) (4)
4 hours	
8 hours	
18 hours	

Based on the submitted data the Division of Bioequivalence proposed the following dissolution specifications:

NLT (b) (4) % of loratadine is dissolved in 30 min

For pseudoephedrine:

1 hour	(b) (4)
2 hours	
4 hours	
8 hours	
18 hours	

Deficiencies:

1. The study was begun in January, 2000 with sample analysis completed in July 2000. However the firm only supplied stability data for a 1 month storage period (vol 1.2, pgs. 194-196. The firm should supply long term stability data for 158 days to cover the actual storage time for the samples.

RECOMMENDATIONS:

1.The fasting bioequivalence study conducted by Impax Pharmaceuticals on its Loratadine/ Pseudoephedrine 10 mg/240 mg ER tablet comparing it to Claritan-D® 10 mg/240 mg 24 hour ER tablet lot # 9-DCS2015 has been found to be incomplete by the Division of

Bioequivalence.

2. The post-prandial bioequivalence study conducted by Impax Pharmaceuticals on its Loratadine/Pseudoephedrine 10 mg/240 mg ER tablet comparing it to Claritan-D® 10 mg/240 mg 24 hour ER tablet lot # 9-DCS2015 has been found to be incomplete by the Division of Bioequivalence.

3. The dissolution study conducted on the 10mg/240 mg ER tablet is acceptable.

4.The dissolution testing should be incorporated into the firm's manufacturing and controls programs. The dissolution testing should be conducted in 900 ml of 0.1N HCL for 1 hour, then replace the medium with 900 mL of 0.05M phosphate buffer at pH 6.8 containing 0.01% sodium lauryl sulfate at37^{0}C using USP XXIV apparatus 1 (basket) at 75 rpm. The test product should meet the following interim specifications:

NLT (b) (4) % of loratadine is dissolved in 30 min

For pseudoephedrine:

	(b) (4)
1 hour	
2 hours	
4 hours	
8 hours	
18 hours	

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG Date: 12/8/2000

Concur: for Barbara M Davit Date: 12/22/00
Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence

cc: ANDA 75989 (original, duplicate), HFD-650(Director), HFD-652 (Huang, Jackson), Drug File, Division File.

FIRM'S DISSOLUTION PROCEDURES

Table 17. Dissolution Data for Loratadine

Product: Loratadine/Pseudoephedrine ER Tablets, 10 mg/240 mg

Lot No.: R99044

Method: UISP apparatus 1 (Basket), 75 rpm, TLPSDR23.03
Medium: 900 mL 0. 1 N HCl for one hour, then to 0.05M phosphate buffer (pH 6.8) w/ 0.01 % SLS

Date Tested	Tablet	Cumulative % dissolved Time (min) 5	10	15	30	60
1/17/00-	1			(b) (4)		
	2					
	3					
	4					
	5					
	6					
1/17/00-	7					
	8					
	9					
	10					
	11					
	12					
	Mean	48.5	74.9	83.0	89.1	92.6
	SD	4.2	4.4	5.2	5.8	5.9
	Max.	55.2	84.0	94.9	102.5	106.4
	Min.	41.6	68.1	73.8	78.4	81.2
	RSD	8.69%	5.84%	6.23%	6.46%	6.42%

Table 18. Dissolution Data for Loratadine

Product: Claritin-D 24 Hour

Lot No.: 9-DCS-2015

Method: USP apparatus 1 (Basket), 75 rpm, TLPSDR23.03
Medium: 900 mL 0.1 N HCl for one hour, then to 0.05M phosphate buffer (pH 6.8) W/ 0.01 % SLS

Date Tested	Tablet	Cumulative % dissolved Time (min) 5	10	15	30	60
1/12/00	1			(b) (4)		
	2					
	3					
	4					
	5					

	6	(b) (4)				
1/12/00	7					
	8					
	9					
	10					
	11					
	12					
Mean		56.9	80.8	89.2	96.6	98.1
SD		5.5	4.8	4.9	6.0	5.5
max.		64.2	87.6	96.6	105.9	106.0
Min.		47.7	73.6	83.1	88.9	91.9
RSD		9.62%	5.99%	5.48%	6.24%	5.57%

Table 19. Dissolution Data for Pseudoephedrine Sulfate
Product: Loratadine/Pseudoephedrine ER Tablets, 10 mg/240 mg
Lot No.: R99044
Method: USP apparatus 1 (Basket), 75 rpm, TLPSDR24.03
Medium: 900 mL 0.1 N HCl for one hour, then to 0.05M phosphate buffer (pH 6.8) w/ 0.01 % SILS

Date Tested	Tablet	Cumulative % dissolved Time (hours)				
		1	2	4	8	18
1/17/00	1	(b) (4)				
	2,					
	3					
	4					
	5					
	6					
1/17/00	7					
	8					
	9					
	10					
	11					
	12					
Mean		23.4	34.31	50.6	72.4	92.7
SD		0.4	0.51	0.7	1.1	1.3
Max.		24.1	35.2	52.1	74.8	95.7
Min.		22.6	33.4	49.7	71.3	91.3
RSD		1.83%	1.54%	1.46%	1.52%	1.41%.

Table 20. Dissolution Data for Pseudoephedrine Sulfate
Product: Claritin-D 24 Hour
Lot No.: 9-DCS-2015
Method: USP apparatus 1 (Basket), 75 rpm, TLPSDR23.03
Medium: 900 mL 0. 1 N HCl for one hour, then to 0.05M phosphate buffer (pH 6.8) w/ 0.01 % SLS

Date Tested	Tablet	Cumulative % dissolved Time (hours)				
		1	2	4	8	18
1/17/00	1	(b) (4)				

	2	(b) (4)				
	3					
	4					
	5					
	6					
1/17100	7					
	8					
	9					
	10					
	11					
	12					
Mean		22.6	34.0	50.2	72.2	94.0
SD		0.6	0.6	0.6	0.9	1.2
Max.		23.4	34.8	51.2	73.4	95.9
Min.		21.6	32.8	49.3	70.8	92.1
RSD		2.52%	1.88%	1.26%	1.27%	1.29%

FDA SUGGESTED METHOD IN RESPONSE TO CONTROL #00-250 DATED JUNE 21, 2000

Table 21. Dissolution Data for Loratadine

Product: Loratadine/Pseudoephedrine ER Tablets, 10 mg/240 mg

Lot No.: R99044

Method: USP apparatus 2 (Paddle), 50 rpm

Medium: 900 mL 0. IN HC1 for one hour, then to 0. 1 M phosphate buffer (pH 7.5)

Date Tested	Tablet	Cumulative % dissolved Time (min)					
		5	10	15	30	45	60
8/7/00-	1	(b) (4)					
	2						
	3						
	4						
	5						
	6						
8/8/00-	7						
	8						
	9						
	10						
Mean		40.0	62.7	71.0	77.5	79.2	79.6
SD		3.6	4.2	5.0	5.9	6.1	6.0
Max.		46.1	70.5	791	87.8	89.7	90.2
Min.		33.9.	56.0.	62.3	67.0	68.4	69.2
RSD		8.93%	6.69%	7.01%	7.62%	7.66%	7.50%

Table 22. Dissolution Data for Loratadine

Product: Claritin-D 24 Hour

Lot No.: 9-DCS-2015

Method: USP apparatus 2 (Paddle), 50 rpm

Medium: 900 ml- 0. 1 N HCl for one hour, then to 0. 1 M phosphate buffer (pH 7.5)

Date Tested	Tablet	Cumulative % dissolved Time (min) 5	10	15	30	45	60
8/7/00-	1			(b) (4)			
	2						
	3						
	4						
	5						
	6						
8/8/00-	7						
	8						
	9						
	10						
	11						
	12						
	Mean	48.6	66.3	73.8	80.9	83.2	84.1
	SD	3.0	3.7	4.3	4.7	4.9	4.9
	Max.	53.3	70.8	79.6	88.4	91.4	92.4
	Min.	43.0	57.5	63.6	70.3	72.5	73.4
	RSD	9.24%	5.59%	5.85%.	5.81%	5.86%	5.81%

Table 23.Dissolution Data for Pseudoephedrine Sulfate

Product: Loratadine/Pseudoephedrine ER Tablets, 10 mg/240 mg

Lot No.: R99044

Method: LISP apparatus 2 (Paddle), 50 rpm

Medium: 900 mL 0.1 N HCl for one hour, then to 0.1M phosphate buffer (pH 7.5)

Date Tested	Tablet	Cumulative % dissolved Time (hours) 1	2	4	6	8	10	12	14	16	18
8/7/00	1					(b) (4)					
	2										
	3										
	4										
	5										
	6										
8/8/00	7										

	8	(b) (4)									
	9										
	10										
	11										
	12										
Mean		20.4	30.1	44.5	55.8	64.8	72.3	78.3	83.2	87.1	90.2
SD		0.5	0.7	1.1	1.2	1.4	1.4	1.5	1.5	1.6	1.5.
Max.		21.3	31.5	46.9	58.5	67.8	75.4	81.6	86.71	90.8	93.7
Min.		19.6	29.0,	42.9	54.1	62.9	70.5	76.3	81.2	85.2	88.3
RSD		2.48%	2.29%	2.54	2.18%	2.10%	1.94%	1.93%	1.83%	1.81%	1.66%

Table 24. Dissolution Data for Pseudoephedrine Sulfate

Product: Claritin-D 24 Hour

Lot No.: 9-DCS-2015

Method: USP apparatus 2 (Paddle), 50 rpm

Medium: 900 mL 0. 1 N HCl for one hour, then to 0. 1 M phosphate buffer (pH 7.5)

Date Tested	Tablet	Cumulative % dissolved Time (hours)									
		1	2	4	6	8	10	12	14	16	18
8/7/00	1	(b) (4)									
	2										
	3										
	4										
	5										
	6										
8/8/00	7										
	8										
	9										
	10										
	11										
	12										
Mean		19.8	28.9	42.5	53.0	61.8	69.2	75.5	80.8	85.1	88.4
SD		0.3	0.3	0.5	0.6	0.7	0.8	0.9	0.9	1.0	0.9
Max.		20.3	29.7	43.6	54.4	63.5	71.0	77.4	82.5	86.8	89.9
Min.		19.4	28.6	41.9	52.5	61.2	68.4	74.5	79.6	83.9	87.4
RSD		1.54%	1.12%	1.10%	1.07%	1.14%	1.16%	1.19%	1.14%	1.12%	1.02

Table 25. Dissolution Data for Loratadine

Product: Loratadine/Pseudoephedrine ER Tablets, 10 mg/240 mg

Lot No.: R99044

Method: LISP apparatus 2 (Paddle), 75 rpm

Medium: 900 mL 0. 1 N HCl for one hour, then to 0. 1 M phosphate buffer (pH 7.5)

Date, Tested	Tablet	Cumulative % dissolved Time (min) 5	10	15	30	45	60
8/9/00-	1	(b) (4)					
	2						
	3						
	4						
	5						
	6						
8/10/00	7						
	8						
	9						
	10						
	11						
	12						
Mean		46.9	67.8	74.7	80.3	81.2	82.1
SD		4.4	5.0	4.5	4.7	4.4	4.4
Max.		51.4	74.6	80.9	86.4	88.0	88.1
Min.		37.6	58.4	66.6	71.9	75.0.	74.4
RSD		9.46%	7.40%	6.03%	5.85%	5.40%	5.36%

Table 26. Dissolution Data for Loratadine

Product: Claritin-D 24 Hour

Lot No.: 9-DCS-2015

Method: USP apparatus 2 (Paddle), 75 rpm

Medium:900 ml- 0. 1 N HCl for one hour, then to 0. 1 M phosphate buffer (pH 7.5)

Date Tested	Tablet	Cumulative % dissolved Time (min) 5	10	15	30	45	60
8/9/00	1	(b) (4)					
	2						
	3						
	4						
	5						
	6						
8/10/00-	7						
	8						
	9						
	10						
	11						
	12						
Mean		54.6	72.4	78.9	84.3	85.6	85.6
SD		3.2	4.8	5.8	6.1	6.4	6.6
Max.		61.3	83.8	91.8	96.4	97.3	98.2
Min.		52.2	66.7	70.2	74.4.	75.1	74.9

RSD	5.91%	6.59%	7.33%	7.27%	7.47%	7.76%

Table 27. Dissolution Data for Pseudoephedrine Sulfate

Product: Loratadine/Pseudoephedrine ER Tablets, 10 mg/240 mg

Lot No.: R99044

Method: USP apparatus 2 (Paddle), 75 rpm

Medium: 900 mL 0.1 N HCl for one hour, then to 0.1 M phosphate buffer (pH 7.5)

Date Tested	Tablet	Cumulative % dissolved Time (hours)									
		1	2	4	6	8	10	12	14	16	18
8/9/00	1	(b) (4)									
	2										
	3										
	4										
	5										
	6										
8/10/00	7										
	8										
	9										
	10										
	11										
	12										
Mean		20.9	30.5	44.8	56.1	65.6	73.2	79.4	84.31	88.3	91.3
SD		0.7	0.9.	1.4	1.7	2.0	2.1	2.0	1.91	1.7	1.5
Max.		22.6	32.9	48.7	61.0	71.3	79.2	84.9	89.1	91.9	93.9
Min.		20.2	29.7	43.7	54.6	63.9	71.3	77.4	82.1	86.1	89.0
RSD		3.12%	2.87%	3.04%	3.08%	3.02%	2.91%	2.56%	2.24%	1.88%	1.62%

Table 28. Dissolution Data for Pseudoephedrine Sulfate

Product: Claritin-D 24 Hour

Lot No.: 9-DCS-2015

Method: USP apparatus 2 (Paddle), 75 rpm

Medium: 900 mL 0. 1 N HCl for one hour, then to 0. 1 M phosphate buffer (pH 7.5)

Date Tested	Tablet	Cumulative % dissolved Time (hours)									
		1	2	4	6	8	10	12	14	16	18
8/9/00	1	(b) (4)									
	2										
	3										
	4										
	5										
	6										
8/10/00	7										
	8										
	9										
	10										
	11										
	12										
Mean		20.5	28.6	42.5	53.2	62.2	69.6	75.7	80.5	84.4	87.4
SD		0.5	1.6	2.3	2.8	3.2	3.4	3.3	2.9	2.6	2.2
Max.		21.1	30.2	46.7	58.5	67.9	75.9	81.8	85.1	88.2	90.0
Min.		20.0	25.9	39.5	49.8	57.9	65.4	71.4	76.0	80.2	83.8
RSD		2.25%	5.72%	5.46%	5.20%	5.17%	4.89%	4.41%	3.62%	3.10%	2.56%

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-652 /Reviewer
HFD-652 /Bio Team Leader 12/8/2000
HFD-617/Project Manager 1/02/01
for HFD-650/Dale Conner 12/22/00

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BIOEQUIVALENCY - DEFICIENCIES Submission Date: September 14, 2000

1. **FASTING STUDY** (STF) OK Strengths: 10mg/240 mg
Clinical: Gateway Medical Research
St. Charles, Mo. **Outcome: IC**
Analytical: (b) (4)

2. **FOOD STUDY** (STP) OK Strengths: 10 mg/240 mg
Clinical: Gateway Medical Research
St. Charles, Mo. **Outcome: IC**
Analytical: (b) (4)

3. **MULTIPLE DOSE STUDY** (STM) OK Strengths:
Outcome: NC

Outcome Decisions:
IC - Incomplete

WinBio Comments

Loratadine and pseudoephedrine sulfate
10 mg/240mg ER Tablet
ANDA No. 75989
Reviewer: Andre Jackson
V:\Firmsam\Impax\Ltrs&Rev\75989A.101

Impax Laboratories, Inc.
Hayward, Ca.
Submission Date:
January 22, 2001

Review of an Amendment to the Single Dose Fasting Study, Single Dose Post-Prandial Study

History

The original application was submitted on September 14, 2000 which included a single dose fasting study, a single dose post-prandial study and a multiple dose study. The studies were found to be incomplete since the firm submitted 1 month stability data while the analytical samples were stored for 158 days. The firm has supplied additional stability data in the current submission. The multiple dose study was not reviewed, only summarized, since these studies are not generally requested for the approval of ER products based upon the "Guidance for Industry: BA and BE studies for orally administered products-general considerations".

Deficiency:

1. The study was begun in January, 2000 with sample analysis completed in July 2000. However the firm only supplied stability data for a 1 month storage period (vol 1.2, pgs. 194-196). The firm should supply long term stability data for 158 days to cover the actual storage time for the samples.

Firm's Response:

The firm conducted a long term stability study at -20°C and both loratadine and pseudoephedrine were found to be stable for 160 days.

FDA Reply:

The firm's reply is acceptable.

RECOMMENDATIONS:

1.The fasting bioequivalence study conducted by Impax Pharmaceuticals on its Loratadine/ Pseudoephedrine 10 mg/240 mg ER tablet comparing it to Claritan-D® 10 mg/240 mg 24 hour ER tablet lot # 9-DCS2015 has been found to be acceptable by the Division of Bioequivalence. The post-prandial bioequivalence study conducted by Impax Pharmaceuticals on its Loratadine/Pseudoephedrine 10 mg/240 mg ER tablet comparing it to Claritan-D® 10 mg/240 mg 24 hour ER tablet lot # 9-DCS2015 has been found to be acceptable by the Division of Bioequivalence. Therefore, Impax Pharmaceuticals Loratadine/Pseudoephedrine 10 mg/240 mg ER tablet is deemed bioequivalent to Claritan-D® 10 mg/240 mg 24 hour ER tablet manufactured by Schering Corporation.

2. The dissolution study conducted on the 10mg/240 mg ER tablet has been previously found

to be acceptable.

3.The dissolution testing should be incorporated into the firm's manufacturing and controls programs. The dissolution testing should be conducted in 900 ml of 0.1N HCL for 1 hour, then replace the medium with 900 mL of 0.05M phosphate buffer at pH 6.8 containing 0.01% sodium lauryl sulfate at37^{0}C using USP XXIV apparatus 1 (basket) at 75 rpm. The test product should meet the following interim specifications:

For Loratadine: NLT (b) (4) % of loratadine is dissolved in 30 min

For pseudoephedrine:

	(b) (4)
1 hour	
2 hours	
4 hours	
8 hours	
18 hours	

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG Date: 1/31/2001

Concur: for Dale P. Conner, Pharm.D. Date: 2/6/2001
Director,
Division of Bioequivalence

cc: ANDA 75989 (original, duplicate), HFD-650(Director), HFD-652 (Huang, Jackson), Drug File, Division File.

CC: ANDA: 75989
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Reviewer

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Printed in final on / /

Endorsements: (Final with Dates)
HFD-652/ Reviewer
HFD-652/ Bio team Leader
HFD-650/ D. Conner

BIOEQUIVALENCY - ACCEPTABLE

submission date: January 22, 2001

1. **STUDY AMENDMENT** (STA)

Strengths: 10mg/240 mg ER tablet
Outcome: AC

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75989 SPONSOR : Impax Laboratories, Inc.

DRUG AND DOSAGE FORM : Loratadine and pseudoephedrine sulfate ER Tablets

STRENGTH(S) : 10 mg/240mg ER Tablet

TYPES OF STUDIES : Single Dose, Food Study, Multiple Dose Study

CLINICAL STUDY SITE(S): Gateway Medical Research, Inc.
St. Charles, Mo.

ANALYTICAL SITE(S) : (b) (4)

STUDY SUMMARY : See Review

DISSOLUTION : See Submission

DSI INSPECTION STATUS

Inspection needed: ~~YES~~ NO	Inspection status:	Inspection results:
First Generic _____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : [signature] DATE : 1/31/2001

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : [signature] DATE : 1/31/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

for INITIAL : [signature] DATE : 2/6/2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-989

PHARMACOLOGY TOXICOLOGY REVIEW

A 1.1

HFD-570: DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Consult for Office of Generic Drugs

ANDA No.: 75-989 **Date of Consult:** 29 OCT 1999

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 12 JAN 2001

Information to be Conveyed to Sponsor: Yes ( ), No (✓)

Sponsor: Impax Laboratories, Inc.

Drug Name: Loratadine / Pseudoephedrine Sulfate Extended Release Tablets (10 mg/240 mg)

Chemical names: Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate
α-[1-(methyl-amino)ethyl]-[S-(R*,R*)]-benzeneMeOH sulfate(2:1) (salt)

Drug Class: Antihistamine/Decongestant

Proposed Clinical Dose: Daily doses of 10 mg loratadine and 240 mg pseudoephedrine.

Clinical formulation:

Ingredient	mg/tablet
Loratadine	(b) (4)
Pseudoephedrine	
Hydroxypropyl methylcellulose	
Hydrogenated vegetable oil	
Polyethylene oxide NF	
Colloidal silicon dioxide NF	
Polyethylene glycol, NF	
Titanium dioxide	
Magnesium stearate	
Total	**809.42**

Rec'd HFD-102
1/25/01
L Rupper

Review:
Harvey Greenberg of the Office of Generic Drugs (HFD-615) requested a safety assessment of the inactive ingredient polyethylene oxide NF ((b) (4) , MW of (b) (4)). Polyethylene oxide is a water soluble resin and a member of a family of polymers with the general formula $(CH_2CHO)_x$. This family of polymers is used in oral drug products, medical devices, and hydrogels used in wound-care applications. The sponsor for the ANDA, Impax Laboratories Inc., proposed use of this inactive ingredient at a level of (b) (4) mg/tablet. The highest amount of this inactive ingredient that is currently approved is ~ 277 mg/tablet (NDA (b) (4) tablet).

Polyethylene oxide NF (b) (4) is supplied to the sponsor by (b) (4) under the proprietary name, (b) (4) and the material meets all compendial requirements of the National Formulary (NF 19). The sponsor provided a Material Safety Data Sheet (MSDS) for polyethylene oxide, NF, a letter from (b) (4) authorizing right of reference to the Drug Master File # (b) (4) for polyethylene oxide, and an independent safety review for a tablet formulation (b) (4) mg polyethylene oxide by Dr. (b) (6) of (b) (4) .

Polyethylene oxides are not highly absorbed *in vivo* as demonstrated by oral administration studies of radio-labeled (b) (4) in which minimal label was detected in urine or expired CO_2, but over 90% was detected in feces.

Oral toxicity studies performed in rats and dogs with polyethylene oxide polymers ranging from a molecular weight of (b) (4) to (b) (4) and for durations ranging from a single dose to 2 years suggest a low level of toxicity. For the purposes of qualifying the proposed level of (b) (4) in the current application, 2 year dietary studies in rats and dogs are the most relevant. In rats, (b) (4) was administered and a NOAEL dose of 5% in the diet was identified. Assuming food consumption of 10-15 g/day (0.5-0.75 g/day (b) (4)) and a body weight of 200-250 g, the NOAEL dose would be equivalent to 2,000 to 3,750 mg/kg. In dogs, (b) (4) was administered and a NOAEL dose of 2% in the diet was identified. Assuming food consumption of 250 g/day (5 g/day (b) (4)) and a body weight of 10 kg, the NOAEL dose would be equivalent to 500 mg/kg. The assumed values for food consumption and body weight were obtained from the NIOSH 1980 Registry of Toxic Effects of Chemical Substances.

The proposed level of the inactive ingredient polyethylene oxide NF (b) (4) is (b) (4) mg/day. This daily dose is equivalent to (b) (4) mg/kg in a 50 kg individual. When comparing the maximum expected human daily dose with the NOAEL doses in the 2 year studies in rats and dogs, the preclinical studies provide safety factors of 230-430 and 57, respectively. Although these preclinical studies were performed with polyethylene oxide (b) (4) (MW (b) (4)), comparable results were obtained with polymers of molecular weight as low as (b) (4) . It is, therefore, reasonable to conclude that the use of polymer (b) (4) (MW (b) (4)) would not significantly increase the toxicity potential.

The proposed level of polyethylene oxide NF (b) (4) is acceptable since the toxicity data base does not indicate an increase in risk in comparison to that at the approved level of 277 mg/tablet.

RECOMMENDATION:

The proposed level of polyethylene oxide ((b) (4)mg/tablet) for use in the extended release tablet of loratadine and pseudoephedrine sulfate is acceptable.

Timothy J. McGovern 1/12/2001
Timothy J. McGovern, Ph.D., Pharmacologist

Chy Lo Joyce Sun Jan. 12, 2001

CC:

HFD-102/L. Hukle
HFD-570/C.J. Sun
HFD-570/T.J. McGovern

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-989

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

September 14, 2000

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

505(j)(2)(A) OK!
08-NOV-2000

Re: ANDA for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg

Dear Mr. Buehler:

In accordance with Section 505 (j) of the Federal Food, Drug and Cosmetic Act, IMPAX Laboratories, Inc hereby submits an Abbreviated New Drug Application (ANDA) for loratadine and pseudoephedrine sulfate extended release tablets, 10 mg/240 mg. The reference listed drug, Claritin-D® 24 Hour (loratadine and pseudoephedrine sulfate, USP) Extended Release Tablets, is the subject of Schering Corporation's approved NDA 20-470. The drug product, which is the subject of this ANDA, differs from the listed product in that the formulation contains different excipients.

The concentration of one of the inactive ingredients, polyethylene oxide, NF (b) (4), exceeds the limit listed in the Inactive Ingredient Guide. The justification for the use of polyethylene oxide, NF, at the proposed concentration is included in Section VII of this ANDA.

This application meets the criteria for an ANDA in that 1) the conditions of use, active ingredient, route of administration, dosage form, and strength are identical to those of the listed drug, 2) bioequivalence has been demonstrated, and 3) patent certification is provided. The labeling complies with all labeling requirements. This application lists IMPAX Laboratories, Inc. as the manufacturing site for the drug product. The submission contains 21 volumes, organized and jacketed in accordance with FDA-OGD guidelines.

Also included with this ANDA is an electronic submission of the package insert word processor file, prepared in Microsoft Word. Two (2) write-protected diskettes are included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission. Four (4) copies of the draft labels and labeling are included in both the archival and review copies of the application.

Two (2) write-protected diskettes containing the pharmacokinetic data resulting from the bioequivalence studies are also included in the archival copy of this submission in a plastic insert.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 18 2000
OGD

Should you have any additional questions regarding this ANDA, please contact me by telephone (510-471-3600; ext 305) or by telefax (510-471-3200).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

Revised 12/99

ANDA CHECKLIST FOR COMPLETENESS and ACCEPTABILITY of the APPLICATION

ANDA# 75989 FIRM NAME Impax

RELATED APPLICATION(S) N/A

DRUG NAME: Loratadine and Pseudoephedrine sulfate

DOSAGE FORM: Extended release Tablets 10 mg/240 mg

FIRST GENERIC? N/A

Electronic Submission (Chem) ✓ E-mail notification sent ✓

Team Leader Dave Giel

Labeling Reviewer Catterson DDC

Random Assignment RN 4

Micro Reviewer N/A

Pharmacodynamic study (Dr. Fanning) N/A

Letter Date 9/14/2000 Received Date 9/18/2000

		YES	NO
	Comments EC 1 ✓ On Cards ✓ Therapeutic Code 6010503 antihistamine/Decongestant	✓	
	Methods Validation Package (3 copies) yes (Required for Non-USP drugs)	✓	
	Archival, and Review copies Field copy certification (original signature)	✓	
	Cover Letter	✓	
	Table of Contents	✓	

9/18

Sec. I	**Signed and Completed Application Form (356h)** (Statement regarding Rx/OTC Status) revised 356h	✓	
Sec. II	**Basis for Submission** RLD Claritin-D 24 Hour Firm Schering Is an ANDA suitability petition required?____ If yes, consult needed for pediatric study requirement.	✓	
Sec. III	**Patent Certification** U-77 6/19/2002; 12/19 2000 PED U-77 4/21/2004 U-142; 10/21/2004 PED U-142; 9/15/2008; 3/15/2009 PED; 1. Paragraph? IV 2. Expiration of Patent 4/23/2013 A. Pediatric Exclusivity Submitted?____ B. Pediatric Exclusivity Tracking System checked?____ 4/23/2013; 4/23/2013 PED	✓	
	Exclusivity Statement	✓	
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** 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 ✓	✓	
Sec. VI	**Bioavailability/Bioequivalence** Vol 1.21 p005265 1. Financial certification (Form FDA 3454) ✓ and Disclosure statement (Form 3455)____ (for BE studies only!) 2. In Vivo Study Protocol(s) ✓ 3. In Vivo Study(ies) ✓ 4. Computer Disk Submitted (2) 1.1 blue 5. Request for Waiver of In Vivo Study(ies) N/A 6. In Vitro Dissolution Data ✓ Vol 1.20 7. Formulation Data Same? (Comparison of all Strengths) ✓ (Ophthalmics, Otics, Externals, Parenterals) 8. Paragraph IV bio study acceptable for filing ✓ 9. Lot numbers of products used in Bio-study ✓ 10. DSI inspection request needed? ~~____~~ ~~1st Generic____ 1st study for site____ Other____~~ ~~E-mail notification to bio PMs sent____~~	✓	

(b) (4) Lot # R99044 (b) (4)

Test: (b) (4)

1000

Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation 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. Certificate(s) of analysis specifications and test results from drug substance manufacturer(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' certificates of analysis (specifications and test results)_____ d. Applicant certificate of analysis_____ Bead # (b) (4) Lot # (b) (4)		
Sec. IX	**Description of Manufacturing Facility** 1. Full Address(es) of the Facility(ies) for the Manufacturing Process, Testing, and Stability Testing_____ 2. CGMP Certification_____ 3. CFN numbers_____		
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address_____ 2. Functions_____ 3. CGMP Certification/GLP_____ 4. CFN numbers_____ 1 CTL (b) (4)		
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_____ 3. If sterile product: Aseptic fill_____ / Terminal sterilization_____ 4. Filter validation (if aseptic fill)_____ 5. Reprocessing Statement		

1 1 Prod

(b) (4)

Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record (Antibiotics/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation ✓ 2. In-process Controls a. Sampling plans and test procedures ✓ b. Specifications and data ✓	✓	
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 supplier's address ✓	✓	
Sec. XIV	**Controls for the Finished Dosage Form** 1. Sampling Plans and Test Procedures ✓ 2. Testing Specifications and Data ✓ 3. 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**	✓	

Lot # R99044 Tab

(b) (4)

(b) (4)

(b) (4)

(b) (4)

1000's =

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) ✓ ✓ 3. List of Convictions statement (original signature) _____	✓	

Reviewing CSO/CST Lacas Patel Date 10/27/00

Recommendation: FILE REFUSE to FILE

Supervisory Concurrence/Date _____

Duplicate copy sent to bio:
(Hold if RF and send when acceptable)

Duplicate copy to HFD _____ for consult

H. Greenberg will send packet out to Pharm. Tox. 11/8

Type of consult:

Comments regarding the ANDA:

① (✓) Safety data for (Polyethylene oxide) Sec. VII. ✓ ok

② 356h → Resubmit b/c not Rx/OTC checked of. ✓ ok

③ Revise patent + exclus. statement. ✓ ok

④ C+C section. Revise section to include [redacted] (b) (4)
ok - only use is for print on tablet. ~ include (amount/tab) + (quantative C+C) ✓ ok

⑤ ✓ [redacted] (b) (4) → included in CTL section but did not provide cGMP or Function of lab. Do not need b/c involved c bio-study. (ok)

⑥ Ask - ? DMF + Studies for Polyethylene oxide. Are the studies included in DMF + can Impax provide contracted study performed by [redacted] (b) (6) Ph.D.

ok - Mark Shaw (Impax) stated that complete study is included in the DMF.

Revised 3/99 - x:\wpfile\nasser\chklst
Revised 12/99 - v:\division\regsupp\chklst

Telecon Record

Date: 10/30/00

ANDA: 75-989

Firm: Impax Pharmaceuticals, Inc.

Drug: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10mg/240mg

FDA Participants: Paras Patel

Industry Participants: Mark Shaw

Phone: 510-429-5883

Agenda:

1. **Paras requested the following:**

   Revision of the patent certification and exclusivity statement.
   Revision of Form 356h to include Rx/OTC designation.

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

October 30, 2000

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

TELEPHONE AMENDMENT
Via FAX: (301) 594-1174
Hardcopy to Follow Separately

NEW CORRESP
NC

Attn: Paras Patel (Regulatory Support Branch)

Re: ANDA 75-989 (Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg)

Dear Mr. Buehler:

This correspondence follows a October 30, 2000 telephone conversation with Mr. Paras Patel of your office concerning the above-referenced ANDA. Mr. Patel requested that IMPAX Laboratories, Inc. (IMPAX) submit additional information to complete the acceptance for filing review of this application.

The following information accompanies this letter:

1. The 356h has been corrected to reflect the prescription status of the proposed product.

2. The patent expiration dates have been corrected to reflect the 6 months pediatric exclusivity. In addition, the Market Exclusivity statement has been revised as suggested.

If you have any questions regarding this amendment please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV - 1 2000
OGD

ANDA 75-989

Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

NOV 8 2000

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated October 30, 2000 and to your correspondence dated October 30, 2000.

NAME OF DRUG: Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg

DATE OF APPLICATION: September 14, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 18, 2000

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Nasser Mahmud, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Ruby Yu
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

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

cc: ANDA 75-989
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/Hgreenberg, Acting Chief, RSB _____ date 08-NOV-2000
HFD-615/PPatel, CSO _____ date 11/1/00
Word File V:\Firmsam\Impax\ltrs&rev\75989.PIV
FT/ PMP/11/1/00
ANDA Acknowledgment Letter!

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

November 27, 2000

PATENT AMENDMENT

NEW CORRESP
NC

Emily Thomas
12/4/00
NAI

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

Re: ANDA 75-989 (Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg)
Documentation of Paragraph IV Patent Notification and Receipt of Notice

Dear Mr. Buehler:

In accordance with 21 CFR 314.95(b), IMPAX Laboratories, Inc. (IMPAX) hereby certifies that it has provided a Notice of Legal and Factual Basis of Non-Infringement for the above-referenced ANDA to the following party and that the Notice met the content requirements specified in 21 CFR 314.95(c):

Legal Department
Schering Corporation (as NDA Holder and Patent Owner)
2000 Galloping Hill Road
Kenilworth, NJ 07033
FEDEX tracking number: 8204-8252-1496

As required by 21 CFR 314.95(e), IMPAX is amending this application to provide documentation of receipt of the Notice of Legal and Factual Basis of Non-Infringement by the above-listed party. A copy of the FEDEX tracking report documenting the delivery of the Notice accompanies this correspondence.

The Notice and documentation of receipt was provided using FEDEX. The acceptability of this form of documentation was agreed to in an October 13, 2000 telephone conversation between the undersigned and Lt. Greg Davis (Regulatory Support Branch), following an October 2, 2000 FAX to the Regulatory Support Branch requesting approval to use FEDEX for Notice delivery.

If you have any questions regarding this amendment please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 28 2000
OGD

Enclosure

1

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION
TO *(Division/Office)* Leah Ripper ,ODE II,HFD-102 Forward: Division of Pulmonary Drug Products, HFD-570 for a harm Tox review	FROM: Office of Generic Drugs(OGD)/RSB HFD-615

DATE:	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 21, 2000		~~75-989~~	Original application	September 18, 2000

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg /240 mg	Medium	Antihistamine/Decongestant	January 21, 2001

NAME OF FIRM Impax Laboratories , Inc

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- X SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICPENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END QF PHASE II MEETING CONTROLLED STUDI ES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III.BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ PROTOCOL-- BIOPHARMACEUTICS
- ☐ IN--VIVO WAIVER REQUEST
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES

IV.DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

x☐ CLINICAL ☐ PRECLINICAL

COMMENTS
The firm is using an inactive ingredient, Polyethylene oxide NF (b) (4) in amount more than what has been approved in a drug product. The highest amount used in a n approved product is (b) (4) mg per tablet, while the firm is proposing to use (b) (4) ng per tablet. The firm has provided some information to support the use of polyethylene oxide (b) (4) at their proposed level. Please review and comment. Please provide an electronic transfer or e-mail of the completed review.

(b) (4) mg/kg

Please return completed to review:

Harvey Greenberg

HFD-615

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)*
Harvey Greenberg	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

RECEIVED
NOV 27 2000
OFFICE OF DRUG EVALUATION II

#2799

COVINGTON & BURLING

1201 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004-2401
TEL 202.662.6000
FAX 202.662.6291
WWW.COV.COM

WASHINGTON, DC
NEW YORK
LONDON
BRUSSELS
SAN FRANCISCO

MICHAEL S. LABSON
TEL 202.662.5220
FAX 202.778.5220
MLABSON@COV.COM

January 2, 2001

BY HAND DELIVERY

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 02 2001
OGD

NC

Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

Re: ANDA No. 75-989
Notice of Filing of Legal Action for Patent Infringement

Ladies and Gentlemen:

Pursuant to 21 C.F.R. § 314.107(f)(2), Schering Corporation ("Schering") hereby notifies FDA that it has filed a legal action for patent infringement within 45 days of receiving notice of a Paragraph IV Certification in connection with the above-referenced abbreviated new drug application ("ANDA"). Schering states as follows:

(i) The ANDA number is 75-989;

(ii) The name of the ANDA applicant is Impax Laboratories, Inc.;

(iii) The established name of the drug is loratadine and pseudoephedrine sulfate extended-release tablets, the strength is 10 mg of loratadine and 240 mg of pseudoephedrine sulfate, and the dosage form is extended-release tablets; and

(iv) Schering hereby certifies that an action for patent infringement was filed in an appropriate court (the United States District Court for the District of New Jersey) on January 2, 2001. Schering will provide the identification number for this action, and a copy of the Complaint, as soon as they are available from the Court.

Schering received notice of a Paragraph IV Certification alleging the noninfringement, invalidity and/or unenforceability of United States Patent Nos. 4,659,716, 4,863,931 and 5,314,697 on November 20, 2000. Schering is the owner of these patents.

Schering brought the above-described action for patent infringement within 45 days of the receipt of notice of the Paragraph IV Certification.

Accordingly, pursuant to Section 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act, ANDA No. 75-989 cannot be approved until the expiration of the thirty-month period beginning on November 20, 2000 and ending on May 20, 2003, or until such time as ordered by the Court.

Thank you for your attention to this matter.

Sincerely yours,

Michael S. Labson

Counsel for Schering Corporation

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

January 12, 2001

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

PATENT AMENDMENT

1/22/01

NEW CORRESP

Re: ANDA 75-989 (Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg)
Documentation of Litigation/Settlement Outcome

Dear Mr. Buehler:

Reference is made to the Office of Generic Drug's November 8, 2000 letter documenting the acceptance for filing of the above-referenced ANDA. The letter requested that IMPAX notify your office in the event that litigation occurred within the 45-day period following notification of the NDA Holder and Patent Owner.

IMPAX hereby confirms that Schering Corporation initiated a lawsuit within the 45-day period as provided for in section 505(j) (4)(B)(iii) of the Act. Accordingly, IMPAX is enclosing with this correspondence a copy of the complaint, filed January 2, 2001 in the United States District Court for the District of New Jersey.

If you have any questions regarding this amendment please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

Enclosure (Civil Action No. 01-CV0009)

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 17 2001
OGD

BIOEQUIVALENCY AMENDMENT

ANDA 75-989

JAN 19 2001

received
Mail 01/19/01

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)

Center for Drug Evaluation and Research
FDA

TO: APPLICANT: IMPAX Laboratories, Inc. TEL: 510-429-5883

ATTN: Mark C. Shaw FAX: 510-429-5886

FROM: Krista M. Scardina, Pharm.D. PROJECT MANAGER: 301-827-5847

Dear Mr. Shaw:

This facsimile is in reference to the bioequivalency data submitted on September 14, 2000, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 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 direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

(15)

JAN 19 2001

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-989 APPLICANT: Impax Laboratories, Inc.

DRUG PRODUCT: Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

1. Your study was begun in January 2000, with sample analysis completed in July 2000. However you only supplied stability data for a 1 month storage period (vol 1.2, pgs. 194-196). You should supply long term stability data for 158 days to cover the actual storage time for the samples.

Sincerely yours,

Barbara Myers Davit

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

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

January 22, 2001

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

BIOEQUIVALENCY AMENDMENT

NDA ORIG AMENDMENT
N/AB

Attn: Krista Scardina, Pharm.D.

Re: ANDA 75-989 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 mg)
Long-Term Stability in Frozen Plasma

Dear Mr. Buehler:

This correspondence follows a January 19, 2001 facsimile from Ms. Krista Scardina of the Division of Bioequivalence for data supporting the long-term stability of loratadine and pseudoephedrine sulfate in frozen human plasma.

The original ANDA submission included long-term data supporting the stability of loratadine and pseudoephedrine sulfate in frozen human plasma for at least one month. Provided in this submission are supplemental data extending the long-term stability to at least 5 and 3/4 months.

If you have any questions regarding this amendment please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Michele Anderson for

Mark C. Shaw
Director, Regulatory Affairs and Compliance

Enclosure

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JAN 22 2001
OGD

COVINGTON & BURLING

1201 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004-2401
TEL 202.662.6000
FAX 202.662.6291
WWW.COV.COM

WASHINGTON, DC
NEW YORK
LONDON
BRUSSELS
SAN FRANCISCO

MICHAEL S. LABSON
TEL 202.662.5220
FAX 202.778.5220
MLABSON@COV.COM

March 1, 2001

Emily Thomas
NDE
3/7/01

BY HAND DELIVERY

Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

NEW CORRESP
NC

Re: ANDA No. 75-989
Supplemental Information Regarding Filing of Legal Action for Patent Infringement

Ladies and Gentlemen:

Reference is made to Schering Corporation's letter of January 2, 2001, which notified FDA that the company had filed a legal action for patent infringement within 45 days of receiving notice of a paragraph IV certification in connection with the above-referenced abbreviated new drug application ("ANDA"). This letter supplements the January 2, 2001 letter and provides additional information, which was unavailable at that time.

The patent infringement action that Schering filed following receipt of a paragraph IV certification for ANDA 75-989 has been assigned Civil Action No. 01-0009 (JAG) by the United States District Court for the District of New Jersey. Copies of the Summons and Complaint in that action are enclosed.

As stated in Schering's January 2, 2001 letter, Schering received notice of a paragraph IV certification for ANDA No. 75-989 on November 20, 2000, brought an action for patent infringement within 45 days of the receipt of the paragraph IV certification, and provided timely notice to FDA of the action. Accordingly, pursuant to Section 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act, ANDA No. 75-989 cannot be approved until the

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expiration of the thirty-month period beginning on November 20, 2000 and ending on May 20, 2003, or until such time as ordered by the Court.

Thank you for your attention to this matter.

Sincerely yours,

Michael S. Labson

Counsel for Schering Corporation

Enclosures

21

IMPAX
Laboratories, Inc.
1780 Whipple Road, Suite 106
Union Union City, CA 94587-1954
Tel. (510) 429-5883 Fax (510) 429-5886

NEW CORRESP

FACSIMILE COVER SHEET

TO: Krista Scardina / Ruby Yu, OGD, FDA DATE: May 13, 2001

FAX NUMBER: 1-301-594-0183

TOTAL NUMBER OF PAGES (INCLUDING THIS COVER SHEET): 3

FROM: Mark C. Shaw PHONE NUMBER: 510-429-5883
Director, Regulatory Affairs and Compliance

Dear Krista:

Thank you for following up on the question I left with Ruby Yu concerning ANDA 75-989. My questions are as follows:

OGD's March 20, 2001 Minor Amendment deficiencies letter included an acknowledgement of IMPAX's proposed in-vitro dissolution test and specifications. An excerpt from that letter accompanies this FAX.

IMPAX has two questions:

1) For loratadine, does (b) (4)

   We wish to confirm whether the reviewer is using USP terminology when acknowledging our proposed in-vitro dissolution specifications.

2) We note in the OGD correspondence that the loratadine sampling timepoint is specified as 30 minutes; however, the media does not change until 60 minutes. IMPAX originally proposed a loratadine specification of NLT (b) (4) %(Q) at 60 minutes. We wish to confirm whether the reference to 30 minutes may be a typographical error since the Division of BE comment appears to acknowledge the dissolution conditions and specifications originally proposed by IMPAX. Please clarify.

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

ANDA: 75-989 APPLICANT: Impax Laboratories, Inc.

DRUG PRODUCT: Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 mg

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

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 ml of 0.1N HCL for 1 hour, then replace the medium with 900 mL of 0.05M phosphate buffer at pH 6.8 containing 0.01% sodium lauryl sulfate at37°C using USP XXIV apparatus 1 (basket) at 75 rpm. The test product should meet the following interim specifications:

For Loratadine: NLT (b) (4) % of loratadine is dissolved in 30 min

For pseudoephedrine:

1 hour	(b) (4)
2 hours	
4 hours	
8 hours	
18 hours	

MLS 05/13/01

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

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

21

TELEPHONE MEMO

TO: Mark C. Shaw
IMPAX Laboratories
510-429-5883

REF# ANDA 75-989

FROM: Krista M. Scardina
Dr. Nhan Tran

DATE: 16 May 2001

SUBJECT: Loratadine/Pseudoephedrine Sulfate ER Tablets

REQUESTED BY: IMPAX Laboratories

The firm faxed a letter to OGD regarding the clarification of the dissolution requirements for Loratadine/Pseudoephedrine Sulfate ER Tablets. The firm's first question was the interpretation of the Q value and its relation to the NLT value. Dr. Tran referred the firm to USP 24, the general chapter on dissolution, p. 1943 that clearly defines Q as the NLT value. Therefore in this particular case, the DBE set the Q value for the loratadine component as (b)(4)% in 30 minutes. For stage one as defined in the acceptance table in the USP, the firm will have to meet Q (b)(4)% for all 6 tablets. The second question asked about the proposed dissolution method in regards to the change in media. The reference to (b)(4)% in 30 minutes is not a typographical error. The (b)(4)% in 30 minutes is for the loratadine component. The loratadine component (immediate release) is measured at 30 minutes, then after on hour, the tablet is placed in a phosphate buffer medium and the pseudoephedrine CR component is measured.

5/17/01

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

July 17, 2001

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

MINOR AMENDMENT

ORIG AMENDMENT
N (Am

Re: ANDA 75-989 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 mg)
Attn: Ruby Yu

Dear Mr. Buehler:

This letter responds to your March 20, 2001, facsimile, listing deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter.

Each deficiency is listed in boldface type followed by IMPAX's response. As required to complete each response, additional data are provided as attachments in this submission. In addition to responding to the Chemistry and Bioequivalence comments, IMPAX also acknowledges the following:

1. IMPAX notes that the labeling portion of the application is under review, and that any deficiencies will be conveyed under separate cover.

2. IMPAX acknowledges that method validation will be performed on the drug product by the FDA field laboratory.

3. We note that the DMFs referenced in ANDA 75-989 must be satisfactory at the time of approval of our ANDA, and that some of the DMF holders may require an inspection by the Division of Manufacturing and Product Quality.

4. IMPAX commits to updating specifications for all inactive compendial ingredients to meet current requirements established in the USP/NF.

5. This submission also includes updated long-term stability data for biobatch lot R99044, provided in **Attachment 8**.

6. IMPAX notes that a satisfactory compliance evaluation of the firms referenced in the ANDA is required for approval.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 9**.

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7/23/01

Should you have any additional questions regarding this response, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

cc: Marshalette Edwards, SFDO

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

August 13, 2001

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

AMENDMENT

ORIG AMENDMENT
N/Am

Attn: Ruby Yu, Project Manager

Re: ANDA 75-989 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 mg)

Dear Mr. Buehler:

Reference is made to IMPAX's July 17, 2001 FAX Amendment to the above-referenced ANDA.

The July 17, 2001 amendment included a revised loratadine drug substance specification, included as Attachment 3, beginning on page 19. During preparation of a related submission that included this same specification as an attachment, IMPAX subsequently decided to (b) (4) the total impurities specification, from (b) (4). A copy of the revised specification is provided in **Attachment 1**.

In addition to the specification listed above, IMPAX is also submitting a current version of the loratadine drug substance test method, 067-4. The chemical names of the known impurities have been added to Section 3 of analytical method 067. In addition, the method has been revised to use the (b) (4). The revised method and associated validation report are provided in **Attachment 2**.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 3**.

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Should you have any additional questions regarding this amendment, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

cc: Marshalette Edwards, SFDO

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

August 16, 2001

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

LABELING AMENDMENT

ORIG AMENDMENT
N/AF

Re: ANDA 75-989: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg

Attn: Lillie Golson, Labeling Review Branch

Dear Mr. Buehler:

This letter responds to your August 7, 2001, facsimile, listing revisions to the IMPAX Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240mg container labels and insert. A copy of your correspondence accompanies this letter.

A side-by-side comparison of the labeling changes and four (4) copies of the draft labels and labeling are included in both the archival and review copies of the amendment. Also included with this amendment is an electronic submission of the package insert word processor file, prepared in Microsoft Word. Two (2) write-protected diskettes are included in the archival copy of the submission in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

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IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

October 8, 2001

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

MINOR AMENDMENT

N\AM

ORIG AMENDMENT

Attn: Ruby Yu, Project Manager

Re: ANDA 75-989 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 mg)

Dear Mr. Buehler:

This letter responds to your August 27, 2001, Fax Amendment, listing deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter. Please note that this amendment has been redesignated a "Minor Amendment", as required by current OGD policies.

Each deficiency is listed in boldface type followed by IMPAX's response. As required to complete each response, additional data are provided as attachments in this submission. In addition to responding to the Chemistry comments, IMPAX also acknowledges the following:

1. IMPAX notes that FDA received our Labeling Amendment dated August 23, 2001, responding to FDA's August 8, 2001 labeling comments.

2. This submission also includes updated long-term stability data for biobatch lot R99044, provided in **Attachment 6**.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 7**.

Should you have any questions regarding this response, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

OFFICE OF GENERIC DRUG
OCT 10 2001
OGD
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cc: Marshalette Edwards, SFDO

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

November 28, 2001

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

AMENDMENT

ORIG AMENDMENT
N/A

Attn: Ruby Wu, Project Manager

Re: ANDA 75-989 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 mg)

Dear Mr. Buehler:

This amendment includes an updated loratadine drug substance specification, updated loratadine drug substance method, and updated method validation report. During preparation of a related submission that included this same specification as an attachment, IMPAX (b) (4) the limits for known impurities I, II and III, from (b) (4) (b) (4). The limit for total impurities remains set at (b) (4)%. The revised specification is provided in **Attachment 1.** Included in **Attachment 2** is an updated analytical method and validation report, revised to include linearity and recovery data generated to incorporate the new lower specifications.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 3**.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

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NOV 30 2001

cc: Marshalette Edwards, SFDO

4.1

RECORD OF TELEPHONE CONVERSATION

Reference is made to the fax dated December 11, 2001. The firm requested a t-con to discuss their Loratadine applications.

OGD Response:

The use of the validated titration method for Assay of loratadine is acceptable. The firm will submit the validation report to all ANDAs, if they have not done so already.

Please (b) (4) the limit of the loratadine assay specification to (b) (4).

For all 3 ANDAs, a limit of (b) (4) % for total impurities for the drug substance and drug product release and stability is acceptable.

The proposed specs for the individual impurities mentioned on the fax are also acceptable.

The firm will provide revised specifications.

The firm will also determine the status of the labeling amendment for ANDA 76-011.

DATE
December 17, 2001

ANDA NUMBER
75-989
76-050
76-011

IND NUMBER

TELECON

INITIATED BY: Firm

PRODUCT NAME
Loratadine Applications

FIRM NAME
Impax

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Mark Shaw & Michelle Anderson

TELEPHONE NUMBER
510-429-5883

SIGNATURE
John Franolic, Acting TL JF 12/18/01
Upinder Atwal UA 12/18/01
Neeru Takiar NT 12/18
Ruby Wu RW 12/18/01

V:\FIRMSAM\IMPAX\TELECONS\75989.76050.76011.tc.121701.doc

CC: T-Con Binder Log
ANDA 75-989
76-050
76-011

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

December 27, 2001

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

FAX AMENDMENT

N|FA

ORIG AMENDMENT

Attn: Ruby Wu, Project Manager

Re: ANDA 75-989 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 mg)

Dear Mr. Buehler:

This letter responds to your November 29, 2001, Fax Amendment, listing deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter.

Each deficiency is listed in boldface type followed by IMPAX's response. As required to complete each response, additional data are provided as attachments in this submission. In addition to responding to the Chemistry comments, IMPAX also acknowledges the following:

1. Reference is made to a teleconference held on December 17, 2001, between Mark Shaw and Michele Anderson of IMPAX, and Ruby Wu, John Franolic, Upinder Atwal and Neeru Takiar of OGD. The commitments contained in this response reflect the agreements reached during the December 17 telecon.

2. IMPAX notes that analytical methods validation is required, since this drug product is not covered by an official monograph in the USP. Samples for the methods validation were shipped to FDA's Northeast Regional Laboratory on December 3, 2001, following a November 16, 2001 FDA request.

3. IMPAX notes that labeling comments, if any, will follow under separate cover.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 8**.

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Should you have any questions regarding this response, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

cc: Marshalette Edwards, SFDO

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

February 27, 2002

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

MINOR AMENDMENT

ORIG AMENDMENT
N/AM

Attn: Ruby Wu, Project Manager

Re: ANDA 75-989 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 mg)

Dear Mr. Buehler:

This letter responds to your February 4, 2002, Minor Amendment, listing deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter.

In addition to responding to the Chemistry comments, IMPAX also acknowledges the following:

1. IMPAX notes that analytical methods validation is required, since this drug product is not covered by an official monograph in the USP. Samples for the methods validation were shipped to FDA's Northeast Regional Laboratory on December 3, 2001, following a November 16, 2001 FDA request.

2. Updated controlled room temperature stability data through 104 weeks are provided in **Attachment 1**.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 2**.

Should you have any questions regarding this response, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Sr. Director, Regulatory Affairs and Compliance

cc: Marshalette Edwards, SFDO

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OGD APPROVAL ROUTING SUMMARY

ANDA # 75-989 Applicant Impax Laboratories
Drug Loratadine and Pseudoephedrine Sulfate ER Tablets Strength 10mg / 240 mg

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

REVIEWER:

1. Project Manager Ruby Wu Team 4 — DRAFT RECEIPT Date 4/22/02 Initials RW — FINAL ACTION Date 4/23/02 Initials RW
   Review Support Br
   Application Summary:
   Original Rec'd date 9/18/00
   Date Acceptable for Filing 9/18/00 J
   Patent Certification (type) III and IV
   Date Patent/Exclus.expires
   Citizens Petition/Legal Case Yes ☐ No ☒
   (If YES, attach email from PM to CP coord)
   First Generic Yes ☒ No ☐
   (If YES, check PETS)
   Pediatric Exclusivity Tracking PETS)
   Date checked 4/24/02 NDA# 20641
   Nothing Submitted ☐ DSG
   Written request issued ☐ Loratadine
   Study Submitted ☒

   EER Status Pending ☐ Acceptable ☒ OAI ☐
   Date of EER Status 3/8/01
   Date of Office Bio Review 12/22/00 · 2/6/01
   Date of Labeling Approv. Sum 1/7/02
   Date of Sterility Assur. App. N/A
   Methods Val. Samples Pending Yes ☐ No ☒
   30 Day Clock Start This is a TA End
   Commitment Rcd. from Firm Yes ☑ No ☐
   Modified-release dosage form: Yes ☒ No ☐
   Interim Dissol. Specs in AP Ltr: Yes ☐ This is TA

   III: 233 12/9/02
   IV: 716 10/21/04
   931 3/15/09
   697 4/23/13

   Previously reviewed and tentatively approved ☐ Date
   Previously reviewed and CGMP def./N/A Minor issued ☐ Date
   Comments:

2. Div. Dir./Deputy Dir. — Date 4/23 Initials DS — Date 4/24 Initials DS
   Chemistry Div. I or II
   Comments:
   CMC OK

3. Frank Holcombe — Date Initials — Date 5/22/02 Initials FH
   Assoc. Dir. For Chemistry
   Comments: (First generic drug review)
   SATISFACTORY

4. Pat Beers Block — Date Initials — Date Initials
   Supv., Review Support Branch
   EER Status: Refer to DLPS review below
   Bioequivalence sites:
   Clinical site:
   Inspection needed: ☐ yes ☐ no
   Status: ☐acceptable ☐unacceptable ☐ pending
   Date of status:
   Reason:
   Analytical site:
   Inspection needed: ☐ yes ☐ no
   Status: ☐acceptable ☐unacceptable ☐pending
   Date of status:
   Reason:
   Bioequivalence office level sign off:
   Labeling Status:
   Microbiology status:
   Patent Certification:
   Controlled Correspondence/Cit.Pet.
   Comments: RLD =

Pat Beers 5/24/2002

REVIEWER: | DRAFT RECEIPT | FINAL ACTION

5. Greg Davis
Supv., Reg. Support Branch

Date 5/24/02 Initials RW | Date 5/24/02 Initials RW for

Contains GDEA certification: Yes ☒ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day Generic Drugs Exclusivity for each strength: Yes ☐ No ☐

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
Date Checked previously granted
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

PIII, PIV

RD=Clarinex 24 Hour Extended Release Tablets 10mg/240mg
Schering Corp. NDA 20-470

Comments: Impax made a "paragraph 3" cert. to the '233 patent expiring 12/19/02. Impax also made "paragraph 4" certifications to the '716, '931 and '697 patents. There is no unexpired exclusivity. Impax was sued by Schering over the 3 patents. Chem/Tox consult on amount of polyethylene oxide acceptable.

6. Peter Rickman
Acting Director, DLPS

Date 5/24/02 Initials RW | Date 5/24/02 Initials RW for

Comments: Acceptable EES dated 3/8/01 (Verified 5/24/02). No O.A.I. alerts noted. Bioequivalence studies (fasting + nonfasting) found acceptable 1/31/01. Dissolution data also acceptable. Bio study performed by [redacted] (b) (4) Medical Research in St. Charles, MO. Analytical studies performed by [redacted] of these facilities have satisfactory DSI inspectional histories. Device-drug BIO endorsed 2/6/01. Label insp. acceptable for TA 1/7/02. CMC found acceptable 4/23/02. Methods validation completed satisfactory.

7. Robert L. West
Acting Deputy Director, OGD

Date 5/24/02 Initials RW | Date 5/24/02 Initials Robert L. West

Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☒ No ☐; Petition: Yes ☐ No ☐

Comments: Impax made PIV certifications to the '716, '931 and '697 patents. Schering sued Impax over the '716 and '697 patents (not '931). Litigation is ongoing. Impax also made a PIII certification to the '233 patent expiring 6/19/02. This ANDA is recommended for tentative approval.

8. Gary Buehler
Director, OGD

Date 5/24/02 Initials RW | Date 5/24/2002 Initials RW for

Comments: Tentative Approval

First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

9. Project Manager Ruby Wu
Review Support Branch

Date RW 5/24/02 Initials | Date RW 5/24/02 Initials

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
3:30 pm Time notified of approval by phone 3:35 pm Time approval letter faxed

FDA Notification:
5/24/02 Date e-mail message sent to "OGD approvals" account
5/24/02 Date Approval letter copied to "//cder/drugapp" directory

\reports\approval\approvrou

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: November 27, 2002

FROM: Gary J. Buehler
Director
Office of Generic Drugs

SUBJECT: Loratadine Over-the-Counter and Patent Certifications

TO: The Records for all active Loratadine ANDA's (list attached)

NOTE: Attachment not found with original

Loratadine Background

Issue:

Now that the Schering NDA supplements converting the status of loratadine to OTC are approved, will an applicant that has already submitted an ANDA for approval of the Rx version of the drug be required to submit new patent certifications as part of the amendment to seek approval for a generic drug with the new OTC labeling?

Background:

The Schering NDA supplements for OTC use of loratadine products were approved on November 27, 2002. The approved product will be the OTC version of loratadine labeled for treatment of rhinitis only. Schering has indicated that it will not continue to market an Rx loratadine product to treat urticaria.

There are various products that contain loratadine that will migrate to over-the-counter status (i.e., oral tablets, orally disintegrating tablets, oral liquid, loratadine and pseudoephedrine sulfate extended release tablets with 12 hour and 24 hour dosing intervals.

The primary patent, U.S.Patent No. 4,282,223, (the '223 patent) barring ANDA/505(b)(2) approvals expires (with its pediatric exclusivity extension) on December 19, 2002. In the case of the other listed patents, the NDA holder did not sue in response to notice of certification for U.S. Patent No. 4,863,931 (the '931 patent). In addition the 30-month stay either remains in place or

in some instances has expired with respect to U.S. Patent No. 4,659,716 (the '716 patent). In the United States District Court,District of New Jersey, Schering Corporation v. Impax Laboratories, Inc. Civil Action No. 01-0520(JWB), claims 1 and 3 of the '716 patent were found invalid. Claims 1 and 3 were the only claims that Schering asserted as being infringed. This was with respect to Impax's ANDA 76-050 for Loratadine/Pseudoephedrine Sulfate Extended-release Tablets, 5mg/120mg (a generic version of Claritin D-12).

Three 505(b)(2) applications have been submitted for loratadine. These were 505(b)(2) applications because the sponsors (Wyeth, (b)(4), Perrigo) were seeking approval for an OTC version of loratadine products (i.e. tablets and orally disintegrating tablets) prior to Schering's submission of an application for an over-the-counter version of Claritin. These three applications would be approvable independent of Claritin going OTC, based upon the agency's stated view that the product may be used safely and effectively OTC. Because these applicants have only been seeking approval for the OTC use, their patent certifications to Schering asserted that their proposed OTC product did not infringe the patent. Only one 505(b)(2), Wyeth's NDA 21-375 for loratadine orally disintegrating tablets, is currently ready for final approval on December 19, 2002.

There are multiple ANDAs for the five different Schering loratadine drug products (syrup, immediate release tablets, rapidly disintegrating tablets, in combination with pseudoephedrine with 12 and 24 hour dosing intervals). These ANDAS are currently for the prescription form of the drug, because that was the approved reference listed drug prior to the switch to OTC. Now that the Schering OTC supplements are approved, and they have withdrawn their prescription product for urticaria, there will no longer be a prescription product to reference. Pending ANDAs, therefore must either be withdrawn or amended to reference the approved OTC form of the drug.

The issue for OGD is what new patent certifications, if any, will be required in ANDA amendments to revise the proposed generic prescription labeling to the new OTC Claritin labeling.

The regulations require that an NDA applicant submit to FDA as part of a supplement (1) any new patents that claim the drug or use of a drug for which approval of the supplement is sought and (2) information on any already submitted patent that claims the changed product. 21 CFR 314.53(d)(2).

According to the review division, Schering is making no changes to its product except to the labeling, and it has submitted no new patents or information on already submitted patents that

protect the new labeling.

FDA has consistently interpreted the FFDCA to require new patent certifications in ANDAs when new patents are submitted for an unchanged RLD before the ANDA is approved. In addition, the agency has required new patent certifications when the RLD is changed in some way (e.g., a new formulation) and a new patent is submitted to claim the change. In addition, the FDA has also required a new patent certification when the ANDA product is changed in some way (e.g., a new formulation) and there are existing patents listed with the FDA. There does not appear to be much experience with changes to the innovator drug product that are not accompanied by new patent information.

Recommendation:

Our view is that, if the ANDA applicant has already submitted adequate patent certifications for those aspects of the drug product that will not be changed by either the NDA supplement or the corresponding ANDA amendment, the inquiry is whether the innovator product has obtained or asserted new protections for the new aspect of the drug that will be duplicated by the generic company or whether existing patents also cover the new aspect of the drug. If the innovator does not assert any new protections for the changed product, the ANDA applicant will have no obligation to submit new patent certifications. If, however, the ANDA applicant changes the proposed generic drug in a way that could change its relation to the patent, then it will be required to certify to the relevant patents. This approach is in accordance with the requirements in 21 CFR 314.94(b)(12)(viii)(C) that "an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate."

In the loratidine case, this would mean that <u>if Schering submits no new patents or patent claims for the OTC loratidine products and the ANDA applicants amend their applications only to conform with the labeling changes Schering made in the listed drug</u>, the ANDA applicants would have no new patent certification obligations. If, however, an ANDA applicant decided to change its product to add the new OTC labeling AND to change the formulation, then that applicant would be required to provide new patent certifications.

Once the new labeling is submitted to an ANDA file, the application may proceed to approval after December 19, 2002, if it is otherwise ready for approval and all scientific and legal issues have been resolved.

q:\issues\loratadine\otcpatentmemo.doc

Drafted by: L. Dickinson, 11/7/02
Revised by: C. Parise 11/15/02
Concur: L. Dickinson 11/22/02
Edited by: R. West 11/27/02
Edited by: G. Buehler 11/27/02

ANDA 75-989

IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 14, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg (24-hour formulation).

On November 27, 2002, the FDA approved Schering's supplemental new drug application providing for the over-the-counter (OTC) use of Claritin® (loratadine/pseudoephedrine sulfate) D-12 and D-24 Extended Release Tablets. With this approval, the approved indications for these products are "for the temporary relief of symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, itchy, watery eyes, itching of the nose or throat; temporary reduction of swelling of nasal passages; temporary relief of sinus pressure; and temporary restoration of freer breathing through the nose." The agency has been informed that with the introduction of products labeled for OTC use, these products will no longer be marketed with prescription (Rx) labeling. Thus, since your ANDA currently references the former product with prescription only labeling, your application cannot be approved.

You may submit a revised Form FDA 356h along with appropriate information to this ANDA to indicate the correct reference listed drug (RLD). In addition, we request that you withdraw your former labeling and submit for our review revised final-printed labeling which is consistent in content and format with that which provides for the OTC use of the RLD.

Furthermore, the agency is unaware of any new patent or patent information submitted by Schering to the NDA supplements providing for the switch from prescription to OTC marketing status for loratadine/pseudoephedrine sulfate drug products. As a result, ANDA applicants who submit an amendment to their pending ANDA providing only to amend their proposed labeling to conform with the labeling for the approved reference listed drug will not be required to submit new patent certifications. Please be advised,

however, that submission of additional patents by Schering for the RLD may require you to submit additional ANDA patent certifications.

If you have any questions, please contact: Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at 301-827-5845.

Sincerely yours,

Gary J. Buehler 12/3/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Claritin Labeling

q:\issues\loratadine\otcanda.doc

Drafted by: C. Parise 11/15/02
Comments by: L. Dickinson 11/22/02

Endorsements(s):

HFD-617/S. Kim/ S. K 11/29/02

V:\FIRMSAM\IMPAX\LTRS&REV\75989~~.OTCANDA.doc~~
F/T by: sk/11/29/02 Loratadine OTC.doc

Claritin-D® 24 hour

10 days of relief

10 Extended Release Tablets

Original Prescription Strength

NEW!

Non-Drowsy*

Claritin-D® 24 hour

Pseudoephedrine Sulfate 240 mg/Nasal Decongestant
Loratadine 10 mg/Antihistamine

RELIEF:
Nasal and Sinus Congestion
Sneezing, Runny Nose
Itchy, Watery Eyes
Itchy Throat or Nose

Extended Release Tablets

Allergy & Congestion

*When taken as directed.
See Drug Facts Panel.

10 EXTENDED RELEASE TABLETS

Actual Size

Claritin-D 24 hour 10 Extended Release Tablets

CODE AREA
NO INK - NO VARNISH

FPO

Claritin-D 24 hour

10 Extended Release Tablets

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Memphis, TN 38151 USA. All rights reserved. 20243-02/2691121

0 41100 08043 1

Claritin-D 24 hour 10 Extended Release Tablets

CODE AREA
NO INK - NO VARNISH

FPO

Drug Facts (continued)

When taking this product do not take more than directed. Taking more than directed may cause drowsiness.

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

If pregnant or nursing, ask a health practitioner 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 crush, chew or dissolve the tablet
- take daily with a full glass of water.

adults and children 12 years and over	1 tablet daily with a full glass of water. Do not take more than 1 tablet in 24 hours
children under 12 years of age	ask a doctor
consumers with liver or kidney disease	ask a doctor

Other information

- safety sealed: do not use if the individual blister unit imprinted with Claritin-D® 24 hour is open or torn
- store between 15° and 25° C (59° and 77° F)
- protect from light and store in a dry place

Inactive ingredients

cellulose, dibasic calcium phosphate, croscarmellose, hypromellose, magnesium stearate, polyethylene glycol, polyethylene oxide, povidone, silicon dioxide, sodium stearate, titanium dioxide, white wax

Questions or comments?

1-800-CLARITIN (1-800-252-7484) or www.claritin.com

Warnings

Do not use
- if you have ever had an allergic reaction to this product or any of its ingredients
- 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
- high blood pressure
- diabetes
- trouble urinating due to an enlarged prostate gland
- liver or kidney disease. Your doctor should determine if you need a different dose.

Uses

temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
- nasal congestion
- runny nose
- sneezing
- itchy, watery eyes
- itching of the nose or throat
- reduce swelling of nasal passages
- temporarily relieves sinus congestion and pressure
- temporarily relieves nasal stuffiness and blocked up nose

Claritin-D 24 hour

Drug Facts

Active Ingredients (in each tablet)	Purpose
Loratadine 10 mg	Antihistamine
Pseudoephedrine sulfate 240 mg	Nasal decongestant

TACH LEGEND ON ALL
IGITAL MECHANICALS

FORMAT
ondensed
ztonal scale adheres to 38 characters

-9 pt Helvetica Cnd. Bold italic
(continued)
ts - 8 pt Helvetica Cnd. Bold italic
ed) - 8 pt Helvetica Cnd.
8 pt Helvetica Cnd. Bold italic
-6 pt Helvetica Cnd. Bold
elvetica Cnd. solid leading 6/6.5
ts - 3.5 pt 2apt Dingbats no compression
r rule, 3/64" gap all around
1 rule
pt tule
BL

Glue NO VARNISH

RECORD OF TELEPHONE CONVERSATION

The following comments were communicated to the firm via a telephone message.

1. Please describe the temper evident packaging methodology that conforms to CFR 211.132 for OTC drugs products. If you have already submitted this information, please cite the volume and page number or the amendment date where the information can be found. This information can be submitted as a new correspondence.

2. If you are proposing a change in packaging, and the packaging is in direct contact with the drug, please provide information about the packaging and 3 months accelerated stability data. This should be submitted as a minor amendment. If the new packaging is not in direct contact with the drug product, please provide a description of the additional packaging as a new correspondence. If no change in packaging has been made, no additional information need be submitted for review.

DATE
December 13, 2002

ANDA NUMBER
75-989
76-050
76-011

IND NUMBER

TELECON

INITIATED BY: FDA

PRODUCT NAME
Loratadine
Applications

FIRM NAME
Impax Laboratories, Inc.

FIRM'S REPRESENTATIVE:
Mark Shaw

TELEPHONE NUMBER
510-476-2018

FDA REPRESENTATIVE:
Sarah Kim

SIGNATURE
Sarah Kim S.Kim 12/16/02

V:\FIRMSAM\IMPAX\TELECONS\76050.76011.75989.tc.121302.doc
CC: T-Con Binder Log
ANDA 75-989
76-050
76-011

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

February 14, 2003

ORIG AMENDMENT
N/AF
LABELING AMENDMENT

FPL

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

Re: ANDA 75-989 (Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/ 240 mg)

Dear Mr. Buehler:

This letter responds to your December 3, 2002, facsimile, regarding the change in marketing status of the above-referenced drug product from Rx to OTC. A copy of your correspondence accompanies this letter.

Accompanying this letter are 12 copies of the final printed container label in the OTC Drug Facts format. IMPAX is submitting OTC labeling for Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg, 1000-count. The FPL conforms to the labeling provided to IMPAX by FDA in your December 3, 2002 correspondence. A side-by-side comparison between the Schering-Plough OTC label for Claritin-D® 24 hour and the IMPAX OTC label is provided.

The OTC marketing status for this application has been indicated on FDA Form 356h. The Statement of Rx/OTC Marketing Status (Section V.5) has also been revised following the November 27, 2002 switch of the Reference Listed Drug, Claritin-D® 24 hour, from Rx to OTC marketing status.

Tamper-Evident Feature

Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg will be initially marketed in 1000-count HDPE bottles as described in Section XIII, pages 4854-4980 of the original ANDA submission. The HDPE bottles are sealed with an inner liner that is imprinted, "Sealed For Your Protection." Please refer to the "Other information" section of the Drug Facts OTC label, submitted in this amendment as Final Printed Labeling.

RECEIVED
FEB 19 2003
OGD / CDER

Should you have any questions regarding this correspondence, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

NAE
MAR
8-19-03
Date of first commercial marketing through OCC. Andrx
under consideration by OCC. Andrx to support & launch
submitted documentation
date of 6/2/03

July 16, 2003

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

GENERAL CORRESPONDENCE

NEW CORRESP
NC

Re: ANDA 75-989 (Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/ 240 mg)

Dear Mr. Buehler:

Accompanying this correspondence is a letter from Mr. James N. Czaban, prepared on behalf of IMPAX Laboratories, Inc. (IMPAX) and Wyeth Corporation. The letter requests that the FDA make a determination as to the date upon which Andrx Corporation first began commercial marketing of its Loratadine and Pseudoephedrine Sulfate Extended Release Tablets (ANDA 75-706).

By copy of this letter IMPAX hereby authorizes representatives from the Office of Generic Drugs to discuss the issues raised by this correspondence directly with Mr. Czaban and/or with the undersigned. This authorization is granted solely with respect to IMPAX's ANDA 75-989 and the issues related to the attached correspondence.

Should you have any questions regarding this correspondence, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
JUL 16 2003
OGD/CDER

MW 8/19/03

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

October 1, 2003

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

MINOR AMENDMENT –
FINAL APPROVAL REQUESTED

ORIG AMENDMENT
N/AM

Attn: Sarah Kim

Re: ANDA 75-989 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 mg)

Dear Mr. Buehler:

This letter follows a September 29, 2003 telephone request from Sarah Kim of your office regarding the above-referenced ANDA. Ms. Kim requested that IMPAX submit a Minor Amendment correspondence requesting final approval of this ANDA. In accordance with this request, IMPAX hereby requests *immediate* final approval of this ANDA, and confirms the following:

CMC Changes

IMPAX Laboratories, Inc. hereby confirms that no CMC changes have been made to the application in the time since FDA issued its May 24, 2002 Tentative Approval letter.

Tamper-Evident Packaging

Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 mg will be initially marketed in 1000-count HDPE bottles as described in Section XIII, pages 4854 - 4980 of the original ANDA submission. The HDPE bottles are sealed with an inner liner that is imprinted, "Sealed For Your Protection." The immediate-container OTC labeling that IMPAX submitted in its February 14, 2003 correspondence contains a reference alerting the end-user to this tamper-evident feature. Please refer to the "Other information" section of the Drug Facts OTC label, submitted as Final Printed Labeling.

IMPAX will be marketing its 1000-count packaged product directly to a marketing partner; this product configuration will not be made available as a retail trade package.

(b) (4)

RECEIVED
OCT 0 6 2003
OGD/CDER

MW 10/8/03

(b) (4)

[redacted]

Final Printed Labeling

Final Printed Labeling was submitted in correspondence dated February 14, 2003.

Litigation Status

There are no remaining 30-month stays applicable to this ANDA.

The District Court for the District of New Jersey issued a ruling on August 8, 2002 in favor of IMPAX in declaring that Claims 1 and 3 of Schering's patent number 4,659,716 are invalid.

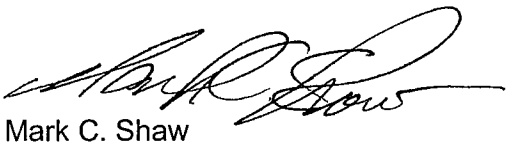
A Motion for Summary Judgment with respect to Schering's patent number 5,314,697 was filed with the District Court for the District of New Jersey. Oral arguments before the Court are scheduled for October 3, 2003.

It is IMPAX's opinion that the only barrier to full approval of IMPAX's ANDA 75-989 is the expiration of Patent Challenge exclusivity awarded to Andrx Pharmaceutical's ANDA 75-706, which is currently listed in the Orange Book as expiring on November 29, 2003. However, IMPAX correspondence dated July 16, and September 16, 2003 to ANDA 75-989, provided documentation indicating that Andrx, the holder of ANDA 75-706, commenced commercial marketing of their D-24 product as early as the approval date of their ANDA, which was on February 21, 2003. As such, the 180-day period of Patent Challenge exclusivity would have expired as early as August 21, 2003.

Accordingly, IMPAX requests the immediate and final approval of its ANDA 75-989.

Should you have any questions regarding this correspondence, please contact me by telephone (*510-476-2018*) or by telefax (*510-476-2091*).

Sincerely,
IMPAX Laboratories, Inc.



Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

November 12, 2003

ORIG AMENDMENT
N/AF

LABELING AMENDMENT

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

Re: ANDA 75-989 (Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/ 240 mg)

Dear Mr. Buehler:

This letter responds to labeling deficiencies cited in an October 23, 2003 telephone conversation between labeling reviewer Debra Catterson of your office and the undersigned.

Accompanying this letter are 12 printer's proofs (with legend) of the final printed container label in the OTC Drug Facts format. The printer's proofs are the true size, color, and text of the production container labels. A side-by-side comparison between the IMPAX OTC label provided in the February 14, 2003 Labeling Amendment and the proposed IMPAX OTC label is provided.

Should you have any questions regarding this correspondence, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
NOV 13 2003
OGD/CL

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-989 Applicant IMPAX Laboratories, Inc.
Drug Loratadine and Pseudoephedrine Sulfate Extended-release Tablets Strength(s) 10 mg / 240 mg

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

VIEWER:	**DRAFT Package**	**FINAL Package**
1. Martin Shimer Chief, Reg. Support Branch	Date 1/16/2004 Initials MMS	Date_____ Initials_____

Contains GDEA certification: Yes ☑ No ☐
(required if sub after 6/1/92)

Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = NDA#_____
Date Checked _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

Patent/Exclusivity Certification: Yes ☑ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☑ No ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐
Has case been settled: Yes ☐ No ☑ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☑
Type of Letter:
Comments: 30 month expired
PC exclusivity has expired

OK for FA

2. Project Manager Sarah Kim Team 4 Review Support Branch	Date 2/27/04 Initials SMS for S.P.	Date_____ Initials_____

Original Rec'd date 9/18/2000
Date Acceptable for Filing 9/18/2000
Patent Certification (type) III, IV
Date Patent/Exclus.expires_____
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Acceptable Bio reviews tabbed Yes ☒ No ☐

EER Status Pending ☐ Acceptable ☐ OAI ☐
Date of EER Status _____
Date of Office Bio Review 12/22/00, 2/6/01
Date of Labeling Approv. Sum 11/26/02
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☒ Received HW on 3/18/02
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☒

PIV exp
7116 - 10/21/04
9931 - 3/15/09
6497 - 4/23/13

Previously reviewed and tentatively approved ☒ Date 5/24/02
Previously reviewed and CGMP def./NA Minor issued ☐ Date _____
Comments:

3. Div. Dir./~~Deputy Dir.~~ Chemistry Div. I or II	Date 3/4/04 Initials [illegible]

Comments:
CMC Satisfactory
EER pending

4. Frank Holcombe Assoc. Dir. For Chemistry	**First Generics Only**	Date_____ Initials_____

Comments: (First generic drug review)
N/A. Andrx's ANDA 75-706 for this drug product was approved on 2/21/03. IMPAX's ANDA was tentatively approved on 5/24/02.

REVIEWER: **FINAL ACTION**

5. Gregg Davis
Deputy Dir., DLPS
Date_____
Initials_____

RLD= Claritin D
Schering Corp. 10mg/240mg NDA 20-470 (001)

6. Peter Rickman
Director, DLPS
Date 3/4/04 Initials [illegible] for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable EES dated 3/3/04. No O.A.T. alerts noted. Refer to the administrative sign-off form completed at the time of the tentative approval on 5/24/02. On 12/3/02, OGD informed Impax that the drug product (RLD) had been changed to OTC status and that no additional patent certifications were required as a result of this change. FP found acceptable for approval 11/26/03. CMC found acceptable 3/1/04. Methods validation was completed and found acceptable.

6. Robert L. West
~~Acting Deputy~~ Director, OGD
Date 3/4/2004 Initials [illegible] for
Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☐
Comments: Impax made paragraph IV certifications to the '716, '931, and '697 patents at the time of filing. Impax was sued by Schering over the '716 and '697 patents. The 30-month statutory hold period expired on 5/20/03. However, final approval of Impax's ANDA was blocked by Andrx's entitlement to 180-day generic drug exclusivity under ANDA 75-706. Andrx's 180-day generic drug exclusivity expired on 11/29/03.

This ANDA is recommended for final approval.

7. Gary Buehler
Director, OGD
Date 3/4/04 Initials [illegible] for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

8. Project Manager, Team Sarah Park
Review Support Branch
Date 3/4/04 Initials SP
NA Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
2:00 Time notified of approval by phone 2:08 Time approval letter faxed
FDA Notification:
3/4/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
3/4/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Note: This ANDA provides for approval of the drug product packaged in bottles of 1000 tablets. These will be sent to a repackager

File V:/division/dlps/approvrou5.doc