CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-557

Name: Loratadine and Pseudoephedrine Sulfate
Extended-release Tablets
10 mg/240 mg

Sponsor: Ranbaxy Inc.

Approval Date: September 22, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-557

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Statistical Review	
Microbiology Review(s)	
Administrative & Correspondence Documents	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-557

APPROVAL LETTER

ANDA 76-557

SEP 22 2004

Ranbaxy Inc.
U.S. Agent for Ranbaxy Laboratories Limited
Attention: Abha Pant
600 College Road East
Princeton, NJ 08540

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 4, 2002, 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 your amendments dated July 23, September 11, October 20, and November 7, 2003; and January 5, March 16, April 20, April 21, May 20, July 1, August 11, and September 8, 2004. We also refer to your correspondence dated March 27, May 14, and October 27, 2003; and April 20, 2004, addressing patent issues related to the reference listed drug product (RLD).

The listed drug product 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 October 23, 2012. 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 on the claims of the '716, '931, or '697 patents. The Act provides that approval of an abbreviated new drug application shall be made effective immediately, unless an action is brought against Ranbaxy

Laboratories Limited (Ranbaxy) for infringement of any of the patents ('716, '931, or '697) that were the subject of the paragraph IV certifications. This action must be brought against Ranbaxy prior to the expiration of 45 days from the date the notice provided by Ranbaxy under section 505(j)(2)(B) is received by the patent and NDA holders.

You have notified the Agency that Ranbaxy complied with the requirements of section 505(j)(2)(B) of the Act. No action was brought by either the patent holder or NDA holder against Ranbaxy within the 45-day period with regard to the '931 or '697 patents. In May 2003, Schering initiated a patent infringement suit against Ranbaxy within the 45-day period, involving the '716 patent in the United States District Court for the District of New Jersey (Schering Corporation v. Ranbaxy Laboratories, Ltd. and Ranbaxy Pharmaceuticals, Inc., Civil Action No. 03-CV-2011 (JWB)). On August 1, 2003, the United States Court of Appeals for the Federal Circuit affirmed a prior decision of the District Court finding the contested claims of the '716 patent to be invalid. On April 20, 2004, you notified the Agency of the settlement between Schering Corporation and Ranbaxy dated March 25, 2004, whereby Civil Action No. 03-2011 (JWB) was dismissed with prejudice by the New Jersey District Court. In addition, we note that the '716 patent was subsequently removed (delisted) from the "Orange Book".

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:

Medium, acid stage	0.1 N HCl for 0-1 hour
Medium, buffer stage	0.1 M phosphate buffer pH 7.5 for 1-16 hours
Volume (mL)	1000 mL
USP Apparatus Type	II (paddle)
Rotation (rpm)	50

Interim Specifications:

Loratadine: NLT (b) (4) % of the labeled amount dissolved 60 minutes

Pseudoephedrine:

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

The "interim" dissolution test 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,

Gary Buehler 9/22/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-557
Division File
Field Copy
HFD-610/RWest
HFD-330/
HFD-205/
HFD-600/C.Parise
HFD-604/D.Hare
HFD-610/Orange Book Staff

Endorsements:
HFD-623/G.Sun/ 8/19/04
HFD-623/D.Gill/ DSGill 8-19-04
HFD-617/S.Park/8-03-04 S.Park 8/19/04
HFD-613/D.Catterson/ > 8/26/04
HFD-613/J.Grace/

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APPROVAL

9/22/2004

conc satisfactory
Lloyd Hoyt
9/21/04

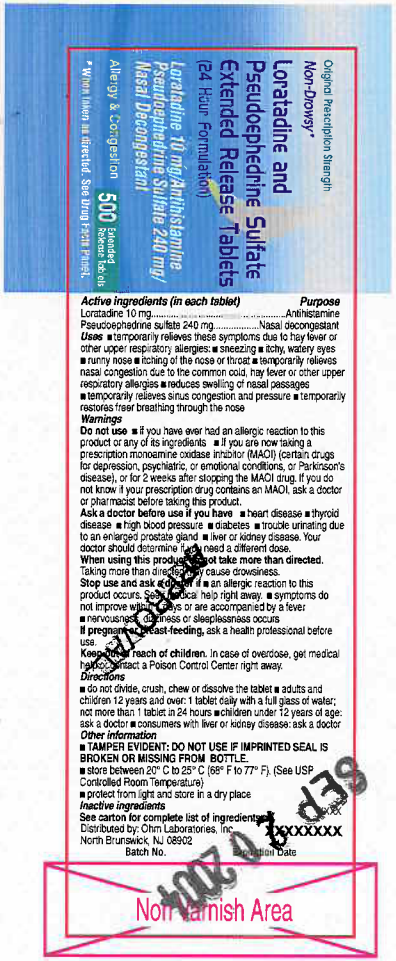
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

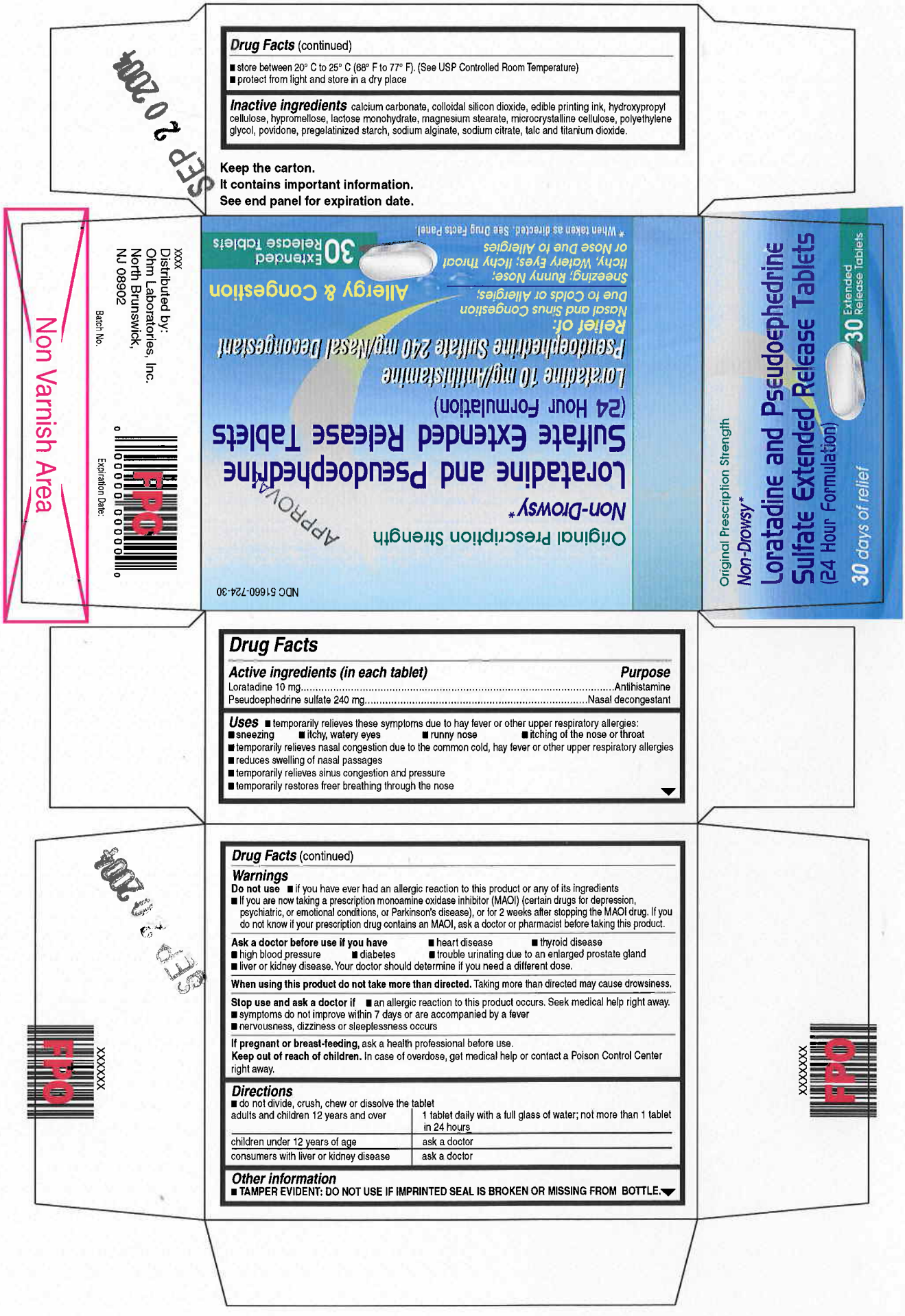
ANDA 76-557

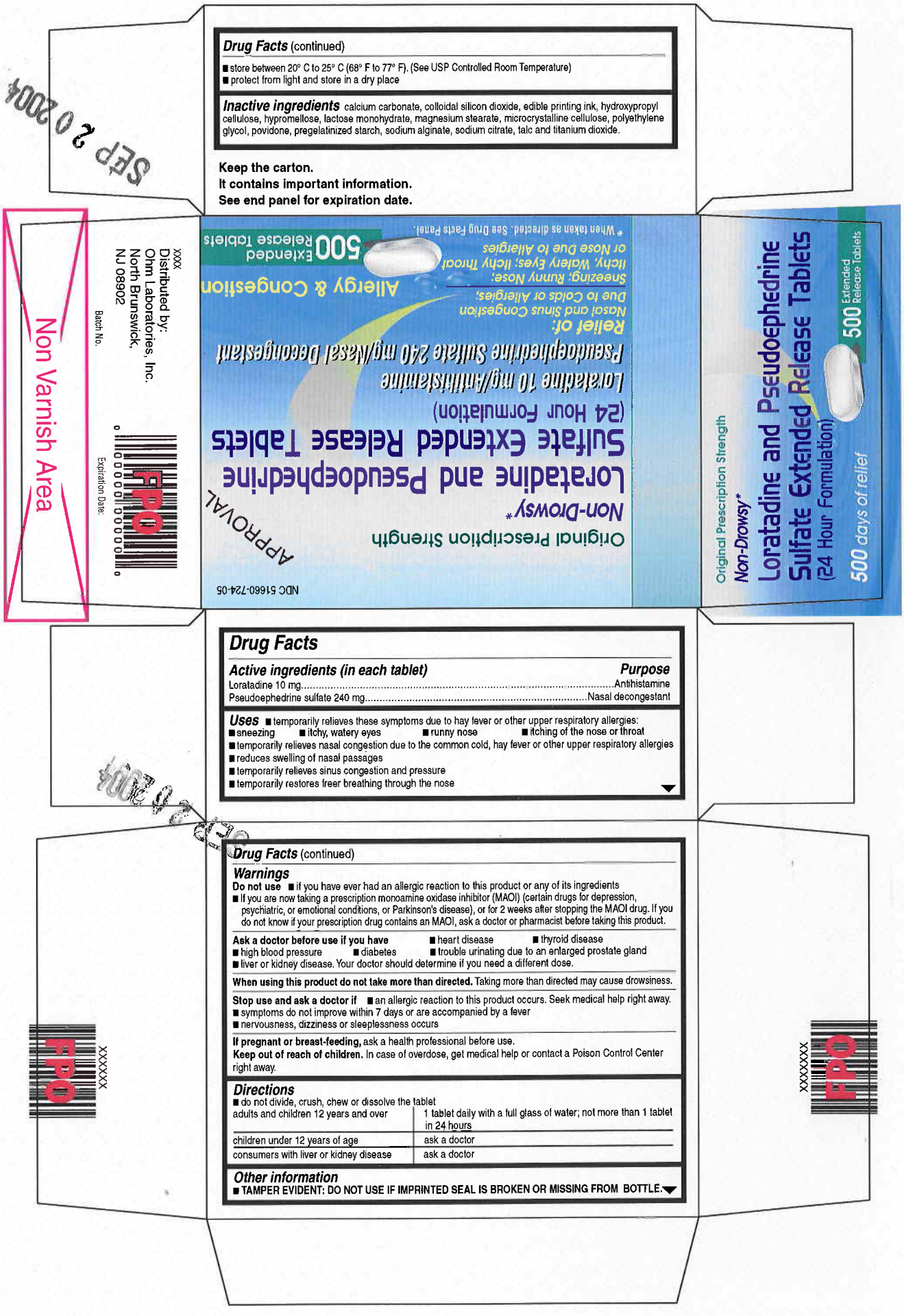
LABELING

(b) (4)


Original Prescription Strength
Non-Drowsy*
Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
(24 Hour Formulation)
Loratadine 10 mg/Antihistamine
Pseudoephedrine Sulfate 240 mg/
Nasal Decongestant
Allergy & Congestion
500 Extended Release Tablets
* When taken as directed. See Drug Facts Panel.
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: ■ sneezing ■ itchy, watery eyes ■ runny nose ■ itching of the nose or throat ■ temporarily relieves nasal congestion due to the common cold, hay fever or other upper respiratory allergies ■ 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.
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
■ TAMPER EVIDENT: DO NOT USE IF IMPRINTED SEAL IS BROKEN OR MISSING FROM BOTTLE.
■ store between 20° C to 25° C (68° F to 77° F). (See USP Controlled Room Temperature)
■ protect from light and store in a dry place
Inactive ingredients
See carton for complete list of ingredients.
Distributed by: Ohm Laboratories, Inc.
North Brunswick, NJ 08902
Batch No.
XXXXXXXX
Expiration Date
Non Varnish Area


Original Prescription Strength
Non-Drowsy*
Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
(24 Hour Formulation)
Loratadine 10 mg/Antihistamine
Pseudoephedrine Sulfate 240 mg/
Nasal Decongestant
Allergy & Congestion
30 Extended Release Tablets
* When taken as directed. See Drug Facts Panel.
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: ■ sneezing ■ itchy, watery eyes ■ runny nose ■ itching of the nose or throat ■ temporarily relieves nasal congestion due to the common cold, hay fever or other upper respiratory allergies ■ 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.
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
■ TAMPER EVIDENT: DO NOT USE IF IMPRINTED SEAL IS BROKEN OR MISSING FROM BOTTLE.
■ store between 20° C to 25° C (68° F to 77° F) (See USP Controlled Room Temperature)
■ protect from light and store in a dry place
Inactive ingredients
XXXX
See carton for complete list of ingredients.
Distributed by: Ohm Laboratories, Inc.
North Brunswick, NJ 08902
XXXXXXXX
Batch No.
Expiration Date
Non Varnish Area


Drug Facts (continued)
■ store between 20° C to 25° C (68° F to 77° F). (See USP Controlled Room Temperature)
■ protect from light and store in a dry place
Inactive ingredients calcium carbonate, colloidal silicon dioxide, edible printing ink, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, sodium alginate, sodium citrate, talc and titanium dioxide.
Keep the carton.
It contains important information.
See end panel for expiration date.
SEP 2 0 2004
Non Varnish Area
XXXX
Distributed by:
Ohm Laboratories, Inc.
North Brunswick,
NJ 08902
Batch No.
Expiration Date:
FPO
Original Prescription Strength
Non-Drowsy*
Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
(24 Hour Formulation)
30 Extended Release Tablets
30 days of relief
Original Prescription Strength
Non-Drowsy*
Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
(24 Hour Formulation)
Loratadine 10 mg/Antihistamine
Pseudoephedrine Sulfate 240 mg/Nasal Decongestant
Relief of:
Nasal and Sinus Congestion
Due to Colds or Allergies;
Sneezing; Runny Nose;
Itchy, Watery Eyes; Itchy Throat
or Nose Due to Allergies
* When taken as directed. See Drug Facts Panel
Allergy & Congestion
30 Extended Release Tablets
NDC 51660-724-30
APPROVAL
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:
■ sneezing ■ itchy, watery eyes ■ runny nose ■ itching of the nose or throat
■ temporarily relieves nasal congestion due to the common cold, hay fever or other upper respiratory allergies
■ reduces swelling of nasal passages
■ temporarily relieves sinus congestion and pressure
■ temporarily restores freer breathing through the nose
Drug Facts (continued)
Warnings
Do not use ■ if you have ever had an allergic reaction to this product or any of its ingredients
■ 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.
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
■ TAMPER EVIDENT: DO NOT USE IF IMPRINTED SEAL IS BROKEN OR MISSING FROM BOTTLE.
SEP 2 0 2004
FPO
XXXXXX
FPO
XXXXXX



Drug Facts (continued)

- store between 20° C to 25° C (68° F to 77° F). (See USP Controlled Room Temperature)
- protect from light and store in a dry place

Inactive ingredients calcium carbonate, colloidal silicon dioxide, edible printing ink, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, sodium alginate, sodium citrate, talc and titanium dioxide.

Keep the carton.
It contains important information.
See end panel for expiration date.

SEP 20 2004

Non Varnish Area

XXXX
Distributed by:
Ohm Laboratories, Inc.
North Brunswick,
NJ 08902

Batch No.

Expiration Date:

APPROVAL

NDC 51660-724-05

Original Prescription Strength
*Non-Drowsy**
Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
(24 Hour Formulation)
500 Extended Release Tablets
500 days of relief

Original Prescription Strength
*Non-Drowsy**
Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
(24 Hour Formulation)
Loratadine 10 mg/Antihistamine
Pseudoephedrine Sulfate 240 mg/Nasal Decongestant
Relief of:
Nasal and Sinus Congestion
Due to Colds or Allergies;
Sneezing; Runny Nose;
Itchy, Watery Eyes; Itchy Throat
or Nose Due to Allergies
Allergy & Congestion
500 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:
  - sneezing
  - itchy, watery eyes
  - runny nose
  - itching of the nose or throat
- temporarily relieves nasal congestion due to the common cold, hay fever or other upper respiratory allergies
- reduces swelling of nasal passages
- temporarily relieves sinus congestion and pressure
- temporarily restores freer breathing through the nose

SEP 20 2004

Drug Facts (continued)

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.

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
- TAMPER EVIDENT: DO NOT USE IF IMPRINTED SEAL IS BROKEN OR MISSING FROM BOTTLE.

XXXXXX

XXXXXXX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-557

LABELING REVIEWS

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

ANDA Number: 76-557

Date of Submission: November 7, 2003, September 11, 2003, July 23, 2003 and December 4, 2002

Applicant's Name: Ranbaxy Pharmaceuticals, Inc.

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

Labeling Deficiencies:

1. **General Comment:**

   Reference is made to your July 23, 2003 submission in which you proposed the proprietary names, (b) (4) and (b) (4), for your drug product. Reference is also made to our November 14, 2003 fax, in which we informed you that the Division of Medication Errors and Technical Support (DMETS) did not recommend the use of these names, due to the potential for confusion with the currently marketed products (b) (4) and (b) (4). Although you have submitted labeling for both the established name and the aforementioned proprietary names, only the labeling with the established name was considered for this review.

2. **CONTAINER** (Bottles of (b) (4) and 500's):
3. **CARTON** (For bottles of (b) (4) and 500's):

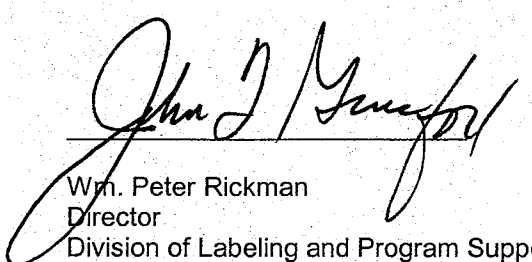
   Please refer to the attached mocked-up copy of your labeling for all of the requested labeling revisions.

Please revise your labels and labeling, as instructed above, and submit in final print.

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

http://www.fda.gov/cder/cdernew/listserv.html

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



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

Attachments: Copy of firm's mocked-up container and carton labeling.

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

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? **The firm proposed the proprietary names, (b) (4) and (b) (4), for their drug product. On November 14, 2003, DMETS concluded that they did not recommend the use of these names, due to the potential for confusion with the currently marketed products (b) (4) (b) (4) and (b) (4). (Consult #03-0166 and #03-0256).**	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) 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	October 23, 2012	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

Ohm Laboratories, Inc.
P.O. Box 7387
1385 Livingston Avenue
North Brunswick, NJ 08902 (Vol. A1.17, Page 6574)

4. CONTAINER/CLOSURE

(b) (4): The firm has not updated their ANDA to include container/closure information for this new package size. (The original container/closure information is for a bottle of 30s.) Sarah Kim spoke with Abha Pant of Ranbaxy on 12/16/03, and Abha said that Ranbaxy will submit the new information on the (b) (4) size.

500s: 500 cc round white opaque HDPE bottle, with 53 mm white polypropylene child-resistant cap. (Vol. A1.18, Page 6997- 6998)

5. 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 at 20 - 25°C (68 - 77°F). (See USP Controlled Room Temperature.) Protect from light and store in a dry place.

6. 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, with the exception of one ingredient: sodium citrate. I have asked the firm to include this ingredient in their listing.

Also, the Drug Facts labeling lists "edible printing ink" under the inactive ingredients, which is (b) (4) Black Ink" in the original components and composition statement. But the firm does not list all of the components of (b) (4) Black Ink in their inactive ingredients. I spoke to John and Lillie about this and was told that it's not necessary to list all of the components of (b) (4) Black Ink, because it is only an imprinting ink and not a film coating agent.
(Vol. A1.17, Pages 6351-6352)

7. NOMENCLATURE:

The firm proposed the proprietary names, (b) (4) and (b) (4), for their drug product. On November 14, 2003, DMETS concluded that they did not recommend the use of these names, due to the potential for confusion with the currently marketed products (b) (4) and (b) (4). (Consult #03-0166 and #03-0256).
The firm also submitted labeling with the established name only, and this labeling was the subject of my review.

Date of Review: 12/10/03 Dates of Submission: 11/07/03, 9/11/03, 7/23/03, and 12/04/02

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 12/16/03

Team Leader: John Grace Date:

John J Grace 12/17/2003

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cc:

ANDA: 76-557
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:\firmsnz\ranbaxy\ltrs&rev\76557-OTC-NA1.L.doc
Review

APPROVAL SUMMARY

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

ANDA Number: 76-557

Date of Submission: January 5, 2004 and December 17, 2003

Applicant's Name: Ranbaxy Pharmaceuticals, 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 30 and 500:
Satisfactory as of the January 5, 2004 submission. [Vol. 3.1]

CARTON Labels: (For bottles of 30 and 500):
Satisfactory as of the January 5, 2004 submission. [Vol. 3.1]

Revisions needed post-approval: **Yes**. The following labeling revision is editorial in nature, and therefore can be a "post-approval" revision. I communicated this post-approval revision to Scott Tomsky, of Ranbaxy Pharmaceuticals, Inc., by telephone and by facsimile on January 13, 2004:

CARTON:

Drug Facts Panel: The "arrow" graphic that leads to the next panel should not appear within the barline, but appear separately from the barline. Please modify both arrows so that they appear just above the barline.

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	October 23, 2012	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? **The firm proposed the proprietary names, (b) (4) and (b) (4), for their drug product. On November 14, 2003, DMETS concluded that they did not recommend the use of these names, due to the potential for confusion with the currently marketed products (b) (4) (b) (4) and (b) (4). (Consult #03-0166 and #03-0256). On December 17, 2003, the firm withdrew the proprietary names and submitted labeling with the established name only.**	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) 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	October 23, 2012	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

Ohm Laboratories, Inc.
P.O. Box 7387
1385 Livingston Avenue
North Brunswick, NJ 08902 (Vol. A1.17, Page 6574)

4. CONTAINER/CLOSURE

30s: 60 cc round white opaque HDPE bottle, with 33 mm white polypropylene child-resistant cap.
500s: 500 cc round white opaque HDPE bottle, with 53 mm white polypropylene child-resistant cap.
(Vol. A1.18, Page 6997- 6998)

5. 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 at 20 - 25°C (68 - 77°F). (See USP Controlled Room Temperature.) Protect from light and store in a dry place.

6. 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.

Also, the Drug Facts labeling lists "edible printing ink" under the inactive ingredients, which is (b) (4) Black Ink" in the original components and composition statement. But the firm does not list all of the components of (b) (4) Black Ink in their inactive ingredients. I spoke to John and Lillie about this and was told that it's not necessary to list all of the components of (b) (4) Black Ink, because it is only an imprinting ink and not a film coating agent.
(Vol. A1.17, Pages 6351-6352)

7. NOMENCLATURE:

The firm proposed the proprietary names, (b) (4) and (b) (4), for their drug product. On November 14, 2003, DMETS concluded that they did not recommend the use of these names, due to the potential for confusion with the currently marketed products (b) (4) and (b) (4). (Consult #03-0166 and #03-0256). On December 17, 2003, the firm withdrew the proprietary names and submitted labeling with the established name only.

Date of Review: 1/13/04 Dates of Submission: 1/05/04, and 12/17/03

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 1/13/04

Team Leader: John Grace Date:

John D Grace 1/14/2004

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cc:

ANDA: 76-557
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
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Review

(This AP Summary supersedes the AP Summary dated 1/14/04.)

APPROVAL SUMMARY

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

ANDA Number: 76-557

Date of Submission: August 11, 2004 (e-submission)

Applicant's Name: Ranbaxy, Inc.
(U.S. Agent for Ranbaxy Laboratories Limited)

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

APPROVAL SUMMARY

Do you have Final Printed Labels and Labeling? Yes. (e-submission)

1. CONTAINER Labels (Bottles of 30 and 500):
   Satisfactory in final print as of the August 11, 2004 submission.
   Network path location: \\Cdsesubogd1\n76557\N_000\2004-08-11\Labeling

2. CARTON (For bottles of 30 and 500):
   Satisfactory in final print as of the August 11, 2004 submission.
   Network path location: \\Cdsesubogd1\n76557\N_000\2004-08-11\Labeling

Revisions needed post-approval: None.

Patent Data – NDA 20-470

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
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	October 23, 2012	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-Plough Healthcare Products, Inc.

Date of Approval of NDA Insert and supplement: NDA 20-470/SE1-022: Approved July 30, 2004

Has this been verified by the MIS system for the NDA? Yes.

Was this approval based upon an OGD labeling guidance? No.

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

REVIEW OF PROFESSIONAL LABELING 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? **The firm proposed the proprietary names, (b) (4) and (b) (4), for their drug product. On November 14, 2003, DMETS concluded that they did not recommend the use of these names, due to the potential for confusion with the currently marketed products (b) (4) and (b) (4). (Consult #03-0166 and #03-0256). On December 17, 2003, the firm withdrew the proprietary names and submitted labeling with the established name only.**	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) Extended Release Tablets by Schering-Plough Healthcare Products, Inc.; NDA 20-470/ SE1-022; approved July 30, 2004. This efficacy supplement provides for a new use of CLARITIN-D in the relief of nasal congestion due to the common cold.

I spoke to the project manager, Elaine Abraham, on August 5, 2004, to see if there was any exclusivity for this new indication. Elaine said that Schering-Plough did not receive exclusivity for this indication, because decongestion for the common cold is already an allowed claim for pseudoephedrine in the OTC Monograph. Therefore, the generic firms may include the new use in their labeling.

2. PATENT/EXCLUSIVITIES

Patent Data – NDA 20-470

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
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	October 23, 2012	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

Ohm Laboratories, Inc.
P.O. Box 7387
1385 Livingston Avenue
North Brunswick, NJ 08902 (Vol. A1.17, Page 6574)

4. CONTAINER/CLOSURE

30s: 60 cc round white opaque HDPE bottle, with 33 mm white polypropylene child-resistant cap.
500s: 500 cc round white opaque HDPE bottle, with 53 mm white polypropylene child-resistant cap.
(Vol. A1.18, Page 6997- 6998)

5. 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°C to 25°C (68°F to 77°F). (See USP Controlled Room Temperature.) Protect from light and store in a dry place.

6. 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.

Also, the Drug Facts labeling lists "edible printing ink" under the inactive ingredients, which is (b) (4) Black Ink" in the original components and composition statement. But the firm does not list all of the components of (b) (4) Black Ink in their inactive ingredients. I spoke to John and Lillie about this and was told that it's not necessary to list all of the components of (b) (4) Black Ink, because it is only an imprinting ink and not a film coating agent.
(Vol. A1.17, Pages 6351-6352)

7. NOMENCLATURE:

The firm proposed the proprietary names, (b) (4) and (b) (4), for their drug product. On November 14, 2003, DMETS concluded that they did not recommend the use of these names, due to the potential for confusion with the currently marketed products (b) (4) and (b) (4). (Consult #03-0166 and #03-0256). On December 17, 2003, the firm withdrew the proprietary names and submitted labeling with the established name only.

Date of Review: 8/17/04 Date of Submission: 8/11/04 (e-submission)

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 8/17/04

Team Leader: John Grace Date:

John J. Grace 8/18/2004

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cc:

ANDA: 76-557
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-557

CHEMISTRY REVIEWS

ANDA 76-557

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

Ranbaxy Laboratories Limited

Guoping Sun, Ph.D.

Division of Chemistry I

Team IV

Table of Contents

Chemistry Review Data Sheet

1. **ANDA:** 76-557

2. **REVIEW #:** 1

3. **REVIEW DATE:** 03-27-03/Revised on 04-08-03, 4-28-03

4. **REVIEWER:** Guoping Sun, Ph.D.

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Original submission	04-DEC-2002
Acceptable for Filing	06-DEC-2002
Additional Information (*Response to 1-9-03 Telephone Contact*)	09-JAN-2003
Additional Information (*Response to 1-10-03 Telephone Contact*)	14-JAN-2003
Amendment (*Response to 1-15-03 Telephone Contact*)	16-JAN-2003
FDA Acknowledgement letter	17-JAN-2003

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

Submission(s) Reviewed	Document Date
Original Submission	04-DEC-2002

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

Applicant:

Name:	**Ranbaxy Laboratories Limited**
Address:	Sector 18, Udyog Vihar Industrial Area Guragon-122 001, India
Representative:	N/A
Telephone:	91-124-6343125
Fax:	N/A

US Agent for Ranbaxy Laboratories Limited:

Name:	**Ranbaxy Pharmaceuticals Inc.**
Address:	600 College Road East Princeton, NJ 08540
Representative:	Abha Pant
Telephone:	609-720-5666
Fax:	609-720-1155

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

a) **Proprietary Name:** N/A

b) **Non-Proprietary Name (USAN):** Loratadine & Pseudoephedrine Sulfate Extended Release Tablets

9. **LEGAL BASIS FOR SUBMISSION:**

Innovator Product:: Claritin-D, 24 Hour® Extended Release Tablets (NDA #: 20-470, Approval Date: 23-AUG-1996)

Innovator Company: Schering

Patent Data: Applicant certifies that to the best of its knowledge no valid or enforceable claim of said patents (see below) will be infringed by the manufacture, use or sale of Ranbaxy's Loratadine and Pseudoephedrine Sulfate Extended Release Tablets for which this abbreviated new drug application is submitted.
Patent data for Claritin-D, 24 Hour®:

Patent #	*Expiration*
4282233	(JUN 19,2002)
4282233*PED	(DEC 19,2002)
4659716	APR 21,2004
4659716*PED	OCT 21,2004
4863931	SEP 15,2008
4863931*PED	MAR 15,2009
5314697	APR 23, 2013
5314697*PED	APR 23, 2013

Exclusivity Data: Applicant certifies that there are no unexpired exclusivities listed in the Orange Book for Claritin-D, 24 Hour® Tablets (Loratadine & Pseudoephedrine Sulfate Extended Release Tablets).

10. **PHARMACOL. CATEGORY:** Antihistamine/Decongestant

11. **DOSAGE FORM:** Tablets

12. **STRENGTH/POTENCY:** 10 mg/240 mg

13. **ROUTE OF ADMINISTRATION:** Oral

14. **Rx/OTC DISPENSED:** ____ Rx ___X___ OTC

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

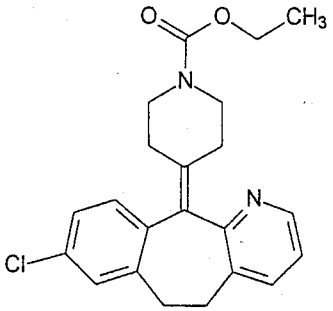
_____ SPOTS product – Form Completed

___X___ Not a SPOTS product

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

Chemical Name: Loratadine:
4-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylic acid, ethyl ester

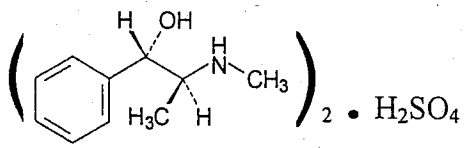
Structural Formula



Molecular Formula: $C_{22}H_{23}ClN_2O_2$
Molecular Weight: 382.89
CAS Number: 79794-75-5

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

Structural Formula



Molecular Formula: $(C_{10}H_{15}NO)_2.H_2SO_4$
Molecular Weight: 428.54
CAS Number: 7460-121-0, USP 26

17. **RELATED/SUPPORTING DOCUMENTS:**

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
15251	II	Ranbaxy Laboratories Limited	Active Ingredient 1: Loratadine	3	*Adequate*	02/22/03	By U. Atwal
(b) (4)	II	(b) (4)	(b) (4)	3	*Adequate*	01/16/03	By N.Takiar
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Claritin-D, 24 Hour®	20-470	Reference Listed Drug (RLD)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	***Acceptable***	27-JAN-2003	
Methods Validation	***Pending***		
Labeling	***Pending***		Debra Catterson
Bioequivalence	***Pending***		Bioequivalence
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW:

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

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

The Chemistry Review for ANDA 76-557

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry manufacturing and controls are *not approvable*. It is recommended that a *Not Approvable*, Minor deficiencies, letter be sent to the applicant.

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

N/A

II. Summary of Chemistry Assessments

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

Basis for ANDA Submission: Ranbaxy's proposed drug product, Loratadine & Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg is based on the reference listed drug (RLD), Claritin-D, 24 Hour® Extended Release Tablets, product of Schering Corporation (NDA #: 20-470, Approval Date: 123-AUG-1996).

Comparison with RLD: Like the innovator's drug product, Ranbaxy's drug product is indicated for the relief of symptoms of seasonal allergic rhinitis. Loratadine & Pseudoephedrine Sulfate Extended Release Tablets should be administered when both the antihistaminic properties of Loratadine and the nasal decongestion activity of Pseudoephedrine Sulfate are desired. Ranbaxy's drug product contains the same active ingredients as the innovator's product. The route of administration (oral), dosage forms (tablets), and strength (10 mg Loratadine and 240 mg Pseudoephedrine Sulfate) are also the same. In conclusion, Ranbaxy's drug product meets the generic drug requirements, i.e. *Same* active ingredient, *Same* route of administration, *Same* strength, *Same* dosage form, *Same* conditions of use, compared to the RLD, Claritin-D, 24 Hour® Extended Release Tablets.

Patent Issues: Ranbaxy certifies that to the best of its knowledge no valid or enforceable claim of the patents under the RLD, Claritin-D, 24 Hour® Extended Release Tablets will be infringed by the manufacture, use or sale of Ranbaxy's Loratadine and Pseudoephedrine Sulfate Extended Release Tablets for which this abbreviated new drug application is submitted.

Product Description: Loratadine & Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg is not listed in the current USP. Ranbaxy's drug product is a White, biconvex,

film coated capsule shaped tablets imprinted with "RX724" in black ink on one side and plain on the other side. It contains the active ingredients, Loratadine and Pseudoephedrine Sulfate, and the inactive ingredients, Microcrystalline Cellulose, Povidone, Hydroxypropyl Methyl Cellulose (HPMC), Hydroxypropyl Cellulose, Sodium Alginate, (b) (4), Colloidal Silicon Dioxide, Talc, Magnesium Stearate, (b) (4) (b) (4)

Drug Substances:
Loratadine is not an USP subject. It is a white to almost white crystalline odorless powder. Its molecular formula is $C_{22}H_{23}ClN_2O_2$ and the molecular weight is 382.89. The drug substance used by the ANDA applicant is manufactured by Ranbaxy Laboratories Limited of India (Type II DMF #15251, reviewed and found ***adequate*** as of 22-FEB-2003, by U. Atwal).

Pseudoephedrine Sulfate is an USP subject and listed on USP 26. It is a white to almost white crystalline substance. Its molecular formula is $(C_{10}H_{15}NO)_2.H_2SO_4$ and the molecular weight is 428.54. The drug substance used by the ANDA applicant is manufactured by (b) (4) (Type II DMF (b) (4), reviewed and found ***adequate*** as of 16-JAN-2003, by N.Takiar).

Packaging: The drug product will be packaged in ***60 cc*** (packaging size: 30 tablets) HDPE bottles with 33 mm CRC cap and ***500 cc*** (packaging size: 500 tablets) HDPE bottles with 53 mm CRC cap for marketing. The stability studies of the test batches described in this application support the proposed commercial packages. According to HOW SUPPLIED section of the insert label, Ranbaxy's Loratadine and Pseudoephedrine Sulfate Extended Release Tablets 10 mg/240 mg contain 10 mg loratadine in the coating for immediate release and 240 mg pseudoephedrine sulfate, USP in an extended-release core. The drug product is supplied as white biconvex, film coated capsule shaped tablets imprinted with "RX724" in black ink on one side and plain on the other. Store at controlled room temperature (b) (4).

In-Process Information: The manufacturing method used for the test batches supporting this ANDA as well as that proposed for the commercial batches comprises a (b) (4)

Analytical methods used by the firm are compendial and in-house.

The firm has provided copies of the three executed batch records for (b) (4) *Tablets.*

Three months accelerated stability data were submitted for all packaging configurations (30, and 500 tablets). Up to *6* months room temperature stability data are provided for all three executed batches (7240202, 7240203, 7240204).

The expiration data for the drug product is *24* months.

The proposed largest production batch is (b) (4) *Tablets*, and a blank batch record for the production batch has been provided.

B. Description of How the Drug Product is Intended to be Used

According to Dosage and Administration of the label insert, adults and children 12 years of age and over: one tablet daily taken with a full glass of water. Patients with renal insufficiency (GFR < 30 mL/min) should be given a lower initial dose (one tablet every other day) because they have reduced clearance of loratadine and pseudoephedrine. Patients who have a history of difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis should not use this product.

C. Basis for Approvability or Not-Approval Recommendation

The application is not approvable due to *minor* CMC deficiencies.

III. Administrative

A. Reviewer's Signature

Guoping Sun, Ph.D./03-27-03/04-08-03

B. Endorsement Block

HFD-623/Guoping Sun, Ph.D./Review Chemist/03-27-03

HFD-623/Dave Gill, Ph.D./Chemistry Team Leader/03-27-03

HFD-617/Sarah Kim, Pharm.D./Project Manager/

C. CC Block

Following this page, 54 pages withheld in full- (b)(4) Chemistry review #1

cc: ANDA 76-557
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/Guoping Sun, Ph.D./03-27-03/Revised on 04-08-03/04-28-03 5/5/03

HFD-623/Dave Gill, Ph.D./03-27-03/Revised on 04-08-03/04-29-03 DSGill 5-5-03

HFD-617/Sarah Kim, Pharm.D./4/30/03 5/13/03

F/T by :ard/5/1/03

V:\FIRMSNZ\RANBAXY\LTRS&REV\76557.cmc.cr1.NA.doc

TYPE OF LETTER: NOT APPROVABLE - **Minor**

ANDA 76-557

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

Ranbaxy Laboratories Limited

Guoping Sun, Ph.D.

Division of Chemistry I

Team IV

Table of Contents

Chemistry Review Data Sheet

1. **ANDA:** 76-557

2. **REVIEW #:** 2

3. **REVIEW DATE:** 10-29-03/Revised on 12-10-03/01-05-04

4. **REVIEWER:** Guoping Sun, Ph.D.

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Original submission	04-DEC-2002
Acceptable for Filing	06-DEC-2002
Additional Information (*Response to 1-9-03 Telephone Contact*)	09-JAN-2003
Additional Information (*Response to 1-10-03 Telephone Contact*)	14-JAN-2003
Amendment (*Response to 1-15-03 Telephone Contact*)	16-JAN-2003
FDA Acknowledgement letter	17-JAN-2003
CMC Deficiency Letter to the firm	14-MAY-2003
Minor Amendment Response from the firm	08-JUL-2003

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

Submission(s) Reviewed	Document Date
Minor Amendment Response from the firm	08-JUL-2003
Telephone deficiencies issued to the firm	13-NOV-2003
T-con with the firm	02-DEC-2003
Telephone Amendment (Revision of product specifications)	08-DEC-2003
Telephone Amendment	12-Dec-2003
Telephone Amendment (Tamper-evident packaging, labeling revision)	17-DEC-2003

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

Applicant:

Name:	**Ranbaxy Laboratories Limited**
Address:	Sector 18, Udyog Vihar Industrial Area Guragon-122 001, India
Representative:	N/A
Telephone:	91-124-6343125
Fax:	N/A

US Agent for Ranbaxy Laboratories Limited:

Chemistry Review Data Sheet

Name:	**Ranbaxy Pharmaceuticals Inc.**
Address:	600 College Road East Princeton, NJ 08540
Representative:	Abha Pant
Telephone:	609-720-5666
Fax:	609-720-1155

8. DRUG PRODUCT NAME/CODE/TYPE:

a) **Proprietary Name:** N/A

b) **Non-Proprietary Name (USAN):** Loratadine & Pseudoephedrine Sulfate Extended Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product:: Claritin-D, 24 Hour® Extended Release Tablets (NDA #: 20-470, Approval Date: 23-AUG-1996)

Innovator Company: Schering

Patent Data: Applicant certifies that to the best of its knowledge no valid or enforceable claim of said patents (see below) will be infringed by the manufacture, use or sale of Ranbaxy's Loratadine and Pseudoephedrine Sulfate Extended Release Tablets for which this abbreviated new drug application is submitted.
Patent data for Claritin-D, 24 Hour®:

Patent #	*Expiration*
4282233	(JUN 19,2002)
4282233*PED	(DEC 19,2002)
4659716	APR 21,2004
4659716*PED	OCT 21,2004
4863931	SEP 15,2008
4863931*PED	MAR 15,2009
5314697	APR 23, 2013
5314697*PED	APR 23, 2013

Exclusivity Data: Applicant certifies that there are no unexpired exclusivities listed in the Orange Book for Claritin-D, 24 Hour® Tablets (Loratadine & Pseudoephedrine Sulfate Extended Release Tablets).

10. PHARMACOL. CATEGORY: Antihistamine/Decongestant

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg/240 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ____ Rx __X__ OTC

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

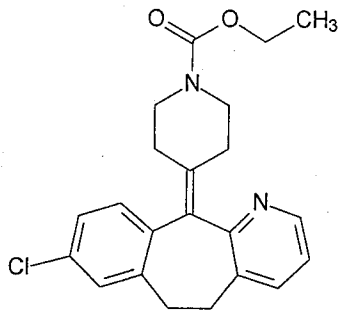
_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

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

Chemical Name: Loratadine:
4-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylic acid, ethyl ester

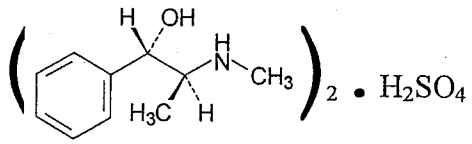
Structural Formula



Molecular Formula: $C_{22}H_{23}ClN_2O_2$
Molecular Weight: 382.89
CAS Number: 79794-75-5

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

Structural Formula



Molecular Formula: $(C_{10}H_{15}NO)_2.H_2SO_4$
Molecular Weight: 428.54
CAS Number: 7460-121-0, USP 26

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
15251	II	Ranbaxy Laboratories Limited	Active Ingredient 1: Loratadine	3	*Adequate*	02/22/03	By U. Atwal
(b) (4)	II	(b) (4)	(b) (4)	3	*Adequate*	01/16/03	By N.Takiar
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Claritin-D, 24 Hour®	20-470	Reference Listed Drug (RLD)

18. STATUS:

Chemistry Review Data Sheet

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	***Acceptable***	27-JAN-2003	
Methods Validation	***Pending***		
Labeling	***Acceptable***	14-Jan-2004	Debra Catterson
Bioequivalence	***Deficient***	27-Feb-2004	H.Nguyen
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW:

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

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

The Chemistry Review for ANDA 76-557

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Bioequivalency is deficient.

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

N/A

II. Summary of Chemistry Assessments

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

Basis for ANDA Submission: Ranbaxy's proposed drug product, Loratadine & Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg is based on the reference listed drug (RLD), Claritin-D, 24 Hour® Extended Release Tablets, product of Schering Corporation (NDA #: 20-470, Approval Date: 123-AUG-1996).

Comparison with RLD: Like the innovator's drug product, Ranbaxy's drug product is indicated for the relief of symptoms of seasonal allergic rhinitis. Loratadine & Pseudoephedrine Sulfate Extended Release Tablets should be administered when both the antihistaminic properties of Loratadine and the nasal decongestion activity of Pseudoephedrine Sulfate are desired. Ranbaxy's drug product contains the same active ingredients as the innovator's product. The route of administration (oral), dosage forms (tablets), and strength (10 mg Loratadine and 240 mg Pseudoephedrine Sulfate) are also the same. In conclusion, Ranbaxy's drug product meets the generic drug requirements, i.e. *Same* active ingredient, *Same* route of administration, *Same* strength, *Same* dosage form, *Same* conditions of use, compared to the RLD, Claritin-D, 24 Hour® Extended Release Tablets.

Patent Issues: Ranbaxy certifies that to the best of its knowledge no valid or enforceable claim of the patents under the RLD, Claritin-D, 24 Hour® Extended Release Tablets will be infringed by the manufacture, use or sale of Ranbaxy's Loratadine and Pseudoephedrine Sulfate Extended Release Tablets for which this abbreviated new drug application is submitted.

Product Description: Loratadine & Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg is not listed in the current USP. Ranbaxy's drug product is a White, biconvex, film coated capsule shaped tablets imprinted with "RX724" in black ink on one side and

plain on the other side. It contains the active ingredients, Loratadine and Pseudoephedrine Sulfate, and the inactive ingredients, Microcrystalline Cellulose, Povidone, Hydroxypropyl Methyl Cellulose (HPMC), Hydroxypropyl Cellulose, Sodium Alginate, (b) (4), Colloidal Silicon Dioxide, Talc, Magnesium Stearate, (b) (4) (b) (4)

Drug Substances:
Loratadine is not an USP subject. It is a white to almost white crystalline odorless powder. Its molecular formula is $C_{22}H_{23}ClN_2O_2$ and the molecular weight is 382.89. The drug substance used by the ANDA applicant is manufactured by Ranbaxy Laboratories Limited of India (Type II DMF #15251, reviewed and found ***adequate*** as of 22-FEB-2003, by U. Atwal).

Pseudoephedrine Sulfate is an USP subject and listed on USP 26. It is a white to almost white crystalline substance. Its molecular formula is $(C_{10}H_{15}NO)_2.H_2SO_4$ and the molecular weight is 428.54. The drug substance used by the ANDA applicant is manufactured by (b) (4) (Type II DMF (b) (4), reviewed and found ***adequate*** as of 16-JAN-2003, by N.Takiar).

Packaging: The drug product will be packaged in the following tamper-evident container/closure systems for marketing:

- ***60 cc*** (packaging size: 30 tablets) HDPE bottles with 33 mm CRC cap
- ***500 cc*** (packaging size: 500 tablets) HDPE bottles with 53 mm CRC cap

The stability studies of the test batches described in this application support the proposed commercial packages. According to HOW SUPPLIED section of the insert label, Ranbaxy's Loratadine and Pseudoephedrine Sulfate Extended Release Tablets 10 mg/240 mg contain 10 mg loratadine in the coating for immediate release and 240 mg pseudoephedrine sulfate, USP in an extended-release core. The drug product is supplied as white biconvex, film coated capsule shaped tablets imprinted with "RX724" in black ink on one side and plain on the other. Store at controlled room temperature (b) (4) (b) (4).

In-Process Information: The manufacturing method used for the test batches supporting this ANDA as well as that proposed for the commercial batches comprises a (b) (4)

Analytical methods used by the firm are compendial and in-house.

The firm has provided copies of the three executed batch records for (b) (4) *Tablets*.

Three months accelerated stability data were submitted for all packaging configurations (30, and 500 tablets). Up to *12* months room temperature stability data are provided for all three executed batches (7240202, 7240203, 7240204).

The expiration data for the drug product is *24* months.

The proposed largest production batch is (b) (4) *Tablets*, and a blank batch record for the production batch has been provided.

B. Description of How the Drug Product is Intended to be Used

According to Dosage and Administration of the label insert, adults and children 12 years of age and over: one tablet daily taken with a full glass of water. Patients with renal insufficiency (GFR < 30 mL/min) should be given a lower initial dose (one tablet every other day) because they have reduced clearance of loratadine and pseudoephedrine. Patients who have a history of difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis should not use this product.

C. Basis for Approvability or Not-Approval Recommendation

Bioequivalency is deficient.

III. Administrative

A. Reviewer's Signature

Guoping Sun, Ph.D./10-29-03/12-10-03/01-05-04

B. Endorsement Block

HFD-623/Guoping Sun, Ph.D./Review Chemist

HFD-623/Dave Gill, Ph.D./Chemistry Team Leader

HFD-617/Sarah Kim, Pharm.D./Project Manager

C. CC Block

Following this page, 23 pages withheld in full- (b)(4) Chemistry review #2

38. Chemistry Comments to be provided to the Applicant

ANDA: 76-557 APPLICANT: Ranbaxy Laboratories Limited

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

The deficiency presented below represent a Minor deficiency.

We refer to the facsimile dated February 27, 2004 regarding deficiencies in the bioequivalence section of your application. These deficiencies must be answered satisfactorily before the application can be approved. Please note that any changes made to the chemistry, manufacturing and controls section of your application as a result of outstanding bioequivalency deficiencies must be submitted and could result in the response being considered a MAJOR Amendment.

Sincerely yours,

DSGill

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

cc: ANDA 76-557
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/Guoping Sun, Ph.D., Review Chemist/10-29-03/revised 12-10-03/1-5-04 3/15/04

HFD-623/Dave Gill, Ph.D., Team Leader/10-29-03/12-10-03/1-5-04/1/6/04 DSGill 3-16-04

HFD-617/Sarah Park, Pharm.D., Project Manager/10-29-03/12-10-03/1-5-04/3/12/04 3/16/04

F/T by: EW 3/15/04

V:\FIRMSNZ\RANBAXY\LTRS&REV\76557.cmc.cr2.APP.doc

TYPE OF LETTER: CMC APPROVABLE, Bio Deficient

ANDA 76-557

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

Ranbaxy Laboratories Limited
(24 – Hour Formulation)

Guoping Sun, Ph.D.

Division of Chemistry III

Team IV

Table of Contents

Chemistry Review Data Sheet

1. **ANDA:** 76-557

2. **REVIEW #:** 3

3. **REVIEW DATE:** 7-22-04/Revised on 7-29-04/9-14-04

4. **REVIEWER:** Guoping Sun, Ph.D.

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Original submission	04-DEC-2002
Acceptable for Filing	06-DEC-2002
Additional Information (*Response to 1-9-03 Telephone Contact*)	09-JAN-2003
Additional Information (*Response to 1-10-03 Telephone Contact*)	14-JAN-2003
Amendment (*Response to 1-15-03 Telephone Contact*)	16-JAN-2003
FDA Acknowledgement letter	17-JAN-2003
CMC Deficiency Letter to the firm	14-MAY-2003
Minor Amendment Response from the firm	08-JUL-2003
Telephone deficiencies issued to the firm	13-NOV-2003
T-con with the firm	02-DEC-2003
Telephone Amendment (Revision of product specifications)	08-DEC-2003
Telephone Amendment	12-Dec-2003
Telephone Amendment (Tamper-evident packaging, labeling revision)	17-DEC-2003
FDA Deficiency Letter	16-MAR-2004
Response to Bioequivalence and CMC Minor	16-MAR-2004
Update of Litigation from Firm	20-APR-2004
Bioequivalence Amendment	20-APR-2004
T-con with the firm	02-SEP-2004

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

Submission(s) Reviewed	Document Date
Additional Information for CMC form Firm	20-MAY-2004
Telephone Amendment	01-JUL-2004
Telephone Amendment	08-SEP-2004

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

Applicant:

Name: **Ranbaxy Laboratories Limited**

Chemistry Review Data Sheet

Address:	Sector 18, Udyog Vihar Industrial Area Guragon-122 001, India
Representative:	N/A
Telephone:	91-124-6343125
Fax:	N/A

US Agent for Ranbaxy Laboratories Limited:

Name:	**Ranbaxy Inc.**
Address:	600 College Road East Princeton, NJ 08540
Representative:	Abha Pant
Telephone:	609-720-5666
Fax:	609-514-9797

8. DRUG PRODUCT NAME/CODE/TYPE:

a) **Proprietary Name:** N/A

b) **Non-Proprietary Name (USAN):** Loratadine & Pseudoephedrine Sulfate Extended Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product:: Claritin-D, 24 Hour® Extended Release Tablets (NDA #: 20-470, Approval Date: 23-AUG-1996)

Innovator Company: Schering

Patent Data: Applicant certifies that to the best of its knowledge no valid or enforceable claim of said patents (see below) will be infringed by the manufacture, use or sale of Ranbaxy's Loratadine and Pseudoephedrine Sulfate Extended Release Tablets for which this abbreviated new drug application is submitted.

Patent data for Claritin-D, 24 Hour®:

Patent #	*Expiration*
4282233	(JUN 19,2002)
4282233*PED	(DEC 19,2002)
4659716	APR 21,2004
4659716*PED	OCT 21,2004
4863931	SEP 15,2008
4863931*PED	MAR 15,2009
5314697	APR 23, 2013
5314697*PED	APR 23, 2013

Exclusivity Data: Applicant certifies that there are no unexpired exclusivities listed in the Orange Book for Claritin-D, 24 Hour® Tablets (Loratadine & Pseudoephedrine Sulfate Extended Release Tablets).

10. PHARMACOL. CATEGORY: Antihistamine/Decongestant

Chemistry Review Data Sheet

11. DOSAGE FORM: Extended – release Tablets

12. STRENGTH/POTENCY: 10 mg/240 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ____ Rx ___X__ OTC

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

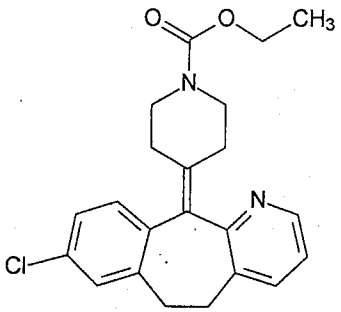
_____ SPOTS product – Form Completed

___X___ Not a SPOTS product

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

Chemical Name: Loratadine:
4-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylic acid, ethyl ester

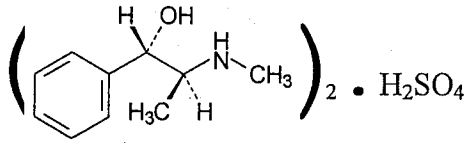
Structural Formula



Molecular Formula: $C_{22}H_{23}ClN_2O_2$
Molecular Weight: 382.89
CAS Number: 79794-75-5

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

Structural Formula



Molecular Formula: $(C_{10}H_{15}NO)_2.H_2SO_4$
Molecular Weight: 428.54

Chemistry Review Data Sheet

CAS Number: 7460-121-0, USP 26

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
15251	II	Ranbaxy Laboratories Limited	Active Ingredient 1: Loratadine	3	*Adequate*	09/30/03	By U. Atwal
(b) (4)	II	(b) (4)	(b) (4)	3	*Adequate*	01/21/03	By N.Takiar
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Claritin-D, 24 Hour®	20-470	Reference Listed Drug (RLD)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	*Acceptable*	27-JAN-2003	
Methods Validation	*N/A*		
Labeling	*Acceptable*	18-Aug-2004	Debra Catterson
Bioequivalence	*Acceptable*	29-APR-2004	H.Nguyen
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW:

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

Yes X No _____ If no, explain reason(s) below:

The Chemistry Review for ANDA 76-557

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry manufacturing and Controls and Bioequivalence are ***Approvable***.

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

N/A

II. Summary of Chemistry Assessments

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

Basis for ANDA Submission: Ranbaxy's proposed drug product, Loratadine & Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg is based on the reference listed drug (RLD), Claritin-D, 24 Hour® Extended Release Tablets, product of Schering Corporation (NDA #: 20-470, Approval Date: 123-AUG-1996).

Comparison with RLD: Like the innovator's drug product, Ranbaxy's drug product is indicated for the relief of symptoms of seasonal allergic rhinitis. Loratadine & Pseudoephedrine Sulfate Extended Release Tablets should be administered when both the antihistaminic properties of Loratadine and the nasal decongestion activity of Pseudoephedrine Sulfate are desired. Ranbaxy's drug product contains the same active ingredients as the innovator's product. The route of administration (oral), dosage forms (tablets), and strength (10 mg Loratadine and 240 mg Pseudoephedrine Sulfate) are also the same. In conclusion, Ranbaxy's drug product meets the generic drug requirements, i.e. *Same* active ingredient, *Same* route of administration, *Same* strength, *Same* dosage form, *Same* conditions of use, compared to the RLD, Claritin-D, 24 Hour® Extended Release Tablets.

Patent Issues: Ranbaxy certifies that to the best of its knowledge no valid or enforceable claim of the patents under the RLD, Claritin-D, 24 Hour® Extended Release Tablets will be infringed by the manufacture, use or sale of Ranbaxy's Loratadine and Pseudoephedrine Sulfate Extended Release Tablets for which this abbreviated new drug application is submitted.

Product Description: Loratadine & Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg is not listed in the current USP. Ranbaxy's drug product is a White, biconvex, film coated capsule shaped tablets imprinted with "RX724" in black ink on one side and

plain on the other side. It contains the active ingredients, Loratadine and Pseudoephedrine Sulfate, and the inactive ingredients, Microcrystalline Cellulose, Povidone, Hydroxypropyl Methyl Cellulose (HPMC), Hydroxypropyl Cellulose, Sodium Alginate, (b) (4), Colloidal Silicon Dioxide, Talc, Magnesium Stearate, (b) (4) (b) (4)

Drug Substances:
Loratadine is an USP subject. It is a white to almost white crystalline odorless powder. Its molecular formula is $C_{22}H_{23}ClN_2O_2$ and the molecular weight is 382.89. The drug substance used by the ANDA applicant is manufactured by Ranbaxy Laboratories Limited of India (Type II DMF #15251, reviewed and found ***adequate*** as of 30-SEP-2003, by U. Atwal).

Pseudoephedrine Sulfate is also an USP subject. It is a white to almost white crystalline substance. Its molecular formula is $(C_{10}H_{15}NO)_2.H_2SO_4$ and the molecular weight is 428.54. The drug substance used by the ANDA applicant is manufactured by (b) (4) (b) (4) (Type II DMF (b) (4), reviewed and found ***adequate*** as of 21-JAN-2003, by N.Takiar).

Packaging: The drug product will be packaged in the following tamper-evident container/closure systems for marketing:

- ***60 cc*** (packaging size: 30 tablets) HDPE bottles with 33 mm CRC cap
- ***500 cc*** (packaging size: 500 tablets) HDPE bottles with 53 mm CRC cap

The stability studies of the test batches described in this application support the proposed commercial packages. According to HOW SUPPLIED section of the insert label, Ranbaxy's Loratadine and Pseudoephedrine Sulfate Extended Release Tablets 10 mg/240 mg contain 10 mg loratadine in the coating for immediate release and 240 mg pseudoephedrine sulfate, USP in an extended-release core. The drug product is supplied as white biconvex, film coated capsule shaped tablets imprinted with "RX724" in black ink on one side and plain on the other. Store at controlled room temperature (b) (4) (b) (4).

In-Process Information: The manufacturing method used for the test batches supporting this ANDA as well as that proposed for the commercial batches comprises a (b) (4)

Analytical methods used by the firm are compendial and in-house.

The firm has provided copies of the three executed batch records for (b) (4) *Tablets.*

Three months accelerated stability data were submitted for all packaging configurations (30, and 500 tablets). Up to *12* months room temperature stability data are provided for all three executed batches (7240202, 7240203, 7240204).

The expiration data for the drug product is *24* months.

The proposed largest production batch is (b) (4) *Tablets*, and a blank batch record for the production batch has been provided.

B. Description of How the Drug Product is Intended to be Used

According to Dosage and Administration of the label insert, adults and children 12 years of age and over: one tablet daily taken with a full glass of water. Patients with renal insufficiency (GFR < 30 mL/min) should be given a lower initial dose (one tablet every other day) because they have reduced clearance of loratadine and pseudoephedrine. Patients who have a history of difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis should not use this product.

C. Basis for Approvability or Not-Approval Recommendation

The firm has resolved all deficiencies issued by the Agency. The ANDA is ***approvable***.

III. Administrative

A. Reviewer's Signature

Guoping Sun, Ph.D./7-22-04/9-14-04 9/14/04

B. Endorsement Block

HFD-623/Guoping Sun, Ph.D./Review Chemist

HFD-623/Dave Gill, Ph.D./Chemistry Team Leader

HFD-617/Sarah Park, Pharm.D./Project Manager

C. CC Block

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

cc: ANDA 76-557
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/Guoping Sun, Ph.D., Review Chemist/7-22-2004/7-29-04/9-14-04

HFD-623/Dave Gill, Ph.D., Team Leader/7-22-2004/7-29-04/9-14-04 DSGill 9-17-04

HFD-617/Sarah Park, Pharm.D., Project Manager/9-14-04 S. Park 9/17/04

F/T by:

V:\FIRMSNZ\RANBAXY\LTRS&REV\76557.cmc.cr3.APP.doc

TYPE OF LETTER: ***CMC Approvable***

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-557

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-557
Drug Product Name	Loratadine/Pseudoephedrine Sulfate Extended-Released Tablets
Strength	10 mg/240 mg
Applicant Name	Ranbaxy Laboratories
Address	Gurgaon, India
Submission Date(s)	December 4, 2002
Amendment Date(s)	N/A
Reviewer	Hoainhon Nguyen
File Location	c:\firmsnz\ranbaxy\ltrs&rev\76557n1202.doc

I. Executive Summary

This application references Claritin-D (loratadine/pseudoephedrine Sulfate, 10 mg/240 mg) 24 Hour ER Tablets and includes one fasting and one fed BE study. The fasting study is a single-dose four-way replicated, crossover study using 27 male and 9 female normal healthy volunteers given a dose of 1x10 mg/240 mg loratadine/pseudoephedrine. The results (point estimate, 90% CI) of the fasting BE study as reported are LAUCt of 1.11, 101.8-121.8% (loratadine), 1.02, 98.2-105.3% (descarboethoxyloratadine(DCL)), 1.03, 100.0-106.5%(pseudoephedrine); LAUCi of 1.12, 101.9-122.3% (loratadine), 1.01, 98.0-105.0% (DCL), 1.01, 97.7-104.3% (pseudoephedrine); and LCmax of 1.07, 96.7-118.5%(loratadine), 1.04, 100.2-108.6% (DCL) and 1.10, 106.4-114.1% (pseudoephedrine). The fed BE study is a single-dose two-way crossover study using 32 male and 5 female normal healthy volunteers given a dose of 1x10 mg/240 mg loratadine/pseudoephedrine. The fed study was conducted before the issuance of the CDER food-effect guidance. The results (point estimate) of the fed BE study are LAUCt of 1.01 (loratadine), 0.99 (DCL) and 1.02 (pseudoephedrine); LAUCi of 1.00 (loratadine), 0.99 (DCL) and 1.02 (pseudoephedrine); and LCmax of 1.06 (loratadine), 1.04 (DCL) and 0.99 (pseudoephedrine). These studies are incomplete due to analytical method validation deficiencies. The dissolution testing is incomplete pending additional dissolution testing using the FDA-recommended method. The application is incomplete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Ranbaxy's Loratadine/Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, Lot# 7240202
Reference Product	Claritin-D (loratadine/pseudoephedrine, 10 mg/240 mg) 24 Hour ER Tablets (NDA # 20-470, Schering, Approved 08/23/96) Lot # 1-DCS-2039
Indication	indicated for the relief of symptoms of seasonal allergic rhinitis.

PK/PD Information

Bioavailability: 80% for loratadine; unquantified for pseudoephedrine.

Metabolism: Loratadine is extensively metabolized in the liver (first-pass metabolism) to an active metabolite, descarboethoxyloratadine (DCL). Pseudoephedrine is also metabolized in the liver with norpseudoephedrine as the active metabolite of pseudoephedrine (less than 1% of the dose).

Half Life: 8.4 hours for loratadine and 28 hours for its metabolite, descarboethoxyloratadine; 6.3 hours for pseudoephedrine and dependent on the pH of the urine.

Tmax: 1 to 2 hours for loratadine; 0.5-1 hour for pseudoephedrine in immediate release tablet and 6-9 hours for pseudoephedrine in sustained-release tablet.

Excretion: For loratadine, approximately 80% of the total dose administered can be found equally distributed between urine and feces as metabolic products. Pseudoephedrine is excreted also mainly via the kidney (70-90%).

Food Effect: In a single-dose study, food increased the AUC of loratadine by approximately 125% and C_{max} by approximately 80%. However, food did not significantly affect the pharmacokinetics of pseudoephedrine sulfate or descarboethoxyloratadine.

Relevant DBE History:

1. ANDA #76-050 (Impax; 12/12/2000): The firm submitteed a single-dose fasting bioequivalence study and a single-dose nonfasting bioequivalence study as well as dissolution testing for the test and reference products. Loratadine, descarboethoxyloratadine, and pseudoephedrine were measured. However, only parent drugs were considered for BE evaluation. For dissolution testing, the following method was recommended for the test product, a generic version of Claritin-D 12 Hour ER tablets (NDA # 19-670; Schering; approved 11/14/94):

Apparatus II (paddle) at 50 rpm
Acid Stage: 900 mL of 0.1 N HCl for 1 hour
Buffer Stage: 900 mL of 0.05 M Phosphate Buffer at pH 8.2 containing 0.01% SLS for 1-12 hours

2. Control Document #02-109 ((b) (4) 02/22/02): The DBE recommended that a single-dose fasting bioequivalence study and a single-dose nonfasting bioequivalence study be conducted for the drug product. Only loaratadine and pseudoephedrine were recommended for measurement.

3. The dissolution method and specification recommended for Claritin-D 24 Hour ER tablet are as follows:

Acid Stage: 1000 mL 0.1N HCl in first hour; then Buffer Stage: 1000 mL 0.1M phosphate buffer pH 7.5 for 16 hours. For both stages: USP Paddle 50 rpm
Specification: NLT (b) (4) 30 min (loratadine)
1 hour (b) (4) , 2 hours (b) (4) , 4 hours (b) (4) , 8 hours (b) (4) , 16 hours (b) (4)
(pseudoephedrine)

B. Contents of Submission

		How many?
Single-dose fasting study	X	1
Single-dose fed study	X	1
In vitro dissolution testing	X	1
Waiver requests		None

C. Bioanalytical Method Validation (Pre-Study, Vol. C1.3, pages. 945-982 and Vol. C1.7, pages 2468-2510)

There were two separate analytical methods for loratadine/ descarboethoxyloratadine (DCL) and pseudoephedrine.

Number of analytes	3 Both parent compounds and one metabolite		
Analyte name	Loratadine	DCL	Pseudoephedrine
Internal Standard	(b) (4)	(b) (4)	(b) (4)
Method description	LC/MS/MS	LC/MS/MS	LC/MS/MS
QC range	60.1 - 8008 pg/mL	60.2-5495 pg/mL	15.11-1209 ng/mL
Standard curve range	20.0-10010 pg/mL	20.1-7019 pg/mL	5.00-1501 ng/mL
Limit of quantitation	20.0 pg/mL	20.1 pg/mL	5.00 ng/mL
Recovery of Drug (%)	Not determined	Not determined	53.7-52.9%
Average Recovery of Int. Std (%)	Not determined	Not determined	54.1%
Intraday precision range (%CV)	3.3-13.9%	0.5-3.9%	1.9-10.7%
Intraday accuracy range (%)	103.8-111.5%	95.8-115.9%	99.9-112.6%
Interday precision range (%CV)	2.6-13.1%	2.5-8.2%	1.9-7.7%
Interday accuracy range (%)	96.8-108.9%	88.5-104.2%	100.7-106.8%
Bench-top stability (hrs)	27 hours	27 hours	16.3 hours
Stock stability (days)	237 days	237 days	187 days
Processed stability (hrs)	155.7 hours	155.7 hours	60.3 hours
Freeze-thaw stability (cycles)	5 cycles	5 cycles	5 cycles
Long-term storage stability (days)	170 days	170 days	105 days
Dilution integrity	1:25 (of 100100 pg/mL) 97.1%	1:25 (59868 pg/mL) 106.2%	Not determined
Specificity	Acceptable	Acceptable	Acceptable
SOPs submitted	No	No	No
Bioanalytical methods are acceptable:	Yes	Yes	Yes
20% Chromatograms included	Yes	Serially Selected? No	

D. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study No.	AA01111
Study Design	randomized, 4-way replicated crossover
No. of subjects enrolled	40 (36 plus 4 alternates)
No. of subjects completing	36
No. of subjects with samples analyzed	37*
Subjects	
Sex(es) included (how many)	Male 27 Female 9
Test product	Ranbaxy's Loratadine/Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, Lot # 7240202

Reference product	Schering's Claritin-D (loratadine/pseudoephedrine sulfate, 10 mg/240 mg) 24 Hour ER Tablets, Lot # 1-DCS-2039
Strength tested	10 mg/240 mg
Dose	1x10 mg/240 mg

*NOTE: Data analyses were performed on data from subjects who completed at least 2 periods of the study. Subjects excluded from the analyses were not necessarily dropout subjects. Dropout subjects were Subjects #11 (prior to Period 4), #12 (prior to Period 2), #24 and # 38 (prior to Period 3). Subjects not included in the study analyses were Subject #12 who did not complete 2 periods, Subject # 23 and 31 who vomited early in Period 3 and Period 4, respectively.

Summary of Statistical Analysis:

Loratadine

Parameter	Point Estimate	90% Confidence Interval
AUCt	111.4	101.8-121.8
AUCi	111.6	101.9-122.3
Cmax	107.0	96.7-118.5

DCL

Parameter	Point Estimate	90% Confidence Interval
AUCt	101.7	98.2-105.3
AUCi	101.4	98.0-105.0
Cmax	104.3	100.2-108.6

Pseudoephedrine

Parameter	Point Estimate	90% Confidence Interval
AUCt	103.2	100.0-106.5
AUCi	100.9	97.7-104.3
Cmax	110.1	106.4-114.1

The study is acceptable

2. Single-dose Nonfasting Bioequivalence Study

Study No.	AA01112
Study Design	randomized, 4-way replicated crossover
No. of subjects enrolled	41 (40 plus 1 alternate)
No. of subjects completing	37
No. of subjects analyzed	37*
Subjects	
Sex(es) included (how many?)	Male 32 Female 5
Test product	Ranbaxy's Loratadine/Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, Lot # 7240202
Reference product	Schering's Claritin-D (loratadine/pseudoephedrine sulfate, 10 mg/240 mg) 24 Hour ER Tablets, Lot # 1-DCS-2039
Strength tested	10 mg/240 mg
Dose	1x10 mg/240 mg

*NOTE: Data analyses were performed on data from subjects who completed at least 2 periods of the study. Subjects excluded from the analyses were not necessarily dropout subjects. Dropout subjects were Subjects #6 (prior to Period 2), #10 and 30 (prior to Period 3) and # 38 (prior to Period 2). Subjects not included in the study analyses were Subjects #6 and 38 who did not complete 2 periods, Subject # 33 who vomited early in Period 3 and Subject#20 who had unacceptable predose DCL levels.

Summary of Statistical Analysis

Loratadine

Parameter	Point Estimate	90% Confidence Interval
LAUCt	100.6	Not determined
LAUCi	100.2	Not determined
Lcmax	105.7	Not determined

DCL

Parameter	Point Estimate	90% Confidence Interval
LAUCt	98.6	Not determined
LAUCi	98.7	Not determined
Lcmax	103.7	Not determined

Pseudoephedrine

Parameter	Point Estimate	90% Confidence Interval
LAUCt	102.3	Not determined
LAUCi	101.9	Not determined
Lcmax	98.9	Not determined

The study is acceptable

E. Formulation

The test product formulations are shown in the Appendix.
Inactive Ingredients are within IIG limits.
Dosage form information
Test drug product:
Tablet: film-coated Shape: capsule-shaped, biconvex Color: white
Imprint/Emboss/engraving: imprinted with "RX724" on one side, and plain on the other side
Other pertinent details: None
Reference drug product:
Tablet: coated Shape: oval, biconvex Color: white to off-white
Imprint/Emboss/engraving: branded with "CLARITIN-D 24 HOUR" in black ink on one side and plain on the other side
Other pertinent details: For both the test and reference products, 10 mg loratadine is in the tablet coating for immediate release, and 240 mg pseudoephedrine sulfate USP is in an extended-release core.

The formulation is acceptable.

F. In Vitro Dissolution

In addition to the proposed method below, the firm conducted dissolution testing using USP apparatus I (basket) at 75 rpm in 900 mL of various media: pH 6.8 phosphate buffer, pH 4.5 buffer, 0.1 N HCl and water.

Methods Submitted	Firm's proposed method
Medium, acid statge	0.1 N HCl for 0-1 hour
Medium, buffer stage	pH 6.8 phosphate buffer for 1-16 hours
Volume (mL)	900 mL
USP Apparatus Type	I (basket)

Rotation (rpm) 75
Firm's specification Loratadine: NLT (b) (4)% dissolved in 60 minutes
Pseudoephedrine: (b) (4) in 1 hour, (b) (4) in 4 hours, (b) (4) in 8 hours and NLT (b) (4) in 16 hours.
F2- value (s): See the data summarized in the Appendix.
The firm is requested to submit additional dissolution data obtained using the FDA-recommended method: 1000 mL 0.1N HCl in the first hour then 1000 mL 0.1M phosphate buffer pH 7.5 for the next 15 hours using USP Paddle at 50 rpm.

G. Waiver Request: Not applicable.

H. Deficiency Comments: The following deficiencies have been identified:

1. The firm is requested to submit long-term stability data for pseudoephedrine covering a freezer storage period of at least 142 days which was the maximum storage period for the actual study samples. Currently, the firm has only provided long-term stability data for a freezer storage period of 105 days.

2. For both blue (archival section) and orange (pharmacokinetic section) jackets of Volume 1.10, the Appendices 5.5 (Adverse Events), 5.6 (Concomitant Medication Report) and 5.7 (Drug Accountability), of the Fasting Study, were left out. The firm is requested to provide these missing sections of the Clinical Report.

3. For Appendix 5.2 (Demographic Information) of the Fasting Study, pp. 3795-3797, the text is illegible. The firm is requested to provide a legible copy of the Appendix 5.2. In addition to the summary information given in the table, the firm is requested to provide additional demographic summary for only subjects that were included in the study (mean, SD and range of age, weight and height), for both Fasting and Nonfasting Studies.

4. For both the Fasting and Nonfasting Studies, the firm is requested to provide raw numerical data which include peak heights and/or peak areas, peak height and/or peak area ratios, and the order in which all study samples, standards and QCs were assayed and reassayed, if any. Currently the firm has only submitted the calculated plasma concentration data for study samples.

5. For both the Fasting and Nonfasting Studies, the firm should provide a list of reassayed samples with the reassay reasons and values. Only a list of pseudoephedrine reassayed samples of the Nonfasting Study was submitted. The SOPs for assay method validation and especially for reassay selection and acceptance should be provided.

6. For the assays of loratadine and DCL, diluted QCs appeared to be included in some of the analytical runs, of the Fasting and Nonfasting Studies. The firm is requested to provide detailed information on how these diluted QCs were prepared.

7. For both the Fasting and Nonfasting Studies, the firm is requested to provide explanation for the split and asymmetrical peaks seen in most of DCL/DCL internal standard chromatograms, and in some of loratadine and pseudoephedrine, and on how these peaks were integrated.

8. For the Nonfasting Study, the firm is requested to provide the reasons for not assaying the samples for Period 2 of Subjects #26 and 27.

9. The firm is requested to conduct additional dissolution testing using the FDA-recommended method: 1000 mL 0.1N HCl in first hour then 1000 mL 0.1M phosphate buffer pH 7.5 for next 15 hours, using USP Paddle at 50 rpm for both the acid and buffer stages. The recommended sampling times are: 5, 10, 20, 30 and 45 minutes for loratadine, 1, 2, 4, 8 and 16 hours for pseudoephedrine.

I. Recommendations

1. The single-dose, fasting bioequivalence study and the single-dose nonfasting bioequivalence study conducted by Ranbaxy on the test product, Loratadine/Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, lot # 7240202,

comparing it with the reference product, Schering's Claritin-D (loratadine/pseudoephedrine sulfate, 10 mg/240 mg) ER Tablets, lot # 1-DCS-2039, have been found **incomplete** due to the deficiencies listed in the Deficiency Comments above.

2. The in-vitro dissolution testing conducted by Ranbaxy on its Loratadine/Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, has been found **incomplete**. The firm is requested to conduct additional dissolution testing using the following FDA-recommended method:

The dissolution testing should be conducted in 1000 mL of 0.1 N HCl for the first hour, and then 1000 mL of 0.1 M pH 7.5 phosphate buffer (0.05 M) for the next 15 hours, both stages at 37°C using USP apparatus II(paddle) at 50 rpm. The recommended sampling times are: 5, 10, 20, 30 and 45 minutes for loratadine, 1, 4, 8 and 16 hours for pseudoephedrine.

8/20/03
Hoainhon Nguyen, Review Branch I

8/22/2003
Yih Chain Huang
Team Leader, Review Branch I

8/25/03
for
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

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IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study (AA01111): Comparative, Randomized, Single-Dose, Fully Replicated, 4-Way Crossover Bioavailability Study of Ranbaxy and Schering (Claritin-D 24 Hour) 10 mg Loratadine/240 mg Pseudoephedrine Sulfate Extended-Release Tablets in Healthy Adult Volunteers Under Fasting Conditions

Study Information

Study Number AA01111
Clinical Site MDS Pharma Services, Quebec, Canada
Principal Investigator Gaetano Morelli, M.D.
Study/Dosing Dates 06/21/02 to 08/29/02
Analytical Site MDS Pharma Services, Quebec, Canada
Analytical Director (b) (6) , Ph.D..
Analysis Dates Loratadine and DCL, 10/04/02 to 11/01/02; pseudoephedrine, 10/25/02 to 11/11/02
Maximum Storage Period 136 days for loratadine and DCL, and 142 days for pseudoephedrine (between the day the first sample was collected and the day the last sample was analyzed).

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Loratadine/Pseudoephedrine Sulfate ER Tablets	Claritin-D 24 Hour ER Tablets
Manufacturer	Ranbaxy	Schering
Batch/Lot No.	7240202	1-DCS-2039
Manufacture Date	Not provided	
Expiration Date	02/2004	10/2002
Strength	10 mg/240 mg	10 mg/240 mg
Dosage Form	ER Tablets	ER Tablets
Batch Size	(b) (4)	
Potency %	96.1/96.7 loratadine/pseudoephedrine	100.8/98.0 loratadine/pseudoephedrine
Content Uniformity %(RSD)*	95.3(3.0)/97.5(1.2) loratadine/pseudoephedrine	101.5(3.5)/98.6(0.7) loratadine/pseudoephedrine
Formulation	See Appendix	
Dose Administered	1x10 mg/240 mg	1x10 mg/240 mg
Route of Administration	Oral	Oral

*NOTE: The difference in content uniformity for loratadine between the test and reference products is >5% (6.2%). However, the potency assay difference is <5% (4.7%) for loratadine.

No. of Sequences		2 (ABAB and BABA)	
No. of Periods		4	
No. of Treatments		2	**Balanced** yes
No. of Groups/Sequence	1		**Washout Period** 21 days
Randomization Scheme		Yes	

Blood Sampling Times	All analytes: Predose, 1, 2, 3, 4, 5, 6, 9, 12, 15, 24, and 36 hours Loratadine and DCL only: 0.25, 0.5, 0.75, 1.25, 1.5, 1.75, 2.5, 3.5, 4.5, 48 and 72 hours DCL only: 96 and 12 hours Pseudoephedrine only: 5.5, 6.5, 7, 7.5 and 30 hours
Blood Volume Collected/Sample	5 mL/sample for loratadine and DCL, 3 mL/sample for pseudoephedrine
Blood Sample Processing/Storage	In vacutainers containing EDTA, plasma was separated after centrifuging, and stored at –20C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See below
Length of Fasting	10 hours predose until 4 hours postdose
Length of Confinement	10 hours predose until 36 hours postdose
Safety Monitoring	Sitting blood pressure and heart rate were measured predose, and at approximately 2, 4, 8 and 12 hours postdose. A 12-lead ECG was performed predose and approximately 5 hours postdose.

Subjects Demographics: Data provided were not legible. The firm is requested to resubmit the demographic data.

Study Results

Clinical: The firm's clinical summary is provided on Pages 3777-3798, Vol. C1.10

Dropout Information Subject # 11 was withdrawn because of low HGB (hemoglobin). Subject #12 was withdrawn because of adverse even prior to Period 2. Subject # 24 did not show up for check-in in Period 3. Subject #38 withdrew from study prior to Period 3 for personal reasons.

Adverse Events	The report of adverse events was left out of the submission. The firm is requested to submit the report.
Protocol Deviations	For minor deviations in blood sampling times and other deviations, see pages 3789-3790, Vol. C1.10

Comments: None of the above adverse events or protocol deviations were judged clinically significant by the study investigator.

During Study Method Validation - Fasting Study AA01111: Loratadine

QC Conc. (pg/mL)	60.1 pg/mL (n=81)	3003 pg/mL (n=82)	8008 pg/mL (n=81)	8008 pg/mL (n=3)*	8008 pg/mL (n=3)*
Inter day Precision (%CV)	10.3	3.5	3.4	1.2	0.4
Inter day Accuracy (% Accuracy)	98.7	101.7	92.4	93.8	89.3
Cal. Standards Conc. (pg/mL)	20.0, 40.0, 100.1, 400.4, 1001, 5005, 7528, 8809, 10010				
Inter day Precision (%CV)	1.6-7.5				
Inter day Accuracy (% Accuracy)	94.4-107.0				
Long-term frozen storage stability (if applicable)	See the prestudy validation data.				
Linearity Range (range of R^2 values)	0.9943-0.9997				
Linearity Range (pg/mL)	20.0-10010				

*These QCs appear to be diluted. However, the dilution was not specified in the analytical report. The firm is requested to provide additional information concerning these QCs.
NOTE: The highest loratadine Cmax concentration measured was 14923 pg/mL. The QC and standard ranges are considered acceptable when dilution is included.

During Study Method Validation - Fasting Study AA01111: DCL

QC Conc. (pg/mL)	60.2 pg/mL (n=83)	2006 pg/mL (n=84)	5515 pg/mL (n=83)	5515 pg/mL (n=3)*	5515 pg/mL (n=3)*
Inter day Precision (%CV)	8.8	4.0	4.5	1.8	1.1
Inter day Accuracy (% Accuracy)	96.0	98.1	92.6	95.5	89.9
Cal. Standards Conc. (pg/mL)	20.1, 40.1, 100.3, 401.1, 1003, 3490, 5014, 6217, 7019				
Inter day Precision (%CV)	2.1-6.2				
Inter day Accuracy (% Accuracy)	93.9-105.5				
Long-term frozen storage stability (if applicable)	See the prestudy validation data.				
Linearity Range (range of R^2 values)	0.9914-0.9991				
Linearity Range (pg/mL)	20.1-7019				

*These QCs appear to be diluted. However, the dilution was not specified in the analytical report. The firm is requested to provide additional information concerning these QCs.
NOTE: The highest DCL Cmax concentration measured was 10356 pg/mL. The QC and standard ranges are considered acceptable when dilution is included.

During Study Method Validation - Fasting Study AA01111: Pseudoephedrine

QC Conc. (ng/mL)	15.00 (n=77)	360.0 (n=78)	1200 (n=78)
Inter day Precision (%CV)	22.1	3.2	2.6
Inter day Accuracy (% Accuracy)	113.3	100.9	98.2
Cal. Standards Conc. (ng/mL)	5.00, 10.0, 25.0, 50.0, 100.0, 250.0, 500.0, 1000, 1350, 1500		
Inter day Precision (%CV)	2.0-6.1		
Inter day Accuracy (% Accuracy)	94.4-109.6		
Long-term frozen storage stability (if applicable)	The prestudy validation data only covered the storage period of 105 days for pseudoephedrine. The firm is requested to submit update long-term stability data to cover the storage period of 142 days for this analyte.		
Linearity Range (range of R^2 values)	0.9951-0.9995		
Linearity Range (ng/mL)	5.00-1500		

NOTE: The highest pseudoephedrine Cmax concentration measured was 836.3 ng/mL. The QC and standard ranges are considered acceptable.

Repeat Assays: No reassay samples were identified. No reassay SOP was submitted. The firm is requested to provide a list of reassay samples with the reassay reasons as well as the SOP for reassay selection and acceptance .

Chromatograms: Split peaks were observed for most of DCL chromatograms and some of loratadine and pseudoephedrine chromatograms. The firm is requested to provide explanation for the split peaks as well as the procedure for measuring peak height/peak area of these chromatograms.

Conclusion: Analytical method is deficient. See Deficiency Comments section.

Pharmacokinetic/Statistical Analysis

Since the analytical validation report was found deficient, the review of the pharmacokinetic/statistical analysis can not be completed at this time. Following is the summary of the study results as provided by the firm and not yet verified by the reviewer.

Mean Pharmacokinetic Parameters and 90% Confidence Intervals:

A. Arithmetic Mean Pharmacokinetic Parameters

Loratadine

Parameter	Units	Test						Reference					
		Replicate 1			Replicate 2			Replicate 1			Replicate 2		
		Mean	N	SD	Mean	N	SD	Mean	N	SD	Mean	N	SD
AUC0-t	Pg.hr/mL	6658	37	4540	7161	34	5975	6358	37	5148	6706	35	6135
AUCi	Pg.hr/mL	7405	33	4994	7883	32	6488	6972	35	5538	7385	34	6636
Cmax	Pg/mL	2336	37	1564	2625	34	2270	2372	37	1952	2691	35	2966
Tmax	Hrs	1.22	37	0.555	1.16	34	0.333	1.11	37	0.308	1.09	35	0.291
T1/2	hrs	15.54	33	10.85	15.02	32	13.87	12.48	35	10.15	14.32	34	13.59

DCL

Parameter	Units	Test						Reference					
		Replicate 1			Replicate 2			Replicate 1			Replicate 2		
		Mean	N	SD	Mean	N	SD	Mean	N	SD	Mean	N	SD
AUC0-t	Pg.hr/mL	47380	37	26292	45909	34	21917	46541	37	23511	45363	35	23860
AUCi	Pg.hr/mL	48924	37	27669	47734	34	24247	48286	37	25132	47023	35	25315
Cmax	Pg/mL	3635	37	1577	3769	34	1604	3480	37	1355	3690	35	1918
Tmax	Hrs	1.83	37	1.08	1.73	34	1.03	1.69	37	1.04	1.60	35	0.917
T1/2	hrs	21.97	37	4.52	23.91	34	6.08	24.25	37	7.35	23.39	35	6.51

Pseudoephedrine

Parameter	Units	Test						Reference					
		Replicate 1			Replicate 2			Replicate 1			Replicate 2		
		Mean	N	SD	Mean	N	SD	Mean	N	SD	Mean	N	SD
AUC0-t	Ng.hr/mL	7306	37	1497	7447	34	1575	7276	37	1727	7249	35	1586
AUCi	Ng.hr/mL	7706	37	1606	7761	34	1750	7785	37	2030	7701	35	1727
Cmax	Ng/mL	467.4	37	115.6	448.3	34	84.67	409.0	37	73.53	423.6	35	104.4
Tmax	Hrs	6.88	37	1.64	6.94	34	2.25	6.22	37	1.52	6.54	35	2.04
T1/2	hrs	6.33	37	1.36	6.18	34	1.41	7.40	37	2.85	7.14	35	2.49

B. Geometric Mean and 90% Confidence Intervals

Loratadine

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	5115	4565	111.4	1.02, 1.22
AUCi	5607	4993	111.6	1.02, 1.22
Cmax	1883	1752	107.0	0.97, 1.18

DCL

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	41970	41231	101.7	0.98, 1.05
AUCi	43278	42625	101.4	0.98, 1.05
Cmax	3396	3273	104.3	1.00, 1.09

Pseudoephedrine

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	7267	7070	103.2	1.00, 1.06
AUCi	7550	7510	100.9	0.98, 1.04
Cmax	448.6	407.9	110.1	1.06, 1.14

C. Total SD and within-subject error (root MSE): Values can not be verified by the reviewer's own analysis at this time due to deficiency found in the analytical report.

Comments: (on pharmacokinetic analysis)

The study is incomplete due to deficiencies found in the analytical validation report.

2. Single-dose Nonfasting Bioequivalence Study (AA01112): Comparative, Randomized, Single-Dose, Fully Replicated, 4-Way Crossover Bioavailability Study of Ranbaxy and Schering (Claritin-D 24 Hour) 10 mg Loratadine/240 mg Pseudoephedrine Sulfate Extended-Release Tablets in Healthy Adult Volunteers Under Fed Conditions

Study Information

Study Number AA01112
Clinical Site MDS Pharma Services, Quebec, Canada
Principal Investigator Gaetano Morelli, M.D.
Study/Dosing Dates 06/29/02 to 09/05/02
Analytical Site MDS Pharma Services, Quebec, Canada
Analytical Director (b) (6), Ph.D.
Analysis Dates 09/15/02 to 10/10/02 for loratadine and DCL; 09/16/02 to 10/22/02 for pseudoephedrine
Maximum Storage Period (between the day the first sample was collected and the day the last sample was analyzed): 103 days for loratadine and DCL and 115 days for pseudoephedrine.

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Loratadine/Pseudoephedrine Sulfate ER Tablets	Claritin-D 24 Hour ER Tablets
Manufacturer	Ranbaxy	Schering
Batch/Lot No.	7240202	1-DCS-2039
Manufacture Date	Not provided	
Expiration Date	02/2004	10/2002
Strength	10 mg/240 mg	10 mg/240 mg
Dosage Form	ER Tablets	ER Tablets
Batch Size	(b) (4)	
Potency %	96.1/96.7 loratadine/pseudoephedrine	100.8/98.0 loratadine/pseudoephedrine
Content Uniformity %(RSD)	95.3(3.0)/97.5(1.2) loratadine/pseudoephedrine	101.5(3.5)/98.6(0.7) loratadine/pseudoephedrine
Formulation	See Appendix	
Dose Administered	1x10 mg/240 mg	1x10 mg/240 mg
Route of Administration	Oral	Oral

No. of Sequences 2 (ABAB and BABA)
No. of Periods 4
No. of Treatments 2 **Balanced** yes
No. of Groups/Sequence 1 **Washout Period** 21 days
Randomization Scheme Yes
Blood Sampling Times All analytes: Predose, 1, 2, 3, 4, 5, 6, 9, 12, 15, 24, and 36 hours
Loratadine and DCL only: 0.25, 0.5, 0.75, 1.25, 1.5, 1.75, 2.5, 3.5, 4.5, 48 and 72 hours
DCL only: 96 and 12 hours
Pseudoephedrine only: 5.5, 6.5, 7, 7.5 and 30 hours
Blood Volume Collected/Sample 5 mL/sample for loratadine and DCL, 3 mL/sample for pseudoephedrine

Blood Sample Processing/Storage	In vacutainers containing EDTA, plasma was separated after centrifuging, and stored at –20C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See below
Length of Fasting	10 hours predose until a standardized breakfast 30 minutes prior to dosing*
Length of Confinement	10 hours predose until 36 hours postdose
Safety Monitoring	Sitting blood pressure and heart rate were measured predose, and at approximately 2, 4, 8 and 12 hours postdose. A 12-lead ECG was performed predose and approximately 5 hours postdose.

***NOTE:** The standard breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 rasher of Canadian bacon, 1 serving of hash brown potatoes, 180 mL of orange juice and 240 mL whole milk.

Subjects Demographics: The firm is requested to provide additional summary for subject demographics which include only the subjects used in the study.

Study Results

Clinical: The firm's clinical summary is provided on Pages 601-634, Vol. C1.2

Dropout Information Subject #6 did not show for check-in, Period 2. Subjects #10 and 30 withdrew prior to Period 3 due to adverse events. Subject #38 was withdrawn due to positive drug test at check-in, Period 2.

Adverse Events	# Total events possibly/probably drug related: 53 (dizziness, headache, feeling weak, nausea, upset stomach, redness on arm, neck, chest, shoulder, runny nose, nasal congestion, cough, feeling cold, sleepiness, sore throat, vomited, itchiness) # received Treatment A: 31 # received Treatment B: 22 All others unrelated to study medication: 13 For additional information see Vol. C1.2, pages # 626-630
Protocol Deviations	Deviations in blood sampling times and other deviations can be found on Vol. C1.2, pages 612-614, and pages 623-625.

Comments: None of the above adverse events or protocol deviations were judged clinically significant by the study investigator.

During Study Method Validation - Nonfasting Study AA01112: Loratadine

QC Conc. (pg/mL)	60.1 (n=157)	3003 (n=158)	8008 (n=158)	8008 (n=4)*	8008 (n=2)*	8008 (n=10)*
Inter day Precision (%CV)	9.6	4.1	4.1	2.9	5.4	5.3
Inter day Accuracy (% Accuracy)	96.8	97.5	96.7	94.9	78.7	89.2
Cal. Standards Conc. (pg/mL)	20.0, 40.0, 100.1, 400.4, 1001, 5005, 7528, 8809, 10010					
Inter day Precision (%CV)	1.6-8.7					
Inter day Accuracy (% Accuracy)	92.8-106.8					
Long-term frozen storage stability (if applicable)	See the prestudy validation data.					
Linearity Range (range of R^2 values)	0.9904-0.9992					
Linearity Range (pg/mL)	20.0-10010					

*These QCs appear to be diluted. However, the dilution was not specified in the analytical report. The firm is requested to provide additional information concerning these QCs.
NOTE: The highest loratadine Cmax concentration measured was 14923 pg/mL. The QC and standard ranges are considered acceptable when dilution is included.

During Study Method Validation - Nonfasting Study AA01112: DCL

QC Conc. (pg/mL)	60.2 (n=157)	2006 (n=158)	5495 (n=148)	5495 (n=4)*	5495 (n=8)*	5515 (n=10)*	5515 (n=2)*
Inter day Precision (%CV)	6.1	4.2	4.3	4.5	9.0	2.5	1.4
Inter day Accuracy (% Accuracy)	93.2	90.4	93.5	89.6	88.7	85.1	87.8
Cal. Standards Conc. (pg/mL)	20.1, 40.1, 100.3, 401.1, 1003, 3490, 5014, 6217, 7019						
Inter day Precision (%CV)	1.8-4.4						
Inter day Accuracy (% Accuracy)	93.4-106.9						
Long-term frozen storage stability (if applicable)	See the prestudy validation data.						
Linearity Range (range of R^2 values)	0.9897-0.9988						
Linearity Range (pg/mL)	20.1-7019						

*These QCs appear to be diluted. However, the dilution was not specified in the analytical report. The firm is requested to provide additional information concerning these QCs.
NOTE: The highest loratadine Cmax concentration measured was 14923 pg/mL. The QC and standard ranges are considered acceptable when dilution is included.

During Study Method Validation - Fasting Study AA01112: Pseudoephedrine

QC Conc. (ng/mL)	15.00 (n=75)	360.0 (n=75)	1200 (n=76)
Inter day Precision (%CV)	18.2	3.7	3.7
Inter day Accuracy (% Accuracy)	107.9	103.3	99.1
Cal. Standards Conc. (ng/mL)	5.00, 10.0, 25.0, 50.0, 100.0, 250.0, 500.0, 1000, 1350, 1500		
Inter day Precision (%CV)	2.4-7.0		
Inter day Accuracy (% Accuracy)	93.4-109.2		
Long-term frozen storage stability (if applicable)	The prestudy validation data only covered the storage period of 105 days for pseudoephedrine. The firm is requested to submit update long-term stability data to cover the storage period of 142 days for this analyte.		
Linearity Range (range of R^2 values)	0.9910-0.9993		
Linearity Range (ng/mL)	5.00-1500		

Repeat Assays:

Repeat Assays: No reassay samples were identified. No reassay SOP was submitted. The firm is requested to provide a list of reassay samples with the reassay reasons as well as the SOP for reassay selection and acceptance .

Chromatograms: Split peaks were observed for most of DCL chromatograms and some of loratadine and pseudoephedrine chromatograms. The firm is requested to provide explanation for the split peaks as well as the procedure for measuring peak height/peak area of these chromatograms.

Conclusion: Analytical method is deficient. See Deficiency Comments section.

Pharmacokinetic/Statistical Analysis

Since the analytical validation report was found deficient, the review of the pharmacokinetic/statistical analysis can not be completed at this time. Following is the summary of the study results as provided by the firm and not yet verified by the reviewer.

Mean Pharmacokinetic Parameters and 90% Confidence Intervals:

A. Arithmetic Mean Pharmacokinetic Parameters

Loratadine

Parameter	Units	Test						Reference					
		Replicate 1			Replicate 2			Replicate 1			Replicate 2		
		Mean	N	SD	Mean	N	SD	Mean	N	SD	Mean	N	SD
AUC0-t	Pg.hr/mL	22423	35	31292	16549	35	18103	18085	37	22160	19114	35	24470
AUCi	Pg.hr/mL	23755	35	33026	17867	34	19574	19495	36	23151	20465	35	25751
Cmax	Pg/mL	5060	35	6102	3861	35	3603	4099	37	4514	4429	35	5118
Tmax	Hrs	2.02	35	0.787	2.34	35	0.90	1.84	37	0.74	2.28	35	1.52
T1/2	hrs	21.93	35	12.74	21.83	34	14.67	20.96	36	12.84	23.16	35	16.77

DCL

Parameter	Units	Test						Reference					
		Replicate 1			Replicate 2			Replicate 1			Replicate 2		
		Mean	N	SD	Mean	N	SD	Mean	N	SD	Mean	N	SD
AUC0-t	Pg.hr/mL	46293	35	26544	46377	35	24506	45256	37	26108	50269	35	31791
AUCi	Pg.hr/mL	48611	35	30084	48246	34	26853	47082	37	28279	52501	35	34158
Cmax	Pg/mL	3434	35	1789	3359	35	1751	3190	37	1512	3378	35	2122
Tmax	Hrs	2.71	35	1.61	2.76	35	1.20	2.32	37	1.06	2.82	35	1.44
T1/2	hrs	25.98	35	6.54	25.87	34	6.19	25.17	37	4.96	27.25	35	5.68

Pseudoephedrine

Parameter	Units	Test						Reference					
		Replicate 1			Replicate 2			Replicate 1			Replicate 2		
		Mean	N	SD	Mean	N	SD	Mean	N	SD	Mean	N	SD
AUC0-t	Ng.hr/mL	7494	35	1422	7421	35	1486	7382	37	1715	7320	35	1540
AUCi	Ng.hr/mL	7781	35	1530	7701	35	1680	7686	37	1877	7654	35	1746
Cmax	Ng/mL	444.8	35	70.94	436.5	35	80.65	450.2	37	84.29	442.6	35	89.10
Tmax	Hrs	7.31	35	2.30	8.03	35	2.12	7.43	37	2.00	7.50	35	1.74
T1/2	hrs	5.81	35	1.29	5.88	35	1.36	6.16	37	1.50	6.33	35	1.79

C. Geometric Mean and 90% Confidence Intervals

Loratadine

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	11261	11197	1.01	Not determined
AUCi	12084	12057	1.00	Not determined
Cmax	2887	2732	1.06	Not determined

DCL

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	41549	42159	0.99	Not determined
AUCi	43104	43661	0.99	Not determined
Cmax	3093	2982	1.04	Not determined

Pseudoephedrine

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	7398	7234	1.02	Not determined
AUCi	7671	7526	1.02	Not determined
Cmax	436.3	441.0	0.99	Not determined

C. Total SD and within-subject error (root MSE): Values can not be verified by the reviewer's own analysis at this time due to deficiency found in the analytical report.

Comments: (on pharmacokinetic analysis)

The study is incomplete due to deficiencies found in the analytical validation report.

Dissolution Data

1. Condition: USP I (basket) at 75 rpm
900 mL 0.1 N HCl for 0-1 hour
900 mL pH 6.8 phosphate buffer for 1-16 hours

Loratadine

Reference Product
Lot No.: 1-DCS-2039
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Time(min.)	Mean	Range	%CV
15	90	(b) (4)	4.0
30	95		4.4
45	97		4.1
60	98		4.3

Test Product
Lot No.: 7240202
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Mean	Range	%CV
74	(b) (4)	4.4
95		3.8
100		3.5
102		3.5

Pseudoephedrine

Reference Product
Lot No.: 1-DCS-2039
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Time(min.)	Mean	Range	%CV
15	9	(b) (4)	4.4
30	14		3.0
45	19		2.8
60	23		3.7
120	41		14
240	56		7.8
360	67		5.8
480	76		3.5
600	82		3.2
720	88		2.5
840	91		1.6
960	94		1.9

F2: 71.90

Test Product
Lot No.: 7240202
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Mean	Range	%CV
4	(b) (4)	10
11		4.3
17		3.1
21		4.1
34		3.8
51		3.2
65		4.4
75		4.0
83		3.8
89		3.6
94		3.0
97		3.1

2. Condition: USP I (basket) at 75 rpm
900 mL 0.1 N HCl for 16 hours

Loratadine

Reference Product
Lot No.: 1-DCS-2039
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Time(min.)	Mean	Range	%CV
15	88	(b) (4)	4.3
30	93		4.6
45	95		5.2
60	96		4.3

Test Product
Lot No.: 7240202
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Mean	Range	%CV
88	(b) (4)	5.6
99		5.4
100		5.1
102		5.6

Pseudoephedrine

Reference Product
Lot No.: 1-DCS-2039
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Test Product
Lot No.: 7240202
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Time(min.)	Mean	Range	%CV	Mean	Range	%CV
15	9	(b) (4)	6.0	7	(b) (4)	19
30	15		4.2	15		14
45	19		3.5	19		5.6
60	24		2.5	23		3.8
120	39		3.6	38		3.1
240	57		1.8	55		3.6
360	70		1.3	69		3.3
480	80		1.2	78		3.2
600	88		1.0	86		3.0
720	92		0.98	91		3.3
840	96		0.94	96		2.7
960	99		0.81	99		2.4

F2: 87.68

3. Condition: USP I (basket) at 75 rpm
900 mL 0.1 N HCl for 0-1 hour
900 mL pH 4.5 buffer for 1-16 hours

Loratadine

Reference Product
Lot No.: 1-DCS-2039
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Test Product
Lot No.: 7240202
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Time(min.)	Mean	Range	%CV	Mean	Range	%CV
15	89	(b) (4)	2.7	82	(b) (4)	4.7
30	95		2.8	96		4.4
45	97		3.1	99		4.5
60	99		3.1	101		4.6

Pseudoephedrine

Reference Product
Lot No.: 1-DCS-2039
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Test Product
Lot No.: 7240202
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Time(min.)	Mean	Range	%CV	Mean	Range	%CV
15	8	(b) (4)	6.4	6	(b) (4)	11
30	14		5.3	13		8.6
45	19		5.3	19		5.8
60	24		3.8	23		4.5
120	37		2.2	38		6.8
240	56		6.4	54		4.0
360	68		4.2	66		3.8
480	77		3.5	76		3.1
600	85		2.9	83		2.8
720	89		2.2	88		2.3
840	93		1.7	93		2.1
960	96		1.3	96		2.1

F2: 87.72

4. **Condition:** USP I (basket) at 75 rpm
900 mL pH 6.8 phosphate buffer for 16 hours

Loratadine

Reference Product
Lot No.: 1-DCS-2039
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Time(min.)	Mean	Range	%CV
15	14	(b) (4)	22
30	19		23
45	20		19
60	21		13

F2=84.95

Test Product
Lot No.: 7240202
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Mean	Range	%CV
13	(b) (4)	13
18		5.3
21		4.5
24		4.7

Pseudoephedrine

Reference Product
Lot No.: 1-DCS-2039
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Time(min.)	Mean	Range	%CV
15	7	(b) (4)	8.6
30	13		4.5
45	17		5.2
60	21		5.0
120	35		2.3
240	52		2.9
360	66		3.0
480	76		3.4
600	85		3.6
720	91		4.0
840	97		4.7
960	100		4.6

F2: 80.75

Test Product
Lot No.: 7240202
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Mean	Range	%CV
6	(b) (4)	30
11		15
17		9.5
21		6.3
36		3.0
55		1.9
70		1.6
79		1.2
87		1.3
93		1.3
97		1.1
99		1.4

5. **Condition:** USP I (basket) at 75 rpm
900 mL 0.1 N HCl for 0-1 hour
900 mL Water for 1-16 hours

Loratadine

Reference Product
Lot No.: 1-DCS-2039
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Time(min.)	Mean	Range	%CV
15	92	(b) (4)	5.1
30	97		5.9
45	99		5.8
60	100		5.2

Test Product
Lot No.: 7240202
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Mean	Range	%CV
82	(b) (4)	7.9
94		3.9
97		3.5
99		3.6

Pseudoephedrine

Reference Product Lot No.: 1-DCS-2039 Strength: 10 mg/240 mg loratadine/pseudoephedrine No. of Units: 12				Test Product Lot No.: 7240202 Strength: 10 mg/240 mg loratadine/pseudoephedrine No. of Units: 12		
Time(min.)	Mean	Range	%CV	Mean	Range	%CV
15	9	(b) (4)	9.4	6	(b) (4)	21
30	15		3.8	12		4.3
45	19		2.6	18		3.0
60	25		1.6	22		4.8
120	39		1.6	35		2.9
240	55		1.0	51		3.2
360	68		0.98	62		4.4
480	77		1.0	71		3.5
600	84		0.94	77		3.3
720	89		1.0	81		2.7
840	94		1.2	85		2.7
960	97		0.86	87		3.2
F2: 64.84						

Comments: The dissolution data as submitted are incomplete. The firm is requested to conduct additional dissolution testing using the FDA-recommended dissolution method.

C. Attachment: Formulation of Ranbaxy's Loratadine and Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg

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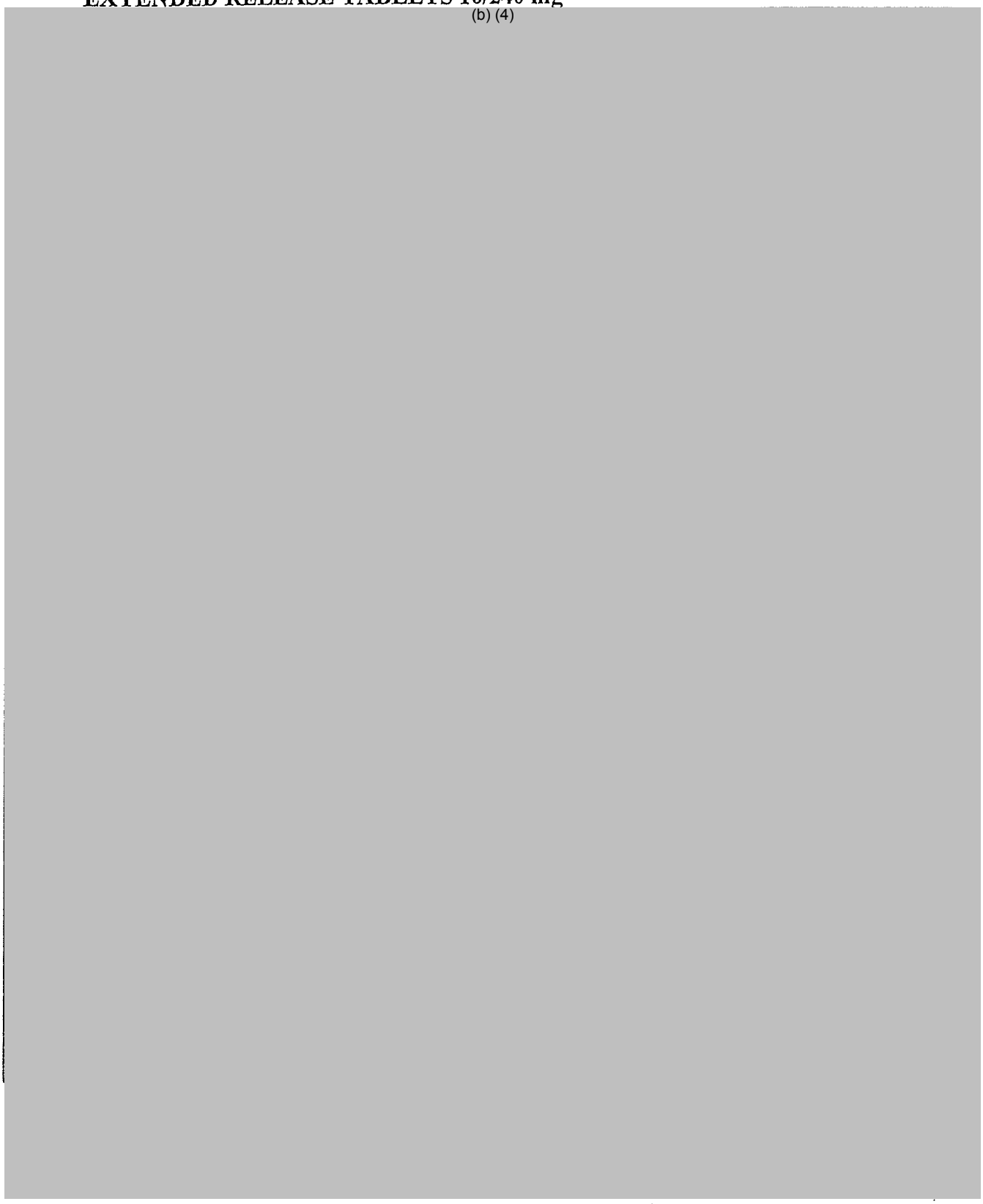
LORATADINE AND PSEUOEPHEDRINE SULFATE
EXTENDED RELEASE TABLETS 10/240 mg

(b) (4)



BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-557 APPLICANT: Ranbaxy Laboratories

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

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

1. Please submit long-term stability data for pseudoephedrine covering a freezer storage period of at least 142 days which was the maximum storage period for the actual study samples. Currently, you have only provided long-term stability data for a freezer storage period of 105 days.

2. For both blue (archival section) and orange (pharmacokinetic section) jackets of Volume 1.10, the Appendices 5.5 (Adverse Events), 5.6 (Concomitant Medication Report) and 5.7 (Drug Accountability), of the Fasting Study, were left out. Please provide these missing sections of the Clinical Report.

3. For Appendix 5.2 (Demographic Information) of the Fasting Study, pp. 3795-3797, the text is illegible. Please provide a legible copy of the Appendix 5.2. In addition to the summary information given in the table, please provide additional demographic summary for only the subjects that were included in the study (mean, SD and range of age, weight and height), for both Fasting and Nonfasting Studies.

4. For both the Fasting and Nonfasting Studies, please provide raw numerical data which include peak heights and/or peak areas, peak height and/or peak area ratios, and the order in which all study samples, standards and QCs were assayed and reassayed, if any. Currently you have only submitted the calculated plasma concentration data for study samples.

5. For both the Fasting and Nonfasting Studies, please provide a list of reassayed samples with the reassay reasons and values. Only a list of pseudoephedrine reassayed samples of the Nonfasting Study was submitted. The SOPs for assay method validation and especially for reassay selection and acceptance should be provided.

6. For the assays of loratadine and descarboethoxyloratadine (DCL), diluted QCs appeared to be included in some of the analytical runs, of the Fasting and Nonfasting Studies. Please provide detailed information on how these diluted QCs were prepared.

7. For both the Fasting and Nonfasting Studies, please provide explanations for the split asymmetrical peaks seen in most of DCL/DCL internal standard chromatograms, and in some of loratadine and pseudoephedrine, and on how these peaks were integrated.

8. For the Nonfasting Study, please provide the reasons for not assaying the samples of Period 2 of Subjects #26 and 27.

9. Please conduct additional dissolution testing using the FDA-recommended method: 1000 mL 0.1N HCl in first hour then 1000 mL 0.1M phosphate buffer pH 7.5 for next 15 hours, using USP Paddle at 50 rpm for both acid and buffer stages. The recommended sampling times are: 5, 10, 20, 30 and 45 minutes for loratadine, 1, 4, 8 and 16 hours for pseudoephedrine.

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

CC:ANDA 76-557
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 8/22/2003
HFD-617/ A. Sigler
HFD-650/ D. Conner 8/25/03

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Printed in final on / /

BIOEQUIVALENCY - INCOMPLETE Submission date: 12-04-02

1. FASTING STUDY (STF) I/C Strength: 10 mg/240 mg
   Clinical: MDS Pharma Services **Outcome: IC**
   Analytical: MDS Pharma Services

2. NON-FASTING STUDY (STP) I/C Strength: 10 mg/240 mg
   Clinical: MDS Pharma Services **Outcome: IC**
   Analytical: MDS Pharma Services

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-557
Drug Product Name	Loratadine/Pseudoephedrine Sulfate Extended-Released Tablets
Strength	10 mg/240 mg
Applicant Name	Ranbaxy Laboratories
Address	Gurgaon, India
Submission Date(s)	October 20, 2003
Amendment Date(s)	N/A
Reviewer	Hoainhon Nguyen
File Location	c:\firmsnz\ranbaxy\ltrs&rev\76557a1003.doc

I. Executive Summary

This is a review of an amendment submitted in response to the DBE's deficiency comments in the review of the original submission dated 12/04/02. This application references Claritin-D (loratadine/pseudoephedrine Sulfate, 10 mg/240 mg) 24 Hour ER Tablets and includes one fasting and one fed BE study. The fasting study is a single-dose four-way replicated, crossover study using 27 male and 10 female normal healthy volunteers given a dose of 1x10 mg/240 mg loratadine/ pseudoephedrine. The fasting study was found acceptable with the following results (point estimate, 90% CI): LAUCT of 1.11, 101.8-121.3% (loratadine), 1.02, 98.3-105.3% (descarboethoxyloratadine(DCL)), 1.03, 100.1-106.4%(pseudoephedrine); LAUCi of 1.12, 102.1-122.0% (loratadine), 1.01, 98.0-104.9% (DCL), 1.01, 97.8-104.4% (pseudoephedrine); and LCmax of 1.07, 96.8-118.2%(loratadine), 1.04, 100.2-108.5% (DCL) and 1.10, 106.4-114.0% (pseudoephedrine). The fed BE study is also a single-dose four-way replicated, crossover study using 31 male and 6 female normal healthy volunteers given a dose of 1x10 mg/240 mg loratadine/pseudoephedrine. The fed study was conducted before the issuance of the CDER food-effect guidance. The nonfasting study was found acceptable with the following results (point estimate): LAUCt of 1.01 (loratadine), 0.99 (DCL) and 1.02 (pseudoephedrine); LAUCi of 1.00 (loratadine), 0.99 (DCL) and 1.02 (pseudoephedrine); and LCmax of 1.06 (loratadine), 1.04 (DCL) and 0.99 (pseudoephedrine).

The dissolution testing and formulation of the test product have been found acceptable. The dissolution results met the FDA-recommended specifications. The application however is considered incomplete since the firm's proposed dissolution method and specifications are different from those recommended by the FDA.

When a fresh test lot is produced, the firm is requested to submit dissolution results for the fresh test lot using the FDA-recommended dissolution method on 12 units since the firm has only tested 6 units of the test lot in the current amendment using the FDA dissolution method, and the test lot was 18 months old at the time of this testing.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Ranbaxy's Loratadine/Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, Lot# 7240202
Reference Product	Claritin-D (loratadine/pseudoephedrine, 10 mg/240 mg) 24 Hour ER Tablets (NDA # 20-470, Schering, Approved 08/23/96) Lot # 1-DCS-2039
Indication	indicated for the relief of symptoms of seasonal allergic rhinitis.

PK/PD Information See the original review (v:\firmsnz\ranbaxy\ltrs&rev\76557n1202)

Relevant DBE History: See the original review (v:\firmsnz\ranbaxy\ltrs&rev\76557n1202)

B. Contents of Submission

		How many?
Study Amendment	X	1

C. Bioanalytical Method Validation (Pre-Study, Vol. C1.3, pages. 945-982 and Vol. C1.7, pages 2468-2510)

See the original review (v:\firmsnz\ranbaxy\ltrs&rev\76557n1202)

D. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study No.	AA01111			
Study Design	randomized, 4-way replicated crossover			
No. of subjects enrolled	40 (36 plus 4 alternates)			
No. of subjects completing	36			
No. of subjects with samples analyzed	37*			
Subjects				
Sex(es) included (how many)	Male	27	Female	10
Test product	Ranbaxy's Loratadine/Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, Lot # 7240202			

Reference product	Schering's Claritin-D (loratadine/pseudoephedrine sulfate, 10 mg/240 mg) 24 Hour ER Tablets, Lot # 1-DCS-2039
Strength tested	10 mg/240 mg
Dose	1x10 mg/240 mg

*NOTE: Data analyses were performed on data from all subjects who completed at least 2 periods of the study. Per protocol, for every subject who did not complete the full 4 periods, an alternate subject was added for laboratory analyses and included in the statistical analyses. Subjects excluded from the analyses were not necessarily dropout subjects. Dropout subjects were Subjects #11 (prior to Period 4), #12 (prior to Period 2), #24 and # 38 (prior to Period 3). **Subjects not included in the study analyses** were **Subject #12** who did not complete 2 periods, **Subjects # 23 and 31** who vomited early in Period 3 and Period 4, respectively. Thus, dropout Subjects #11, 24 and 38 were included in the study analyses.

Summary of Statistical Analysis: (N=37)

Loratadine

Parameter	Point Estimate	90% Confidence Interval
AUCt	1.11	101.8-121.3
AUCi	1.12	102.1-122.0
Cmax	107.0	96.8-118.2

DCL

Parameter	Point Estimate	90% Confidence Interval
AUCt	1.02	98.3-105.3
AUCi	1.01	98.0-104.9
Cmax	1.04	100.2-108.5

Pseudoephedrine

Parameter	Point Estimate	90% Confidence Interval
AUCt	1.03	100.1-106.4
AUCi	1.01	97.8-104.4
Cmax	1.10	106.4-114.0

The fasted study is acceptable.

2. Single-dose Nonfasting Bioequivalence Study

Study No.	AA01112
Study Design	randomized, 4-way replicated crossover
No. of subjects enrolled	41 (40 plus 1 alternate)
No. of subjects completing	37
No. of subjects analyzed	37*
Subjects	
Sex(es) included (how many?)	Male 31 Female 6
Test product	Ranbaxy's Loratadine/Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, Lot # 7240202
Reference product	Schering's Claritin-D (loratadine/pseudoephedrine sulfate, 10 mg/240 mg) 24 Hour ER Tablets, Lot # 1-DCS-2039
Strength tested	10 mg/240 mg
Dose	1x10 mg/240 mg

*NOTE: Data analyses were performed on data from subjects who completed at least 2 periods of the study. Per protocol, for every subject who did not complete the full 4 periods, an alternate subject was added for laboratory analyses and included in the statistical analyses. Subjects excluded from the analyses were not necessarily dropout subjects. Dropout subjects were Subjects #6 (prior to Period 2), #10 and 30 (prior to Period 3) and # 38 (prior to

Period 2). **Subjects not included in the study analyses** were **Subjects #6 and 38** who did not complete 2 periods, **Subject # 33** who vomited early in Period 3 and **Subject#20** who had unacceptable predose DCL levels. Thus, dropout Subjects # 10 and 30 were included in the study analyses.

Summary of Statistical Analysis (N=37)

Loratadine

Parameter	Point Estimate	90% Confidence Interval
LAUCt	1.01	91.4-111.0
LAUCi	1.00	90.9-110.8
Lcmax	1.06	95.5-117.0

DCL

Parameter	Point Estimate	90% Confidence Interval
LAUCt	0.99	94.2-104.0
LAUCi	0.99	94.2-104.0
Lcmax	1.04	98.7-108.9

Pseudoephedrine

Parameter	Point Estimate	90% Confidence Interval
LAUCt	1.02	99.8-104.9
LAUCi	1.02	99.1-104.4
Lcmax	0.99	95.6-102.4

The fed study is acceptable.

E. Formulation

See the review of the original submission (v:\firmsnz\ranbaxy\ltrs&rev\76557n1202).

F. In Vitro Dissolution

In the original submission dated 12/04/02, the firm conducted dissolution testing using USP apparatus I (basket) at 75 rpm in 900 mL of various media: pH 6.8 phosphate buffer, pH 4.5 buffer, 0.1 N HCl and water, in addition to the firm's proposed method (basket 75 rpm in 900 mL of 0.1 N HCl for 1 hour and in 900 mL of pH 6.8 phosphate buffer for an additional 15 hours). For the summary of these data, see the review of the original submission. The firm was requested to submit additional dissolution data obtained using the following FDA-recommended method:

Methods Submitted	FDA
Medium, acid statge	0.1 N HCl for 0-1 hour
Medium, buffer stage	pH 7.5 phosphate buffer for 1-16 hours
Volume (mL)	1000 mL
USP Apparatus Type	II (paddle)
Rotation (rpm)	50
FDA's specifications	NLT (b) (4)%, 30 min (loratadine) 1 hour (b) (4) 2 hours (b) (4), 4 hours (b) (4) 8 hours (b) (4) 16 hours (b) (4) (pseudoephedrine)
F2- value (s):	Not calculated since only the dissolution data for the test product were submitted.

G. Waiver Request: Not applicable.

H. Deficiency Comments: In the current amendment, the firm has addressed the following deficiencies identified in the review of the original submission:

1. The firm is requested to submit long-term stability data for pseudoephedrine covering a freezer storage period of at least 142 days which was the maximum storage period for the actual study samples. Currently, the firm has only provided long-term stability data for a freezer storage period of 105 days.

Firm's Response: The firm has provided long-term stability data for pseudoephedrine covering a freezer storage period of 354 days.

DBE's Comment: The long-term stability data are acceptable.

2. For both blue (archival section) and orange (pharmacokinetic section) jackets of Volume 1.10, the Appendices 5.5 (Adverse Events), 5.6 (Concomitant Medication Report) and 5.7 (Drug Accountability), of the Fasting Study, were left out. The firm is requested to provide these missing sections of the Clinical Report.

Firm's Response: The clinical report has been regenerated by MDS Pharma Services and provided in the current amendment.

DBE's Comment: The clinical report as submitted in the current amendment is acceptable. The Adverse Event data are summarized in the Appendix of this review.

3. For Appendix 5.2 (Demographic Information) of the Fasting Study, pp. 3795-3797, the text is illegible. The firm is requested to provide a legible copy of the Appendix 5.2. In addition to the summary information given in the table, the firm is requested to provide additional demographic summary for only subjects that were included in the study (mean, SD and range of age, weight and height), for both Fasting and Nonfasting Studies.

Firm's Response: The firm has provided legible demographic information in the current amendment, even though it did not summarize the demographic data for the fasting and nonfasting studies as requested.

DBE's Comment: The demographic information is acceptable. The demographic data excluding unanalyzed subjects are summarized by the reviewer in the Appendix of this review.

4. For both the Fasting and Nonfasting Studies, the firm is requested to provide raw numerical data which include peak heights and/or peak areas, peak height and/or peak area ratios, and the order in which all study samples, standards and QCs were assayed and reassayed, if any. Currently the firm has only submitted the calculated plasma concentration data for study samples.

Firm's Response: The firm has submitted raw numerical data of loratadine, pseudoephedrine and DCL (descarboethoxyloratadine) for both fasting and nonfasting studies.

DBE's Comment: The raw numerical data as submitted in the current amendment are adequate and acceptable.

5. For both the Fasting and Nonfasting Studies, the firm should provide a list of reassayed samples with the reassay reasons and values. Only a list of pseudoephedrine reassayed samples of the Nonfasting Study was submitted. The SOPs for assay method validation and especially for reassay selection and acceptance should be provided.

Firm's Response: The firm has provided tables of samples reassayed for loratadine, DCL and pseudoephedrine from both fasting and nonfasting studies. The firm has also submitted the SOPs for assay method validation and reassay selection and acceptance.

DBE's Comment: The tables of reassayed samples and SOP's as submitted in the current amendment are adequate and acceptable. All samples were reassayed for analytical reasons only.

6. For the assays of loratadine and DCL, diluted QCs appeared to be included in some of the analytical runs, of the Fasting and Nonfasting Studies. The firm is requested to provide detailed information on how these diluted QCs were prepared.

Firms' Response: *"Dilution integrity, (dilutional linearity), has been assessed for a concentration of 100099.8 pg/mL for loratadine and 59868.3 pg/mL for DCL as indicated in the validation report of 90252-SCE. This assessment involves the preparation of quality control samples at the concentrations described above, and diluting these quality controls appropriately to within the validated analytical range with blank matrix. In addition, in every analytical run with diluted subject samples, 2 quality control samples with the same dilution factor are extracted. There must be a minimum of 1 out of 2 diluted quality control samples within 15% of the actual concentration in order to accept the result for a diluted subject sample."*

DBE's Comment: In addition to the firm's response concerning dilution integrity above, the reviewer was able to find out (from the raw numerical data submitted) the dilution factor for each of the diluted quality control samples listed in the within-study validation report. As indicated by the firm, the diluted quality control samples had the same dilution factor as the diluted subject samples of the same run. The dilution factors of these QC samples are included in the During Study Method Validation tables of this review. The firm's response is considered adequate.

7. For both the Fasting and Nonfasting Studies, the firm is requested to provide explanation for the split and asymmetrical peaks seen in most of DCL/DCL internal standard chromatograms, and in some of loratadine and pseudoephedrine, and on how these peaks were integrated.

Firm's Response: *"The asymmetrical peak observed in most of the DCL and DCL internal standard are most probably due to analytical column performance and not the presence of any interfering peak. The DCL and DCL internal standard peak are fully integrated as no peak separation was observed in the chromatograms."*

DBE's Comment: The firm's explanation is adequate. Observed split peaks appeared to be from electronic noises (spikes) rather than from chemical interferences. The asymmetrical tailing peak shapes are consistent with the peak pattern generated by interaction between eluting sample and column solid support and/or liquid phase.

8. For the Nonfasting Study, the firm is requested to provide the reasons for not assaying the samples for Period 2 of Subjects #26 and 27.

Firm's Response: *"The identity of the 1.5 hour blood draw could not be confirmed for Subjects #26 and 27 in Period 2 for Formulation A (See Protocol Deviations section of the Clinical Conduct of Study Report for further details). Since Tmax is expected to be close to 1.5 hours, all samples from Subject Nos. 26 and 27 in Period 2 were not analyzed to avoid any potential bias. This is the most conservative approach when crucial samples are not available and when we suspect that the pharmacokinetic of a product may not be described adequately. Moreover, this approach does not impact significantly the statistical power since this was a 4-way fully replicate study, and the Cmax parameters pertaining to Formulation A for Subject Nos 26 and 27 in Period 4 were properly characterized (both subjects had the sequence BABA). As a result, the conservative approach we have used is likely to minimize any potential bias associated with the missing 1.5 hour sample in Period 2 for Subject Nos. 26 and 27."*

DBE's Comment: The firm's response is adequate. The reviewer agrees with the firm's approach.

9. The firm is requested to conduct additional dissolution testing using the FDA-recommended method: 1000 mL 0.1N HCl in first hour then 1000 mL 0.1M phosphate buffer pH 7.5 for next 15 hours, using USP Paddle at 50 rpm for both the acid and buffer stages. The recommended sampling times are: 5, 10, 20, 30 and 45 minutes for loratadine, 1, 2, 4, 8 and 16 hours for pseudoephedrine.

Firm's Response: The firm has conducted additional dissolution testing using the FDA-recommended method on Loratadine and Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg (Batch #7240202, **18 months old**). In addition to the dissolution results which are summarized in the review Appendix, the firm has the following comments: *"The results indicate incomplete release of Loratadine in 45 minutes. Although the Agency had requested dissolution of Loratadine up to 45 minutes only, Ranbaxy deliberately conducted dissolution profile of Loratadine up to 60 minutes. At 60 minutes also, the results indicate incomplete release of Loratadine. In fact, going by the present Ranbaxy specification, the product does not meet dissolution testing criteria for Loratadine component ((b)(4) % (Q) in 60 minutes) at S-1 stage. There is no significant change in the release profile of Pseudoephedrine component and it very well meets the present drug release specifications.*

During dissolution testing the tablets exhibited a sticking tendency to the bottom of the dissolution vessel; an observation generally observed with polymeric matrix tablets tested using paddle apparatus. The incomplete release of Loratadine is possibly due to the sticking tendency of the tablets to the bottom of the dissolution vessel. In Ranbaxy's product, Loratadine is contained in the coating of the tablets. Since one face of the tablet may not be getting completely exposed to the dissolution medium (due to sticking), no complete release of Loratadine is observed in one hour.

In view of the above observation, it appears that the new dissolution methodology may not be suitable for this product."

DBE's Comment: The dissolution testing is considered **incomplete**. The firm has proposed the following method and specification:

Medium, acid statge	0.1 N HCl for 0-1 hour
Medium, buffer stage	pH 6.8 phosphate buffer for 1-16 hours
Volume (mL)	900 mL
USP Apparatus Type	I (basket)
Rotation (rpm)	75
Firm's specifications	Loratadine: NLT (b) (4)% dissolved in 60 minutes Pseudoephedrine: (b) (4) in 1 hour, (b) (4) in 4 hours, (b) (4) in 8 hours and NLT (b) (4)% in 16 hours.

However, the Agency recommends the following method and specifications (based on the submitted data):

Medium, acid statge	0.1 N HCl for 0-1 hour
Medium, buffer stage	0.1 M phosphate buffer pH 7.5 for 1-16 hours
Volume (mL)	1000 mL
USP Apparatus Type	II (paddle)
Rotation (rpm)	50
FDA's specification	Loratadine: NLT (b) (4)% of the labeled amount dissolved 30 min Pseudoephedrine: 1 hour (b) (4) 2 hours 4 hours 8 hours 16 hour

The firm is recommended to incorporate the FDA-recommended dissolution method and specifications into its stability and quality control programs. The firm is requested to submit dissolution data on 12 units when a fresh lot becomes available and to include the 2-hour sampling time in the pseudoephedrine dissolution profile. **The firm is requested to provide response to the Agency's recommendations.**

It should be noted that the additional dissolution data as submitted in the current amendment are considered acceptable. The firm tested only 6 units of the test product. The firm did not provide the pseudoephedrine data for 2-hour sampling time which was left out of the DBE request inadvertently. However, both loratadine and pseudoephedrine data met the FDA-recommended specifications for the sampling times submitted. The FDA-recommended specification for loratadine is NLT (b) (4)%(Q) dissolved in 30 minutes. The mean percent of loratadine dissolved at 30 minutes was 87 (b) (4) for the test product.

I. Recommendations

1. The single-dose, fasting bioequivalence study and the single-dose nonfasting bioequivalence study conducted by Ranbaxy on the test product, Loratadine/Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, lot # 7240202, comparing it with the reference product, Schering's Claritin-D® (loratadine/pseudoephedrine sulfate, 10 mg/240 mg) ER Tablets, lot # 1-DCS-2039, have been found **acceptable** by the Division of Bioequivalence. The test

product, Ranbaxy's Loratadine & Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, is deemed bioequivalent to the reference product, , Schering's Claritin-D® (loratadine/pseudoephedrine sulfate, 10 mg/240 mg) ER Tablets.

2. The dissolution testing is considered **incomplete**. The firm has proposed the following method and specification:

Medium, acid statge	0.1 N HCl for 0-1 hour
Medium, buffer stage	pH 6.8 phosphate buffer for 1-16 hours
Volume (mL)	900 mL
USP Apparatus Type	I (basket)
Rotation (rpm)	75
Firm's specifications	Loratadine: NLT (b)(4)% dissolved in 60 minutes Pseudoephedrine: (b)(4) % in 1 hour, (b)(4) % in 4 hours, (b)(4) n 8 hours and NLT (b)(4)% in 16 hours.

However, the Agency recommends the following method and specifications (based on the submitted data):

Medium, acid statge	0.1 N HCl for 0-1 hour
Medium, buffer stage	0.1 M phosphate buffer pH 7.5 for 1-16 hours
Volume (mL)	1000 mL
USP Apparatus Type	II (paddle)
Rotation (rpm)	50
FDA's specification	Loratadine: NLT (b)(4)% of the labeled amount dissolved 30 min Pseudoephedrine: 1 hour (b)(4) 2 hours 4 hours 8 hours 16 hour

The firm is recommended to incorporate the FDA-recommended dissolution method and specifications into its stability and quality control programs. The firm is requested to submit dissolution data on 12 units when a fresh lot becomes available and to include the 2-hour sampling time in the pseudoephedrine dissolution profile. **The firm is requested to provide response to the Agency's recommendations.**

2/24/04
Hoaihon Nguyen, Review Branch I

2/24/2004
Yih Chain Huang
Team Leader, Review Branch I

for Barbara M Sauz 2/24/04
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

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IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study (AA01111): Comparative, Randomized, Single-Dose, Fully Replicated, 4-Way Crossover Bioavailability Study of Ranbaxy and Schering (Claritin-D 24 Hour) 10 mg Loratadine/240 mg Pseudoephedrine Sulfate Extended-Release Tablets in Healthy Adult Volunteers Under Fasting Conditions

Study Information See the review of the original submission for a summary of study design and conduct. The Subject Demographic and Adverse Events data were submitted in the current amendment and are summarized below in addition to the revised During Study Method Validation tables and the study results.

Table 1 Demographics of Study Subjects*

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0			Caucasian	97.3
Mean	33.51	Mean	70.36	18-40	78.4	Male	73.0	Afr. Amer.	2.7
SD	6.53	SD	9.08	41-64	21.6	Female	27.0	Hispanic	0.0
Range	21-45	Range	54.1-87.4	65-75	0.0			Asian	0.0
				>75	0.0			Others	0.0

***NOTE:** Data analyses were performed on data from all subjects who completed at least 2 periods of the study. Per protocol, for every subject who did not complete the full 4 periods, an alternate subject was added for laboratory analyses and included in the statistical analyses. Subjects excluded from the analyses were not necessarily dropout subjects. Dropout subjects were Subjects #11 (prior to Period 4), #12 (prior to Period 2), #24 and # 38 (prior to Period 3). **Subjects not included in the study analyses** were **Subject #12** who did not complete 2 periods, **Subjects # 23 and 31** who vomited early in Period 3 and Period 4, respectively. The demographics summary was based on all enrolled subjects. Thus, dropout Subjects # 11, 24 and 38 were included in the study analyses.

Study Results

Table 2 Dropout Information

Subject No	11	12	24	38
Reason	Low hemoglobin	Predose adverse event	Personal reasons	Personal reasons
Period	4	II	III	III
Replacement	Yes	Yes	Yes	No

Was there a difference in side effects for the test versus the reference? See Table 3.

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Headache	7	5
Dryness of mouth	1	0
Dryness of skin	1	0
Dryness of hands	1	0
Deep breath when sleeping at times	0	2
Pain in thoraci region	0	1
Low hemoglobin	0	1
Hypersalivation	1	0
Pain in jaw	1	0
Runny nose	1	0
Feeling tired	1	0
Dizziness	2	1
Fainted	1	0
Burning sensation at venipuncture site	1	0
Feeling achy	1	0
Burning sensation at urinary tract	0	1
Redness to right forearm	0	1
Vomited	1	1
Pain in kidney region right side	0	1
Pain in abdominal region upper right quadrant	0	1
Hot flush	1	0
Palpitations	1	0
Bruise to venipuncture site on right arm	1	0
Total:	**23**	**15**

Comments: There were slightly more adverse effects reported for the Test Treatment than the Reference Treatment. Overall, there were relatively few adverse events reported for the entire study (4 periods). Severity of the adverse events ranged from mild to moderate.

Was there a difference in protocol deviations for the test versus the reference? No

Protocol Deviations There were no significant protocol deviations that might have compromised the integrity of the study. Significant blood sampling deviations were corrected for actual times using ClinQuick™ program.

Table 4 Assay Validation – Within Study

During Study Method Validation - Fasting Study AA01111: Loratadine

QC Conc. (pg/mL)	60.1 pg/mL (n=81)	3003 pg/mL (n=82)	8008 pg/mL (n=81)	8008 pg/mL (n=3)Diluted x2	8008 pg/mL (n=3) Diluted x5
Inter day Precision (%CV)	10.3	3.5	3.4	1.2	0.4
Inter day Accuracy (% Accuracy)	98.7	101.7	92.4	93.8	89.3
Cal. Standards Conc. (pg/mL)	20.0, 40.0, 100.1, 400.4, 1001, 5005, 7528, 8809, 10010				

Inter day Precision (%CV)	1.6-7.5
Inter day Accuracy (% Accuracy)	94.4-107.0
Long-term frozen storage stability (if applicable)	170 days
Linearity Range (range of R^2 values)	0.9943-0.9997
Linearity Range (pg/mL)	20.0-10010

NOTE: The highest loratadine Cmax concentration measured was 14923 pg/mL. The QC and standard ranges are considered acceptable when dilution is included.

During Study Method Validation - Fasting Study AA01111: DCL

QC Conc. (pg/mL)	60.2 pg/mL (n=83)	2006 pg/mL (n=84)	5515 pg/mL (n=83)	5515 pg/mL (n=3)Diluted x2	5515 pg/mL (n=3)Diluted x5
Inter day Precision (%CV)	8.8	4.0	4.5	1.8	1.1
Inter day Accuracy (% Accuracy)	96.0	98.1	92.6	95.5	89.9
Cal. Standards Conc. (pg/mL)	20.1, 40.1, 100.3, 401.1, 1003, 3490, 5014, 6217, 7019				
Inter day Precision (%CV)	2.1-6.2				
Inter day Accuracy (% Accuracy)	93.9-105.5				
Long-term frozen storage stability (if applicable)	170 days				
Linearity Range (range of R^2 values)	0.9914-0.9991				
Linearity Range (pg/mL)	20.1-7019				

NOTE: The highest DCL Cmax concentration measured was 10356 pg/mL. The QC and standard ranges are considered acceptable when dilution is included.

During Study Method Validation - Fasting Study AA01111: Pseudoephedrine

QC Conc. (ng/mL)	15.00 (n=77)	360.0 (n=78)	1200 (n=78)
Inter day Precision (%CV)	22.1	3.2	2.6
Inter day Accuracy (% Accuracy)	113.3	100.9	98.2
Cal. Standards Conc. (ng/mL)	5.00, 10.0, 25.0, 50.0, 100.0, 250.0, 500.0, 1000, 1350, 1500		
Inter day Precision (%CV)	2.0-6.1		
Inter day Accuracy (% Accuracy)	94.4-109.6		
Long-term frozen storage stability (if applicable)	354 days		
Linearity Range (range of R^2 values)	0.9951-0.9995		
Linearity Range (ng/mL)	5.00-1500		

NOTE: The highest pseudoephedrine Cmax concentration measured was 836.3 ng/mL. The QC and standard ranges are considered acceptable.

Table 5 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
AL-G-1520-10	04/19/02	Reporting of Data Generated from the Analysis of Biological Matrices

- **Comments on repeat assays.** All samples were repeated for analytical reasons only.

Conclusion: Analytical method is acceptable.

Table 6 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 9 and Figures 1

Loratadine

Test Treatment Replicate 1 -Loratadine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	37	6657.70	68.1884130	805.7125000	16419.36
AUCI pg.hr/mL	33	7405.12	67.4278758	868.2908148	17574.92
CMAX pg/mL	37	2336.41	66.9432871	437.1000000	6283.00
LAUCL	37	8.5392634	9.2281305	6.6917270	9.7062166
LAUCI	33	8.6363589	9.4247670	6.7665267	9.7742282
LCMAX	37	7.5318389	9.3780355	6.0801620	8.7456029
TMAX hr	37	1.2229730	45.3997772	0.5000000	4.0000000
THALF hr	33	15.5291970	69.8656629	1.4221634	37.8906765
KEL hr^{-1}	33	0.1003481	108.5236585	0.0182933	0.4873893
AUC RATIO	33	0.9160266	5.0870383	0.7796730	0.9722352

Test Treatment Replicate 2 -Loratadine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	34	7163.89	83.4264656	1023.38	27428.61
AUCI pg.hr/mL	32	7884.89	82.3062769	1107.18	28619.44
CMAX pg/mL	34	2625.06	86.4707939	405.4000000	10872.70
LAUCL	34	8.5411583	10.0586097	6.9308613	10.2193420
LAUCI	32	8.6275008	10.2165440	7.0095752	10.2618414
LCMAX	34	7.5500963	10.8914522	6.0048742	9.2940103
TMAX hr	34	1.1617647	28.4705688	0.5000000	2.0000000
THALF hr	32	14.9861990	92.2392820	1.3499305	48.4596079
KEL hr^{-1}	32	0.1250836	107.5687868	0.0143036	0.5134688
AUC RATIO	32	0.9327561	3.5455691	0.8277929	0.9671269

Reference Treatment Replicate 1 -Loratadine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	37	6369.21	80.8173620	759.7000000	19389.25
AUCI pg.hr/mL	35	6974.55	79.3784238	858.1311779	20007.25
CMAX pg/mL	37	2372.33	82.2834617	346.3000000	7839.90
LAUCL	37	8.4254999	10.1705202	6.6329236	9.8724741
LAUCI	35	8.5065441	10.3382099	6.7547570	9.9038499
LCMAX	37	7.4574493	10.9424071	5.8473055	8.9669814
TMAX hr	37	1.1081081	27.9066595	0.5000000	2.0000000
THALF hr	35	12.4854293	81.3259987	1.6308814	39.2166212
KEL hr^{-1}	35	0.1189011	86.8817156	0.0176748	0.4250139
AUC RATIO	35	0.9231341	5.1912738	0.7795142	0.9691113

Reference Treatment Replicate 2 -Loratadine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	35	6694.59	90.8937829	462.4500000	24873.05
AUCI pg.hr/mL	34	7367.42	89.4020186	507.6733900	25763.86
CMAX pg/mL	35	2691.33	110.1967040	248.0000000	14923.10
LAUCL	35	8.4307513	10.7467481	6.1365384	10.1215402
LAUCI	34	8.5258094	10.7206003	6.2298383	10.1567282
LCMAX	35	7.4801608	12.0628102	5.5134287	9.6106656
TMAX hr	35	1.0857143	26.7499975	0.5000000	1.7500000
THALF hr	34	14.2509522	93.7125994	1.1258889	59.1832285
KEL hr^{-1}	34	0.1268030	107.9123459	0.0117119	0.6156444
AUC RATIO	34	0.9233387	4.8382126	0.7875680	0.9701967

DCL

Test Treatment Replicate 1 - DCL

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	37	47375.62	55.4843834	19253.21	134923.73
AUCI pg.hr/mL	37	48919.60	56.5479116	20314.82	137022.18
CMAX pg/mL	37	3635.04	43.3939954	1595.80	7453.90
LAUCL	37	10.6496439	4.3644885	9.8654332	11.8124649
LAUCI	37	10.6790538	4.3797637	9.9191058	11.8278981
LCMAX	37	8.1134721	5.0828430	7.3751305	8.9164927
TMAX hr	37	1.8310811	58.9051979	0.7500000	5.0000000
THALF hr	37	21.9637329	20.5716213	15.3619925	36.7924267
KEL hr^{-1}	37	0.0327546	18.8507315	0.0188394	0.0451209
AUC RATIO	37	0.9711517	1.6588368	0.9036279	0.9892514

Test Treatment Replicate 2 - DCL

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	34	45894.64	47.7535916	19965.26	107675.61
AUCI pg.hr/mL	34	47721.72	50.8082609	20812.28	124664.95
CMAX pg/mL	34	3769.45	42.5479146	1714.90	7799.30
LAUCL	34	10.6389700	4.0505395	9.9017492	11.5868784
LAUCI	34	10.6711453	4.1341981	9.9432983	11.7333850
LCMAX	34	8.1484887	5.1790306	7.4471100	8.9617893
TMAX hr	34	1.7205882	60.2559970	1.0000000	6.0000000
THALF hr	34	23.9610322	25.4244436	14.0225263	41.9078645
KEL hr^{-1}	34	0.0306109	23.6283585	0.0165398	0.0494310
AUC RATIO	34	0.9686169	2.3799798	0.8637200	0.9904524

Reference Treatment Replicate 1 - DCL

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	37	46535.97	50.5174651	18539.86	115580.20
AUCI pg.hr/mL	37	48280.87	52.0501360	19597.72	121996.13
CMAX pg/mL	37	3480.20	38.9432824	1494.70	7549.80
LAUCL	37	10.6402836	4.3062446	9.8276784	11.6577199
LAUCI	37	10.6734756	4.3396572	9.8831684	11.7117446
LCMAX	37	8.0806046	4.9012458	7.3096808	8.9292764
TMAX hr	37	1.6891892	61.2613346	0.7500000	6.0000000
THALF hr	37	24.2508275	30.3005669	14.4944511	51.7818137
KEL hr^{-1}	37	0.0308091	26.6466545	0.0133859	0.0478216
AUC RATIO	37	0.9675050	1.7724750	0.8932704	0.9873592

Reference Treatment Replicate 2 - DCL

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	35	45342.41	52.5633345	21080.65	125164.61
AUCI pg.hr/mL	35	47002.19	53.8101410	22134.64	133682.25
CMAX pg/mL	35	3689.67	51.9812533	1641.60	10356.60
LAUCL	35	10.6124500	4.2973790	9.9561108	11.7373850
LAUCI	35	10.6457572	4.3134184	10.0048993	11.8032210
LCMAX	35	8.1071541	5.5433972	7.4034267	9.2453793
TMAX hr	35	1.6000000	57.3723808	0.7500000	5.0000000
THALF hr	35	23.3807925	27.8651690	14.2153119	48.8046979
KEL hr^{-1}	35	0.0315529	24.0987296	0.0142025	0.0487606
AUC RATIO	35	0.9673778	1.6861574	0.9084261	0.9884021

Pseudoephedrine

Test Treatment Replicate 1 - Pseudoephedrine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL ng.hr/mL	37	7405.86	20.2019112	4356.97	11618.26
AUCI ng.hr/mL	37	7708.47	20.8292845	4397.01	12025.32
CMAX ng/mL	37	467.4586486	24.7350162	309.2900000	836.3400000
LAUCL	37	8.8890854	2.3788029	8.3795310	9.3603331
LAUCI	37	8.9274968	2.4683501	8.3886795	9.3947693
LMAX	37	6.1219130	3.6109451	5.7342793	6.7290352
TMAX hr	37	6.8783784	23.8892138	4.0000000	12.0000000
THALF hr	37	6.4069113	20.4608009	4.3841330	10.2294852
KEL hr^{-1}	37	0.1124950	19.9484958	0.0677453	0.1580700
AUC RATIO	37	0.9625980	2.4274927	0.8874992	0.9929732

Test Treatment Replicate 2 - Pseudoephedrine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL ng.hr/mL	34	7449.16	21.0934832	4083.36	12194.75
AUCI ng.hr/mL	34	7772.56	22.5981872	4083.36	12962.01
CMAX ng/mL	34	448.3229412	18.8851330	289.8600000	750.7100000
LAUCL	34	8.8937475	2.4331755	8.3146755	9.4087606
LAUCI	34	8.9329487	2.5991023	8.3146755	9.4697780
LMAX	34	6.0892032	2.9875839	5.6693980	6.6210194
TMAX hr	34	6.9411765	32.3977725	4.0000000	15.0000000
THALF hr	34	6.4274404	22.2857190	3.9576500	10.0641791
KEL hr^{-1}	34	0.1130675	22.3787167	0.0688581	0.1751039
AUC RATIO	34	0.9618872	2.6348498	0.8905634	1.0000000

Reference Treatment Replicate 1 - Pseudoephedrine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL ng.hr/mL	37	7277.67	23.7123750	3251.86	11928.21
AUCI ng.hr/mL	37	7764.14	25.7314389	3251.86	13025.88
CMAX ng/mL	37	408.9535135	17.9811484	272.1000000	603.2600000
LAUCL	37	8.8642924	2.7751349	8.0869832	9.3866617
LAUCI	37	8.9239897	2.9952417	8.0869832	9.4746932
LMAX	37	5.9981485	2.9677388	5.6061696	6.4023483
TMAX hr	37	6.2162162	24.4662622	5.0000000	12.0000000
THALF hr	37	7.4152853	25.9420134	4.8181373	13.0673629
KEL hr^{-1}	37	0.0988145	22.6009699	0.0530329	0.1438315
AUC RATIO	37	0.9429738	4.3838051	0.8185018	1.0000000

Reference Treatment Replicate 2 - Pseudoephedrine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL ng.hr/mL	35	7250.20	21.8330256	3345.29	11523.95
AUCI ng.hr/mL	35	7715.77	22.5986997	3345.29	12029.50
CMAX ng/mL	35	423.5674286	24.6408694	293.1400000	831.9500000
LAUCL	35	8.8637073	2.6415579	8.1153079	9.3521825
LAUCI	35	8.9234511	2.7723799	8.1153079	9.3951169
LMAX	35	6.0246161	3.5431133	5.6806503	6.7237723
TMAX hr	35	6.5428571	31.1450105	5.0000000	15.0000000
THALF hr	35	7.4491493	29.3999660	4.3210784	16.1979875
KEL hr^{-1}	35	0.0995710	25.2013903	0.0427831	0.1603766
AUC RATIO	35	0.9430274	4.5658262	0.7681042	1.0000000

Table 7 Least Square Geometric Means and 90% Confidence Intervals (N=37)

Loratadine

Parameter	Test	Reference	T/R	90% CI
AUC0-t	5226	4701	1.11	101.8-121.3
AUC∞	5685	5093	1.12	102.1-122.0
Cmax	1923	1797	1.07	96.8-118.2

DCL

Parameter	Test	Reference	T/R	90% CI
AUC0-t	42100	41399	1.02	98.3-105.3
AUC∞	43421	42813	1.01	98.0-104.9
Cmax	3394	3254	1.04	100.2-108.5

Pseudoephedrine

Parameter	Test	Reference	T/R	90% CI
AUC0-t	7243	7021	1.03	100.1-106.4
AUC∞	7528	7450	1.01	97.8-104.4
Cmax	447.7	406.4	1.10	106.4-114.0

Table 8 Additional Study Information

Within Subject Variance: Values as taken from the Covariance Parameter Estimates Table of PROC MIXED output are shown below (for ln-transformed AUCt and Cmax only)

Loratadine

	lnCmax	LnAUCt	LnAUCi
Test	0.1002	0.1001	0.09910
Reference	0.1441	0.08510	0.07592

DCL

	lnCmax	LnAUCt	LnAUCi
Test	0.01996	0.01765	0.01738
Reference	0.02017	0.01208	0.01198

Pseudoephedrine

	lnCmax	LnAUCt	LnAUCi
Test	0.01744	0.008156	0.008635
Reference	0.01307	0.01464	0.01643

Comments:

- kel and AUC∞ were determined for how many subjects? See N values provided in the Arithmetic Mean Pharmacokinetic Parameters tables above (pages 12-15). The reviewer agreed with the firm's determination of KEL.
- Indicate the number of subjects with the following:

a. measurable drug concentrations at 0 hr: Subject # 19 (Period I, Reference Treatment) with pseudoephedrine predose level of 14.83 ng/mL or 2.5% of corresponding Cmax.

b. first scheduled post-dose sampling time as Tmax: Subjects #20 (Period I, II, II and IV) and 40 (Period IV, Test Treatment) both for loratadine.

c. first measurable drug concentration as Cmax: Same as listed in Tmax.

- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Are the 90% confidence intervals for AUC0-t, AUC∞, Cmax within the acceptable limits of 80-125%? Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect. N/A.

Conclusion: The single-dose fasting bioequivalence study is acceptable.

Table 9 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Loratadine

Test Treatment Replicate 1 - Loratadine (pg/mL)

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	37	0	0	0	0
Hour0.25	36	50.9138889	189.8622089	0	1139.70
Hour0.50	37	603.2918919	775.1523837	0	3722.80
Hour0.75	37	1557.76	1375.46	0	6283.00
Hour1	37	1845.95	1322.66	20.6000000	5785.20
Hour1.25	37	1971.16	1390.79	22.3000000	5500.90
Hour1.50	37	1785.83	1302.90	102.2000000	5112.60
Hour1.75	37	1581.69	1127.44	159.9000000	4097.40
Hour2	37	1404.06	1027.60	112.5000000	3919.40
Hour2.50	37	1113.46	796.0389187	84.7000000	3126.00
Hour3	37	832.3729730	604.8420628	77.8000000	2232.00
Hour3.50	37	690.9918919	529.1905445	50.1000000	2310.00
Hour4	37	542.0216216	477.7040054	43.9000000	2565.80
Hour4.50	37	419.9378378	425.9416766	28.5000000	2456.20
Hour5	37	324.1837838	351.6561045	30.5000000	2076.00
Hour6	37	222.7594595	232.7158370	0	1316.40
Hour9	37	95.4621622	70.7062364	0	279.5000000
Hour12	35	63.9257143	43.3721471	0	143.6000000
Hour15	36	43.6472222	34.6144519	0	115.4000000
Hour24	35	25.4257143	21.2608912	0	77.9000000
Hour36	37	24.1027027	23.1050077	0	86.0000000
Hour48	37	7.7135135	13.7275708	0	53.3000000
Hour72	36	1.4805556	6.1944131	0	27.5000000
Hour96	37	0	0	0	0
Hour120	37	0	0	0	0

Test Treatment Replicate 2 - Loratadine (pg/mL)

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	34	0	0	0	0
Hour0.25	34	58.0911765	123.9680393	0	552.3000000
Hour0.50	34	584.2000000	653.0239673	27.9000000	2560.30
Hour0.75	34	1743.24	1669.37	155.7000000	8095.80
Hour1	34	2243.03	2131.62	306.9000000	10872.70
Hour1.25	34	2391.96	2255.63	319.9000000	10727.80
Hour1.50	34	2187.88	2029.22	276.6000000	9306.10
Hour1.75	34	1878.56	1647.41	222.9000000	7330.10
Hour2	34	1581.89	1318.44	177.7000000	5725.90
Hour2.50	34	1187.67	953.6418665	127.1000000	4278.10
Hour3	34	865.1470588	661.4385293	91.5000000	2862.70
Hour3.50	34	660.2000000	503.9629388	89.0000000	2230.20
Hour4	34	508.2000000	371.1157820	64.0000000	1487.50
Hour4.50	34	383.3029412	266.7000057	49.9000000	991.1000000
Hour5	34	285.0823529	198.2941288	33.8000000	742.2000000
Hour6	34	201.6705882	136.3596326	23.3000000	508.8000000
Hour9	34	97.0176471	72.8904303	0	269.0000000
Hour12	34	60.3323529	45.6160240	0	176.3000000
Hour15	34	44.1558824	38.8253993	0	134.7000000
Hour24	33	25.0242424	25.5963502	0	90.6000000
Hour36	34	17.3058824	22.0807052	0	72.5000000
Hour48	33	8.9939394	15.0863958	0	49.8000000
Hour72	33	4.2696970	10.6258966	0	39.7000000
Hour96	34	2.0764706	6.8497759	0	28.1000000
Hour120	33	0	0	0	0

Reference Treatment Replicate 1 - Loratadine (pg/mL)

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	37	0	0	0	0
Hour0.25	37	95.3081081	266.5915638	0	1525.70
Hour0.50	37	716.0891892	894.5650339	58.9000000	4610.40
Hour0.75	37	1913.61	1961.89	234.5000000	7839.90
Hour1	37	2124.58	1846.02	346.3000000	7295.60
Hour1.25	37	2092.45	1744.10	309.5000000	7625.40
Hour1.50	37	1845.35	1499.96	257.2000000	6081.20
Hour1.75	37	1644.04	1333.23	167.2000000	5573.90
Hour2	37	1391.29	1154.60	130.9000000	4714.20
Hour2.50	37	1059.02	853.4457860	105.4000000	3458.40
Hour3	37	766.0189189	577.3730148	69.4000000	2008.30
Hour3.50	37	604.6756757	467.2771384	71.9000000	1655.40
Hour4	37	466.3378378	349.1634999	57.7000000	1197.50
Hour4.50	37	347.3432432	265.7499760	36.2000000	927.9000000
Hour5	37	260.2216216	198.5685386	33.8000000	669.1000000
Hour6	37	170.1162162	124.6120725	0	437.8000000
Hour9	37	86.1351351	67.7945803	0	262.2000000
Hour12	37	54.6108108	44.9443964	0	157.3000000
Hour15	37	39.4945946	36.1395439	0	111.7000000
Hour24	33	21.1545455	23.4911964	0	62.3000000
Hour36	37	17.4810811	22.1157415	0	86.8000000
Hour48	36	6.0777778	11.8273801	0	37.7000000
Hour72	36	1.3305556	5.5675498	0	24.8000000
Hour96	37	0	0	0	0
Hour120	37	0	0	0	0

Reference Treatment Replicate 2 - Loratadine (pg/mL)

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	35	0	0	0	0
Hour0.25	35	87.1942857	221.3769409	0	1292.00
Hour0.50	35	883.8942857	1428.30	41.5000000	7941.70
Hour0.75	35	2217.89	2979.13	153.5000000	14923.10
Hour1	35	2354.78	2586.98	194.2000000	12009.20
Hour1.25	35	2262.51	2194.65	163.5000000	10666.10
Hour1.50	35	1905.12	1681.52	125.8000000	7361.00
Hour1.75	35	1628.31	1350.20	101.8000000	5637.20
Hour2	35	1406.39	1073.46	98.0000000	4360.60
Hour2.50	35	1056.90	821.5868086	78.4000000	3590.90
Hour3	35	783.8600000	616.4447817	51.0000000	2379.10
Hour3.50	35	595.7857143	452.2504051	46.9000000	1696.60
Hour4	35	494.7371429	404.3534615	38.3000000	1441.10
Hour4.50	35	356.8714286	285.9616897	26.8000000	1089.30
Hour5	35	259.3885714	199.6159176	22.8000000	707.4000000
Hour6	35	179.1200000	142.9994998	0	588.4000000
Hour9	34	89.6882353	70.3353343	0	255.5000000
Hour12	35	58.1457143	48.8409805	0	169.6000000
Hour15	35	39.8857143	37.6210450	0	124.3000000
Hour24	35	20.4942857	25.8702412	0	93.6000000
Hour36	35	16.3057143	21.7248021	0	94.7000000
Hour48	35	6.3371429	13.8552196	0	57.6000000
Hour72	35	3.3600000	10.2876053	0	49.4000000
Hour96	35	0	0	0	0
Hour120	35	0	0	0	0

DCL

Test Treatment Replicate 1 - DCL (pg/mL)

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	37	0	0	0	0
Hour0.25	36	13.8694444	26.3256726	0	110.3000000
Hour0.50	37	643.6621622	665.0266989	0	2612.20
Hour0.75	37	2027.22	1359.73	33.2000000	5305.30
Hour1	37	2789.43	1447.63	71.7000000	6363.60
Hour1.25	37	3143.91	1536.42	83.4000000	6790.70
Hour1.50	37	2980.50	1404.83	333.0000000	7453.90
Hour1.75	37	3046.24	1324.38	1216.30	6894.70
Hour2	37	2809.32	1088.74	1064.90	5118.20
Hour2.50	37	2815.96	1218.57	1398.00	5852.00
Hour3	37	2429.98	1066.40	1226.40	6019.50
Hour3.50	37	2542.52	1133.13	1224.60	6194.10
Hour4	37	2225.72	982.7261140	768.1000000	5962.50
Hour4.50	37	2337.04	1147.38	830.7000000	7166.30
Hour5	37	2145.02	992.5407374	1010.50	6290.10
Hour6	37	1930.22	930.2736400	917.2000000	5625.50
Hour9	37	1327.33	679.5781069	558.3000000	3972.20
Hour12	37	1089.44	603.4405320	410.5000000	3427.50
Hour15	37	896.3135135	506.3153816	323.4000000	2703.80
Hour24	37	531.3675676	337.4933333	164.2000000	1743.40
Hour36	37	362.9864865	283.8869837	110.8000000	1499.20
Hour48	37	235.0459459	193.3375956	55.6000000	885.9000000
Hour72	36	102.4027778	99.8214878	0	540.5000000
Hour96	37	57.2324324	66.9089143	0	352.9000000
Hour120	37	26.3729730	45.0681314	0	221.2000000

Test Treatment Replicate 2 - DCL (pg/mL)

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	34	0	0	0	0
Hour0.25	34	24.7588235	57.2007953	0	284.9000000
Hour0.50	34	649.8147059	619.5120382	43.8000000	3255.20
Hour0.75	34	2082.66	1211.21	391.4000000	5397.70
Hour1	34	2975.30	1685.25	717.6000000	7700.10
Hour1.25	34	3438.67	1538.37	1337.90	7799.30
Hour1.50	34	3358.04	1454.14	1471.30	7173.80
Hour1.75	34	3177.07	1355.65	975.0000000	6346.60
Hour2	34	3136.24	1197.61	1587.50	5850.70
Hour2.50	34	2852.58	1162.32	1424.20	5927.90
Hour3	34	2562.04	918.8888662	1207.80	4734.50
Hour3.50	34	2307.27	869.8084973	1083.70	4609.90
Hour4	34	2158.64	790.2058531	852.9000000	4096.50
Hour4.50	34	2209.09	833.1657851	805.6000000	4299.70
Hour5	34	2195.37	868.5987121	1123.70	4446.30
Hour6	34	1880.95	678.2845565	1023.80	3716.60
Hour9	34	1306.92	548.1568426	561.6000000	2771.40
Hour12	34	994.9323529	484.7336261	468.9000000	2431.10
Hour15	34	802.9352941	391.9506925	317.0000000	1816.00
Hour24	34	504.2470588	271.7125980	223.7000000	1255.90
Hour36	34	343.2088235	228.5272471	125.9000000	1186.80
Hour48	34	217.2117647	163.1573729	68.7000000	840.2000000
Hour72	34	110.4470588	101.5920339	28.4000000	529.3000000
Hour96	34	58.9147059	72.2769133	0	377.9000000
Hour120	33	32.4090909	54.5153669	0	281.0000000

Reference Treatment Replicate 1 - DCL (pg/mL)

Variable	N	Mean	Std Dev	Minimum	Maximum
Hour0	37	0	0	0	0
Hour0D25	37	72.5270270	194.2354937	0	1076.80
Hour0D50	37	897.6459459	900.1364639	68.3000000	4299.90
Hour0D75	37	2280.18	1503.01	433.9000000	6841.70
Hour1	37	2940.37	1493.28	787.7000000	7393.90
Hour1D25	37	3143.02	1367.24	1155.30	7549.80
Hour1D50	37	2988.59	1210.63	1364.20	6778.00
Hour1D75	37	3066.44	1277.27	1131.60	6738.40
Hour2	37	2813.37	1149.85	1249.50	6524.90
Hour2D50	37	2709.29	1113.87	1146.40	5633.90
Hour3	37	2296.40	935.6302942	1024.00	4798.40
Hour3D50	37	2342.75	919.4586395	1099.00	4845.40
Hour4	37	2005.55	784.6073925	1007.20	4273.00
Hour4D50	37	2224.01	913.2834520	960.0000000	4735.20
Hour5	37	2051.04	803.3758534	928.1000000	4746.70
Hour6	37	1838.17	666.8708391	907.5000000	3522.20
Hour9	37	1316.59	574.5452356	565.6000000	2734.80
Hour12	37	1067.32	506.4292923	441.9000000	2304.90
Hour15	37	871.2756757	452.7710830	316.2000000	2035.30
Hour24	37	517.4891892	294.6293998	171.9000000	1434.30
Hour36	37	347.9837838	243.4682611	98.8000000	1139.90
Hour48	36	235.9388889	184.6891524	58.9000000	801.9000000
Hour72	36	115.8388889	113.0411664	24.4000000	496.4000000
Hour96	37	61.3783784	69.3868749	0	314.8000000
Hour120	37	30.6729730	47.7574407	0	237.8000000

Reference Treatment Replicate 2 - DCL (pg/mL)

Variable	N	Mean	Std Dev	Minimum	Maximum
Hour0	35	0	0	0	0
Hour0D25	35	62.1942857	116.3200983	0	521.3000000
Hour0D50	35	858.7885714	859.8799888	53.9000000	4050.70
Hour0D75	35	2512.36	1964.67	467.5000000	10356.60
Hour1	35	3051.30	1988.07	1028.40	9397.80
Hour1D25	35	3320.28	1645.37	1553.80	8420.60
Hour1D50	35	3211.14	1596.45	1419.80	8197.50
Hour1D75	35	3049.37	1477.70	1516.50	7614.10
Hour2	35	2935.61	1353.87	1433.00	6846.30
Hour2D50	35	2767.45	1399.83	1246.70	6678.30
Hour3	35	2522.67	1227.87	1243.40	6381.60
Hour3D50	35	2372.85	1117.81	1177.20	5854.60
Hour4	35	2141.47	984.0817190	1088.00	5147.80
Hour4D50	35	2140.96	932.5264740	1014.30	5072.70
Hour5	35	2171.31	992.2704007	1082.50	5534.20
Hour6	35	1898.46	800.0813316	1013.20	4211.20
Hour9	35	1262.15	589.2340444	662.5000000	2929.10
Hour12	35	990.3200000	464.2440850	418.4000000	2178.90
Hour15	35	787.9171429	402.6836340	319.0000000	1976.40
Hour24	35	503.1142857	282.1648435	226.7000000	1366.90
Hour36	35	341.9942857	259.0686395	128.0000000	1186.50
Hour48	35	213.8428571	156.5329514	71.9000000	748.0000000
Hour72	35	112.0657143	108.8712163	25.3000000	501.6000000
Hour96	35	53.4514286	60.5548433	0	272.8000000
Hour120	35	28.1914286	46.0426169	0	189.1000000

Pseudoephedrine

Test Treatment Replicate 1 - Pseudoephedrine (ng/mL)

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	37	0	0	0	0
Hour1	37	92.1381081	40.3344187	0	210.0700000
Hour2	37	187.1729730	52.5064958	77.3500000	307.2900000
Hour3	37	267.1954054	61.9033589	147.7400000	394.2700000
Hour4	37	346.7683784	73.5072635	199.4600000	469.5600000
Hour5	37	418.9783784	74.6546878	267.2200000	682.0900000
Hour5.50	37	430.8329730	102.6148545	289.3000000	836.3400000
Hour6	37	418.5232432	82.5846639	307.3000000	746.5600000
Hour6.50	37	424.5024324	83.5476351	300.4200000	751.2200000
Hour7	37	426.1029730	97.6350706	283.1200000	816.0200000
Hour7.50	37	433.1535135	95.4966558	273.9600000	769.9200000
Hour9	37	414.9108108	100.1120231	223.2600000	774.0000000
Hour12	37	352.8145946	94.6837913	181.4900000	671.0100000
Hour15	37	278.9370270	72.2556097	135.7200000	443.7400000
Hour24	37	109.4097297	37.8443659	32.8500000	174.1100000
Hour30	37	56.4989189	23.0149586	12.7800000	102.3500000
Hour36	37	30.0118919	15.4151139	5.5600000	57.5500000

Test Treatment Replicate 2 - Pseudoephedrine (ng/mL)

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	34	0	0	0	0
Hour1	34	97.5229412	42.3929596	30.2000000	210.9200000
Hour2	34	194.2920588	52.2955417	92.5000000	318.3500000
Hour3	34	282.9820588	69.2816330	159.0300000	420.8600000
Hour4	34	342.6900000	76.6275168	174.5800000	509.4400000
Hour5	34	415.9741176	79.8066615	203.6900000	608.8800000
Hour5.50	34	410.0723529	82.2405034	202.8700000	657.3500000
Hour6	34	404.9120588	74.4493496	211.2100000	636.2500000
Hour6.50	34	415.0488235	79.7914721	220.4100000	675.5900000
Hour7	34	417.6926471	81.0446036	238.5400000	684.1200000
Hour7.50	34	418.7261765	87.4364840	247.0000000	750.7100000
Hour9	34	410.1782353	90.3749121	262.3200000	676.5100000
Hour12	34	336.6714706	73.1824329	201.8100000	511.7400000
Hour15	34	285.5488235	71.9420165	119.0200000	465.2000000
Hour24	34	115.5176471	41.8529405	23.1800000	203.0300000
Hour30	34	61.8729412	31.5753400	8.7500000	132.3500000
Hour36	34	31.0900000	18.7524633	0	72.1900000

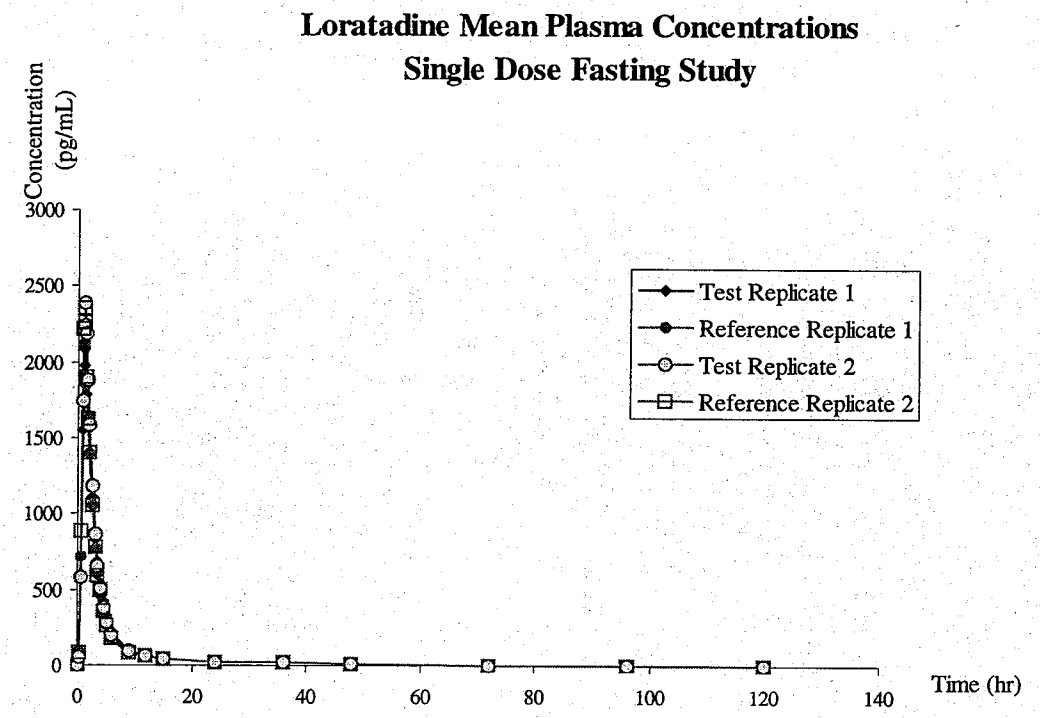
Reference Treatment Replicate 1 - Pseudoephedrine (ng/mL)

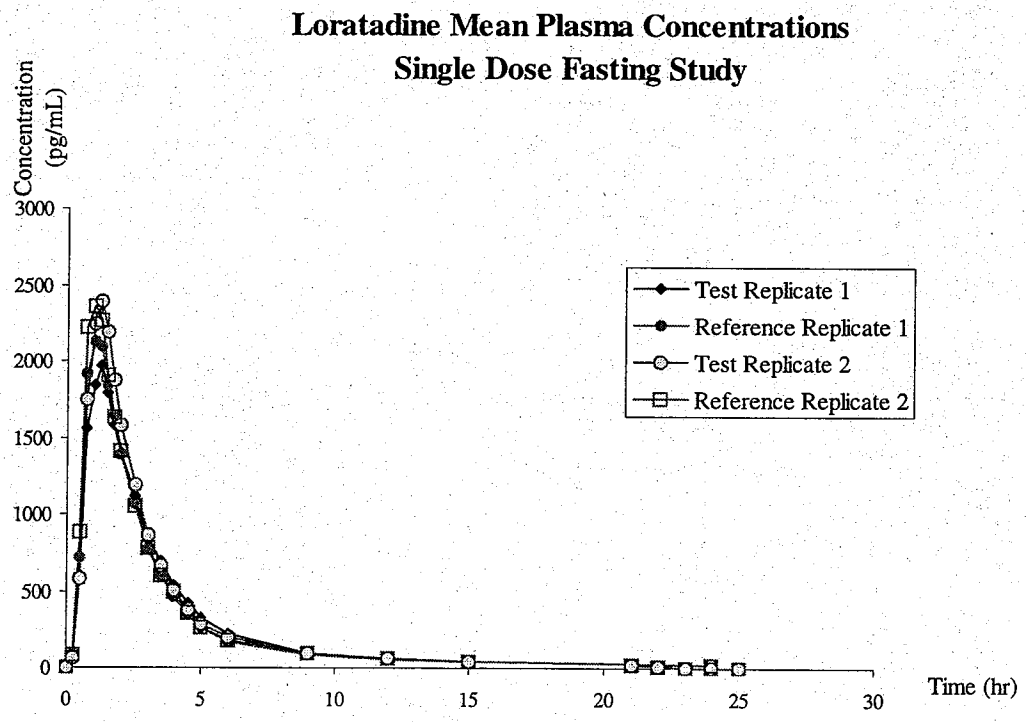
Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	37	0.4008108	2.4380370	0	14.8300000
Hour1	37	93.8191892	39.4101265	44.7200000	197.4100000
Hour2	37	183.0048649	48.2302935	92.9000000	304.9600000
Hour3	37	252.6527027	55.4712064	144.4600000	380.8400000
Hour4	37	310.0891892	58.2202805	208.6400000	444.9500000
Hour5	37	384.6129730	66.0262179	254.7700000	597.1600000
Hour5.50	37	383.8208108	66.7697871	256.1200000	603.2600000
Hour6	37	381.9848649	63.8699640	272.1000000	583.7700000
Hour6.50	37	378.7802703	65.9939707	261.6500000	571.2400000
Hour7	37	383.7005405	70.6623053	237.3700000	573.1400000
Hour7.50	37	386.0481081	74.7844753	247.8600000	592.1300000
Hour9	37	374.2945946	75.9294212	214.7600000	574.0500000
Hour12	37	320.0272973	85.0019361	128.9200000	537.1800000
Hour15	37	281.2197297	85.1392183	81.5700000	489.8900000
Hour24	37	126.7010811	44.9995368	23.5100000	255.8800000
Hour30	37	73.1745946	31.9028493	11.0100000	153.3400000
Hour36	37	40.1283784	24.8847898	0	102.3900000

Reference Treatment Replicate 2 - Pseudoephedrine (ng/mL)

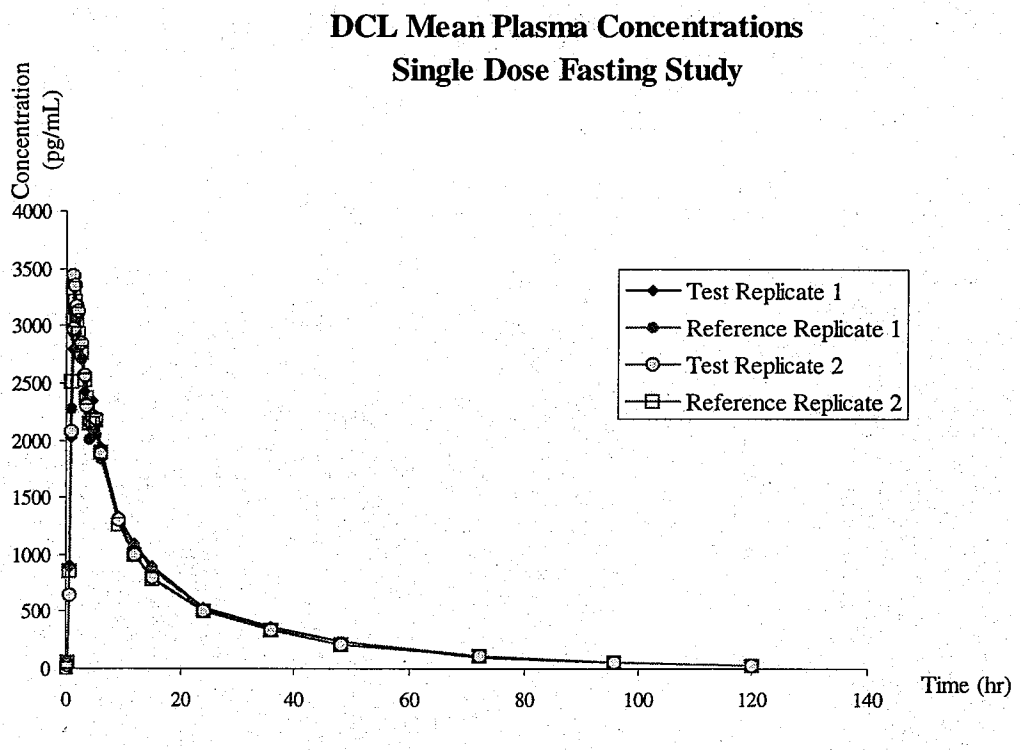
Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	35	0	0	0	0
Hour1	35	98.5597143	40.0686729	40.4000000	236.1200000
Hour2	35	184.8574286	47.2335115	100.2400000	306.3400000
Hour3	35	269.7397143	61.8885769	137.2800000	372.4200000
Hour4	35	324.1382857	65.2541303	208.8500000	518.0800000
Hour5	35	394.9694286	71.5083545	280.5100000	628.9500000
Hour5.50	35	380.8614286	62.8428138	293.1400000	628.8700000
Hour6	35	378.9371429	70.9450535	283.1200000	637.3800000
Hour6.50	35	382.4217143	77.0871674	282.3800000	667.5100000
Hour7	35	395.6568571	107.2590846	255.9600000	831.9500000
Hour7.50	35	381.9440000	82.5034448	232.7700000	653.5300000
Hour9	35	370.9442857	90.4444907	209.5400000	666.3600000
Hour12	35	317.1582857	78.0983891	136.3600000	505.3700000
Hour15	35	274.4714286	72.2181701	89.4600000	412.7300000
Hour24	35	126.2982857	44.9727709	25.9900000	212.4800000
Hour30	35	71.6820000	30.7870166	11.0500000	133.2700000
Hour36	35	38.5131429	20.2317963	0	79.4600000

Figures 1A &1B





Figures 2A & 2B



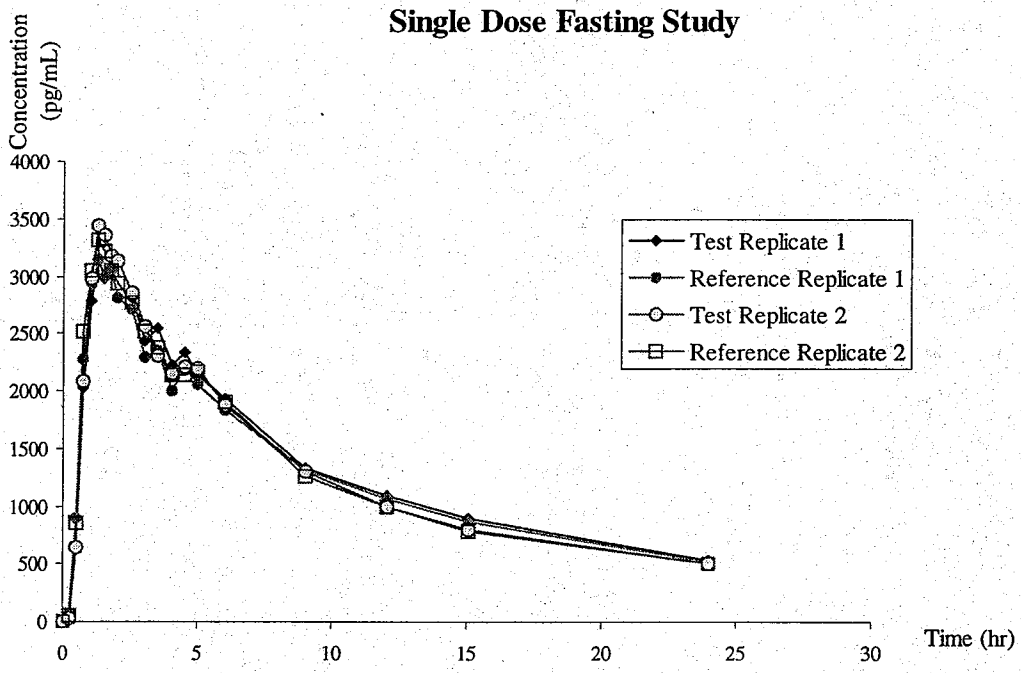
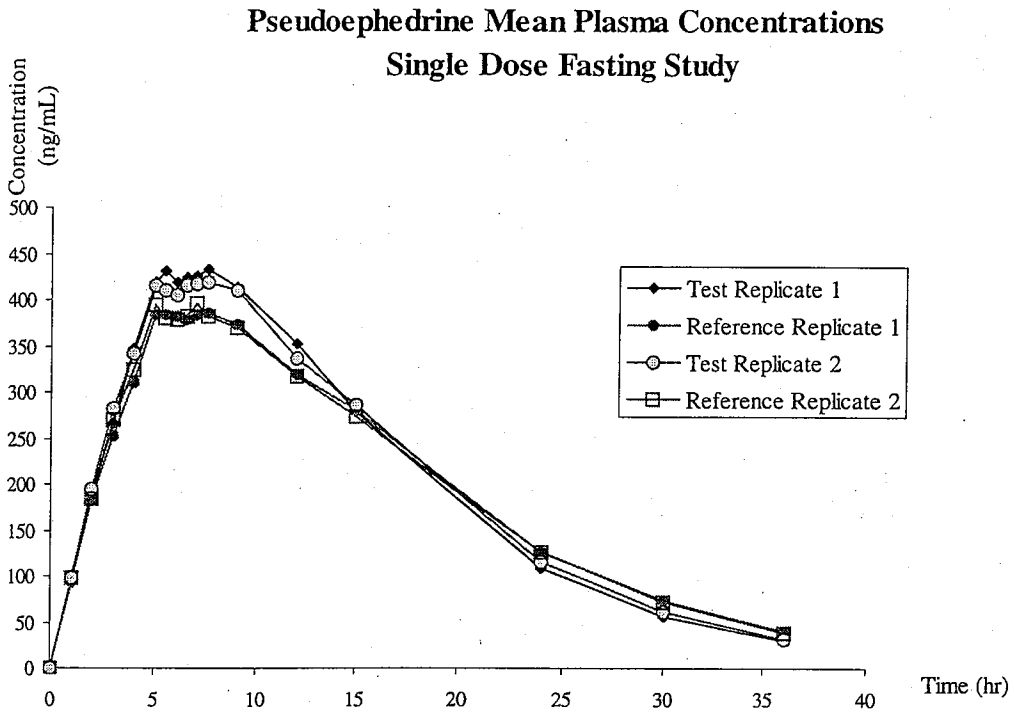


Figure 3


Pseudoephedrine Mean Plasma Concentrations
Single Dose Fasting Study
Concentration (ng/mL)
500
450
400
350
300
250
200
150
100
50
0
0
5
10
15
20
25
30
35
40
Time (hr)
Test Replicate 1
Reference Replicate 1
Test Replicate 2
Reference Replicate 2

2. Single-dose Nonfasting Bioequivalence Study (AA01112): Comparative, Randomized, Single-Dose, Fully Replicated, 4-Way Crossover Bioavailability Study of Ranbaxy and Schering (Claritin-D 24 Hour) 10 mg Loratadine/240 mg Pseudoephedrine Sulfate Extended-Release Tablets in Healthy Adult Volunteers Under Fed Conditions

Study Information See the review of the original submission for a summary of study design and conduct. The Subject Demographic and Adverse Events data were submitted in the current amendment and are summarized below in addition to the revised During Study Method Validation tables and the study results.

Table 10 Demographics of Study Subjects*

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0			Caucasian	91.9
Mean	33.11	Mean	72.97	18-40	83.8	Male	83.8	Afr. Amer.	2.7
SD	6.55	SD	7.20	41-64	16.2	Female	16.2	Hispanic	2.7
Range	20-45	Range	55.5-88.5	65-75	0.0			Asian	2.7
				>75	0.0			Others	0.0

***NOTE:** Data analyses were performed on data from subjects who completed at least 2 periods of the study. Per protocol, for every subject who did not complete the full 4 periods, an alternate subject was added for laboratory analyses and included in the statistical analyses. Subjects excluded from the analyses were not necessarily dropout subjects. Dropout subjects were Subjects #6 (prior to Period 2), #10 and 30 (prior to Period 3) and # 38 (prior to Period 2). **Subjects not included in the study analyses** were **Subjects #6 and 38** who did not complete 2 periods, **Subject # 33** who vomited early in Period 3 and **Subject#20** who had unacceptable predose DCL levels. The demographics summary was based on all enrolled subjects. Thus, dropout Subjects # 10 and 30 were included in the study analyses.

Study Results

Table 11 Dropout Information

Subject No	6	10	30	38
Reason	Personal reasons	Adverse event	Adverse event	Positive drug test
Period	II	III	III	II
Replacement	Yes	No	No	No

Was there a difference in side effects for the test versus the reference? See Table 12.

Table 12 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Feeling cold	1	0
Nausea	2	5
Sleepiness	1	0
Redness to left inner ankle	0	1
Sore throat	1	0
Headache	3	7
Shivers	1	0
Sore ears	0	1
Sore lower back	0	1
Dryness in the throat	0	1
Pain in right thigh	0	1
Pain in left thigh	0	1
Pain in right ear	1	0
Vomited	2	0
Redness to right eye lid	0	1
Swelling to right eye lid	0	1
Itchiness all over	1	0
Pain to upper and mid chest and back	1	0
Bump on inner right ankle	1	0
Total:	**15**	**20**

Comments: There were slightly more adverse effects reported for the Reference Treatment than the Test Treatment. Overall, there were relatively few adverse events reported for the entire study (4 periods). Severity of the adverse events ranged from mild to moderate.

Was there a difference in protocol deviations for the test versus the reference? No

Protocol Deviations There were no significant protocol deviations that might have compromised the integrity of the study. Significant blood sampling deviations were corrected for actual times using ClinQuick™ program.

Table 13 Assay Validation – Within Study

During Study Method Validation - Nonfasting Study AA01112: Loratadine

QC Conc. (pg/mL)	60.1 (n=157)	3003 (n=158)	8008 (n=158)	8008 (n=4) Diluted x2	8008 (n=2) Diluted x25	8008 (n=10) Diluted x5
Inter day Precision (%CV)	9.6	4.1	4.1	2.9	5.4	5.3
Inter day Accuracy (% Accuracy)	96.8	97.5	96.7	94.9	78.7	89.2
Cal. Standards Conc. (pg/mL)	20.0, 40.0, 100.1, 400.4, 1001, 5005, 7528, 8809, 10010					
Inter day Precision (%CV)	1.6-8.7					
Inter day Accuracy (% Accuracy)	92.8-106.8					
Long-term frozen storage stability (if applicable)	See the prestudy validation data.					
Linearity Range (range of R^2 values)	0.9904-0.9992					
Linearity Range (pg/mL)	20.0-10010					

NOTE: The highest loratadine Cmax concentration measured was 14923 pg/mL. The QC and standard ranges are considered acceptable when dilution is included.

During Study Method Validation - Nonfasting Study AA01112: DCL

QC Conc. (pg/mL)	60.2 (n=157)	2006 (n=158)	5495 (n=148)	5495 (n=4) Diluted x2	5495 (n=10) Diluted x5	5515 (n=10)	5515 (n=2) Diluted x5
Inter day Precision (%CV)	6.1	4.2	4.3	4.5	9.0	2.5	1.4
Inter day Accuracy (% Accuracy)	93.2	90.4	93.5	89.6	88.7	85.1	87.8
Cal. Standards Conc. (pg/mL)	20.1, 40.1, 100.3, 401.1, 1003, 3490, 5014, 6217, 7019						
Inter day Precision (%CV)	1.8-4.4						
Inter day Accuracy (% Accuracy)	93.4-106.9						
Long-term frozen storage stability (if applicable)	See the prestudy validation data.						
Linearity Range (range of R^2 values)	0.9897-0.9988						
Linearity Range (pg/mL)	20.1-7019						

NOTE: The highest loratadine Cmax concentration measured was 14923 pg/mL. The QC and standard ranges are considered acceptable when dilution is included.

During Study Method Validation - Nonfasting Study AA01112: Pseudoephedrine

QC Conc. (ng/mL)	15.00 (n=75)	360.0 (n=75)	1200 (n=76)
Inter day Precision (%CV)	18.2	3.7	3.7
Inter day Accuracy (% Accuracy)	107.9	103.3	99.1
Cal. Standards Conc. (ng/mL)	5.00, 10.0, 25.0, 50.0, 100.0, 250.0, 500.0, 1000, 1350, 1500		
Inter day Precision (%CV)	2.4-7.0		
Inter day Accuracy (% Accuracy)	93.4-109.2		
Long-term frozen storage stability (if applicable)	354 days		
Linearity Range (range of R^2 values)	0.9910-0.9993		
Linearity Range (ng/mL)	5.00-1500		

Table 14 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
AL-G-1520-10	04/19/02	Reporting of Data Generated from the Analysis of Biological Matrices

Comments on repeat assays: All samples were assayed for analytical reasons only.

Conclusion: Analytical method is acceptable.

Table 15 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figures 4

Loratadine

Test Treatment Replicate 1 - Loratadine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	35	22420.32	139.4941601	2749.10	141787.68
AUCI pg.hr/mL	35	23751.65	138.9806925	3119.01	146633.08
CMAX pg/mL	35	5060.36	120.5785108	863.5000000	26226.60
LAUCL	35	9.4270515	10.7981262	7.9190289	11.8620860
LAUCI	35	9.5030341	10.4475458	8.0452712	11.8956887
LCMAX	35	8.0644889	11.3741580	6.7609939	10.1745294
TMAX hr	35	2.0214286	38.9216593	1.2500000	4.5000000
THALF hr	35	21.9138000	58.0594631	4.2070201	55.3975153
KEL hr^{-1}	35	0.0459788	74.2455205	0.0125122	0.1647597
AUC RATIO	35	0.9279082	4.7618749	0.7990264	0.9813681

Test Treatment Replicate 2 - Loratadine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	35	16611.90	108.9906757	2478.21	78653.23
AUCI pg.hr/mL	34	18002.49	110.7011603	2805.66	86037.65
CMAX pg/mL	35	3861.02	93.3083183	638.3000000	15813.80
LAUCL	35	9.3226836	9.2809443	7.8152928	11.2728039
LAUCI	34	9.3968454	9.2387793	7.9393928	11.3625403
LCMAX	35	7.9462601	9.8455695	6.4588084	9.6686383
TMAX hr	35	2.3357143	38.5865379	1.2500000	4.5000000
THALF hr	34	22.9922262	77.6747520	1.9468508	85.4506851
KEL hr^{-1}	34	0.0533219	113.9833599	0.0081117	0.3560351
AUC RATIO	34	0.9315017	3.3219580	0.8457278	0.9822389

Reference Treatment Replicate 1 - Loratadine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	37	18090.56	122.5694847	1912.01	94050.90
AUCI pg.hr/mL	36	19500.61	118.7848678	2588.39	95298.42
CMAX pg/mL	37	4098.56	110.1351278	420.2000000	20646.20
LAUCL	37	9.3026355	10.3075891	7.5559116	11.4515914
LAUCI	36	9.4165255	9.6528387	7.8587908	11.4647685
LCMAX	37	7.8980816	11.2232415	6.0407308	9.9352866
TMAX hr	37	1.8445946	40.3255872	1.0000000	4.5000000
THALF hr	36	20.9620110	61.2679594	3.9699078	56.8286249
KEL hr^{-1}	36	0.0507880	80.4816760	0.0121971	0.1746003
AUC RATIO	36	0.9373465	3.6434890	0.8319691	0.9869093

Reference Treatment Replicate 2 - Loratadine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	35	19133.30	128.0076627	2273.30	122942.00
AUCI pg.hr/mL	35	20483.65	126.0416696	2394.26	126487.43
CMAX pg/mL	35	4428.69	115.5767187	507.2000000	21562.00
LAUCL	35	9.3717162	10.0635318	7.7289878	11.7194680
LAUCI	35	9.4429057	10.0029746	7.7808292	11.7478982
LCMAX	35	7.9451417	11.6521059	6.2289054	9.9786878
TMAX hr	35	2.2785714	66.7796867	1.0000000	9.0000000
THALF hr	35	23.2569112	72.4641959	3.5983988	62.5202116
KEL hr^{-1}	35	0.0534081	83.3973394	0.0110868	0.1926266
AUC RATIO	35	0.9320460	4.0219919	0.8231122	0.9719701

DCL

Test Treatment Replicate 1 -DCL

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	35	46291.69	57.3203330	22504.38	133869.91
AUCI pg.hr/mL	35	48608.80	61.8679219	23739.41	144782.37
CMAX pg/mL	35	3434.12	52.0953796	1145.00	10537.40
LAUCL	35	10.6372058	4.0135060	10.0214650	11.8046238
LAUCI	35	10.6741388	4.1691922	10.0748919	11.8829870
LCMAX	35	8.0395761	5.5004754	7.0431599	9.2626861
TMAX hr	35	2.7071429	59.4062331	1.0000000	9.0000000
THALF hr	35	25.9749358	25.1922714	18.5940835	51.5580279
KEL hr^{-1} AUC	35	0.0279726	19.8746590	0.0134440	0.0372778
RATIO	35	0.9641873	2.9714784	0.8234734	0.9855791

Test Treatment Replicate 2 - DCL

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	35	46674.37	52.1866506	23472.60	134215.80
AUCI pg.hr/mL	34	48436.03	55.3057740	24292.26	141812.11
CMAX pg/mL	35	3359.46	52.1123567	1770.80	10019.30
LAUCL	35	10.6594528	3.7960183	10.0635891	11.8072042
LAUCI	34	10.6884962	3.9132330	10.0979132	11.8622583
LCMAX	35	8.0291910	4.9734508	7.4791867	9.2122685
TMAX hr	35	2.7571429	43.3454789	1.5000000	6.0000000
THALF hr	34	25.8519323	23.8475636	14.4527750	41.5369447
KEL hr^{-1}	34	0.0283756	24.9714929	0.0166875	0.0479595
AUC RATIO	34	0.9634801	2.6573560	0.8498073	0.9861208

Reference Treatment Replicate 1 - DCL

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	37	45257.99	57.6943995	17508.34	138252.15
AUCI pg.hr/mL	37	47083.67	60.0696012	18844.47	144205.47
CMAX pg/mL	37	3190.19	47.3805764	943.8000000	8915.40
LAUCL	37	10.6086486	4.2115354	9.7704325	11.8368345
LAUCI	37	10.6425864	4.2614591	9.8439747	11.8789944
LCMAX	37	7.9810793	5.1389969	6.8499143	9.0955354
TMAX hr	37	2.3243243	45.4117367	1.0000000	5.0000000
THALF hr	37	25.1684079	19.6854889	16.6494370	38.3599610
KEL hr^{-1}	37	0.0285472	19.0581358	0.0180695	0.0416319
AUC RATIO	37	0.9667900	1.8095278	0.8997397	0.9862900

Reference Treatment Replicate 2 - DCL

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL pg.hr/mL	35	50281.19	63.3053091	24212.75	159118.64
AUCI pg.hr/mL	35	52534.01	65.1790764	25156.39	167838.08
CMAX pg/mL	35	3377.60	62.8180443	1281.80	12021.00
LAUCL	35	10.6893318	4.5806872	10.0946346	11.9774054
LAUCI	35	10.7264845	4.6590561	10.1328674	12.0307550
LCMAX	35	8.0071080	5.5748356	7.1560206	9.3944104
TMAX hr	35	2.8214286	50.9724283	1.0000000	6.0000000
THALF hr	35	27.3869355	21.0237306	19.3964781	40.0727592
KEL hr^{-1}	35	0.0263302	19.4364802	0.0172972	0.0357357
AUC RATIO	35	0.9637458	2.1240641	0.8908038	0.9883952

Pseudoephedrine

Test Treatment Replicate 1 - Pseudoephedrine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL ng.hr/mL	35	7501.28	18.8522115	4892.04	10462.18
AUCI ng.hr/mL	35	7755.83	20.0587097	4977.35	11058.49
CMAX ng/mL	35	444.8542857	15.9469393	293.0500000	660.7200000
LAUCL	35	8.9055275	2.1264864	8.4953637	9.2555219
LAUCI	35	8.9367236	2.2461160	8.5126532	9.3109541
LMAX	35	6.0856710	2.5877452	5.6803432	6.4933301
TMAX hr	35	7.3142857	31.4175769	4.0000000	12.0000000
THALF hr	35	6.0853124	27.3190694	4.3259045	13.7710714
KEL hr^{-1}	35	0.1194895	19.2754002	0.0503229	0.1601977
AUC RATIO	35	0.9694791	2.0107546	0.9016142	1.0000000

Test Treatment Replicate 2 - Pseudoephedrine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL ng.hr/mL	35	7420.44	20.0208343	4848.03	11104.89
AUCI ng.hr/mL	35	7701.76	21.6912987	4898.79	12481.51
CMAX ng/mL	35	436.5125714	18.4755883	288.3300000	646.3400000
LAUCL	35	8.8932337	2.1977542	8.4863267	9.3151408
LAUCI	35	8.9276056	2.3403009	8.4967428	9.4320035
LMAX	35	6.0627900	2.9820128	5.6641057	6.4713257
TMAX hr	35	8.0285714	26.3764595	5.0000000	12.0000000
THALF hr	35	5.9933704	20.0975300	4.3005673	9.4633136
KEL hr^{-1}	35	0.1198760	18.5435319	0.0732302	0.1611415
AUC RATIO	35	0.9664752	2.3422694	0.8897074	0.9924404

Reference Treatment Replicate 1 - Pseudoephedrine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL ng.hr/mL	37	7382.09	23.2346446	4884.51	12509.43
AUCI ng.hr/mL	37	7687.09	24.3397732	4927.19	12720.14
CMAX ng/mL	37	450.2029730	18.7229109	325.0400000	788.4300000
LAUCL	37	8.8824897	2.4817713	8.4938243	9.4342380
LAUCI	37	8.9202083	2.6167208	8.5025234	9.4509415
LMAX	37	6.0950369	2.7593718	5.7839483	6.6700436
TMAX hr	37	7.4324324	26.9633292	5.0000000	12.0000000
THALF hr	37	6.2539417	22.3050156	4.3041720	10.2366329
KEL hr^{-1}	37	0.1157761	20.3341468	0.0676980	0.1610066
AUC RATIO	37	0.9633213	2.6564165	0.8887197	0.9919392

Reference Treatment Replicate 2 - Pseudoephedrine

Variable	N	Mean	Coeff of Variation	Minimum	Maximum
AUCL ng.hr/mL	35	7321.59	21.0528399	5207.99	11083.35
AUCI ng.hr/mL	35	7650.56	22.6874721	5324.56	11797.25
CMAX ng/mL	35	442.6417143	20.1296368	303.4400000	748.5000000
LAUCL	35	8.8777506	2.3195059	8.5579488	9.3131990
LAUCI	35	8.9186097	2.4679381	8.5800854	9.3756220
LMAX	35	6.0744065	3.1627223	5.7151839	6.6180712
TMAX hr	35	7.5000000	23.2069406	5.0000000	12.0000000
THALF hr	35	6.3634863	21.8565216	4.3293199	10.0158116
KEL hr^{-1}	35	0.1136738	20.3756821	0.0691906	0.1600713
AUC RATIO	35	0.9603355	2.7898315	0.8832939	0.9934704

Table 16 Geometric Means and 90% Confidence Intervals (N=37)

Loratadine

Parameter	Test	Reference	T/R	90% CI
AUC0-t	11285	11206	1.01	91.4-111.0
AUC∞	12100	12059	1.00	90.9-110.8
Cmax	2887	2731	1.06	95.5-117.0

DCL

Parameter	Test	Reference	T/R	90% CI
AUC0-t	41727	42163	0.99	94.2-104.0
AUC∞	43213	43669	0.99	94.2-104.0
Cmax	3093	2982	1.04	98.7-108.9

Pseudoephedrine

Parameter	Test	Reference	T/R	90% CI
AUC0-t	7402	7234	1.02	99.8-104.9
AUC∞	7659	7527	1.02	99.1-104.4
Cmax	436.3	441.0	0.99	95.6-102.4

Table 17 Additional Study Information

Within Subject Variance: Values as taken from the Covariance Parameter Estimates Table of PROC MIXED output are shown below (for ln-transformed AUCt and Cmax only)

Loratadine

	LnCmax	LnAUCt	LnAUCi
Test	0.09392	0.08957	0.08674
Reference	0.1707	0.1512	0.1591

DCL

	lnCmax	LnAUCt	LnAUCi
Test	0.02911	0.01948	0.01983
Reference	0.03208	0.04252	0.04147

Pseudoephedrine

	lnCmax	LnAUCt	LnAUCi
Test	0.009602	0.006384	0.006772
Reference	0.01190	0.008811	0.009850

Comments:

- ke and AUC∞ were determined for how many subjects? See N values given in the Arithmetic Mean Pharmacokinetic Parameters tables above (pages 30-33). If there are cases in which Ke cannot be calculated, indicate if you agree or disagree with firm's decision: The reviewer agreed with the firm's determination of KEL.
- Indicate the number of subjects with the following:

a. measurable drug concentrations at 0 hr: Subject # 7(Period IV, Reference Treatment) for both loratadine and DCL. Predose loratadine level was 96.4 pg/mL or 2.34% of corresponding Cmax. Predose DCL level was 52.1 pg/mL or 2.01% of corresponding Cmax. The subject was included in the study analyses. Subject #20 had DCL predose levels of 131.1 pg/mL (or 5.27% of corresponding Cmax) for Period II, 123.5 pg/mL (or 4.51 % of Cmax) for Period III, and 129.5 pg/mL (or 5.22% of corresponding Cmax) for Period IV. This subject was dropped from the study analyses per the current general BA/BE guidance.

b. first scheduled post-dose sampling time as T_{max}: None

c. first measurable drug concentration as C_{max}: None

- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes for the PK parameters and point estimates. The firm did not calculate 90% confidence intervals.
- Are the 90% confidence intervals for AUC_{0-t}, AUC∞, Cmax within the acceptable limits of 80-125%? Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect: N/A

Conclusion: The single-dose fed bioequivalence study is acceptable.

Table 18 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Test Treatment Replicate 1 - Loratadine (pg/mL)

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	35	0	0	0	0
Hour0.50	35	214.9057143	572.3565296	0	3193.30
Hour0.75	35	852.1000000	2206.84	0	12761.00
Hour1	35	1972.35	3767.36	0	21765.10
Hour1.25	35	3236.49	4773.01	0	26226.60
Hour1.50	35	4003.28	5110.29	0	22976.80
Hour1.75	35	4227.16	5182.04	56.9000000	21639.10
Hour2	35	4260.09	5123.23	124.0000000	23616.70
Hour2.25	35	4144.98	5211.29	232.1000000	25553.40
Hour2.50	35	3807.73	4696.19	501.1000000	22295.80
Hour2.75	35	3452.39	4405.95	558.3000000	21995.50
Hour3	35	3139.63	4029.16	412.6000000	20375.10
Hour3.50	35	2718.23	3401.93	354.0000000	16698.40
Hour4	35	2173.25	2755.10	280.2000000	13350.10
Hour4.50	35	1859.81	2365.34	231.1000000	11643.40
Hour5	35	1473.26	1953.88	183.4000000	9483.40
Hour6	35	982.3742857	1376.67	114.5000000	6951.50
Hour9	35	420.5885714	595.7138707	45.1000000	2966.60
Hour12	35	263.2685714	410.8686027	35.2000000	2093.60
Hour15	35	198.4771429	301.1812373	33.2000000	1490.70
Hour24	35	103.1285714	167.1648914	0	797.8000000
Hour36	35	82.9371429	148.8852679	0	676.6000000
Hour48	34	39.4058824	85.7690484	0	372.2000000
Hour72	34	24.0617647	62.0033920	0	287.6000000
Hour96	35	16.8885714	46.0381094	0	222.2000000
Hour120	35	11.3171429	33.5013036	0	172.1000000

Test Treatment Replicate 2 - Loratadine (pg/mL)

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	35	0	0	0	0
Hour0.50	35	71.4228571	163.4863784	0	857.0000000
Hour0.75	35	329.1171429	670.0814198	0	3745.10
Hour1	35	991.8600000	1343.86	0	6033.40
Hour1.25	35	1869.74	2232.06	0	11175.80
Hour1.50	35	2483.86	2793.32	0	14495.00
Hour1.75	35	3010.09	3073.04	0	14586.10
Hour2	35	3278.17	3521.92	125.1000000	15813.80
Hour2.25	35	3110.81	3123.03	466.1000000	13159.20
Hour2.50	35	3137.48	3336.47	498.3000000	14928.10
Hour2.75	35	2997.13	3254.61	493.5000000	14963.90
Hour3	35	2722.24	2941.93	397.4000000	14214.80
Hour3.50	35	2359.68	2549.69	349.4000000	12387.00
Hour4	35	2045.94	2432.36	240.5000000	12533.70
Hour4.50	35	1672.77	2044.10	176.6000000	10864.40
Hour5	35	1344.63	1794.55	153.0000000	10035.00
Hour6	35	921.1342857	1467.30	91.3000000	8430.00
Hour9	35	283.9228571	273.7167472	45.3000000	1089.60
Hour12	35	160.9142857	159.1814302	21.4000000	720.1000000
Hour15	35	116.9971429	107.4062505	0	523.0000000
Hour24	35	60.8142857	63.3457327	0	318.7000000
Hour36	34	46.8411765	64.8260475	0	354.9000000
Hour48	33	29.6636364	50.4499431	0	214.0000000
Hour72	33	17.0454545	37.1857927	0	176.6000000
Hour96	33	10.4090909	27.3993997	0	120.8000000
Hour120	32	7.7281250	20.7373317	0	91.9000000

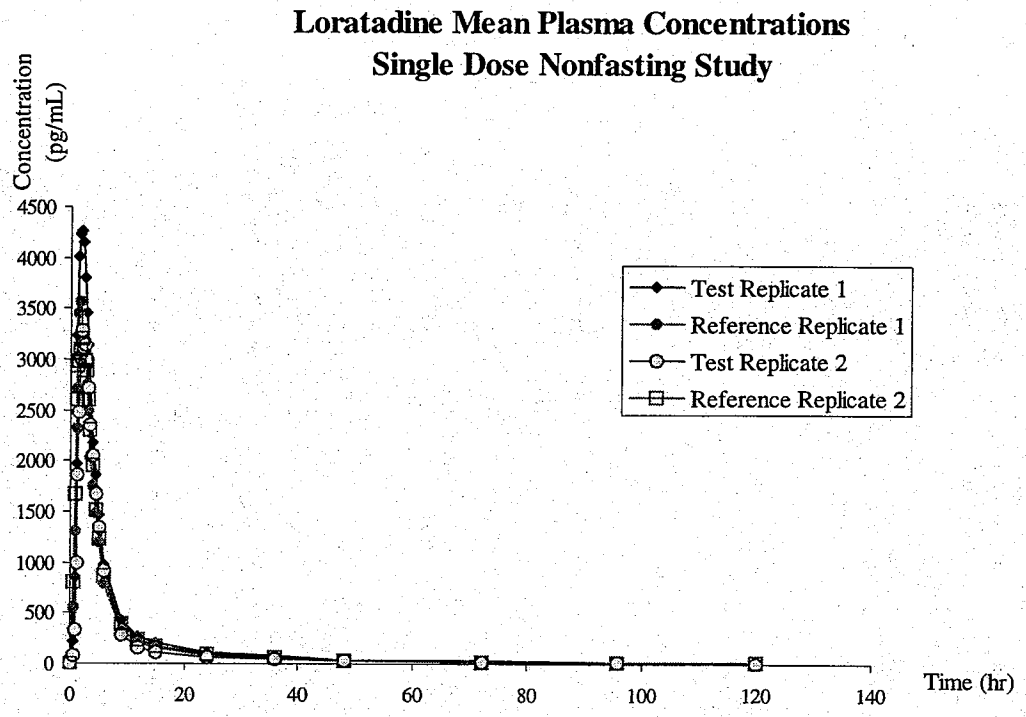
Reference Treatment Replicate 1 - Loratadine

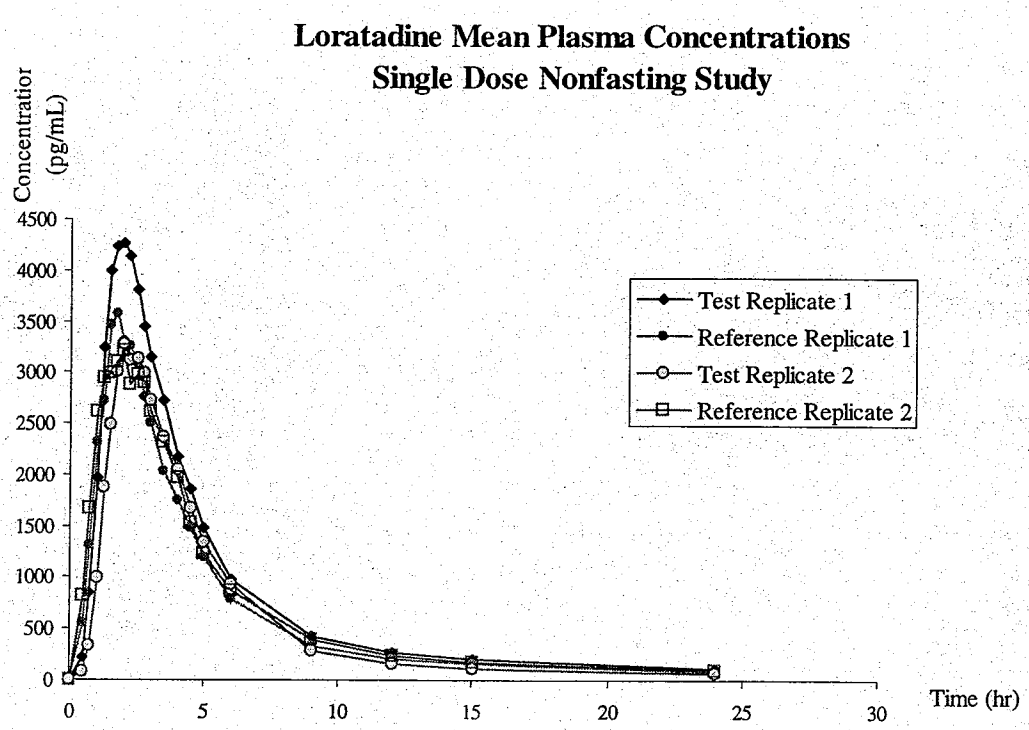
Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	37	0	0	0	0
Hour0.50	36	545.8027778	1079.70	0	5331.00
Hour0.75	37	1307.89	2129.73	0	9899.40
Hour1	37	2317.37	2864.93	54.3000000	11939.60
Hour1.25	36	2719.25	3174.54	97.9000000	13565.50
Hour1.50	37	3456.69	4200.13	96.3000000	17216.30
Hour1.75	37	3574.94	4430.01	205.7000000	20646.20
Hour2	37	3303.08	3744.92	396.8000000	15272.20
Hour2.25	37	3251.78	3823.15	365.7000000	16880.60
Hour2.50	37	3072.02	3629.70	328.0000000	16224.80
Hour2.75	37	2746.51	3055.89	323.6000000	12564.40
Hour3	37	2496.08	2766.46	306.7000000	11147.70
Hour3.50	37	2036.92	2134.89	282.0000000	8728.90
Hour4	37	1744.86	2023.44	241.2000000	9132.60
Hour4.50	37	1483.91	1795.32	211.7000000	8655.80
Hour5	37	1195.89	1558.57	164.7000000	7821.90
Hour6	37	784.7540541	1001.99	91.0000000	4873.20
Hour9	37	327.6567568	402.0787054	35.4000000	1856.60
Hour12	36	206.4166667	257.1453324	36.8000000	1119.70
Hour15	37	157.7918919	196.3862243	24.8000000	896.1000000
Hour24	36	83.4305556	110.4170945	0	448.7000000
Hour36	37	59.2351351	89.2347597	0	373.0000000
Hour48	37	36.0081081	59.0176545	0	253.5000000
Hour72	36	18.1750000	38.5805678	0	189.3000000
Hour96	36	10.0861111	25.5430746	0	136.3000000
Hour120	37	6.6486486	19.4817525	0	106.6000000

Reference Treatment Replicate 2 - Loratadine

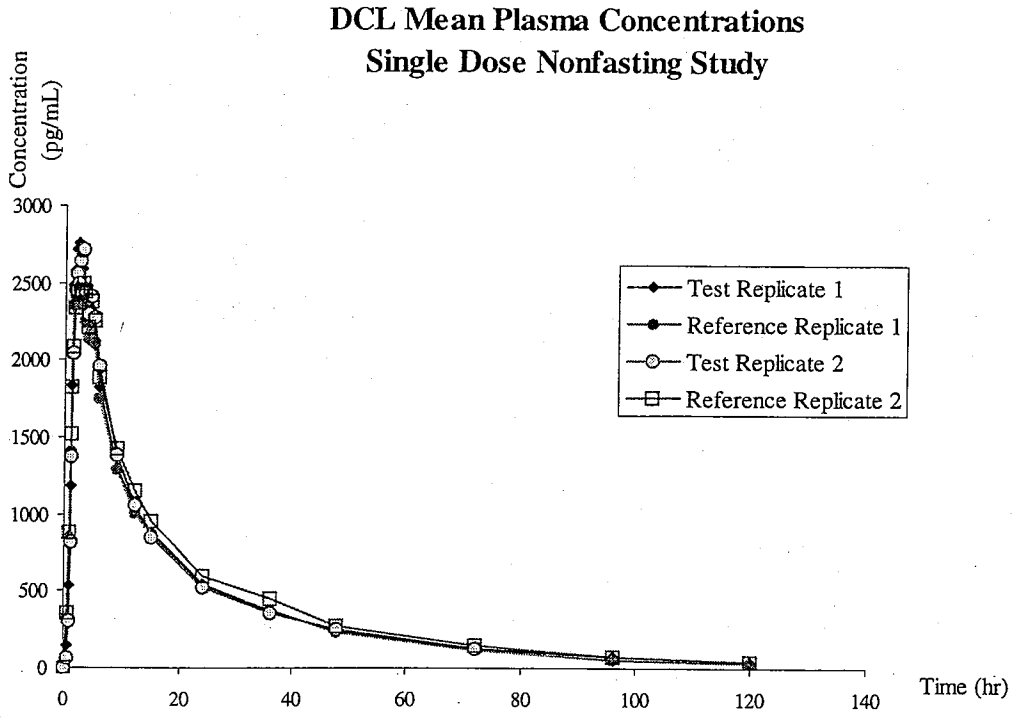
Variable	N	Mean	Std Dev	Minimum	Maximum
Hour0	35	2.7542857	16.2945740	0	96.4000000
Hour0.50	35	811.0657143	1740.15	0	7564.20
Hour0.75	35	1669.54	3104.72	0	15030.50
Hour1	35	2604.28	4311.81	34.8000000	20892.40
Hour1.25	35	2936.91	3887.57	96.1000000	17914.50
Hour1.50	35	2989.52	3595.58	141.7000000	17471.80
Hour1.75	35	3099.31	3409.49	173.2000000	16193.50
Hour2	35	3207.56	3353.05	222.1000000	12521.40
Hour2.25	35	2884.43	2758.19	336.5000000	10637.40
Hour2.50	35	2980.11	3545.67	393.1000000	18223.30
Hour2.75	35	2888.31	3890.58	364.8000000	21562.00
Hour3	35	2605.61	3609.07	383.2000000	20701.40
Hour3.50	35	2312.89	3341.31	427.9000000	19417.20
Hour4	35	1964.80	3089.99	337.4000000	18161.00
Hour4.50	35	1520.96	2274.80	240.5000000	13525.00
Hour5	35	1233.80	1892.77	169.3000000	11386.80
Hour6	35	863.6457143	1526.64	102.9000000	9150.30
Hour9	35	389.9657143	593.1965119	46.5000000	3029.00
Hour12	35	237.1971429	362.9834687	21.0000000	1784.10
Hour15	35	176.3428571	255.5359101	23.3000000	1219.50
Hour24	34	89.1911765	120.9668809	0	489.8000000
Hour36	35	69.0057143	105.6809153	0	470.4000000
Hour48	35	34.6714286	65.4424784	0	280.7000000
Hour72	34	20.8823529	45.3265356	0	196.5000000
Hour96	35	12.9028571	32.8351899	0	148.8000000
Hour120	35	8.3171429	24.8393365	0	124.7000000

Figures 4A & 4B





Figures 5A & 5B



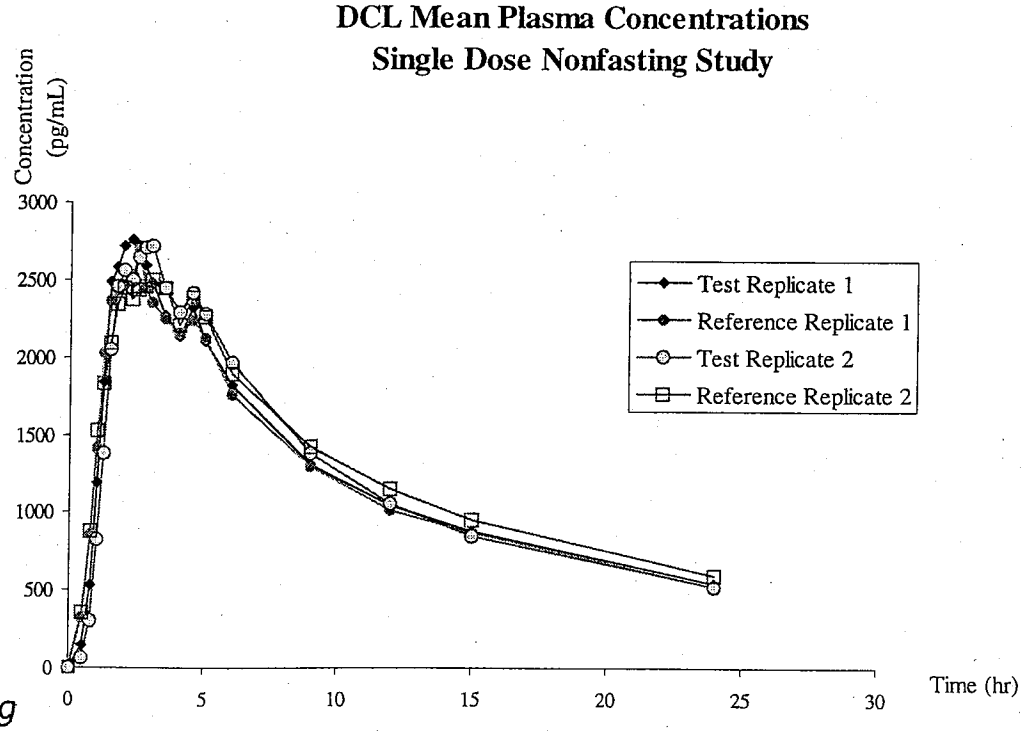
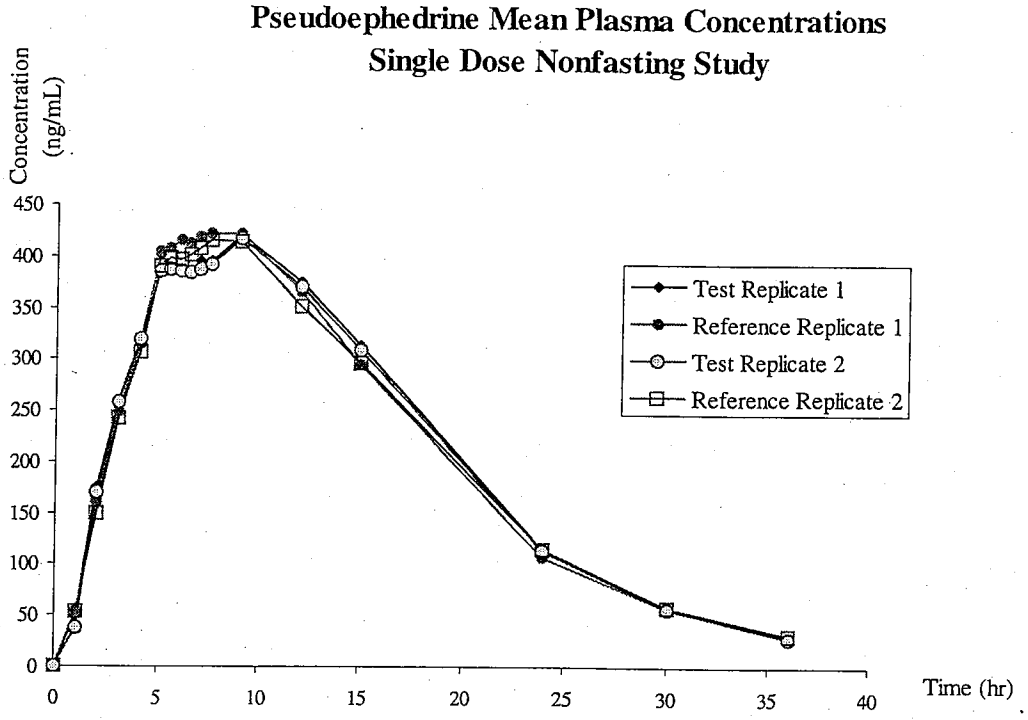


Figure 6


Pseudoephedrine Mean Plasma Concentrations
Single Dose Nonfasting Study
Concentration (ng/mL)
450
400
350
300
250
200
150
100
50
0
0
5
10
15
20
25
30
35
40
Time (hr)
Test Replicate 1
Reference Replicate 1
Test Replicate 2
Reference Replicate 2

B. Formulation Data: The formulation was found acceptable. See the review of the original submission.

C. Dissolution Data: (Additional testing – FDA recommended method) For other dissolution testing of the test and reference products, see the review of the original submission.

Condition: USP II (paddle) at 50 rpm
1000 mL 0.1 N HCl for 0-1 hour
1000 mL pH 7.5 phosphate buffer for 1-16 hours

Loratadine
Test Product
Lot No.: 7240202
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 6

Time(min.)	Mean	Range	%CV
5	42	(b) (4)	8.3
10	64		5.1
20	81		5.2
30	87		5.7
45	89		4.9
60	90		5.4

Pseudoephedrine
Test Product
Lot No.: 7240202
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 6

Time(min.)	Mean	Range	%CV
60	21	(b) (4)	5.2
240	51		3.0
480	73		2.4
960	97		1.8

F2: N/A

Comments: The dissolution data as submitted are accetable. However, the firm only tested 6 units, the test lot was over 18 months old, and the 2-hour sampling time point for pseudoephedrine dissolution testing was not included in the above results. The firm is requested to provide additional dissolution testing using the FDA-recommended dissolution method on a fresh test lot, when it becomes available, using 12 units and including the 2-hour sampling time point for pseudoephedrine profile.

D. SAS Output

1. Fasting Study

Microsoft Word
Document

2. Nonfasting Study

Microsoft Word
Document

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-557 APPLICANT: Ranbaxy Laboratories

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

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

The dissolution testing is considered **incomplete.** You have proposed the following method and specifications:

Medium, acid statge	0.1 N HCl for 0-1 hour
Medium, buffer stage	pH 6.8 phosphate buffer for 1-16 hours
Volume (mL)	900 mL
USP Apparatus Type	I (basket)
Rotation (rpm)	75

Your proposed specifications:

Loratadine: NLT (b)(4)% dissolved in 60 minutes
Pseudoephedrine: (b)(4)
1 hour
4 hours
8 hours
16 hours

However, the FDA recommends the following method and specifications (based on the submitted data):

Medium, acid stage	0.1 N HCl for 0-1 hour
Medium, buffer stage	0.1 M phosphate buffer pH 7.5 for 1-16 hours
Volume (mL)	1000 mL
USP Apparatus Type	II (paddle)
Rotation (rpm)	50

FDA's specifications:

Loratadine: NLT (b)(4)% of the labeled amount dissolved 30 min
Pseudoephedrine: (b)(4)
1 hour
2 hours
4 hours
8 hours
16 hours

We recommend that you test the FDA-recommended dissolution method on 12 units of your product taken when a **fresh lot** becomes available. Please include **the 2-hour sampling time** in the pseudoephedrine dissolution profile.

Please provide your response to the FDA's above recommendations.

Sincerely yours,

for Barbara M. Davit

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

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CC:ANDA 76-557
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang
HFD-617/ A. Sigler
HFD-650/ D. Conner

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Printed in final on / /

BIOEQUIVALENCY - INCOMPLETE Submission date: 10-20-03

1. STUDY AMENDMENT (STA) Strength: 10 mg/240 mg
Outcome: IC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-557
Drug Product Name	Loratadine/Pseudoephedrine Sulfate Extended-Released Tablets
Strength	10 mg/240 mg
Applicant Name	Ranbaxy Laboratories
Address	Gurgaon, India
Submission Date(s)	March 16, 2004
Amendment Date(s)	April 21, 2004
Reviewer	Hoainhon Nguyen
File Location	c:\firmsnz\ranbaxy\ltrs&rev\76557a0304.doc

I. Executive Summary

This is a review of an amendment submitted in response to the DBE's deficiency comments in the review of the previous submission dated 10/20/03. The fasting and nonfasting bioequivalence studies, dissolution testing and formulation of the test product had previously been found acceptable. The application however was considered incomplete since the firm's proposed dissolution method and specifications were different from those recommended by the FDA. In addition, the firm was requested to submit dissolution results for the fresh test lot when a fresh test lot is produced, using the FDA-recommended dissolution method on 12 units since the firm had only tested 6 units of the test lot in the current amendment using the FDA dissolution method, and the test lot was 18 months old at the time of this testing.

In the current amendments, the firm submitted the dissolution data for a fresh lot using the FDA-recommended method. The firm has also proposed different specifications based on the data of the fresh lot. The specifications were proposed such that the fresh lot can pass Stage 1 dissolution testing. The DBE agrees with the firm's newly proposed specifications. The revised specifications are considered as *interim* specifications and the firm is requested to submit dissolution data for 3 fresh lots when they become available to confirm the specifications.

The application is considered acceptable with no further deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Ranbaxy's Loratadine/Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, Lot# 7240202
Reference Product	Claritin-D (loratadine/pseudoephedrine, 10 mg/240 mg) 24 Hour ER Tablets (NDA # 20-470, Schering, Approved 08/23/96) Lot # 1-DCS-2039
Indication	indicated for the relief of symptoms of seasonal allergic rhinitis.

PK/PD Information See the original review (v:\firmsnz\ranbaxy\ltrs&rev\76557n1202)

Relevant DBE History: See the original review (v:\firmsnz\ranbaxy\ltrs&rev\76557n1202)

B. Contents of Submission

		How many?
Study Amendments	X	2 (including 1 Telephone Amendment)

C. Bioanalytical Method Validation

See the original review (v:\firmsnz\ranbaxy\ltrs&rev\76557n1202)

D. In Vivo Studies

See the reviews v:\firmsnz\ranbaxy\ltrs&rev\76557n1202 and v:\firmsnz\ranbaxy\ltrs&rev\76557a1003.doc.

1. Single-dose Fasting Bioequivalence Study

Study No.	AA01111
Study Design	randomized, 4-way replicated crossover
Test product	Ranbaxy's Loratadine/Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, Lot # 7240202
Reference product	Schering's Claritin-D (loratadine/pseudoephedrine sulfate, 10 mg/240 mg) 24 Hour ER Tablets, Lot # 1-DCS-2039
Strength tested	10 mg/240 mg
Dose	1x10 mg/240 mg

Summary of Statistical Analysis: (N=37)

Loratadine

Parameter	Point Estimate	90% Confidence Interval
AUCt	1.11	101.8-121.3
AUCi	1.12	102.1-122.0
Cmax	107.0	96.8-118.2

DCL

Parameter	Point Estimate	90% Confidence Interval
AUCt	1.02	98.3-105.3
AUCi	1.01	98.0-104.9
Cmax	1.04	100.2-108.5

Pseudoephedrine

Parameter	Point Estimate	90% Confidence Interval
AUCt	1.03	100.1-106.4
AUCi	1.01	97.8-104.4
Cmax	1.10	106.4-114.0

2. Single-dose Nonfasting Bioequivalence Study

Study No. AA01112
Study Design randomized, 4-way replicated crossover
Test product Ranbaxy's Loratadine/Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, Lot # 7240202
Reference product Schering's Claritin-D (loratadine/pseudoephedrine sulfate, 10 mg/240 mg) 24 Hour ER Tablets, Lot # 1-DCS-2039
Strength tested 10 mg/240 mg
Dose 1x10 mg/240 mg

Summary of Statistical Analysis (N=37)

Loratadine

Parameter	Point Estimate	90% Confidence Interval
LAUCt	1.01	91.4-111.0
LAUCi	1.00	90.9-110.8
Lcmax	1.06	95.5-117.0

DCL

Parameter	Point Estimate	90% Confidence Interval
LAUCt	0.99	94.2-104.0
LAUCi	0.99	94.2-104.0
Lcmax	1.04	98.7-108.9

Pseudoephedrine

Parameter	Point Estimate	90% Confidence Interval
LAUCt	1.02	99.8-104.9
LAUCi	1.02	99.1-104.4
Lcmax	0.99	95.6-102.4

E. Formulation

See the review of the original submission (v:\firmsnz\ranbaxy\ltrs&rev\76557n1202).

F. In Vitro Dissolution

In the previous submission dated 10/20/03, upon the DBE's request, the firm conducted dissolution testing using the FDA-recommended method on Loratadine and Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg. The bio batch (Lot No. 7240202) was 18 months old at the time of the dissolution testing. The DBE reviewed the dissolution data and found the following deficiencies:

The dissolution testing was considered **incomplete**. The firm had proposed the following method and specification:

Medium, acid stage 0.1 N HCl for 0-1 hour
Medium, buffer stage pH 6.8 phosphate buffer for 1-16 hours
Volume (mL) 900 mL
USP Apparatus Type I (basket)
Rotation (rpm) 75
Firm's specifications Loratadine: NLT (b)(4)% dissolved in 60 minutes

Pseudoephedrine: (b) (4) in 1 hour, (b) (4) in 4 hours, (b) (4) in 8 hours and NLT (b) (4)% in 16 hours.

However, the Agency recommends the following method and specifications (based on the submitted data):

Medium, acid stage	0.1 N HCl for 0-1 hour
Medium, buffer stage	0.1 M phosphate buffer pH 7.5 for 1-16 hours
Volume (mL)	1000 mL
USP Apparatus Type	II (paddle)
Rotation (rpm)	50
FDA's specification	Loratadine: NLT (b) (4)% of the labeled amount dissolved 30 min
	Pseudoephedrine: 1 hour (b) (4)
	2 hours
	4 hours
	8 hours
	16 hours

The firm was requested to submit dissolution data on 12 units when a fresh lot becomes available and to include the 2-hour sampling time in the pseudoephedrine dissolution profile. The firm was also requested to provide response to the Agency's recommendations.

In the current amendment, the firm has submitted dissolution data for a recently manufactured batch (Lot No. 7240302) of Loratadine and Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg. The dissolution testing was performed using the FDA-recommended method. (See Appendix for the summary of the dissolution data). The results showed 4 units of the tested 12 units were below (b) (4) at 30 minutes for loratadine. The pseudoephedrine results met the FDA-recommended specifications for all units. In addition, the firm has submitted the dissolution data (using the FDA-recommended dissolution method) for each lot of the currently marketed products, Claritin-D 24 HR (the RLD product) by Schering and Allergy Relief D-24 by Andrx. The dissolution data for these two marketed lots did not meet the FDA-recommended specification for loratadine at S1 level. Based on the submitted results, the firm has requested a telephone conference with the DBE to discuss the appropriate loratadine specification for its product. The conference was held on 04/20/04. Per the discussion between the FDA and firm's representatives, the following was determined:

1. For loratadine, the immediate-release component, the firm is requesting the specification to be changed to NLT (b) (4)% (Q) in 60 minutes. This proposed specification will allow the submitted fresh lot (Lot No. 7240302) to pass Stage 1 of the dissolution testing (for immediate release product).

2. For pseudoephedrine, although the submitted fresh lot met the FDA-recommended specifications at L1 level, the firm is requesting that the specifications to be changed as follows:

1 hour	(b) (4)	(originally recommended (b) (4)
2 hours		(originally recommended
4 hours		(originally recommended
8 hours		(no change)
16 hours	NLT (b) (4)%	(no change)

The above proposed specifications by the firm were considered reasonable and therefore, acceptable (See the firm's Telephone amendment dated 04/21/04 and Dr. Nhan Tran's confirmation email in the review Appendix). However, the revised specifications are considered only as *interim* specifications, and the firm is requested to submit dissolution data for 3 fresh lots when they become available to confirm the specifications.

G. Waiver Request: Not applicable.

H. Comments:

As requested in the teleconference dated April 20, 2004, the firm submitted a written request in a Telephone Amendment dated 04/21/04 for the revised specifications for loratadine and pseudoephedrine as stated in the In Vitro Dissolution section above. The specifications are found acceptable by the DBE. The dissolution testing is now considered **complete**.

The following method and specifications (based on the dissolution data of the bio lot submitted in the previous submission as well as the dissolution data of the fresh lot submitted in the current amendment) are proposed by the firm in the Telephone Amendment and recommended by the DBE:

Medium, acid stage	0.1 N HCl for 0-1 hour
Medium, buffer stage	0.1 M phosphate buffer pH 7.5 for 1-16 hours
Volume (mL)	1000 mL
USP Apparatus Type	II (paddle)
Rotation (rpm)	50
FDA's specification	Loratadine: NLT (b) (4) % of the labeled amount dissolved 60 min
	Pseudoephedrine: 1 hour (b) (4)
	2 hours
	4 hours
	8 hours
	16 hours

The revised specifications are considered only as *interim* specifications, and the firm is requested to submit dissolution data for 3 fresh lots when they become available to confirm the specifications.

I. Recommendations

From the previous review:

1. The single-dose, fasting bioequivalence study and the single-dose nonfasting bioequivalence study conducted by Ranbaxy on the test product, Loratadine/Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, lot # 7240202, comparing it with the reference product, Schering's Claritin-D® (loratadine/pseudoephedrine sulfate, 10 mg/240 mg) ER Tablets, lot # 1-DCS-2039, have been found **acceptable** by the Division of Bioequivalence. The test product, Ranbaxy's Loratadine & Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg, is deemed bioequivalent to the reference product, , Schering's Claritin-D® (loratadine/pseudoephedrine sulfate, 10 mg/240 mg) ER Tablets.

From the review of the current amendment:

2. The dissolution testing for the test product has been found **acceptable.** The following method and specifications (based on the dissolution data of the bio lot submitted in the previous submission as well as the dissolution data of the fresh lot submitted in the current amendment) are proposed by the firm and recommended by the DBE:

Medium, acid stage	0.1 N HCl for 0-1 hour
Medium, buffer stage	0.1 M phosphate buffer pH 7.5 for 1-16 hours
Volume (mL)	1000 mL
USP Apparatus Type	II (paddle)
Rotation (rpm)	50
FDA's specification	Loratadine: NLT (b) (4) % of the labeled amount dissolved 60 min
	Pseudoephedrine: 1 hour (b) (4)
	2 hours
	4 hours
	8 hours
	16 hours

The revised specifications are considered only as *interim* specifications, and the firm is requested to submit dissolution data for 3 fresh lots when they become available to confirm the specifications.

4/28/04
Hoainhon Nguyen, Review Branch I

4/29/2004
Shriniwas Nerurkar, Ph.D.
Team Leader, Review Branch I

4/29/04
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Hnguyen/04-21-04/W#76557a0304.doc

IV. Appendix

A. Dissolution Data: (Additional testing of a recently manufactured lot, using the FDA recommended method, per the DBE's request) For other dissolution testing of the test and reference products, see the review of the original submission.

Condition: USP II (paddle) at 50 rpm
1000 mL 0.1 N HCl for 0-1 hour
1000 mL pH 7.5 phosphate buffer for 1-16 hours

Loratadine
Test Product
Lot No.: 7240302
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Time(min.)	Mean	Range	%CV
30	83	(b) (4)	6.2
60	88		4.8

Pseudoephedrine
Test Product
Lot No.: 7240302
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 12

Time(min.)	Mean	Range	%CV
60	21	(b) (4)	3.5
120	32		3.6
240	47		3.4
480	69		2.9
960	92		2.0

Loratadine
Claritin-D 24 HR Tablets
Lot No.: 3 DCS 554 (Exp. 10/05)
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 6

Time(min.)	Mean	Range	%CV
30	81	(b) (4)	4.6
60	83		4.3

Pseudoephedrine Not tested

Loratadine
Allergy Relief D 24 HR
Lot No.: 3K1067 (Exp. 06/05)
Strength: 10 mg/240 mg loratadine/pseudoephedrine
No. of Units: 6

Time(min.)	Mean	Range	%CV
30	67	(b) (4)	4.1
60	73		1.2

Pseudoephedrine Not tested

B. Dissolution Consult:

From: Tran, Nhan L
Sent: Wednesday, April 21, 2004 6:36 AM
To: Nguyen, Hoainhon T
Cc: Nerurkar, Shriniwas G; Sigler, Aaron
Subject: RE: Revised Dissolution Specifications for ANDA 76-557

Yes, that was discussed and agreed upon between us and the firm. For Loratadine, the spec of NLT (b) (4) %/60 minutes is good enough to be discriminating and the firm will not need to go to Stage 2 of dissolution testing.

Thanks,

-----Original Message-----
From: Nguyen, Hoainhon T
Sent: Tuesday, April 20, 2004 2:26 PM
To: Tran, Nhan L
Cc: Nerurkar, Shriniwas G; Sigler, Aaron; Nguyen, Hoainhon T
Subject: Revised Dissolution Specifications for ANDA 76-557

Hi Tran,
Per our discussion and our telephone conference with Ranbaxy today, we have agreed to the following revised specifications for ANDA 76-557 (Loratadine and Pseudoephedrine Sulfate ER Tablets):
Method: FDA-recommended method (USP Apparatus II(paddle), 1000 mL of 0.1 N HCl for the first hour and 1000 mL of pH7.5 phosphate buffer (0.1M) for 2-16 hours.
Specifications:
Loratadine: NLT (b) (4) %(Q) in 60 minutes
Pseudoephedrine:
1 hour (b) (4) (originally (b) (4))
2 hours (originally)
4 hours (originally)
8 hours
16 hours NLT (b) (4) %

The above specifications will allow the submitted fresh lot (#7240302) to pass Stage 1 of the dissolution testing. The firm will be informed that this is the *interim* specifications and is requested to submit the dissolution data for 3 additional fresh lots when available to confirm the revised specifications.

PLEASE CONFIRM OUR DISSOLUTION RECOMMENDATIONS ABOVE.

Thanks,
Hoai

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-557 APPLICANT: Ranbaxy Laboratories

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

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

We agree with your proposed dissolution method and specifications as follows:

Medium, acid stage	0.1 N HCl for 0-1 hour
Medium, buffer stage	0.1 M phosphate buffer pH 7.5 for 1-16 hours
Volume (mL)	1000 mL
USP Apparatus Type	II (paddle)
Rotation (rpm)	50
Interim Specifications	

Loratadine:	NLT (b)(4)% of the labeled amount dissolved 60 minutes
Pseudoephedrine:	1 hour (b)(4)
	2 hours
	4 hours
	8 hours
	16 hours NLT (b)(4)%

The revised specifications are considered only as *interim* specifications, and you are requested to submit dissolution data for 3 fresh lots when they become available to confirm the specifications.

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

Sincerely yours,

for Barbara M Davit

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

CC:ANDA 76-557
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ SNerurkar

4/29/04

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ SNerurkar
HFD-617/ A. Sigler
HFD-650/ D. Conner 4/29/04

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Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE Submission date: 03-16-04, 04-20-04
21

1. STUDY AMENDMENTS (STA) Additional Dissolution Data & New Proposed Specifications Strength: 10 mg/240 mg
Outcome: AC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-557

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

505(j)(2)(A) OK
15-JAN-2003
Gregory S. Davis

December 4, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg
Abbreviated New Drug Application

Dear Sir/Madam:

Ranbaxy Laboratories Limited (RLL) herewith submits an abbreviated new drug application (ANDA) for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act.

This ANDA refers to the listed drug, Claritin-D® 24 Hour Tablets which are manufactured by Schering Pharmaceuticals the holder of NDA 20-470 as published in the Electronic Orange Book of the U. S. Department of Health and Human Services..

With reference to patent nos. US 4,659,716; US 4,863,931 and US 5,314,697, the applicant certifies that in the opinion and to the best of its knowledge said patents will not be infringed by the manufacture, use, or sale of Loratadine and Pseudoephedrine Sulfate Extended Release Tablets for which this abbreviated new drug application is submitted.

With respect to U.S. Patent No. 4,282,233, Ranbaxy Laboratories Limited certifies that in its opinion and to the best of its knowledge, said patent will expire on December 19, 2002. Ranbaxy Laboratories Limited, therefore, requests the approval of this ANDA effective after December 19, 2002.

RECEIVED
DEC 0 6 2002
OGD / CDER

The manufacturer of the Loratadine drug substance used to produce the ANDA batches of drug product is Ranbaxy Laboratories Limited, Toansa, India. The Drug Master File (DMF) No. 15251 was filed on January 17, 2001. A sample of the bulk raw material is available and will be provided to the Agency upon request.

The manufacturer of the Pseudoephedrine Sulfate, USP drug substance used to produce the ANDA batches of the drug product is (b) (4). A letter of access from the manufacturer for Drug Master File (DMF) No. (b) (4) is included in this application. A sample of the bulk raw material is available and will be provided to the Agency upon request.

This application provides for the manufacture, processing and packaging at Ohm Laboratories, Inc., North Brunswick, New Jersey. The release and stability studies on the finished drug product are also carried out at the same location. Ohm Laboratories, Inc. is 100% owned by Ranbaxy Pharmaceuticals Inc. (RPI). RPI is a 100% wholly owned subsidiary of Ranbaxy Laboratories Limited (RLL), the Parent Company and sponsor of this ANDA. Abha Pant is RLL's U.S. Agent and RPI's Director of Regulatory Affairs. This application submitted by RLL will therefore contain information with either RLL, RPI or OHM's name on the document. An authorization letter from RLL appointing Abha Pant as the official U.S. Agent and representative for Ranbaxy Laboratories Limited is attached.

The required bioavailability/bioequivalence studies were conducted on Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg and Claritin-D® 24 Hour Tablets 10 mg/240 mg by MDS Pharma Services., Saint Laurent (Montreal), Quebec, Canada. The studies indicate that Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg are equivalent to Claritin-D® 24 Hour Tablets 10 mg/240 mg. The in-vitro dissolution profile for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg is comparable to that of and Claritin-D® 24 Hour Tablets 10 mg/240 mg.

Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg are stable and a two year expiration dating is requested. The two year expiration dating of this product is supported by one, two, and three months accelerated stability data (40°C± 2°C/75% ± 5% relative humidity). The stability studies were conducted under a stability protocol that is in conformance with the current FDA stability guidelines.

The dosage form, active ingredient, uses, directions, warnings, potency and labeling (except Description, How Supplied and Manufacturer Sections) for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, are the same as those for Claritin-D® 24 Hour Tablets 10 mg/240 mg.

The ANDA is submitted in 19 volumes:

Volume I:	Section I through Section V
Volume II Through Volume XVI:	Section VI
Volume XVII:	Section VII through Section XI
Volume XVIII:	Section XII through Section XIV
Volume XIX:	Section XV through Section XXII

FIELD COPY: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the FDA New Jersey District Office, Parsippany, NJ since the manufacturing is done at Ranbaxy's facility, Ohm Laboratories, Inc. in North Brunswick, NJ.

Please contact Abha Pant at 609-720-5666, or Anthony M. Maffia at 609-720-5336 if you have any questions regarding this submission.

Sincerely,

Abha Pant.

Abha Pant
US Agent for Ranbaxy Laboratories Ltd.

RANBAXY
PHARMACEUTICALS INC.

January 9, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NC
NEW CORRESP

UPS

ADDITIONAL INFORMATION

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg
ANDA 76-557

Dear Ms. Emily Thomas, Project Manager:

Reference is made to the above approved ANDA 76-557 for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg. Reference is made to our telephone contact of January 9, 2003.

As per our telephone contact the following additional information was requested and is included in this amendment:

1) **Letters with original signatures should appear on *Ranbaxy Pharmaceuticals Inc.* Letterhead**
   - The following letters are included in **Attachment 1**: Cover letter, Field Copy Certification, cGMP Certification, Environmental Assessment Statement, and Debarment Statement.

2) **Letter of Access for** (b) (4) **DMF** (b) (4)
   - The correct DMF Letter of Access is included in **Attachment 2.**

3) (b) (4)

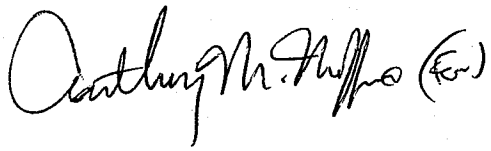
RECEIVED
JAN 10 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this additional information has been provided to the Food and Drug Administration, New Jersey District Office in Parsippany, New Jersey.

If you have any questions or comments regarding this supplement, please call me at 609-720-5336 or Abha Pant at 609-720-5666. Thank you.

Sincerely,



Anthony M. Maffia, III
Regulatory Affairs Associate (for)
Abha Pant
Director Regulatory Affairs

RANBAXY
PHARMACEUTICALS INC.
600 COLLEGE ROAD EAST PRINCETON, NEW JERSEY 08540
PHONE: 1-888-RANBAXY

NEW CO

NC

January 14, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

ADDITIONAL INFORMATION

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg
ANDA 76-557

Dear Ms. Emily Thomas, Project Manager:

Reference is made to the above approved ANDA 76-557 for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg. Reference is made to our telephone contact of January 10, 2003.

As per our telephone contact the following additional information was requested and is included in this amendment:

1) (b) (4)

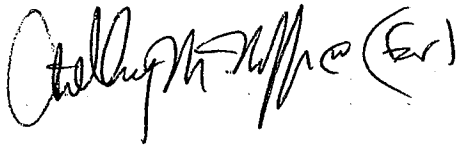
- The manufacturer has provided their specification for (b) (4) (b) (4). This may be found in **Attachment 1.**
- (b) (4)

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this additional information has been provided to the Food and Drug Administration, New Jersey District Office in Parsippany, New Jersey.

RECEIVED
JAN 15 2003
OGD / CDER

If you have any questions or comments regarding this supplement, please call me at 609-720-5336 or Abha Pant at 609-720-5666. Thank you.

Sincerely,



Anthony M. Maffia, III
Regulatory Affairs Associate (for)
Abha Pant
Director Regulatory Affairs

RANBAXY
PHARMACEUTICALS INC.
600 COLLEGE ROAD EAST PRINCETON, NEW JERSEY 08540
PHONE: 1-888-RANBAXY

January 16, 2003

NEW CORRESP

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Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

AMENDMENT TO A PENDING APPLICATION

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg
ANDA 76-557

Dear Ms. Emily Thomas, Project Manager:

Reference is made to the above approved ANDA 76-557 for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg. Reference is made to our telephone contact of January 15, 2003.

With reference to US Patent no. 4,282,233, the applicant certifies that in the opinion and to the best of its knowledge, said patent expired on December 19, 2002. Accordingly, Ranbaxy is submitting a revised Patent Certification to reflect patent no. 4,282,233 as Paragraph II. Please find the revise Patent Certification attached.

If you have any questions, regarding this amendment, please call me at 609-720-5336, or Abha Pant at 609-720-5666.

Sincerely,

Anthony M. Maffia, III
Regulatory Affairs Associate (for)
Abha Pant
U.S. Agent for Ranbaxy Laboratories Limited

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Ethomy NA I 4/8/03

RANBAXY
PHARMACEUTICALS INC.

March 27, 2003

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Patent Amendment

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg
ANDA 76-557

Dear Sir/Madam:

Ranbaxy Laboratories Limited references our abbreviated ANDA 76-557 for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg submitted to the agency December 4, 2002.

Ranbaxy Laboratories Ltd. has complied with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of said patents or their representatives and to the holder of the approved drug application for the listed drug, and with the requirements under 21 CFR 314.95(c) with respect to the content of the notice.

We are amending this application to certify that Ranbaxy Laboratories Limited has notified the appropriate holder via U. S. certified mail on March 19, 2003. The certified letter was delivered to Schering Corp. on March 20, 2003. Attached are copies of the certified receipt and the notice by Ranbaxy to the listed drug holder, Schering Corp.

If you have any questions regarding this amendment, please contact me at (609) 720-5609 or, Abha Pant at (609) 720-5666.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited.

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MAR 2 8 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

6/9/03 P.V.P
1 - Copy of Civil Action (CA # 03-CV-716
2 - Sent only on

NEW CORRESP
NC

May 14, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Patent Amendment

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg
ANDA 76-557
Notice of Civil Action

Dear Sir/Madam:

Ranbaxy Laboratories Limited references our abbreviated ANDA 76-557 for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg submitted to the agency December 4, 2002. Reference is also made to our Patent Amendment dated March 27, 2003.

The holder of the approved drug application for the listed drug, Schering Corp. was notified of Ranbaxy's ANDA 76-557 for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg via certified mail on March 20, 2003.

We are including a copy of the Civil Action, filed on behalf of Schering Corp. to the U.S District Court of NJ on May 2, 2003.

If you have any questions regarding this amendment, please contact me at (609) 720-5609 or, Abha Pant at (609) 720-5666.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited.

RECEIVED
MAY 15 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 FAX: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

May 19, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

NEW CORRESP
NC

ADDITIONAL INFORMATION

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg
ANDA 76-557

Dear Sir/Madam:

Reference is made to the above pending ANDA 76-557 for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg. Reference is made to our telephone contact with Ms. Sarah Kim.

As per our telephone contact the following additional information was requested and is included in this amendment:

1) **Information regarding** (b) (4) **and whether or not they have changed names from** (b) (4) **.**
   - The lab has provided a letter in which they explain the relation of (b) (4) See **Attached letter.**

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this additional information has been provided to the Food and Drug Administration, New Jersey District Office in North Brunswick, New Jersey.

If you have any questions or comments regarding this supplement, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
Director Regulatory Affairs, US Agent for Ranbaxy Laboratories Limited

RECEIVED
MAY 20 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 FAX: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

ORIG AMENDMENT
N/AM

July 8, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and FAX

Minor Amendment Response

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
10 mg/240 mg
ANDA # 76-557

Dear Sir/Madam:

Reference is made to the above pending ANDA for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, submitted to the Agency on December 4, 2002.

Reference is also made to the Minor deficiency comments received May 14, 2003.

The deficiency questions and responses are addressed and detailed on the following pages.

Field Copy: We certify that a true copy of the technical sections described in 21 CFR 314.94 (d)(5) of this submission has been provided to the FDA New Jersey District Office in North Brunswick, New Jersey since the manufacturing is done at Ohm Laboratories, in North Brunswick, NJ.

If you have any questions or comments regarding this information, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky (for)
Manager, Regulatory Affairs (*for*)
Abha Pant
Official US Agent for Ranbaxy Laboratories Limited

RECEIVED
JUL 09 2003
OGD/CDER

7-15-03

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 FAX: (609) 720-1155

MINOR AMENDMENT

NDA 76-557

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)

MAY 14 2003

TO: APPLICANT: Ranbaxy Laboratories Limited TEL: 609-720-5666

ATTN: Abha Pant, U.S. Agent FAX: 609-720-1155

FROM: Sarah Kim PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 4, 2002, 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.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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

SPECIAL INSTRUCTIONS:

Chemistry comments provided. Bioequivalency and Labeling comments will be provided under separate cover.

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.

MAY 14 2003

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-557
APPLICANT: Ranbaxy Laboratories Limited
DRUG PRODUCT: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets 10 mg/240 mg

The deficiencies presented below represent **Minor** deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.
9.
10.

(b) (4)

11.

12.

13.

14.

15.

16.

17.

18.

19.

20.

21.

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

1. Please make a commitment in your retesting statements that your compendial specifications for the raw materials will be revised in accordance with any official compendial update and will be included in your annual reports.

2. Please update your room temperature stability data and provide all available data in your next amendment.

3. A review of the bioequivalence portion of your application is pending. After the review is complete, any deficiencies found will be communicated to you under separate cover.

4. A review of the labels and labeling is pending. Any deficiencies found will be sent to you under separate cover.

5. Acceptance of your dissolution method and specifications are contingent upon the results of the bioequivalence review by our Division of Bioequivalence.

6. The FDA district office will be performing methods validation on the new drug substance and the finished dosage form after the completion of the bioequivalence review and related impurities issues are resolved.

7. Your drug product, Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, is now an OTC drug. Please revise the form 356h accordingly.

Sincerely yours,

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

RANBAXY
PHARMACEUTICALS INC.

ORIGINAL

July 23, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and FAX

Labeling Amendment

ORIG AMENDMENT
N/AFT

Reference: **Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg**
ANDA # 76-557

Dear Sir/Madam:

Reference is made to the above pending ANDA for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg submitted to the Agency on December 4, 2002.

Ranbaxy is hereby submitting draft labeling for a proprietary name. The purpose of this submission is only for review and approval of proprietary name, therefore the side panels which will contain the drug facts text will be submitted at a later time. We request that you forward these labels to the Office of Drug Safety/Division of Medication Errors and Technical Support.

The names are in order of preference:

1. (b) (4) (Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg)

2. (b) (4) (Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg)

Please note, (b) (4) and (b) (4) have been submitted for Loratadine Syrup, 5 mg/5mL, ANDA # 76-529, on April 8, 2003 by Ranbaxy.

If you have any questions or comments regarding this information, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky (for)

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
Official US Agent for Ranbaxy Laboratories Limited

RECEIVED
JUL 2 4 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

September 11, 2003

ORIG AMENDMENT
N/AF

ORIGINAL

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS & FAX

LABELING INFORMATION

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg
ANDA 76-557

Dear Sir/Madam:

Reference is made to the above ANDA 76-557 for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg. Reference is made to the Labeling Amendment submitted July 23, 2003 for review of a proprietary name. Reference is also made to the telephone contact of September 9, 2003.

As per our telephone contact the following additional information was requested and is included in this amendment:

1) **Labeling for the proposed Cartons and labels with the proposed Proprietary names containing the Drug Facts labeling on the side panels.**
2) **Side-by-side comparison of our proposed labeling and the RLD labeling**

If you have any questions or comments regarding this amendment, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
Director Regulatory Affairs

RECEIVED
SEP 12 2003
OGD/OBP

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 FAX: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

ORIG AMENDMENT

N/AB

October 20, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and FAX

Bioequivalency Amendment Response

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets 10 mg/240 mg
ANDA # 76-557

Dear Sir/Madam:

Reference is made to the above pending ANDA for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, submitted to the Agency on December 4, 2002.

Reference is also made to the Bioequivalency Amendment received August 27, 2003.

The deficiency questions and responses are addressed and detailed on the following pages.

If you have any questions or comments regarding this information, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky (for)

RECEIVED
OCT 21 2003
OGD/CDER

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
Official US Agent for Ranbaxy Laboratories Limited

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

11/12/03 NAS S. Middleton '716 - invalid

October 27, 2003

FAX AND
UPS OVERNIGHT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC

Reference: **Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg**
ANDA 76-557

Dear Sir/Madam:

Ranbaxy Laboratories Limited references our abbreviated ANDA 76-557 for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg submitted to the agency December 4, 2002. Reference is also made to the letter sent to the Agency on May 14, 2003 updating the Agency on the status of the Civil Action suit (03-2011) regarding this ANDA.

Ranbaxy was notified that the United States District Court for the District of New Jersey has administratively terminated the Civil Action suit (03-2011) pending final resolution of the Consolidated Appeals by the U.S. Court of Appeals for the Federal Circuit. (See **attachment 1**)

The '716 patent, has been declared invalid (August 1, 2003) by the United States Court of Appeals for the Federal Circuit in Schering Corporation v. Geneva Pharmaceuticals, Inc., Novartis Corporation, Teva Pharmaceuticals, USA, Inc., Zenith Goldline Pharmaceuticals, Inc., Andrx Corporation, Mylan Pharmaceuticals, American Home Products, and Impax Laboratories, Inc., 2002 U.S. Dist. Lexis 14587; 64 U.S.P.Q.2d (BNA) 1032. This consolidated litigation had civil action numbers 99-2237, 98-1259, 00-255 99-2820, 00-1439, 00-1657, 00-2944, 01-9, 01-279, and 01-520. (See **attachment 2**) As such, the patent that has been asserted against Ranbaxy has been declared invalid in a consolidated litigation over Loratadine.

Based on the fact that the '716 patent has been declared invalid in the above mentioned consolidated litigation, the Schering v. Ranbaxy civil action # 03-2011 has been finally terminated.

RECEIVED
OCT 29 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX:** (609) 720-1155

If you have any questions regarding this submission please contact me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RANBAXY
PHARMACEUTICALS INC.

November 7, 2003

ORIG AMENDMENT
N/AF

ORIGINAL

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS & FAX

LABELING INFORMATION

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg
ANDA 76-557

Dear Sir/Madam:

Reference is made to the above ANDA 76-557 for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg. Reference is made to the Labeling Amendment submitted September 16, 2003 for review of a proprietary name.

Ranbaxy hereby submits final printed labeling for the established name of this product. This is being submitted so the Agency has on file Drug Facts labeling for this product containing both the established name and a proprietary name. Ranbaxy wishes to market both as soon as approval is received for this ANDA. Please note, there are no changes to the drug facts text from the labeling submitted September 16, 2003 for the proposed proprietary name. The following information is included in this amendment:

1) **Cartons and container labels with the Established name containing the Drug Facts format.**
2) **Side-by-side comparison of our labeling with the established name and the labeling submitted September 16, 2003 with the proposed proprietary name.**

If you have any questions or comments regarding this amendment, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
Official U.S. Agent for Ranbaxy Laboratories Limited

RECEIVED
NOV 10 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RECORD OF TELEPHONE CONVERSATION

Reference is made to the unapproved ANDA 76-557 and the Minor Amendment dated July 8, 2003. The following deficiencies/comments were communicated to the firm.

1. (b) (4)

2.

3.

The firm's response may be submitted as a telephone amendment.

DATE
November 13, 2003

ANDA NUMBER
76-557

IND NUMBER

TELECON

INITIATED BY

SPONSOR __

FDA X

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

FIRM NAME
Ranbaxy Laboratories Limited

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Abha Pant
Anthony Maffia
Scott Thompsky

TELEPHONE NUMBER
609-720-5666

SIGNATURE
Guoping Sun 11/13/03
Sarah Kim 12/10/03

CC: ANDA 76-557
Chem. I Telecon Binder
Division File
V:\FIRMSNZ\RANBAXY\TELECONS\76557.tc.111303.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
FD-420, PKLN Rm 6-34, Office of Drug Safety/Division of ,cation Errors and Technical Support (DMETS) - mie Beam, Project Manager			FROM: Debra Catterson, HFD-613, Labeling Review Branch, OGD	
DATE: October 10, 2003	IND NO. N/A	ANDA NO. 76-557	TYPE OF DOCUMENT: Labeling Amendment	DATE OF DOCUMENT September 11, 2003
NAME OF DRUG Loratadine (10 mg) and Pseudoephedrine Sulfate (240 mg) Extended Release Tablets (24 Hour Formulation) (OTC)		REFERENCE LISTED DRUG: Claritin-D 24 Hour® Tablets NDA 20-470	CLASSIFICATION OF DRUG: Antihistamine/Decongestant	DESIRED COMPLETION DATE December 10, 2003
NAME OF FIRM Ranbaxy Pharmaceuticals, Inc.				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ PRE NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ CONTROL SUPPLEMENT
- ■ OTHER: **Proposed Proprietary Name**
- ☐ MEETING PLANNED BY _____

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL EVALUATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ OF PHASE II MEETING TROLLED STUDI ES TOCOL REVIEW ☐ OTHER	☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDI ES ☐ PROTOCOL REVIEW ☐ 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 ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

******PLEASE NOTE: THIS IS AN ADDENDUM TO A PREVIOUSLY SUBMITTED CONSULT REQUEST.******

Ranbaxy submitted two proposed proprietary names, (b) (4) for their drug product. A consult request was submitted to DMETS on September 4, 2003. However, the firm's draft labeling was missing the Drug Facts Panel information. Per Sammie Beam's email request of Sept. 9, 2003, I asked the o resubmit their labeling with the complete information. On September 11, 2003, the firm submitted the d labeling, and it is attached for your review.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)*
Debra M. Catterson 10/10/03 827-5835	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

3.1

DATES RECEIVED: May 14, 2003 and Sept. 9, 2003 **DOCUMENT DATES:** May 14, 2003 and Sept. 4, 2003	**DUE DATE:** November 9, 2003 76-557	**ODS CONSULT #:** 03-0166 and 03-0256

TO: Peter Rickman
Director, Division of Labeling and Program Support, Office of Generic Drugs
HFD-610

THROUGH: Harvey Greenberg
Project Manager
HFD-615

PRODUCT NAME: (b) (4) (Primary) (b) (4) (Alternate) (Loratidine Syrup) 5 mg/mL and (b) (4) (Primary) (b) (4) (Alternate) (Loratidine and Pseudoephedrine Extended Release Tablets) 10 mg/240 mg **NDA#:** 76-529 and 76-557	**MANUFACTURER:** Ranbaxy Pharmaceuticals, Inc.

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

SUMMARY: In response to a consult from the Division of Labeling and Program Support, Office of Generic Drugs (HFD-613), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary names (b) (4) (Primary) and (b) (4) (alternate), to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

1. DMETS does not recommend the use of the proprietary names (b) (4) or (b) (4)
2. DMETS recommends implementation of the labeling revisions as outlined in Section III of this review.
3. DDMAC finds the names (b) (4) and (b) (4) unacceptable from a promotional perspective because they are overly fanciful. DDMAC finds the names (b) (4) and (b) (4) acceptable from a promotional perspective.
4. The Division of Over-the-Counter Drug Products (HFD-560) did not have any concerns with the proposed names.

Carol Holquist 11/14/03

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist for 11/14/03

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

DDC

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 14, 2003

ANDA# 76-529 and 76-557

NAME OF DRUG: (b) (4) (Primary)
(b) (4) (Alternate)
(Loratidine Syrup) 5 mg/mL
and
(b) (4) (Primary)
(b) (4) (Alternate)
(Loratidine and Pseudoephedrine Extended Release Tablets) 10 mg/240 mg

ANDA HOLDER: Ranbaxy Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Labeling Review Branch in the Division of Labeling and Program Support, Office of Generic Drugs (HFD-613), for an assessment of the proposed proprietary names (b) (4). The container labels and carton labeling were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

(b) (4) (primary name) and (b) (4) (alternate name) are the proposed proprietary names for loratidine syrup. They are indicated for the temporary relief of symptoms such as sneezing, runny nose, itching, watery eyes, and itching of the nose or throat due to hay fever or other respiratory allergies. The recommended dose for adults and children six years of age and older is two teaspoonfuls daily. For children ages two to six years old, the recommended dose is one teaspoonful daily. (b) (4) will be available in a strength of 5 mg/5 mL. The reference listed drug (RLD) for (b) (4) is *Claritin Syrup.*

(b) (4) (primary name) and (b) (4) (alternate name) are the proposed proprietary names for loratidine and pseudoephedrine sulfate extended release tablets. They are indicated for the temporary relief of symptoms due to hay fever or other upper respiratory allergies, such as nasal congestion, runny nose, itchy, watery eyes and throat, sneezing, reduction of nasal passage swelling, and relief of sinus congestion and pressure. The recommended dose for adults and children twelve years of age and older is one tablet daily with a full glass of water. The maximum dose is one tablet per 24 hours. (b) (4) will be available in a strength of 10 mg loratidine and 240 mg pseudoephedrine. The reference listed drug for (b) (4) is *Claritin-D 24 hour tablets.*

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1, 2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to (b) (4), to a degree where potential confusion between these drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the Saegis[5] Pharma-In-Use database were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted six prescription analysis studies consisting of four written prescription studies (inpatient and outpatient) and two verbal prescription studies, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the names.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names (b) (4). Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. (b) (4)

   a. The DMETS Expert Panel identified a currently marketed distributor product with an identical name, (b) (4), to have potential for confusion with both (b) (4). This product is listed in Table 1 (see page 4), along with the usual dosage and available dosage form.

   b. DDMAC did not recommend the use of the names (b) (4) unacceptable because they are overly fanciful.

---

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

2. (b) (4)

a. The Expert Panel identified Clemastine, Amnesteem, Anectine, and Dehistine, as having potential for confusion with (b) (4). These products are listed in table 2 (see below and page 5), along with the usual dosage and available dosage forms.

b. DDMAC did not have concerns about the names (b) (4) with regard to promotional claims

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel for (b) (4)

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
(b) (4)	Loratidine Syrup 5 mg/5 mL Loratidine and Pseudoephedrine Extended Release Tablets 10 mg/240 mg	Take 2 teaspoonfuls daily. Take 1 tablet daily.	
(b) (4) (Rx)	(b) (4)	Take 1 tablet every 12 hours, not to exceed 2 tablets in 24 hours.	**S/A, L/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

Table 2: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel for (b) (4)

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
(b) (4)	Loratidine Syrup 5 mg/5 mL Loratidine and Pseudoephedrine Extended Release Tablets 10 mg/240 mg	Take 2 teaspoonfuls daily. Take 1 tablet daily.	
Clemastine (Rx) Clemastine (OTC)	Clemastine Fumarate Tablets 2.68 mg (equiv. to 2 mg clemastine) Syrup: 0.67 mg (equiv. to 0.5 mg base)/5 mL 1.34 mg (equiv. to 1 mg clemastine)	Urticaria/angioedema: 2.68 mg tablet 1 to 3 times per day, maximum. Allergic rhinitis: 1.34 mg tablet every 12 hours or twice daily.	**L/A
Amnesteem (Rx)	Isotretinoin Capsules, USP 10 mg, 20 mg, and 40 mg (Reference Listed Drug – Accutane)	0.5 mg/kg/day to 1 mg/kg/day divided into 2 doses for 15 to 20 weeks. Maximum dose is 2 mg/kg/day.	**S/A, L/A

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
(b) (4)	Loratidine Syrup 5 mg/5 mL Loratidine and Pseudoephedrine Extended Release Tablets 10 mg/240 mg	Take 2 teaspoonfuls daily. Take 1 tablet daily.	
Anectine (Rx)	Succinylcholine Chloride 20 mg/mL	Dosage is individualized. Short surgical procedures 0.6 mg/kg intravenously. (Can vary depending on procedure.) Long surgical procedures 0.3 mg/kg to 1.1 mg/kg intravenously. (Can vary depending on duration of procedure.)	**S/A, L/A
Dehistine (Rx)	Chlorpheniramine and Methscopolamine syrup 2 mg/1.25 mg	Take 10 mL every 4 to 6 hours, up to a maximum of 40 mL per day.	**S/A, L/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PHONETIC ORTHOGRAPNIC COMPUTER ANALYSIS (POCA)

As part of the assessment, proposed names are evaluated via a phonetic/orthographic database that is in the final stages of development for DMETS. At the time of this review, the database was not available. Therefore, (b) (4) were not evaluated using this method.

C. DIVISION COMMENTS

The Division of Over-the-Counter Drug Products (HFD-560) did not have any concerns with the proposed names.

D. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Twelve separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of (b) (4), with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. Each study employed a total of 129 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for (b) (4) (see pages 6 and 7). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the

participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

i. (b) (4)

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: (b) (4) 10ml qam #120ml	(b) (4), give 10 mL every morning, dispense 120 mL.
Inpatient RX: (b) (4)	

ii. (b) (4)

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: (b) (4) #1	(b) (4), take as directed, dispense #1.
Inpatient RX: (b) (4)	

iii. (b) (4)

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: (b) (4) 1 tsp QD # 120ml	(b) (4) give 2 teaspoonfuls daily, dispense 120 mL.
Inpatient RX: (b) (4) 1 tsp QD #1	

iv. (b) (4)

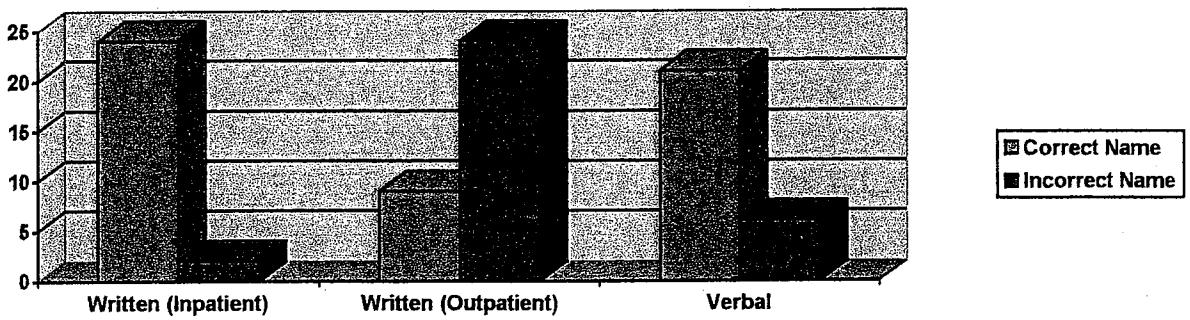
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: (b) (4) ao Dlv. daily #30	(b) (4), take as directed, dispense #30l.
Inpatient RX: (b) (4) po QD !	

2. Results:

i. The results for (b) (4) are summarized in Table 3.

Table 3

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	43	26 (60%)	24 (92%)	2 (8%)
Written Outpatient	43	33 (77%)	9 (27%)	24 (73%)
Verbal	43	27 (63%)	21 (78%)	6 (22%)
Total	129	86 (67%)	54 (63%)	32 (37%)



Among the verbal prescription study participants for (b) (4), 6 of 27 (22%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of (b) (4). The responses were (b) (4).

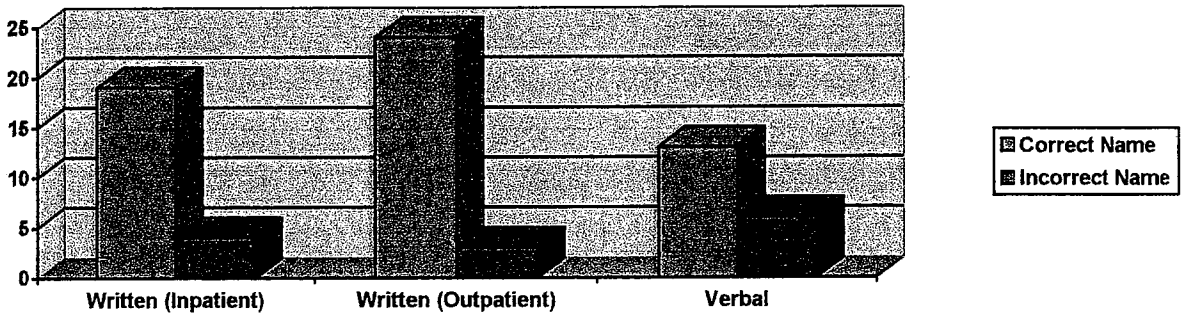
Among the written inpatient prescription study participants for (b) (4), 2 of 26 (8%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of (b) (4). The responses were (b) (4).

Among the written outpatient prescription study participants for (b) (4) 24 of 33 (73%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of (b) (4). The responses were (b) (4) (b) (4).

ii. The results for (b) (4) are summarized in Table 4.

Table 4

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	43	23 (53%)	19 (83%)	4 (17%)
Written Outpatient	43	27 (63%)	24 (89%)	3 (11%)
Verbal	43	19 (44%)	13 (68%)	6 (32%)
Total	129	69 (53%)	56 (81%)	13 19%)



Among the verbal prescription study participants for (b) (4), 6 of 19 (32%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of (b) (4) (b) (4). The responses were, (b) (4) (b) (4).

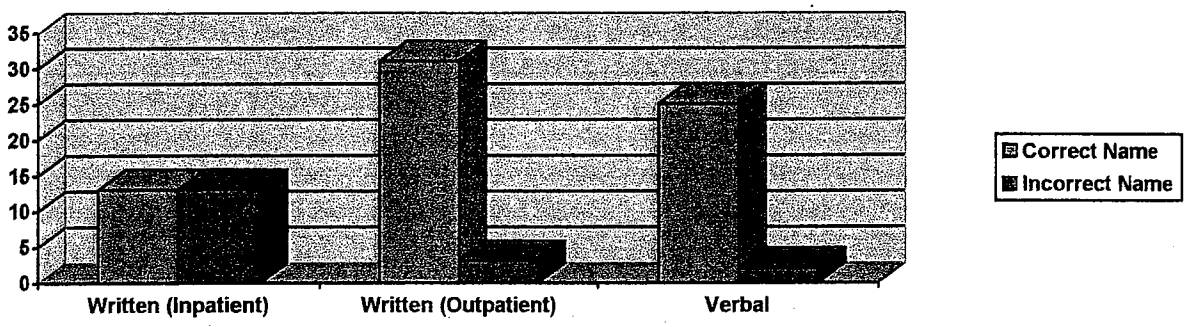
Among the written inpatient prescription study participants for (b) (4), 4 of 23 (17%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of (b) (4). The responses were (b) (4).

Among the written outpatient prescription study participants for (b) (4), 3 of 27 (11%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of (b) (4). The responses were (b) (4).

iii. The results for (b) (4) are summarized in Table 4.

Table 4

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	43	26 (60%)	13 (50%)	13 (50%)
Written Outpatient	43	34 (79%)	31 (91%)	3 (9%)
Verbal	43	27 (63%)	25 (93%)	2 (7%)
Total	129	87 (67%)	69 (79%)	18 (21%)



Among the verbal prescription study participants for (b) (4), 2 of 27 (7%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of (b) (4). The responses were (b) (4).

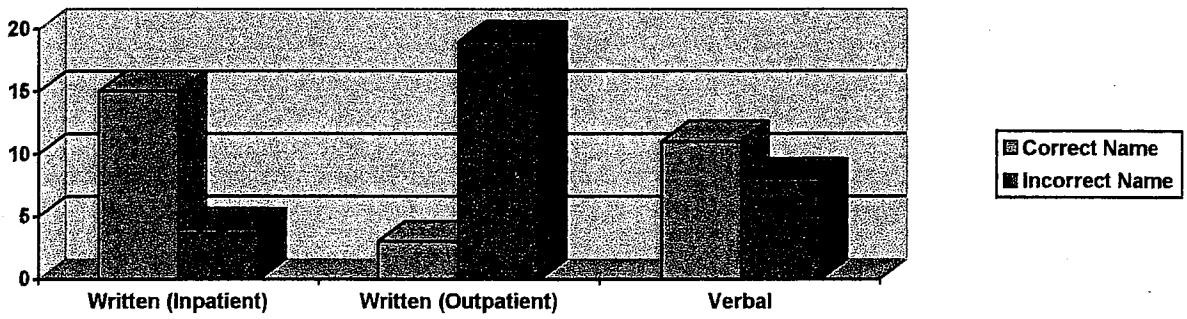
Among the written inpatient prescription study participants for (b) (4), 13 of 26 (50%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of (b) (4). The responses were (b) (4) (b) (4).

Among the written outpatient prescription study participants for (b) (4), 3 of 34 (9%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of (b) (4). The responses were (b) (4).

iv. The results for (b) (4) are summarized in Table 5.

Table 5

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	43	19 (44%)	15 (79%)	4 (21%)
Written Outpatient	43	22 (51%)	3 (14%)	19 (86%)
Verbal	43	19 (44%)	11 (58%)	8 (42%)
Total	129	60 (47%)	29 (48%)	31 (52%)



Among the verbal prescription study participants for (b) (4), 8 of 19 (44%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of (b) (4). The responses were (b) (4).

Among the written inpatient prescription study participants for (b) (4), 4 of 19 (21%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of (b) (4). The responses were (b) (4).

Among the written outpatient prescription study participants for (b) (4), 19 of 22 (86%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of (b) (4). The responses were (b) (4)

E. SAFETY EVALUATOR RISK ASSESSMENT:

1. Sound-alike and Look-alike Names for (b) (4)

In reviewing the proprietary names (b) (4) and (b) (4), the primary concern raised involved one sound-alike and look-alike product currently in the U.S. marketplace: (b) (4).

We conducted prescription studies to simulate the prescription ordering process. Our study confirmed confusion between (b) (4) and (b) (4) and the prescription drug product (b) (4). Eight respondents in the written studies identified the drug name as (b) (4). Additionally, three participants in the verbal study identified the proposed name as (b) (4), and one respondent identified the name as (b) (4), both similar to the currently marketed drug product, (b) (4). The remaining incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed names, (b) (4) and (b) (4). Although there are limitations to the predictive value of these studies primarily due to sample size, we have acquired safety concerns due to positive interpretations. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

(b) (4), a prescription drug product currently marketed by (b) (4), is identical to the proposed names (b) (4) and (b) (4), with the exception of the space between the terms (b) (4) and (b) (4), and the dash before the letter (b) (4). These editorial differences will not be evident in a written prescription or verbal order. (b) (4) contains (b) (4) in strengths of (b) (4). (b) (4) is indicated for (b) (4) (b) (4). The recommended dose of (b) (4) is one tablet every 12 hours, not to exceed two tablets in a 24 hour time period. In addition to identical sound-alike and look-alike characteristics of the names (see page 13), the products share an overlapping indication of use (b) (4), route of administration (oral), and dosage form (tablet). The products differ in dosing regimen (every 12 hours vs. once daily) and active ingredients. Both products contain (b) (4). In addition, (b) (4) also contains (b) (4), whereas the proposed name, (b) (4) contains loratidine. A prescription order, for example for "(b) (4) 2 tsp daily" could be misinterpreted as "(b) (4) 2 daily", and vice versa. If the patient is sensitive or allergic to a particular ingredient, and received the incorrect medication, this could put them at risk for experiencing an allergic reaction. Also, because (b) (4) appears in reference texts and on internet websites, if a healthcare provider or patient were to look up information using the term (b) (4), it would be possible for them to obtain information on the wrong drug product. DMETS believes that similarities in the look-alike and sound-alike characteristics of the names, in the addition to the similarities in indication, route of administration and dosage form increases the risk of confusion and errors between (b) (4) (b) (4).

2. Sound-alike and Look-alike Names for (b) (4)

In reviewing the proprietary name (b) (4) and (b) (4), the primary concerns raised were related to three look-alike and/or sound-alike names currently in the U.S. marketplace: Clemastine, Amnesteem, and Anectine.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between (b) (4) or (b) (4) and Clemastine, Amnesteem, Anectine, or Dehistine. A negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size. However, one respondent in the written study identified the proposed name as (b) (4), which is similar to the currently marketed drug product Amnesteem. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed names, (b) (4) and (b) (4).

a. Clemastine (generic Tavist) has look-alike similarities to the proposed names (b) (4) (b) (4) (see page 15). Clemastine is an antihistamine, indicated for the relief of symptoms associated with allergic rhinitis, such as sneezing rhinorrhea, pruritis, and lacrimation. It is also indicated for the relief of mild, uncomplicated allergic skin manifestations of urticaria and angioedema. Clemastine is available as an over-the-counter tablet in a strength of 1 mg; as a prescription in a strength of 2 mg; and as a syrup with a concentration of 0.5 mg/5 mL. The names have look-alike similarities in that each name has an identical (b) (4). Additionally, when scripted, the letter combination of (b) (4) in Clemastine can look similar to (b) (4), as found in (b) (4). The products also share an overlapping indication of use (allergic rhinitis), route of administration (oral), dosage form (tablet and syrup), and dosing regimen (every 12 hours). Both products are also available in only one strength, therefore prescriptions for Clemastine and (b) (4) can be written without a strength being indicated. However, the letter combinations located in the middle of the names (b) (4) look different when written. DMETS believes that a difference in the look-alike characteristics of the

product names makes the risk for confusion and error between (b) (4) (b) (4) minimal.

(b) (4)

b. Amnesteem was identified to have sound-alike and look-alike similarities to the proposed names (b) (4). Amnesteem contains isotretinoin, and is indicated for the treatment of severe recalcitrant nodular acne that has been unresponsive to conventional therapy. The names share look-alike and sound-alike similarities in that each name consists of (b) (4) (b) (4). Additionally, there are similar letter combinations at the beginning (b) (4) and ending (b) (4) of each name. The products also share an overlapping route of administration (oral), and have overlapping numerals in their strength (10 mg vs. 10 mg/240 mg). However because (b) (4) are combination products, the strength of the additional active ingredient, pseudoephedrine, is also included when if the strength is written. The products differ in dosing regimen (twice daily vs. once daily). Additionally, Amnesteem has been designated as a pregnancy category X medication. It is prescribed under the *System to Prevent Isotretinoin-Related Issues of Teratogenicity (S.P.I.R.I.T.)*. This system consists of pregnancy testing in females who are prescribed Amnesteem, as well as counseling in all patients who are prescribed the medication. Patients sign a consent form and meet the pre-determined criteria for treatment with Amnesteem before qualifying stickers are placed on their prescriptions, which can then be filled within 7 days from the date they are written. Also, valid Amnesteem prescriptions can only be dispensed with no more than a 30 day supply of the medication. Refills require a new prescription with the appropriate qualifying stickers. Telephone or computerized prescriptions for Amnesteem are not permitted. Despite the similarities in the look-alike and sound-alike characteristics, as well as the similarities in route of the administration, the differences in strength and dosing regimen in addition to the required monitoring procedures for Amnesteem, makes the likelihood of confusion between (b) (4) minimal.

(b) (4)

c. Anectine can have look-alike and sound-alike similarities to the proposed names (b) (4) (b) (4). Anectine contains succinylcholine, and is indicated as an adjunct to general anesthesia to facilitate intubation, and to induce skeletal muscle relaxation during surgery or mechanical ventilation. Both names consist of (b) (4), and have identical (b) (4) and (b) (4). However, the products differ in route of administration (intravenous or intramuscular vs. oral), dosage form (injection vs. syrup or tablet). The dosing strength for Anectine is individualized according to the patient's weight. As a result, there is no overlap in dosing strength between Anectine and (b) (4). Due to these differences in addition to the fact that Anectine is used during surgical procedures, and under the close

supervision of medical personnel, DMETS believes that there is minimal risk of confusion between Anectine, (b) (4).

(b) (4)

d. Dehistine was identified to have look-alike and sound-alike similarities to the proposed names (b) (4). Dehistine is a combination product containing 10 grams of phenylephrine, 2 mg of Chlorpheniramine, and 1.25 mg of methoscopolamine, and is indicated for the treatment of symptoms associated with the common cold, allergies, hay fever, sinusitis, and other respiratory illnesses. Both names consist of (b) (4) syllables, and have an identical (b) (4) (b) (4). Additionally, the upper case (b) (4) and (b) (4) can look similar when written. The products share an overlapping indication (allergies and respiratory illnesses), route of administration (oral), and dosage form (syrup). The products differ in strength (10 mg/2 mg/1.25 mg vs. syrup: 5 mg/5mL and tablet: 10 mg/240 mg), as well as dosing regimen (every 4 to 6 hours vs. once daily). Dehistine, (b) (4) are all available in only one strength, and thus prescriptions can be written without a strength indicated. For example, a prescription order written for "(b) (4) 2 tsp qd" could be misinterpreted as "Dehistine 2 tsp qid". This could result in harm to a patient, particularly if the patient is allergic to one of the ingredients found in Dehistine. Due to the similarities in the look-alike and sound-alike characteristics of the medications, in addition to the similarities indication, route of administration, and dosage form, DMETS believes that there is an increased risk of confusion and error between Dehistine and (b) (4).

(b) (4)

III. COMMENTS TO THE SPONSOR:

The Division of Medication Errors and Technical Support (DMETS) does not recommend the use of the proprietary names (b) (4).

In reviewing the proprietary names (b) (4), the product considered having the greatest potential for name confusion with (b) (4) was (b) (4). In reviewing the proposed proprietary names (b) (4), the primary concern raised was related to the drug product, Dehistine.

A. (b) (4)

(b) (4), a prescription drug product currently marketed by (b) (4), is identical to the proposed names (b) (4), with the exception of the space between the terms (b) (4) and (b) (4), and the dash before the letter (b) (4). These editorial differences will not be evident in a written prescription or verbal order. (b) (4) contains (b) (4) in strengths of (b) (4). (b) (4) is indicated for (b) (4) (b) (4). The recommended dose of (b) (4) is one tablet every 12 hours, not to exceed two tablets in a 24 hour time period. In addition to identical sound-alike and look-alike characteristics of the names (see below), the products share an overlapping indication of use (b) (4), route of administration (oral), and dosage form (tablet). The products differ in dosing regimen (every 12 hours vs. once daily) and active ingredients. Both products contain (b) (4). In addition, (b) (4) also contains (b) (4), whereas the proposed name, (b) (4) contains loratidine. A prescription order, for example for "(b) (4) 2 tsp daily" could be misinterpreted as "(b) (4) 2 daily", and vice versa. If the patient is sensitive or allergic to a particular ingredient, and received the incorrect medication, this could put them at risk for experiencing an allergic reaction. Also, because (b) (4) appears in reference texts and on internet websites, if a healthcare provider or patient were to look up information using the term (b) (4), it would be possible for them to obtain information on the wrong drug product. DMETS believes that similarities in the look-alike and sound-alike characteristics of the names, in the addition to the similarities in indication, route of administration and dosage form increases the risk of confusion and errors between (b) (4) (b) (4).

(b) (4)

B. (b) (4)

Dehistine was identified to have look-alike and sound-alike similarities to the proposed names (b) (4). Dehistine is a combination product containing 10 grams of phenylephrine, 2 mg of Chlorpheniramine, and 1.25 mg of methoscopolamine, and is indicated for the treatment of symptoms associated with the common cold, allergies, hay fever, sinusitis, and other respiratory illnesses. Both names consist of (b) (4) syllables, and have an identical (b) (4) (b) (4). Additionally, the upper case (b) (4) and (b) (4) can look similar when written. The products share an overlapping indication (allergies and respiratory illnesses), route of administration (oral), and dosage form (syrup). The products differ in strength (10 mg/2 mg/1.25 mg vs. syrup: 5 mg/5mL and tablet: 10 mg/240 mg), as well as dosing regimen (every 4 to 6 hours vs. once daily). Dehistine, (b) (4) are all available in only one strength, and thus prescriptions can be written without a strength indicated. For example, a prescription order written for "(b) (4) 2 tsp qd" could be misinterpreted as "Dehistine 2 tsp qid". This could result in harm to a patient, particularly if the patient is allergic to one of the ingredients found in Dehistine. Due to the similarities in the look-alike and sound-alike characteristics of the medications, in addition to the similarities indication, route of administration, and dosage form, DMETS believes that there is an increased risk of confusion and error between Dehistine and (b) (4).

(b) (4)

Additionally, DMETS reviewed the container labels and carton labeling, and has focused on safety issues relating to possible medication errors. DMETS has no comments on the labeling.

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary names (b) (4) (b) (4).

B. DMETS recommends implementation of the labeling revisions as outlined in Section III of this review.

C. DDMAC finds the names (b) (4) unacceptable because they are overly fanciful. DDMAC finds the names (b) (4) acceptable from a promotional perspective.

D. The Division of Over-the-Counter Drug Products did not have any concerns with the proposed names.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud 11/14/03

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

cc: ANDA # 76-529 and 76-557
HFD-610: Division Files
HFD-613: Debra Catterson, Labeling Reviewer
HFD-613: John F. Grace, Team Leader
HFD-610: Peter Rickman, Division Director
HFD-510: Harvey Greenberg, Project Manager
HFD-040: Andy Haffer, Senior Regulatory Review Officer, DDMAC
HFD-430: Patrick Guinn, Project Manager, DDRE
HFD-420: Sammie Beam, Project Manager, DMETS
HFD-420: Alina Mahmud, Team Leader, DMETS
HFD-420: Tia M. Harper-Velazquez, Safety Evaluator, DMETS

L:ODS03/Med Errors/Consults Completed/03-0166 & 03-0256 (b) (4)

RECORD OF TELEPHONE CONVERSATION

Reference is made to the unapproved ANDA 76-557 and the Minor Amendment dated July 8, 2003. Reference is also made to the t-con dated November 13, 2003 and the firm's telephone call on November 26, 2003, requesting another telephone conference.

Firm: The firm stated that currently, the specification for total impurities for drug product release and stability is NMT (b) (4), and the firm is unable to meet the specification of NMT (b) (4)% that was agreed upon during the last telephone conference. The impurities for the two APIs, which are MNT (b) (4)% for Loratadine and NMT (b) (4)% for Pseudoephedrine, already equal NMT (b) (4)%.

FDA: The drug product stability specification for total impurities need only address impurities for the degradation products. The impurities for the drug substance need only be included if they are degradation products. Please differentiate between the in-process impurities and degradation products. For impurities that are not included in the total impurities specification, please provide justification for the exclusion.

Firm: The firm asked for guidance regarding the release specifications.

FDA: You may do the same for the release specifications.

The firm response to today's telephone conference and that from November 13, 2003, may be submitted as a telephone amendment.

DATE
December 2, 2003

ANDA NUMBER
76-557

IND NUMBER

TELECON

INITIATED BY

SPONSOR _X_

FDA __

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

FIRM NAME
Ranbaxy Laboratories Limited

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Abha Pant
Scott Thompsky

TELEPHONE NUMBER
609-720-5666

SIGNATURE
Dave Gill DSGill
Guoping Sun 12/2/03
Sarah Kim 12/10/03

CC: ANDA 76-557
Chem. I Telecon Binder
Division File
V:\FIRMSNZ\RANBAXY\TELECONS\76557.tc.120203.doc

RANBAXY
PHARMACEUTICALS INC.
600 COLLEGE ROAD EAST PRINCETON, NEW JERSEY 08540
PHONE: 1-888-RANBAXY

December 8, 2003

ORIG AMENDMENT
N/ATM

UPS and FAX

TELEPHONE Response
CHEMISTRY

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
10 mg/240 mg
ANDA # 76-557

Dear Sir/Madam:

Reference is made to the above pending ANDA for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, submitted to the Agency on December 4, 2002.

Reference is also made to the Telephone contacts of November 13, 2003 and December 2, 2003.

The deficiency questions and responses are addressed and detailed on the following pages.

Field Copy: We certify that a true copy of the technical sections described in 21 CFR 314.94 (d)(5) of this submission has been provided to the FDA New Jersey District Office in North Brunswick, New Jersey since the manufacturing is done at Ohm Laboratories, in North Brunswick, NJ.

If you have any questions or comments regarding this information, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
Official US Agent for Ranbaxy Laboratories Limited

RECEIVED
DEC 0 9 2003
OGD/CDER

RANBAXY
PHARMACEUTICALS INC.

ORIG AMENDMENT

December 12, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS & FAX

ADDITIONAL INFORMATION

Reference: **Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg**
ANDA 76-557

Dear Sir or Madam:

Reference is made to the above approved ANDA 76-557 for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg. Reference is made to our telephone contact of December 12, 2003.

As per our telephone contact the following additional information was requested:

Please provide a commitment to resolve any issues identified in the method validation process after approval.

Ranbaxy Laboratories Limited commits to resolve any issues identified in the method validation process after approval.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this additional information has been provided to the Food and Drug Administration, New Jersey District Office in Parsippany, New Jersey.

If you have any questions or comments regarding this supplement, please call me at 609-720-5336 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
Official US Agent for Ranbaxy Laboratories Limited

RECEIVED
DEC 15 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RECORD OF TELEPHONE CONVERSATION

On this date, I called the firm and made reference to the unapproved ANDA 76-557.

I stated that the firm has submitted labeling for (b) (4) count and 500 count packaging, but in the chemistry section, the packing is for 30 count and 500 count bottles. I asked the firm whether the (b) (4) count or the 30 count is the correct packaging.

The firm stated that the (b) (4) count is the current packaging and agreed to submit a chemistry amendment with the packaging changes.

I also asked the firm to submit the tamper-evident packaging methodology.

The firm's response to the above requested information may be submitted as a telephone amendment.

DATE
December 16, 2003

ANDA NUMBER
76-557

IND NUMBER

TELECON

INITIATED BY

SPONSOR __

FDA _X_

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

FIRM NAME
Ranbaxy Laboratories Limited

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Abha Pant

TELEPHONE NUMBER
609-720-5666

SIGNATURE

Sarah Kim SKim 12/16/03

CC: ANDA ~~76-557~~
Chem. I Telecon Binder
Division File
V:\FIRMSNZ\RANBAXY\TELECONS\76557.tc.121603.doc

RANBAXY
PHARMACEUTICALS INC.

December 17, 2003

ORIG AMENDMENT
N/APM

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and FAX

TELEPHONE Response
CHEMISTRY & LABELING

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
10 mg/240 mg
ANDA # 76-557

Dear Sir/Madam:

Reference is made to the above pending ANDA for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, submitted to the Agency on December 4, 2002.

Reference is also made to the Telephone contact of December 16, 2003.

As per the Agency's request Ranbaxy is providing the following information:

- information on the description of the tamper-evident packaging for the above referenced product. (Please see the attached summary of information.)
- labeling for bottles of 30's as supported by the stability included in the original ANDA. We mistakenly submitted labeling for bottles packs of (b) (4) and 500's in the labeling amendments dated September 11, 2003 and November 7, 2003, rather than labeling for the bottle packs of 30's and 500's. Therefore, we hereby withdraw the labeling dated September 11, 2003 as the proposed proprietary name has been rejected by DMETS on November 14, 2003. In addition, we withdraw the labeling for the bottles of (b) (4) and hereby submit labeling for bottles of 30.

Field Copy: We certify that a true copy of the technical sections described in 21 CFR 314.94 (d)(5) of this submission has been provided to the FDA New Jersey District Office in North Brunswick, New Jersey since the manufacturing is done at Ohm Laboratories, in North Brunswick, NJ.

RECEIVED
DEC 1 8 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

If you have any questions or comments regarding this information, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
Official US Agent for Ranbaxy Laboratories Limited

RANBAXY
PHARMACEUTICALS INC.

ORIGINAL

January 5, 2004

ORIG AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and FAX

TELEPHONE Response
LABELING

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
10 mg/240 mg
ANDA # 76-557

Dear Sir/Madam:

Reference is made to the above pending ANDA for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, submitted to the Agency on December 4, 2002. Reference is also made to the labeling deficiency of December 18, 2003.

The deficiency questions and responses are addressed and detailed on the following pages.

If you have any questions or comments regarding this information, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
Official US Agent for Ranbaxy Laboratories Limited

RECEIVED
JAN 0 6 2004
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

March 16, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and FAX

Bioequivalence and CMC Minor Amendment Response

ORIG AMENDMENT
N/am
BIOAVAILABILITY

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets 10 mg/240 mg
ANDA # 76-557

Dear Sir/Madam:

Reference is made to the above pending ANDA for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, submitted to the Agency on December 4, 2002.

Reference is also made to the Bioequivalence comments fax received February 27, 2004 and the Minor Amendment fax received March 16, 2004.

The deficiency questions and responses are addressed and detailed on the following pages.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this additional information has been provided to the Food and Drug Administration, New Jersey District Office in North Brunswick, New Jersey.

Please contact me at 609-720-8017, or Abha Pant at 609-720-5666 if you have any questions regarding this amendment. Thank you.

Sincerely,

Brett Johnson (for)

Brett Johnson
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

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MAR 17 2004
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RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

April 20, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and FAX

Bioequivalence Amendment

ORIG AMENDMENT
N/AB

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets 10 mg/240 mg
ANDA # 76-557

Dear Sir/Madam:

Reference is made to the above pending ANDA for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, submitted to the Agency on December 4, 2002. Reference is also made to the telephone contact on April 20th between Ranbaxy and the Agency.

Based on the Agency's request, Ranbaxy hereby submits the dissolution specifications as discussed in the telephone conference today. Please find below the Agency earlier proposed specifications and the revised, proposed specifications using the same method:

Condition	**Medium/Media**	
	Initial - 1 hour	**1 - 16 hour**
USP Apparatus # II (paddle), 50 RPM	0.1N HCl	0.1M phosphate buffer pH 7.5
Media volume 1000 ml		
Temperature 37 ± 0.5°C		

Component	FDA Specifications		Proposed Specifications	
Loratadine *(Immediate release)*	NLT (b)(4) % (Q) is dissolved in 30 minutes		**NLT (b)(4) % (Q) is dissolved in 60 minutes**	
Pseudoephedrine Sulfate *(Extended release)*	Time in hours	% Release (b)(4)	Time in hours	% Release (b)(4)
	1 hour		1 hour	
	2 hours		2 hours	
	4 hours		4 hours	
	8 hours		8 hours	
	16 hours		16 hours	

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Please contact me at 609-720-5609, or Abha Pant at 609-720-5666 if you have any questions regarding this amendment. Thank you.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

April 20, 2004

NEW CORRESP
MC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and FAX

Update of Litigation

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
10 mg/240 mg
ANDA 76-557

Dear Sir/Madam:

Reference is made to the above pending ANDA for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, submitted to the Agency on December 4, 2002.

As per the Agency's request, please find a copy of the New Jersey District Court's settlement between Schering Corporation and Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Inc., dated March 25, 2004, whereby Civil Action No. 03-2011 (JWB) was dismissed with prejudice.

If you have any further questions regarding this submission, please contact the undersigned at 609-720-5390 or Ms. Abha Pant at 609-720-5666.
Thank you.

Sincerely,

Richard Leone (for)

Richard Leone
Regulatory Affairs Associate (for)
Abha Pant
U.S. Agent for Ranbaxy Laboratories Limited

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RANBAXY ORIGINAL

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

May 20, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and FAX

Additional Information
Chemistry

ORIG AMENDMENT
N/AM

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
10 mg/240 mg
ANDA #76-557

Dear Sir/Madam:

Reference is made to the above pending ANDA for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, submitted to the Agency on December 4, 2002. Reference is also made to the telephone contact on April 20, 2004 between Ranbaxy and the Agency, to our Bioequivalence Amendment dated the same wherein we submitted revised dissolution specifications as discussed in the telephone contact, and to the telephone contact between the Agency and Ranbaxy on May 17, 2004.

Based on the May 17, 2004 telephone contact with the Division of Bioequivalence, we understand that the Amendment submitted on April 20, 2004 is acceptable and the bioequivalence review is now closed.

Based on the information above, Ranbaxy hereby submits the revised drug product standard test procedure (**Attachment 1**), revised drug product release specification (**Attachment 2**) and revised stability specification (**Attachment 3**) incorporating the new dissolution specifications.

Field Copy: We certify that a true copy of the technical sections described in 21 CFR 314.94 (d)(5) of this submission has been provided to the FDA New Jersey District Office in North Brunswick, New Jersey.

Please contact me at 609-720-8016, or Abha Pant at 609-720-5666 if you have any questions regarding this submission. Thank you.

Sincerely,

RECEIVED
MAY 21 2004
OGD/CDER

Sean M. Russell
Regulatory Affairs Associate (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECORD OF TELEPHONE CONVERSATION

Reference is made to the unapproved ANDA 76-557. The following deficiency was communicated to the firm.

The Agency asked the firm to submit stability data for dissolution based on the new dissolution specifications. The firm may provide dissolution data from retained samples from accelerated stability studies. Three meaningful test points may be submitted.

The firm stated that they are testing the validation batches using the old and new methods. The firm stated that 24 month stability test was already conducted. The firm agreed to obtain stability data for dissolution based on retained samples from accelerated stability studies. If they do not have retained samples, the firm will propose another way to provide the data.

The firm's response may be submitted as a Telephone Amendment if they are able to respond within 10 days.

DATE
June 22, 2004

ANDA NUMBER
76-557

IND NUMBER

TELECON

INITIATED BY

SPONSOR __

FDA _X_

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

FIRM NAME
Ranbaxy Laboratories Limited

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Abha Pant
Manjett Bindra
Mini Nair

TELEPHONE NUMBER
609-720-5666

SIGNATURE
Dave Gill DSGill
Guoping Sun 6/22/04
Sarah Park S. Park 6/28/04

CC: ANDA 76-557
Division File
V:\FIRMSNZ\RANBAXY\TELECONS\76557tc062204.doc

RECORD OF TELEPHONE CONVERSATION

Reference is made to the Telephone Conference on June 22, 2004, and the firm's voice mail message to Sarah Park on June 22, 2004, regarding the dissolution data. These recommendations are provided by Dave Gill communicated through Sarah Park

The firm stated that they have already crossed the 24 month test point, so they will be testing that batch at the 26 month station. The firm will test for dissolution at 26 months and submit the results. In addition, the firm has retention samples from another batch which has been packed in (b) (4) bottles. The firm requested if they can submit 2 test points from the retention samples on this particular batch, and provide the dissolution data generated at accelerated time points.

Agency agreed with the firm's request to submit the 26 month test point from the test batch plus two accelerated time points from the retention samples of another batch, which are packaged in (b) (4) (b) (4) bottles.

DATE
June 23, 2004

ANDA NUMBER
76-557

IND NUMBER

TELECON

INITIATED BY

SPONSOR __

FDA _X_

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

FIRM NAME
Ranbaxy Laboratories Limited

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Mini Nair

TELEPHONE NUMBER
609-720-5666

SIGNATURE
Sarah Park S. Park 6/23/04

CC: ANDA 76-557
Division File
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RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

July 1, 2004

ORIG AMENDMENT
IN/AM.

UPS and FAX

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Telephone Response
Chemistry

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
10 mg/240 mg
ANDA # 76-557

Dear Sir/Madam:

Reference is made to the above pending ANDA for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, submitted to the Agency on December 4, 2002. Reference is also made to the Telephone contact between the Agency and Ranbaxy dated June 22, 2004.

During this Telephone contact the Agency made reference to an additional information amendment dated May 20, 2004. In this amendment Ranbaxy supplied all revised specifications incorporating Agency agreed upon dissolution specifications. The Agency stated that although all relevant specifications were updated, stability data incorporating these specifications must be performed and supplied for three stability time points.

As per the Agency's request Ranbaxy is providing stability data using the newly adopted dissolution specifications for the three time points, twenty-eight month CRT, 3 month ACC and 2 month ACC data. Additionally, as per the Agency's comments, Ranbaxy commits to retain retention samples in the future for all non USP drug products for Accelerated Stability purposes.

Field Copy: We certify that a true copy of the technical sections described in 21 CFR 314.94 (d)(5) of this submission has been provided to the FDA New Jersey District Office in North Brunswick, New Jersey since the manufacturing is done at Ohm Laboratories, in North Brunswick, NJ.

If you have any questions or comments regarding this information, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,
Brett Johnson (for)

Brett Johnson
Regulatory Affairs Associate (*for*)
Abha Pant
Official US Agent for Ranbaxy Laboratories Limited

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JUL 0 2 2004
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RANBAXY ORIGINAL

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

August 11, 2004

ORIG AMENDMENT
N/AF

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS & FAX

TELEPHONE RESPONSE
LABELING

Reference: **Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg**
ANDA 76-557

Dear Sir/Madam:

Reference is made to the above pending ANDA for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, submitted to the Agency on December 4, 2002. Reference is also made to the telephone contact with the Agency dated August 10, 2004.

The Agency requested, in the telephone contact dated August 10, 2004, that updated labeling be submitted to reflect the RLD's newly approved labeling.

With respect to the Agency's request, Ranbaxy is providing updated bottle and carton labeling in **Attachment 1** and a side-by-side comparison of the updated labeling versus the RLD labeling in **Attachment 2**.

Additionally, on the following page, a CD containing all electronic labeling is included.

If you have any questions or comments regarding this information, please call me at 609-720-8017 or Abha Pant at 609-720-5666.

Sincerely,

Brett Johnson (for)

Brett Johnson
Regulatory Affairs Associate *(for)*
Abha Pant
Official US Agent for Ranbaxy Laboratories Limited

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RECORD OF TELEPHONE CONVERSATION

Reference is made to the unapproved ANDA 76-557. The following deficiencies/ comments were communicated to the firm.

1. (b) (4)

2.

The firm's response may be submitted as a telephone amendment.

DATE
September 2, 2004

ANDA NUMBER
76-557

IND NUMBER

TELECON

INITIATED BY

SPONSOR __

FDA _X_

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

FIRM NAME
Ranbaxy Laboratories Limited

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Abha Pant
Brad Johnson
Scott Thompsky

TELEPHONE NUMBER
609-720-5666

SIGNATURE
Dave Gill
Guoping Sun 9/10/04
Sarah Park 9/10/04

CC: ANDA 76-557
Division File
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RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

September 8, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and FAX

Telephone Amendment
Chemistry
ORIG AMENDMENT
N/AM

Reference: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
10 mg/240 mg
ANDA # 76-557

Dear Sir/Madam:

Reference is made to the above pending ANDA for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 10 mg/240 mg, submitted to the Agency on December 4, 2002.

Reference is also made to the facsimile sent from the Agency on September 1, 2004 and the Telephone contact between the Agency and Ranbaxy dated September 2, 2004.

The deficiency questions and responses are addressed and detailed on the following pages.

Field Copy: We certify that a true copy of the technical sections described in 21 CFR 314.94 (d)(5) of this submission has been provided to the FDA New Jersey District Office in North Brunswick, New Jersey since the manufacturing is done at Ohm Laboratories, in North Brunswick, NJ.

If you have any questions or comments regarding this information, please call me at 609-720-8017 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Brett Johnson (for)

Brett Johnson
Regulatory Affairs Associate (*for*)
Abha Pant
Official US Agent for Ranbaxy Laboratories Limited

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SEP 09 2004
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OGD APPROVAL ROUTING SUMMARY

ANDA # 76-557 Applicant Ranbaxy Laboratories Limited
Drug Loratadine and Pseudoephedrine Sulfate Strength(s) 10 mg/240 mg
Extended Release Tablets

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

REVIEWER:	DRAFT Package	FINAL Package
1. Martin Shimer Chief, Reg. Support Branch	Date 2 Aug 2004 Initials MS	Date 9/20/04 Initials for

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = NDA# 20-470
Patent/Exclusivity Certification: Yes ☑ No ☐
Date Checked Previously granted
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☑ No ☐
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐
Study Submitted ☐
Has case been settled: Yes ☑ No ☐ Date settled:
Is applicant eligible for 180 day Eligible for Full Approval
Generic Drugs Exclusivity for each strength: Yes ☐ No ☑
Type of Letter:
Comments: Ranbaxy was not sued on the '302 '697 patents. Their PIV to '776 resulted in Integra's lawsuit on the '776 patent was found invalid by the district court & affirmed by the Appellate court. Furthermore, Schering has requested that the Agency delist this patent. Hence NDA 75-766 pc exclusivity has expired

2. Project Manager, Sarah Park Team 4 Review Support Branch	Date 7/30/04 Initials SBP	Date Initials

Original Rec'd date 12/6/2002
Date Acceptable for Filing 12/6/2002
Patent Certification (type) IV
Date Patent/Exclus.expires see attached
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 ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 1/27/2003
Date of Office Bio Review 4/29/2004; 8/26/03; 2/24/03
Date of Labeling Approv. Sum 8/18/2004
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☐ N/A
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☑ No ☐

Previously reviewed and tentatively approved NO ☐ Date
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

3. David Read (PP IVs Only) Pre-MMA Language luded ☐ NA OGD Regulatory Counsel, Post-MMA Language Included ☐ Comments: see revisions		Date 8/5/04 Initials DTR

4. Div. Dir./Deputy Dir. Chemistry Div. I II OR III Comments: conc satisfactory		Date 9/20/04 Initials SAR

1

REVIEWER: FINAL ACTION

5. Frank Holcombe **First Generics Only** Date______
Assoc. Dir. For Chemistry Initials______
Comments: (First generic drug review)
N/A - Andrx's ANDA 75-706 was approved on 2/21/03. Impax's ANDA 75-989 was approved on 3/4/04.

6. Vacant RLD = Claritin-D 24 Hour 10mg/240mg Date______
Deputy Dir., DLPS Extended-release Tablets Initials______

7. Peter Rickman Schering Corp NDA 20-470 (002) Date 9/22/04
Director, DLPS Initials Per Robert West for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Acceptable EES dated 12/7/03 (verified 9/22/04). No OAI alerts noted. Bioequivalence studies (fasting and nonfasting) found acceptable 2/24/04. "Intercom" dissolution testing found acceptable 4/29/04. Bio test sites have acceptable DSI inspection histories. Office level bio endorsed 4/29/04. FPL found acceptable for approval 8/18/04. CMC found acceptable 9/17/04. Methods validation was not requested for the drug product. Both APIs are compendial.

8. Robert L. West Date 9/22/2004
Deputy Director, OGD Initials Robert West
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☐
Comments: Ranbaxy made paragraph IV certifications to the '931 and '716 '697 patents. Schering sued Ranbaxy for infringement of the '716 patent (not currently listed in the Orange Book). On 8/1/03 the '716 patent was found invalid by the appellate court.

This ANDA is recommended for approval.

9. Gary Buehler Date 9/22/04
Director, OGD Initials GB
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

10. Project Manager, Team Sarah Park Date 9/22/04
Review Support Branch Initials SP
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
10:00AM Time notified of approval by phone 10:05AM Time approval letter faxed
FDA Notification:
9/22/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
9/22/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou8.doc