CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 076134

Name: Loratadine Tablets
10 mg

Sponsor: Ranbaxy Pharmaceuticals, Inc.

Approval Date: August 18, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076134

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076134

APPROVAL LETTER

ANDA 76-134

AUG 18 2003

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

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 15, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Loratadine Tablets, 10 mg (OTC).

Reference is made to the Tentative Approval letter issued by this Office on December 20, 2001, and to your amendments dated July 3, August 13, October 21, and October 30, 2002; and January 22, January 30, February 26, March 12, April 7, and June 24, 2003. We also refer to your correspondence dated March 27, July 22, and August 1, 2003, addressing patent litigation issues discussed below.

The listed drug product referenced in your application (RLD), Claritin® Tablets, 10 mg, of Schering Corporation (Schering), is subject to periods of patent protection that expire on October 21, 2004 (U.S. Patent No. 4,659,716, the '716 patent), and March 15, 2009 (U.S. Patent No. 4,863,931, the '931 patent). Your application contains patent certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Loratadine Tablets, 10 mg, will not infringe on the claims of the '716 and '931 patents, or that the claims of these patents are otherwise invalid or unenforceable. Section 505(j)(5)(B)(iii) of 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 one or more of the patents that are the subject of the certifications. This action must be brought against Ranbaxy prior to the expiration of forty-five (45) days from the date the notice provided by Ranbaxy under Section 505(j)(2)(B)(i) is

received by the patent and NDA holders.

You notified the Agency that Ranbaxy complied with the requirements of Section 505(j)(2)(B) of the Act. As a result, in June 2001, Schering initiated a patent infringement suit against you 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. 01-CV-2990 (JAG)). In an order decided, filed, and entered on the Docket on August 8, 2002, the Chief Judge of the United States District Court for the District of New Jersey ruled in a related and consolidated case (Civil Action No.98-1259 (JWB) et al.) that the contested claims of the '716 patent were invalid. On August 8, 2002, Schering appealed the district court's decision in the consolidated case to the United States Court of Appeals for the Federal Circuit. Subsequently, you informed the Agency that in an order dated February 28, 2003, the district court stayed Ranbaxy's civil action, pending a decision in Schering's appeal of the consolidated District Court's decision. To conclude this matter and to provide for final approval of this application, you informed the Agency that on August 1, 2003, the United States Court of Appeals for the Federal Circuit affirmed the District Court's prior decision finding the contested claims of the '716 patent to be invalid. In addition, we note that no action was brought by either the patent holder or NDA holder against Ranbaxy within the 45-day period with regard to the '931 patent.

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 Tablets, 10 mg, to be bioequivalent to the listed drug, Claritin® Tablets, 10 mg, of Schering Corporation. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application

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 8/18/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

ANDA 76-134
Division File
FIELD COPY
HFD-610/RWest
HFD-330/
HFD-205/
HFD-610/Orange Book Staff

Endorsements:
HFD-623/G.Sun/ 8/1/03
HFD-623/D.Gill/ DSGill 8-4-03
HFD-617/S.Kim/7-21-03/8-01-03 S. Kim 8/07/03
HFD-613/D.Catterson/ RWu for 8/8/2003
HFD-613/J.Grace/ 8/7/03

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F/T by: sk/7-21-03/8-01-03

APPROVAL

RAC filed 8/15/03
(EER overall ok
7/16/03

Robert Lost
8/18/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076134

TENTATIVE APPROVAL LETTER

ANDA 76-134

DEC 20 2001

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

Dear Madam:

This is in reference to your abbreviated new drug application dated March 15, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Loratadine Tablets, 10 mg.

Reference is also made to your amendments dated May 16, August 30, October 10, and November 7, 2001.

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

The listed drug product (RLD) referenced in your application, Claritin Tablets of Schering Corp., is subject to periods of patent protection which expire on December 19, 2002 (U.S. Patent No. 4,282,233, the '233 patent), October 21, 2004 (U.S. Patent No. 4,659,716, the `716 patent), and March 15, 2009 (U.S. Patent No. 4,863,931, the '931 patent). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(III) of the Act for the '233 patent. Your application also contains patent certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe upon the '716 or '931 patents, or that these patents

are invalid or unenforceable. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Ranbaxy Laboratories Limited (Ranbaxy) for infringement of one or more of the patents that are the subject of the certifications. This action must be brought against Ranbaxy prior to the expiration of forty-five (45) days from the date the notice provided by Ranbaxy under paragraph (2)(B)(I) is received. You have notified FDA that Ranbaxy has complied with the requirements of Section 505(j)(2)(B) of the Act and that litigation is underway in the United States District Court for the District of New Jersey involving a challenge to the '716 patent (Schering Corporation v. Ranbaxy Laboratories, Ltd. and Ranbaxy Pharmaceuticals, Inc., Civil Action No. 01-2990 (JAG)). Therefore, final approval cannot be granted until:

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

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

   c. the '716 patent has expired, and

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

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

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

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

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

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

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

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

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

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

Sincerely yours,

Gary Buehler
Director 12/20/01
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-134
Division File
FIELD COPY
HFD-610/RWest
HFD-210/B.Poole
HFD-330/
HFD-205/

Endorsements:
HFD-623/J.Franolic/ John J. Franolic 11/19/01
HFD-623/D.Gill/ DSGill 11-19-01
HFD-617/R.Wu/11/19/01 RWu 11/19/01
HFD-613/D.Catterson/ Debra M. Catterson 11/20/01
HFD-613/J.Grace/ 11/26/2001
V:\FIRMSNZ\RANBAXY\LTRS&REV\76134.ta.doc
F/T by: gp/11/19/01

Robert Lusfest
12/20/2001
EES Acceptable

TENTATIVE APPROVAL

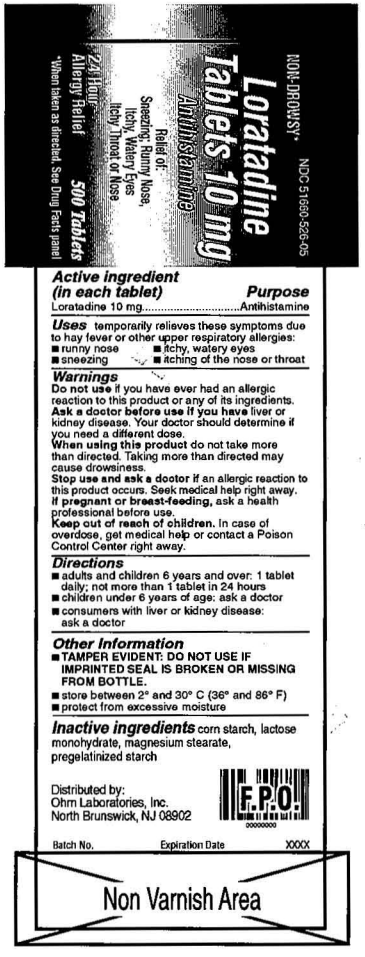
MVB EER dtd pending
11/20/01

CENTER FOR DRUG EVALUATION AND RESEARCH

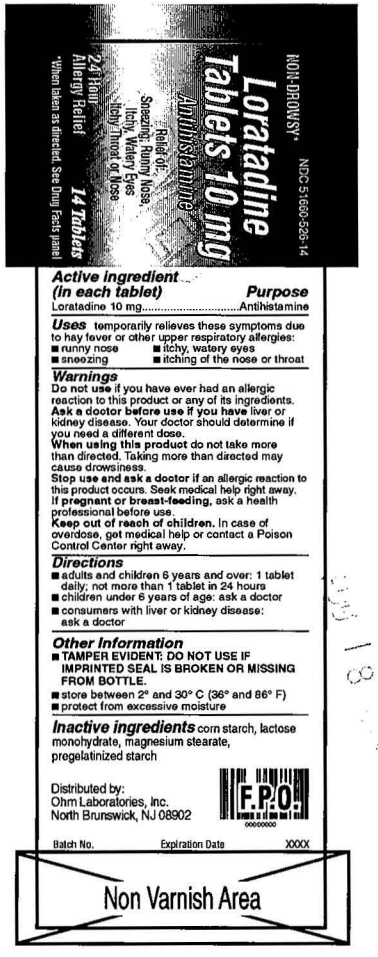
APPLICATION NUMBER:

ANDA 076134

LABELING

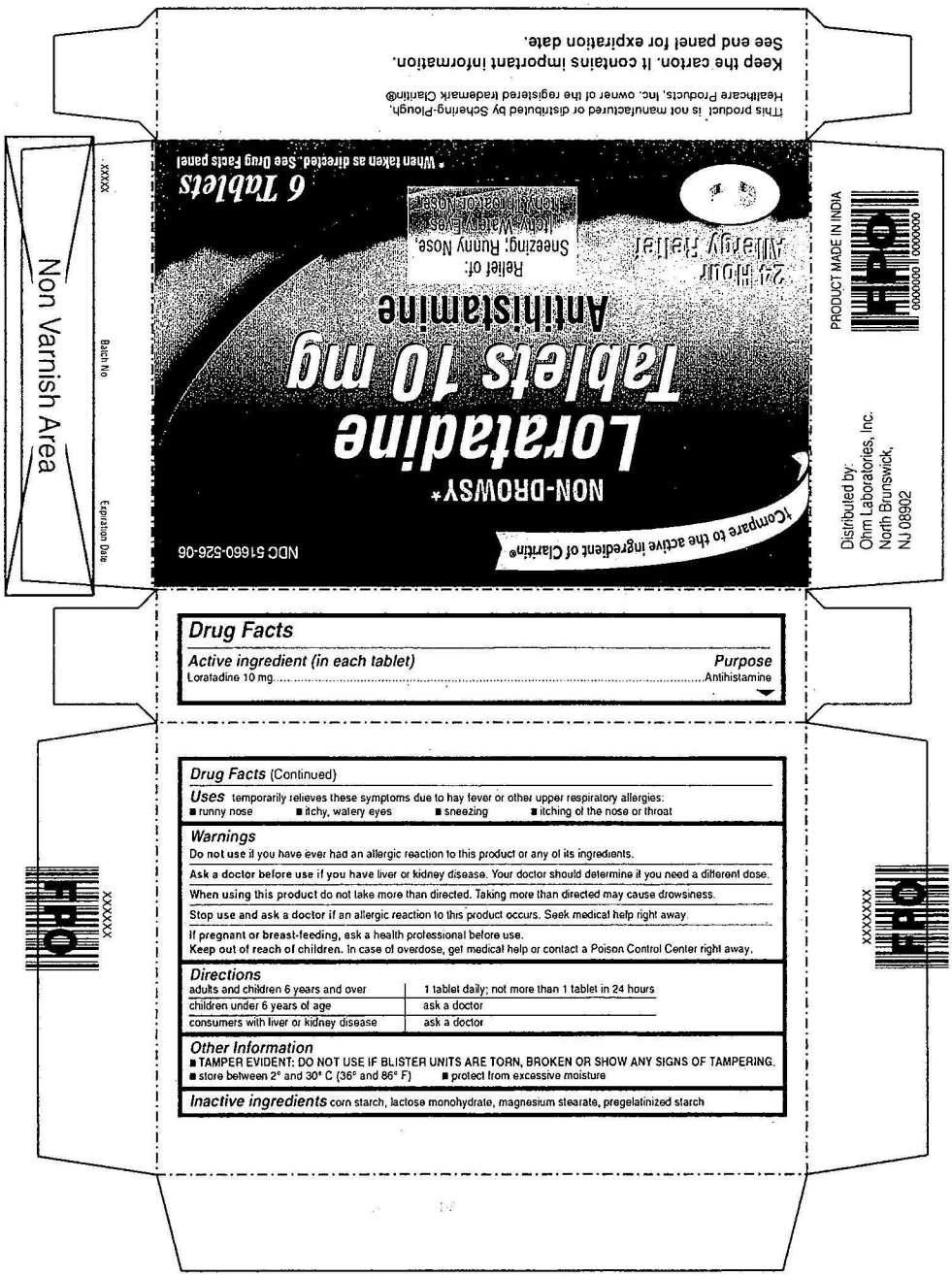

NON-DROWSY*
NDC 51660-526-05
Loratadine
Tablets 10 mg
Antihistamine
Relief of:
Sneezing, Runny Nose,
Itchy, Watery Eyes
Itchy Throat or Nose
24 Hour
Allergy Relief
500 Tablets
*when taken as directed. See Drug Facts panel
Active Ingredient
(in each tablet)
Purpose
Loratadine 10 mg.....Antihistamine
Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
■ runny nose
■ itchy, watery eyes
■ sneezing
■ itching of the nose or throat
Warnings
Do not use if you have ever had an allergic reaction to this product or any of its ingredients.
Ask a doctor before use if you have 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.
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
■ adults and children 6 years and over: 1 tablet daily; not more than 1 tablet in 24 hours
■ children under 6 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 2° and 30° C (36° and 86° F)
■ protect from excessive moisture
Inactive ingredients corn starch, lactose monohydrate, magnesium stearate, pregelatinized starch
Distributed by:
Ohm Laboratories, Inc.
North Brunswick, NJ 08902
F.P.O.
Batch No.
Expiration Date
XXXX
Non Varnish Area

(b) (4)


NON-DROWSY*
NDC 51660-526-14
Loratadine
Tablets 10 mg
Antihistamine
Relief of:
Sneezing, Runny Nose,
Itchy, Watery Eyes
Itchy Throat or Nose
24 Hour
Allergy Relief
14 Tablets
*when taken as directed. See Drug Facts panel
Active Ingredient
(in each tablet)
Purpose
Loratadine 10 mg.....Antihistamine
Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
■ runny nose
■ itchy, watery eyes
■ sneezing
■ itching of the nose or throat
Warnings
Do not use if you have ever had an allergic reaction to this product or any of its ingredients.
Ask a doctor before use if you have 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.
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
■ adults and children 6 years and over: 1 tablet daily; not more than 1 tablet in 24 hours
■ children under 6 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 2° and 30° C (36° and 86° F)
■ protect from excessive moisture
Inactive ingredients corn starch, lactose monohydrate, magnesium stearate, pregelatinized starch
Distributed by:
Ohm Laboratories, Inc.
North Brunswick, NJ 08902
F.P.O.
Batch No.
Expiration Date
XXXX
Non Varnish Area

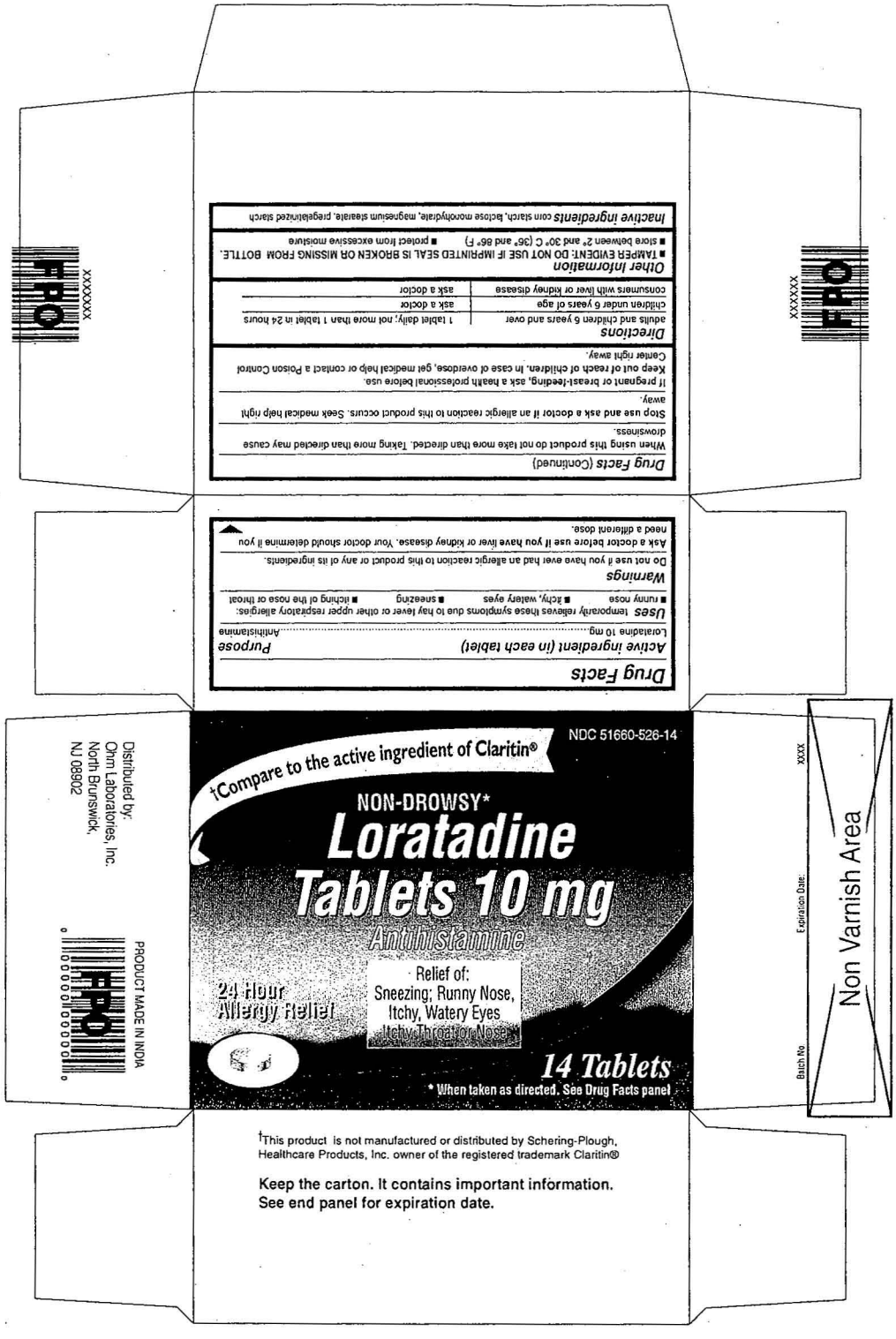
(b) (4)

(b) (4)


Non Varnish Area
Batch No
Expiration Date
XXXXX
6 Tablets
* When taken as directed. See Drug Facts panel
Relief of:
Sneezing; Runny Nose;
Itchy, Watery Eyes;
Itchy Throat; Nose
24 hour
Allergy Relief
NON-DROWSY*
Loratadine
Tablets 10 mg
Antihistamine
Compare to the active ingredient of Claritin®
NDC 51660-526-06
PRODUCT MADE IN INDIA
Distributed by:
Ohm Laboratories, Inc.
North Brunswick,
NJ 08902
This product is not manufactured or distributed by Schering-Plough,
HealthCare Products, Inc. owner of the registered trademark Claritin®
Keep the carton. It contains important information.
See end panel for expiration date.
Drug Facts
Active ingredient (in each tablet) Purpose
Loratadine 10 mg Antihistamine
Drug Facts (Continued)
Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
■ runny nose ■ itchy, watery eyes ■ sneezing ■ itching of the nose or throat
Warnings
Do not use if you have ever had an allergic reaction to this product or any of its ingredients.
Ask a doctor before use if you have 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.
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
adults and children 6 years and over | 1 tablet daily; not more than 1 tablet in 24 hours
children under 6 years of age | ask a doctor
consumers with liver or kidney disease | ask a doctor
Other Information
■ TAMPER EVIDENT: DO NOT USE IF BLISTER UNITS ARE TORN, BROKEN OR SHOW ANY SIGNS OF TAMPERING.
■ store between 2° and 30° C (36° and 86° F) ■ protect from excessive moisture
Inactive ingredients corn starch, lactose monohydrate, magnesium stearate, pregelatinized starch
XXXXXX
XXXXXXX


Drug Facts (Continued)
Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
■ runny nose ■ itchy, watery eyes ■ sneezing ■ itching of the nose or throat
Warnings
Do not use if you have ever had an allergic reaction to this product or any of its ingredients
Ask a doctor before use if you have 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.
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
adults and children 6 years and over 1 tablet daily; not more than 1 tablet in 24 hours
children under 6 years of age ask a doctor
consumers with liver or kidney disease ask a doctor
Other information
■ TAMPER EVIDENT: DO NOT USE IF BLISTER UNITS ARE TORN, BROKEN OR SHOW ANY SIGNS OF TAMPERING.
■ store between 2° and 30° C (36° and 86° F) ■ protect from excessive moisture
Inactive ingredients corn starch, lactose monohydrate, magnesium stearate, pregelatinized starch
Drug Facts
Active ingredient (in each tablet) Purpose
Loratadine 10 mg ..... Antihistamine
XXXXXXX
XXXXXX
Distributed by:
Ohm Laboratories, Inc.
North Brunswick,
NJ 08902
PRODUCT MADE IN INDIA
†Compare to the active ingredient of Claritin®
NDC 51660-526-11
NON-DROWSY*
Loratadine
Tablets 10 mg
Antihistamine
24 Hour
Allergy Relief
Relief of:
Sneezing; Runny Nose,
Itchy, Watery Eyes;
Itchy Throat or Nose
10 Tablets
* When taken as directed. See Drug Facts panel
Expiration Date:
Batch No.
XXXXX
Non Varnish Area
†This product is not manufactured or distributed by Schering-Plough, Healthcare Products, Inc. owner of the registered trademark Claritin®
Keep the carton. It contains important information.
See end panel for expiration date.

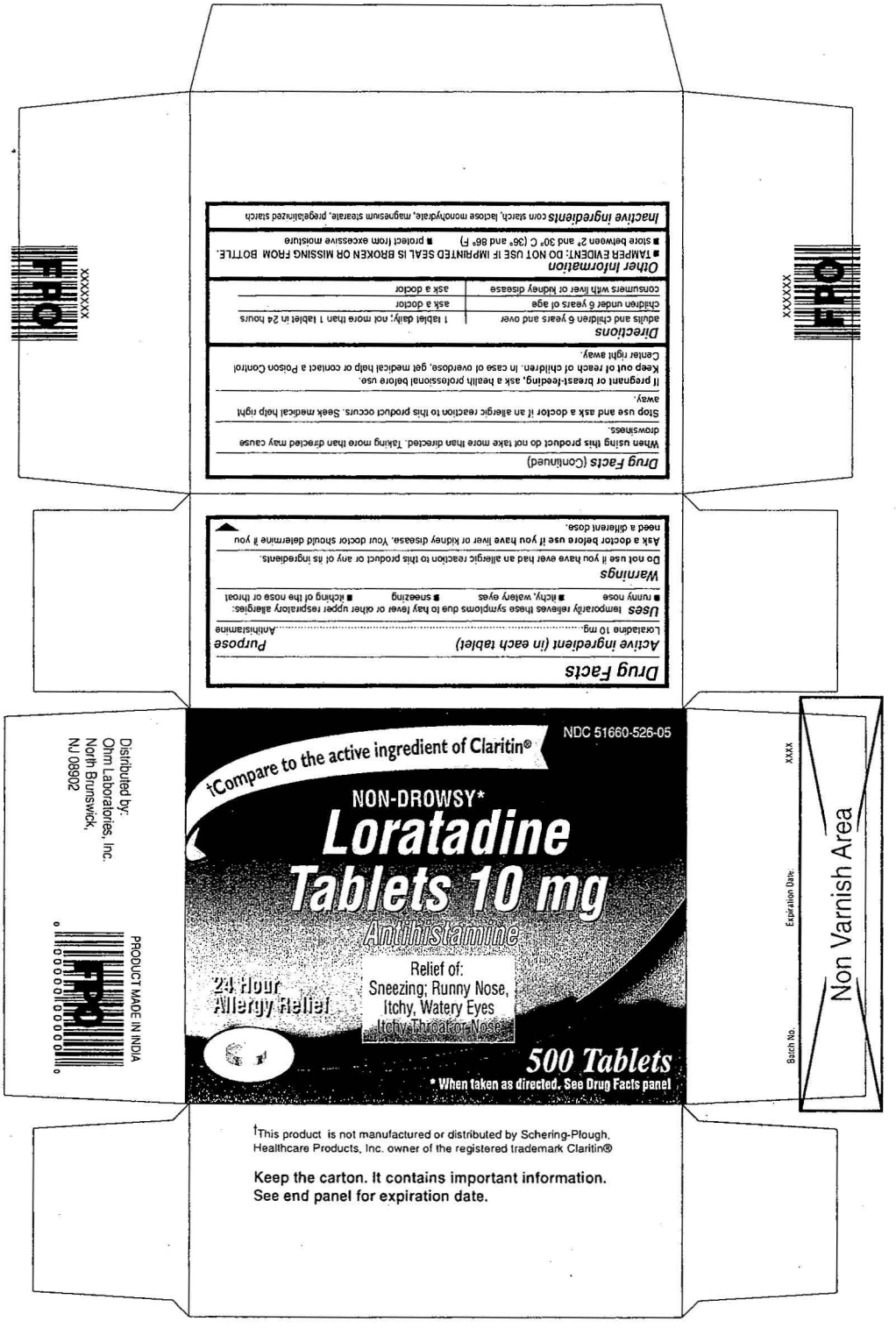
(b) (4)



†This product is not manufactured or distributed by Schering-Plough, Healthcare Products, Inc. owner of the registered trademark Claritin®

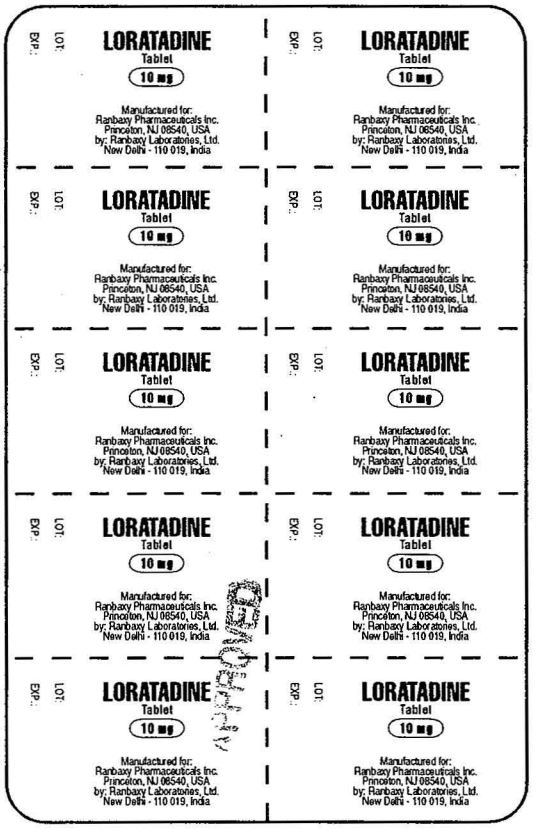
Keep the carton. It contains important information.
See end panel for expiration date.

(b) (4)


Drug Facts (Continued)
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.
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
adults and children 6 years and over | 1 tablet daily; not more than 1 tablet in 24 hours
children under 6 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 2° and 30° C (36° and 86° F)
protect from excessive moisture
Inactive ingredients corn starch, lactose monohydrate, magnesium stearate, pregelatinized starch
Drug Facts
Active ingredient (in each tablet) Purpose
Loratadine 10 mg Antihistamine
Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
runny nose
itchy, watery eyes
sneezing
itching of the nose or throat
Warnings
Do not use if you have ever had an allergic reaction to this product or any of its ingredients.
Ask a doctor before use if you have liver or kidney disease. Your doctor should determine if you need a different dose.
Distributed by:
Ohm Laboratories, Inc.
North Brunswick,
NJ 08902
PRODUCT MADE IN INDIA
†Compare to the active ingredient of Claritin®
NDC 51660-526-05
NON-DROWSY*
Loratadine
Tablets 10 mg
Antihistamine
24 Hour Allergy Relief
Relief of:
Sneezing; Runny Nose,
Itchy, Watery Eyes
Itchy Throat or Nose
500 Tablets
* When taken as directed. See Drug Facts panel
Non Varnish Area
XXXX
Expiration Date:
Batch No.
†This product is not manufactured or distributed by Schering-Plough, Healthcare Products, Inc. owner of the registered trademark Claritin®
Keep the carton. It contains important information.
See end panel for expiration date.

(b) (4)

H 2 23/32" x W 4 1/4"



Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Princeton, NJ 08540 USA
by: Ranbaxy Laboratories Ltd.
New Delhi - 110 019, India

RANBAXY

NDC 63304-526-80

LORATADINE
Tablets
10 mg

Rx only

100 Unit-Dose Tablets
(10 Blister Strips of 10 Unit-Dose Tablets)

Each tablet contains: 10 mg loratadine

Usual Dosage: See package insert. Read accompanying directions carefully.

Dispense in a tight container as defined in USP/NF.

Protect from excessive moisture.

Store at controlled room temperature
15° to 30° C (59° to 86° F) (see USP).

To Open: Tear blister at perforations and peel back at corner tab to remove foil.

RANBAXY

NDC 63304-526-80

APPROVED

LORATADINE
Tablets
10 mg

Rx only

100 Unit-Dose Tablets
(10 Blister Strips of 10 Unit-Dose Tablets)

RANBAXY

NDC 63304-526-80

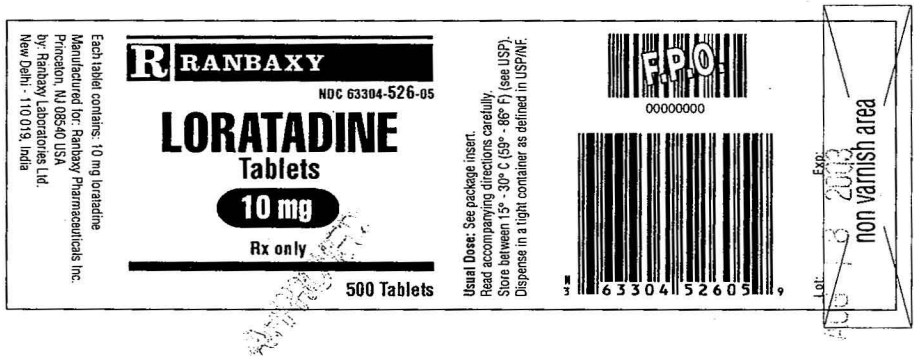
LORATADINE
Tablets
10 mg

Rx only

100 Unit-Dose Tablets
(10 Blister Strips of 10 Unit-Dose Tablets)

Label Size = 45cc 1 1/8" x 4 1/4"

Label Size = 120cc 4 5/8" x 1 1/2"



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076134

LABELING REVIEWS

TENTATIVE APPROVAL SUMMARY

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

ANDA Number: 76-134

Dates of Submission: March 15, 2001 (Original) and November 7, 2001 (Amendment)

Applicant's Name: Ranbaxy Laboratories Limited

Established Name: Loratadine Tablets, 10 mg

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

Do you have 12 Final Printed Labels and Labeling? **No**. – The firm submitted 4 draft copies of their labels and labeling, which is acceptable for a Tentative Approval. Final Printed Labeling will be submitted by the firm 60 days prior to full approval of this application. Full approval is expected on Dec. 19, 2002.

CONTAINER Labels – [Bottles of 14's and 500's]:
Satisfactory in **draft** as of the March 15, 2001 submission.

Professional Package INSERT:
Satisfactory in **draft** as of the November 7, 2001 submission.

Revisions needed post-tentative approval: **Yes**. There were several labeling revisions that were mostly editorial in nature, and therefore could be "post-tentative approval" revisions. I communicated these revisions to Iris Feliciano, U.S. Agent for Ranbaxy Laboratories, Ltd., by telephone and by facsimile on November 14, 2001.

Patent Data – NDA 19-658

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

Exclusivity Data– NDA 19-658

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®

NDA Number: 19-658

NDA Drug Name: Loratadine Tablets 10 mg

NDA Firm: Schering Corporation

Date of Approval of NDA Insert and supplement: December 4, 2000; NDA 20-641/SE5-007 (combined insert)

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

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

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

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	

If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	

Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for CLARITIN® by Schering; NDA 20-641/SE5-007; approved December 4, 2000. The CLARITIN insert labeling is a combined one for CLARITIN Tablets, Syrup, and Rapidly Disintegrating Tablets (REDITABS). All references to the REDITABS and Syrup should be carved out of the generic firm's labeling. But certain references pertaining to the Syrup provide pertinent information relating to the pharmacokinetics, pediatric use, adverse reactions, and overdosage of loratadine. The "First Generic" for loratadine tablets included these Syrup references. Therefore, I will have the firm include these particular loratadine syrup references into their labeling.

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 19-658

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

Exclusivity Data– NDA 19-658

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

Ranbaxy Laboratories Limited
Paonta Sahib
District Sirmour
Himachal Pradesh – 173 025
INDIA [Vol. 1.14 pg. 5492.]

4. CONTAINER/CLOSURE

14s: 45 cc round white HDPE bottle, with 33 mm white (b) (4) child-resistant cap.
500s: 120 cc round white HDPE bottle, with 38 mm white (b) (4) child-resistant cap.
[Vol. 1.14 pg. 5664, 5665, & 5667.]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears to be accurate according to the components/composition statement. [Vol. 1.14 pg. 5441.]

6. PACKAGING CONFIGURATIONS

RLD: Bottles of 100 and 500 tablets, Unit-of-Use packages of 30 tablets (10 tablets per blister card), and 10 x 10 tablet Unit Dose-Hospital Packs.
ANDA: Bottles of 14 and 500 tablets.
[Vol. 1.1 pg. 027.]

7. STORAGE/DISPENSING STATEMENTS COMPARISON

NDA: Store between 2° and 30°C (36° and 86°F).
Dispense in tight container as defined in USP/NF. (Container label only)
ANDA: Store tablets at room temperature 15° to 30°C (59°to 86°F) (See USP). Dispense in a tight container as defined in the USP/NF.
[Vol. 1.1, pg. 027 & 028]

8. CAPSULE IMPRINT

The capsule imprintings have been accurately described in the HOW SUPPLIED section of the Insert according to the firm's Finished Product Specifications:

'white uncoated, round tablets; debossed with **RX526** on one side
and plain on the other.'

[Vol. A1.14 pg. 5804.]

9. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on June 18, 2001, that the firm's single dose fasting, post-prandial, and dissolution studies were all acceptable.

Date of Review: 11/13/01 Dates of Submission: 3/15/01 and 11/7/01

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 11/14/01

Team Leader: John Grace Date:

John D Grace 11/15/2001

cc:

ANDA: 76-134
DUP/DIVISION FILE
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Review

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

ANDA Number: 76-134

Date of Submission: July 3, 2002 (Amendment)

Applicant's Name: Ranbaxy Laboratories Limited

Established Name: Loratadine Tablets, 10 mg

Labeling Deficiencies:

1. **CONTAINER:**

   a. Bottles of 14 and 500: Satisfactory in draft as of the March 15, 2001 submission.

   b. Unit Dose Blister Card of 10 Tablets:

      Revise "Tablets" to read "Tablet" on each of the ten unit dose blister labels.

2. **CARTON** Label [For box of 100 (10 x 10) unit dose tablets]:

   a. Revise "100 Unit-Dose Capsules" to read "100 Unit-Dose Tablets" wherever it appears on your label.

   b. Revise "(10 Strips of 10 Unit-Dose Capsules)" to read "(10 Blister Strips of 10 Unit-Dose Tablets)" wherever it appears on your label.

   c. Insert the following text after the "This unit-dose package is not child resistant." statement:

      "This package is intended for institutional inpatient use. If dispensed for outpatient use, appropriate safety packaging must be provided."

3. **INSERT:**

   a. DESCRIPTION: Revise "monhydrate" to read "monohydrate".

   b. ADVERSE REACTIONS: Loratadine Syrup:

      Delete the entire paragraph that begins with the sentence: (b) (4) [The information should be deleted because this patient population is not referenced in the Dosage and Administration section.]

   c. HOW SUPPLIED

      i. Revise "Unit-dose package of 100" to read "Unit-dose package of 100 (10 blister strips of 10 tablets)".
      ii. Insert the following text immediately preceding the temperature storage statement:

      "Protect unit-dose packaging from excessive moisture."

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

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

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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

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

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	

Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for CLARITIN® by Schering; NDA 20-641/SE5-007; approved December 4, 2000. The CLARITIN insert labeling is a combined one for CLARITIN Tablets, Syrup, and Rapidly Disintegrating Tablets (REDITABS). All references to the REDITABS and Syrup should be carved out of the generic firm's labeling. But certain references pertaining to the Syrup provide pertinent information relating to the pharmacokinetics, pediatric use, adverse reactions, and overdosage of loratadine. The "First Generic" for loratadine tablets included these Syrup references. Therefore, I will have the firm include these particular loratadine syrup references into their labeling.

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 19-658

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

Exclusivity Data– NDA 19-658

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

Ranbaxy Laboratories Limited
Paonta Sahib
District Sirmour
Himachal Pradesh – 173 025
INDIA [Vol. 1.14 pg. 5492.]

4. CONTAINER/CLOSURE

14s: 45 cc round white HDPE bottle, with 33 mm white (b) (4) child-resistant cap.
500s: 120 cc round white HDPE bottle, with 38 mm white (b) (4) child-resistant cap.
Unit Dose 100's (10 x 10): (b) (4)
[Vol. 1.14 pg. 5664, 5665, & 5667; Vol. 2.1 pg. 10 and 22]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears to be accurate according to the components/composition statement. [Vol. 1.14 pg. 5441.]

6. PACKAGING CONFIGURATIONS

RLD: Bottles of 100 and 500 tablets, Unit-of-Use packages of 30 tablets (10 tablets per blister card), and 10 x 10 tablet Unit Dose-Hospital Packs.
ANDA: Bottles of 14 and 500 tablets; and Unit-Dose packages of 100 (10 X 10).
[Vol. 1.1 pg. 027.]

7. STORAGE/DISPENSING STATEMENTS COMPARISON

NDA: Store between 2° and 30°C (36° and 86°F).
Dispense in tight container as defined in USP/NF. (Container label only)
Protect unit dose packaging from excessive moisture.
ANDA: Store tablets at room temperature 15° to 30°C (59°to 86°F) (See USP). Dispense in a tight container as defined in the USP/NF.
Protect unit dose packaging from excessive moisture.
[Vol. 1.1, pg. 027 & 028]

8. TABLET IMPRINT

The tablet imprintings have been accurately described in the HOW SUPPLIED section of the Insert according to the firm's Finished Product Specifications:

'white uncoated, round tablets; debossed with **RX526** on one side and plain on the other.'

[Vol. A1.14 pg. 5804.]

9. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on June 18, 2001, that the firm's single dose fasting, post-prandial, and dissolution studies were all acceptable.

Date of Review: 10/4/02 Date of Submission: 7/03/02

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 10/4/02

Team Leader: John Grace Date:

John J Grace 10/7/2002

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cc:

ANDA: 76-134
DUP/DIVISION FILE
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Review

APPROVAL SUMMARY

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

ANDA Number: 76-134

Dates of Submission: October 21, 2002 (Amendment-FPL) and October 30, 2002 (Amendment-FPL)

Applicant's Name: Ranbaxy Laboratories Limited

Established Name: Loratadine Tablets, 10 mg

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 –

a. Bottles of 14's and 500's:
Satisfactory as of the October 30, 2002 submission. [Vol. 2.1, "Attachment 1"]

b. Unit Dose Blister Card of 10 Tablets:
Satisfactory as of the October 21, 2002 submission. [Vol. 2.1, "Attachment 1"]

CARTON Labels – [For box of 100 (10 x 10) unit dose tablets]:
Satisfactory as of the October 21, 2002 submission. [Vol. 2.1, "Attachment 1"]

PROFESSIONAL PACKAGE INSERT:
Satisfactory as of the October 21, 2002 submission. [Vol. 2.1, "Attachment 1", Revised October 2002]

Revisions needed post-approval: None.

Patent Data – NDA 19-658

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

Exclusivity Data– NDA 19-658

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®

NDA Number: 19-658

NDA Drug Name: Loratadine Tablets 10 mg

NDA Firm: Schering Corporation

Date of Approval of NDA Insert and supplement: December 4, 2000; NDA 20-641/SE5-007 (combined insert)

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

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

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

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	

Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	

Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for CLARITIN® by Schering; NDA 20-641/SE5-007; approved December 4, 2000. The CLARITIN insert labeling is a combined one for CLARITIN Tablets, Syrup, and Rapidly Disintegrating Tablets (REDITABS). All references to the REDITABS and Syrup should be carved out of the generic firm's labeling. But certain references pertaining to the Syrup provide pertinent information relating to the pharmacokinetics, pediatric use, adverse reactions, and overdosage of loratadine. The "First Generic" for loratadine tablets included these Syrup references. Therefore, I will have the firm include these particular loratadine syrup references into their labeling.

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 19-658

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4282233	June 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4282233*PED	December 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4659716	April 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4659716*PED	October 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None

4863931	September 15, 2008	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
4863931*PED	March 15, 2009	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 19-658

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

Ranbaxy Laboratories Limited
Paonta Sahib
District Sirmour
Himachal Pradesh – 173 025
INDIA [Vol. 1.14 pg. 5492.]

4. CONTAINER/CLOSURE

14s: 45 cc round white HDPE bottle, with 33 mm white (b) (4) child-resistant cap.
500s: 120 cc round white HDPE bottle, with 38 mm white (b) (4) child-resistant cap.
Unit Dose 100's (10 x 10): (b) (4) .
[Vol. 1.14 pg. 5664, 5665, & 5667; Vol. 2.1 pg. 10 and 22]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears to be accurate according to the components/composition statement. [Vol. 1.14 pg. 5441.]

6. PACKAGING CONFIGURATIONS

RLD: Bottles of 100 and 500 tablets, Unit-of-Use packages of 30 tablets (10 tablets per blister card), and 10 x 10 tablet Unit Dose-Hospital Packs.
ANDA: Bottles of 14 and 500 tablets; and Unit-Dose packages of 100 (10 X 10).
[Vol. 1.1 pg. 027.]

7. STORAGE/DISPENSING STATEMENTS COMPARISON

NDA: Store between 2° and 30°C (36° and 86°F).
Dispense in tight container as defined in USP/NF. (Container label only)
Protect unit dose packaging from excessive moisture.
ANDA: Store tablets at room temperature 15° to 30°C (59°to 86°F) (See USP). Dispense in a tight container as defined in the USP/NF.
Protect unit dose packaging from excessive moisture.
[Also, the firm removed all "not child-resistant" language from their unit-dose packaging. In their 10.21.02 submission, they submitted an actual sample of their blister card to demonstrate that it was in fact, child-resistant.]
[Vol. 1.1, pg. 027 & 028]

8. TABLET IMPRINT

The tablet imprintings have been accurately described in the HOW SUPPLIED section of the Insert according to the firm's Finished Product Specifications:

'white uncoated, round tablets; debossed with **RX526** on one side and plain on the other.'

[Vol. A1.14 pg. 5804.]

9. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on June 18, 2001, that the firm's single dose fasting, post-prandial, and dissolution studies were all acceptable.

Date of Review: 11/8/02 Date of Submission: 10/21/02 and 10/30/02

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 11/8/02

Team Leader: John Grace Date:

John J Grace 11/12/2002

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cc:

ANDA: 76-134
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:\firmsnz\ranbaxy\ltrs&rev\76134APL.doc
Review

APPROVAL SUMMARY

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

ANDA Number: 76-134

Dates of Submission: March 12, 2003 and January 22, 2003 (Amendments)

Applicant's Name: Ranbaxy Laboratories Limited

Established Name: Loratadine Tablets, 10 mg (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 –

a. Unit Dose Blister Cards of 6 Tablets and 10 Tablets:
Satisfactory as of the January 22, 2003 submission. [Vol. 3.1, "Attachment 1", pages 13 & 14]

b. Bottles of 14's and 500's:
Satisfactory as of the March 12, 2003 submission. [Vol. 3.1, "Attachment 1", page 4]

CARTON Labels –

a. For unit dose blister cards of 6 tablets and 10 tablets:
Satisfactory as of the March 12, 2003 submission. [Vol. 3.1, "Attachment 1", pages 5 & 6]

b. For bottles of 14's and 500's:
Satisfactory as of the March 12, 2003 submission. [Vol. 3.1, "Attachment 1", pages 7 & 8]

Revisions needed post-approval: **Yes**. There were two labeling revisions that were editorial in nature, and therefore could be "post-approval" revisions. I communicated these post-approval revisions to Mary C. Goyette, of Ranbaxy by telephone on March 24, 2003.

Patent Data – NDA 19-658

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

4863931*PED	March 15, 2009	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 19-658

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®

NDA Number: 19-658

NDA Drug Name: Loratadine Tablets 10 mg

NDA Firm: Schering Corporation

Date of Approval of NDA Insert and supplement: Nov. 27, 2002; NDA 19-658/SE6-018 (Rx to OTC Switch)

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

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

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

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			

Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	

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

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for CLARITIN® Tablets by Schering; NDA 19-658/SE6-018 (Rx to OTC switch); approved November 27, 2002.

2. PATENTS/EXCLUSIVITIES

   Patent Data – NDA 19-658

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

4863931*PED	March 15, 2009	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 19-658

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

3. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

NDA - Store between 2° and 30°C (36° and 86°F). Protect from excessive moisture. (Moisture statement is only on the unit dose carton.)
ANDA - Store between 2° and 30°C (36° and 86°F). Protect from excessive moisture. (Moisture statement is on all labels.)

4. 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 statement of Components and Composition appearing on page 66. [Vol. 1.14 pg. 5441.]

5. CONTAINER/CLOSURE SYSTEM

14s: 45 cc round white HDPE bottle, with 33 mm white (b) (4) child-resistant cap.
500s: 120 cc round white HDPE bottle, with 38 mm white (b) (4) child-resistant cap.
Unit Dose Blister Card of 6's and 10's: (b) (4).
[Vol. 1.14 pg. 5664, 5665, & 5667; Vol. 2.1 pg. 10 and 22]

Date of Review: 3/21/03 Dates of Submission: 3/12/03 and 1/22/03

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 3/24/03

Team Leader: John Grace Date: 3/25/03

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cc:

ANDA: 76-134
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076134

CHEMISTRY REVIEWS

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO:** 1

2. **ANDA:** 76-134 (Loratadine Tablets, 10 mg)

3. **NAME AND ADDRESS OF APPLICANT:**
Ranbaxy Laboratories Limited
Sector 18, Udyog Vihar Industrial Area
Gurgaon - 122 001, India

Ranbaxy Pharmaceuticals Inc.
Attention: Shirley Ternyik, US Agent
600 College Road East
Princeton, NJ 08540

4. **LEGAL BASIS for ANDA SUBMISSION:**
The ANDA submission is based on the following reference listed drug: Claritin®(Loratadine Tablets, 10 mg): NDA 19-658 from Schering Corporation (approved 4/12/93).

According to the *Approved Drug Products with Therapeutic Equivalence, 20th Edition, (2000), Cumulative Supplement 9, Sept 2000,* there are three US Patents listed in connection with this product: US Patent # 4,282,233, # 4,659,716, and #4,863,931.

The firm has filed Paragraph IV Patent Certification for US Patent #4,863,931 and #4,659,716. The applicant certifies that in its opinion and to the best of its knowledge, no valid or enforceable claim of the above patents will be infringed by the manufacture, use, or sale of Loratadine Tablets for which this abbreviated new drug application is submitted.

The firm has filed Paragraph III Patent Certification for US Patent #4,282,233. The applicant certifies that in its opinion and to the best of its knowledge, that said patent will expire on June 19, 2002. The six months pediatric exclusivity will expire on December 19, 2002. The firm has requested approval of this ANDA effective December 19, 2002.

The firm states that there is no unexpired exclusivity for Loratadine Tablets.

5. **SUPPLEMENT(s):** N/A

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

7. **NONPROPRIETARY NAME:** Loratadine Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Ranbaxy:	
03/15/01	Submission of ANDA (received on 03/19/01)
04/10/01	Updated exclusivity statement
05/16/01	Notification of patent holder
FDA	
04/12/01	ANDA Acknowledgment letter
06/18/01	Bioequivalence review (acceptable)

10. **PHARMACOLOGICAL CATEGORY:** Long-acting Antihistamine

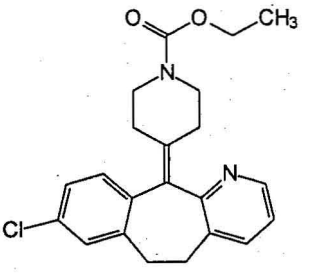
11. **HOW DISPENSED:** Rx

12. **RELATED IND/NDA/DMF(s):** See Item 37

13. **DOSAGE FORM:** Oral Tablets

14. **Strength:** 10 mg

15. **CHEMICAL NAMES AND STRUCTURE:**
Chemical name: 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-, ethyl ester
Formula: $C_{22}H_{23}ClN_2O_2$
Molecular weight: 382.89
CAS registry number(s): 79794-75-5
Chemical structure:



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

17. **COMMENTS:**
Both the bulk drug substance and the drug product do not have USP monographs.

DMF #15251 (Type II) for the bulk drug substance was reviewed in connection with this submission, and was found deficient.

There are other CMC deficiencies. The bioequivalence review was found acceptable on 6/18/01.

The Labeling review is pending.

Method validation request has been issued this review cycle.

EER is pending 3/19/01.

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Not approvable (MINOR)

19. **REVIEWER:** John D. Franolic, Ph.D.

DATE COMPLETED: 7/28/01, 8/09/01, 8/24/01

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO**: 2

2. **ANDA**: 76-134 (Loratadine Tablets, 10 mg)

3. **NAME AND ADDRESS OF APPLICANT**:
Ranbaxy Laboratories Limited
Sector 18, Udyog Vihar Industrial Area
Gurgaon - 122 001, India

Ranbaxy Pharmaceuticals Inc.
Attention: Shirley Ternyik, US Agent
600 College Road East
Princeton, NJ 08540

4. **LEGAL BASIS for ANDA SUBMISSION**:
The ANDA submission is based on the following reference listed drug: Claritin®(Loratadine Tablets, 10 mg): NDA 19-658 from Schering Corporation (approved 4/12/93).

According to the *Approved Drug Products with Therapeutic Equivalence, 20th Edition, (2000), Cumulative Supplement 9, Sept 2000,* there are three US Patents listed in connection with this product: US Patent # 4,282,233, # 4,659,716, and #4,863,931.

The firm has filed Paragraph IV Patent Certification for US Patent #4,863,931 and #4,659,716. The applicant certifies that in its opinion and to the best of its knowledge, no valid or enforceable claim of the above patents will be infringed by the manufacture, use, or sale of Loratadine Tablets for which this abbreviated new drug application is submitted.

The firm has filed Paragraph III Patent Certification for US Patent #4,282,233. The applicant certifies that in its opinion and to the best of its knowledge, that said patent will expire on June 19, 2002. The six months pediatric exclusivity will expire on December 19, 2002. The firm has requested approval of this ANDA effective December 19, 2002.

The firm states that there is no unexpired exclusivity for Loratadine Tablets.

5. **SUPPLEMENT(s)**: N/A

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

7. **NONPROPRIETARY NAME**: Loratadine Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES**:
Ranbaxy:

03/15/01	Submission of ANDA (received on 03/19/01)
04/10/01	Updated exclusivity statement
05/16/01	Notification of patent holder
08/30/01	Notice of Civil Action
09/26/01	Notice of filing of legal action (Schering counsel)
10/10/01	Minor Amendment

FDA

04/12/01	ANDA Acknowledgment letter
06/18/01	Bioequivalence review (acceptable)
09/06/01	Deficiency (MINOR) Letter

10. **PHARMACOLOGICAL CATEGORY:** Long-acting Antihistamine

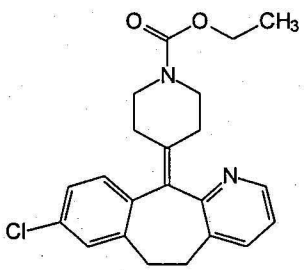
11. **HOW DISPENSED:** Rx

12. **RELATED IND/NDA/DMF(s):** See Item 37

13. **DOSAGE FORM:** Oral Tablets

14. **Strength:** 10 mg

15. **CHEMICAL NAMES AND STRUCTURE:**
Chemical name: 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-, ethyl ester
Formula: $C_{22}H_{23}ClN_2O_2$
Molecular weight: 382.89
CAS registry number(s): 79794-75-5
Chemical structure:



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

17. **COMMENTS:**
Both the bulk drug substance and the drug product do not have USP monographs.

DMF #15251 (Type II) for the bulk drug substance is adequate.

The bioequivalence review was found acceptable on 6/18/01. The Labeling review was found acceptable 11/19/01. EER is pending 10/12/01.

Method validation request was issued and samples were sent on 9/7/01.

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Approvable (Tentative Approval pending EER)

19. **REVIEWER:** John D. Franolic, Ph.D. **DATE COMPLETED:** 10/26/01

ANDA 76-134 TENTATIVE APPROVAL SUMMARY

(Pending: EES, and Methods Validation)

PRODUCT: Loratadine Tablets
FIRM: Ranbaxy Laboratories Limited
DOSAGE FORM: Tablet
STRENGTHS: 10 mg
cGMP STATEMENT/EIR UPDATE STATUS: Pending 10/12/01
BIO STUDY: APPROVE, Bio Review Dated 6/18/01
VALIDATION: Pending (Methods Validation Package sent out 8/13/01)

STABILITY: Three (3) months accelerated stability data, 40°C ± 2°C/75% ± 5% RH, and twelve (12) months, long-term room temperature data, 25°C ± 2°C/60% ± 5% RH, for both 14's (45cc HDPE bottle) and 500's (120cc HDPE bottle) container/closure system is submitted for ANDA batch #1074046. The container/closure system used for the stability study is equivalent to the system proposed for commercial use. All reported data are within specifications as listed. Thus, a 24 month expiration date is justified.

The firm submits 6 months (0, 3, and 6 months) of room temperature data for the simulated bulk shipment pack (500 tablets, (b) (4)). The data submitted supports the proposed 6 months holding period for tablets inside the bulk packaging (b) (4) tablets).

Tests and specifications for the drug product on stability include:
Description (Conforms); Assay (90.0 - 110.0% of Label Claim); Dissolution (NLT (b) (4) % (Q) dissolved in 60 minutes); Related Compounds (Any individual known related compound: NMT (b) (4) %, Any individual Unknown Related Compound: NMT (b) (4) %, Total Impurities: NMT (b) (4) %); (b) (4) w/w).

LABELING: Acceptable 11/15/01

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH: (b) (4) tablets (Batch #1074046)

SIZE OF STABILITY BATCHES: The stability batch is the same as the bio-batch.

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

CHEMIST: John D. Franolic, Ph.D. John D. Franolic 11/20/01 DATE: 10/26/01

SUPERVISOR: D. Gill, Ph.D. DSGill 11-20-01 DATE: 10/30/01

CHEMISTRY REVIEW

ANDA 76-134

Loratadine Tablets, 10 mg

Ranbaxy Laboratories Limited

Guoping Sun, Ph.D.

Office of Generic Drugs, Division of Chemistry I

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Chemistry Assessment 9

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data ..... N/A

S DRUG SUBSTANCE [Name, Manufacturer] ..... N/A

P DRUG PRODUCT [Name, Dosage form] ..... N/A

A APPENDICES ..... N/A

R REGIONAL INFORMATION ..... N/A

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 ..... N/A

A. Labeling & Package Insert ..... N/A

B. Environmental Assessment Or Claim Of Categorical Exclusion ..... N/A

III. List Of Deficiencies To Be Communicated ..... N/A

Chemistry Review Data Sheet

1. ANDA 76-134

2. REVIEW #3

3. REVIEW DATE: March 27, 2003

4. REVIEWER: Guoping Sun, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Firm:	
Submission of ANDA (received on 03/19/01)	15-Mar-2001
Updated exclusivity statement	10-Apr-2001
Notification of patent holder	16-May-2001
Notice of Civil Action	30-Aug-2001
Notice of filing of legal action	26-Sept-2001
Minor Amendment	10-Oct-2001
Labeling Amendment	07-Nov-2001
Labeling Amendment	22-JAN-2003
FDA:	
Acceptable for filing	12-Apr-2001
Bioequivalence Acceptable	18-Jun-2001
NA (MINOR) Letter	06-Sep-2001
Labeling Tentative Approval	15-Nov-2001
Tentative Approval Letter	20-Dec-2001
Telephone Deficiency	08-Aug-2002
Telephone Contact	07-JAN-3003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (Gratuitous)	03-JUL-2002
Telephone Amendment	13-AUG-2002
New Correspondence	13-DEC-2002
Amendment	30-JAN-2003
Amendment	26-FEB-2003

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Ranbaxy Laboratories Limited
Address:	Sector 18, Udyog Vihar Industrial Area Gurgaon – 122 001, India
Representative:	Abha Pant (US Agent)
Telephone:	(609) 720-5666

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Loratadine Tablets

9. LEGAL BASIS FOR SUBMISSION:

   The ANDA submission is based on the following reference listed drug: Claritin® (Loratadine Tablets, 10 mg): NDA 19-658 from Schering Corporation (approved 4/12/93).

   According to the *Approved Drug Products with Therapeutic Equivalence, 20th Edition, (2000), Cumulative Supplement 9, Sept 2000,* there are three US Patents listed in connection with this product: US Patent # 4,282,233, # 4,659,716, and #4,863,931.

   The firm has filed Paragraph IV Patent Certification for US Patent #4,863,931 and #4,659,716. The applicant certifies that in its opinion and to the best of its knowledge, no valid or enforceable claim of the above patents will be infringed by the manufacture, use, or sale of Loratadine Tablets for which this abbreviated new drug application is submitted.

   The firm has filed Paragraph III Patent Certification for US Patent #4,282,233. The applicant certifies that in its opinion and to the best of its knowledge, that said patent expire on June 19, 2002. The six months pediatric exclusivity will expire on December 19, 2002. The firm has requested approval of this ANDA effective December 19, 2002. The firm states that there is no unexpired exclusivity for Loratadine Tablets.

10. PHARMACOL. CATEGORY: Long-acting Antihistamine

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _____Rx __X___. OTC

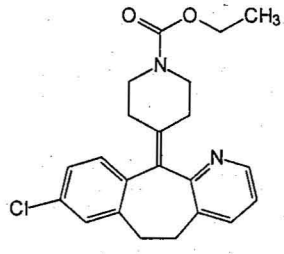
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Chemical Name: 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-, ethyl ester
Molecular Formula: $C_{22}H_{23}ClN_2O_2$
Molecular Weight: 382.89
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
15251	II	Ranbaxy Labs Toansa	Loratadine	1	Adequate	22-FEB-2003	Reviewed by U. Atwal
[redacted] (b) (4)				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	16-Jul-02	
Methods Validation	Acceptable	30-Jan-02	
Labeling	Acceptable	25-MAR-03	
Bioequivalence	Acceptable	18-Jun-01	
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. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-134

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)

Drug Product: Loratadine Tablets, 10 mg, is a non-sterile product and a non-USP drug. The active agent in this immediate release dosage form is Loratadine, a long-acting antihistaminic agent. The approved, reference listed drug is Claritin® (Loratadine Tablets, 10 mg) the subject of NDA 19-658 from Schering Corporation (approved 4/12/93). The proposed commercial packaging configurations for Loratadine Tablets 10 mg are high-density polyethylene (HDPE) round bottles (14's - 45 cc; 500's - 120 cc) with child resistant closures (CRC)(33 mm and 38 mm), with (b) (4). In addition, the product will be packaged in unit dose blisters of 10. The container closure systems are hermetically sealed for tamper evident packaging.

Drug Substance: Loratadine is an off-white to white crystalline that is soluble in methanol. The chemical name/formula/MW are as follow: 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-, ethyl ester, $C_{22}H_{23}ClN_2O_2$, 382.89. Loratadine is a non-USP drug. The firm uses its own in-house specifications to monitor the quality of the drug substance. The key physicochemical properties monitored that influence batch-to-batch reproducibility are loss on drying, melting range, and particle size.

Formulation and Manufacturing Process: The product formulation, in addition to Loratadine, contains Lactose Monohydrate NF, Starch NF, Pregelatinized Starch NF, and Magnesium Stearate NF. These inactive ingredients are widely used in the pharmaceutical industry and are not expected to effect the safety and effectiveness of the drug product. The product is manufactured by (b) (4). No inks or dyes are used to imprint the tablets. The size of the production batches will be the same as that of the biobatch, (b) (4) Tablets.

Method Validation: The firm's analytical methods validation were found acceptable by FDA's Northeast Regional Laboratory on 1/30/2002.

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

See Labeling.

C. Basis for Approvability or Not-Approval Recommendation

The firm's application was tentatively approved on 12/20/01. However a gratuitous amendment was issued on 7/3/02 providing for an additional packaging configuration for blisters and the addition of an outside firm to package the blisters. The review of this amendment resulted in additional deficiencies which were satisfactorily addressed by the firm by the 8/13/02 telephone amendment. Also the firm submitted tamper evident statement for OTC on 1/30/03 and an amendment on 2/26/03 to request for an increase of the (b) (4) specification for the Blister Packs from a limit of NMT (b) (4)% to a limit of NMT (b) (4)%. After reviewing the amendments, it is concluded that firm's justifications for an a increase of the (b) (4) specification for the Blister Packs are not satisfactory. This ANDA is Not Approvable due to a Minor deficiency.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

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

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

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

F/T by

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TYPE OF LETTER: NOT APPROVABLE

C. CC Block

ANDA 76-134
ANDA DUP
DIV FILE
Field Copy

12 pages have been withheld as b4 (CCI/TS) immediately following this page

#4

CHEMISTRY REVIEW

ANDA 76-134

Loratadine Tablets, 10 mg

Ranbaxy Laboratories Limited

Guoping Sun, Ph.D.

Office of Generic Drugs, Division of Chemistry I

Table of Contents

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I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A 8

II. Summary of Chemistry Assessments 8

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 9

III. Administrative 9

A. Reviewer's Signature 9

B. Endorsement Block 9

Chemistry Assessment 10

B) Supporting Information and testing for the Container/Closure systems : Satisfactory in CR#3 15

Chemistry Review Data Sheet

1. ANDA 76-134

2. REVIEW #4

3. REVIEW DATE: July 18, 2003

4. REVIEWER: Guoping Sun, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Firm:	
Submission of ANDA (received on 03/19/01)	15-Mar-2001
Updated exclusivity statement	10-Apr-2001
Notification of patent holder	16-May-2001
Notice of Civil Action	30-Aug-2001
Notice of filing of legal action	26-Sept-2001
Minor Amendment	10-Oct-2001
Labeling Amendment	07-Nov-2001
Amendment (Gratuitous)	03-JUL-2002
Telephone Amendment	13-AUG-2002
New Correspondence	13-DEC-2002
Labeling Amendment	22-JAN-2003
Amendment	30-JAN-2003
Amendment	26-FEB-2003
Labeling Amendment	12-MAR-2003
Patent and Court Case Information	27-MAR-2003
FDA:	
Acceptable for filing	12-Apr-2001
Bioequivalence Acceptable	18-Jun-2001
NA (MINOR) Letter	06-Sep-2001
Labeling Tentative Approval	15-Nov-2001
Tentative Approval Letter	20-Dec-2001
Telephone Deficiency	08-Aug-2002
Telephone Contact	07-JAN-3003
NA (Minor) Letter	03-APR-2003

6. SUBMISSION(S) BEING REVIEWED:

Chemistry Review Data Sheet

Submission(s) Reviewed	Document Date
Amendment (Response to CMC deficiency letter)	07-APR-2003
Additional Information (24 months stability data)	24-JUN-2003
Patent Amendment	22-JUL-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Ranbaxy Laboratories Limited
Address:	Sector 18, Udyog Vihar Industrial Area Gurgaon – 122 001, India
Representative:	Abha Pant (US Agent)
Telephone:	(609) 720-5666

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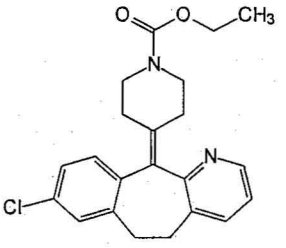

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DOCUMENT	APPLICATION NUMBER	DESCRIPTION

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Chemistry Review Data Sheet

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EA	N/A		
Radiopharmaceutical	N/A		

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The Chemistry Review for ANDA 76-134

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Chemistry manufacturing and controls are ***approvable***.

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

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Formulation and Manufacturing Process: The product formulation, in addition to Loratadine, contains Lactose Monohydrate NF, Starch NF, Pregelatinized Starch NF, and Magnesium Stearate NF. These inactive ingredients are widely used in the pharmaceutical industry and are not expected to effect the safety and effectiveness of the drug product. The product is manufactured by (b) (4) No inks or dyes are used to imprint the tablets. The size of the production batches will be the same as that of the biobatch, (b) (4) Tablets.

Method Validation: The firm's analytical methods validation were found acceptable by FDA's Northeast Regional Laboratory on 1/30/2002.

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

See Labeling.

C. Basis for Approvability or Not-Approval Recommendation

The firm's application was tentatively approved on 12/20/01. After that, some minor deficiency issues regarding CMC were communicated between the firm and the Agency. The last CMC deficiency letter was issued on April 3, 2003 regarding the firm's request for an increase of the (b) (4) specification for the Blister Packs from a limit of NMT (b) (4)% to a limit of NMT (b) (4)%. Firm has responded on April 7, 2003 and June 24, 2003 by providing test data and 24-months stability data to justify the increase. Firm's response was considered satisfactory, and therefore, this ANDA is *Approvable*.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-623/Guoping Sun, Ph.D./ 7/18/03

HFD-623 /Dave Gill, Ph.D./

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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076134

BIOEQUIVALENCE REVIEWS

Loratadine Tablets
10 mg
ANDA #76-134
Reviewer: Mamata Gokhale
v:\firmsnz\ranbaxy\ltrs&rev\76134SD.301

Ranbaxy Laboratories Ltd.
Gurgaon 122 001 India
U.S. Agent: Ranbaxy
Princeton NJ 08540
Submission Date: 3/19/01
15

Review of Bioequivalence Studies and Dissolution Data

I. Introduction

Indication: Long-acting tricyclic antihistamine with selective H_1-receptor antagonistic activity for seasonal allergic rhinitis and idiopathic urticaria.
Type of Submission: ANDA for 10 mg strength of Loratadine Tablets.
Contents of Submission: Single dose fasting and post-prandial bioequivalence studies and dissolution data.
RLD: Claritin® Tablets, 10 mg, manufactured by Schering Corporation.
Recommended dose: For adults and children, 12 years or older, 10 mg once daily and for patients with hepatic or renal impairment, 10 mg every other day.

II. Background

Following oral administration, loratadine undergoes rapid absorption and extensive first pass metabolism catalyzed by P450 3A4. Tmax is reached within 1.3 hours for loratadine and 2.5 hours for its major active metabolite descarboethoxyloratadine. Exposure (AUC) to the metabolite is greater than to the parent loratadine. About 80% of the administered dose is eliminated equally in urine and feces. Mean elimination half life is 8.4 hours for loratadine and 28 hours for descarboethoxyloratadine. Food increases systemic bioavailability of loratadine and descarboethoxyloratadine by 40 and 15% respectively. Food intake does not affect Cmax but delays Tmax by 1 hour for loratadine and descarboethoxyloratadine. Considerable variability in the pharmacokinetic data of Claritin® tablets has been documented.

III. Single-dose Replicate Fasting Bioequivalence Study

A. Study Information

Study Number 001185
Medical Director Samuel Serfati, M.D.
Analytical Director (b) (4)
Clinical Site MDS Pharma Services Inc., Montreal Canada
Study Dates Period I: 10/7-10/9/00 Period II: 10/28-10/30/00
Period III: 11/18-20/00 Period IV: 12/9-11/00
Analytical Site (b) (4)

Analysis Dates 12/18/00-1/26/01
Sample Storage Period Up to 111 days

Treatment ID	A (A1 designated the formulation given the first time, A2 designated the formulation given the second time).	B (B1 designated the formulation given the first time, B2 designated the formulation given the second time)
Test or Reference	Test	Reference
Product Name	Loratadine	Claritin®
Manufacturer	Ranbaxy Laboratories Ltd.	Schering Corporation
Lot No.	1074046	9RXF375
Manufacture Date	5/00	N/A
Expiration Date	4/02 (proposed)	6/01
Strength	10 mg	10 mg
Dosage Form	Tablets	Tablets
ANDA Batch Size	(b) (4)	N/A
Production Batch Size	(b) (4)	N/A
Potency	(b) (4)%	(b) (4)%
Content Uniformity (mean, %cv, range, n)	101.0, 1.4, 98.6-103.5, 10	96.7, 1.32, 94.4-98.5, 10
Formulation	See Table #1	N/A
Dose Administered	10 mg	10 mg
Route of Administration	Oral	Oral
Length of Fasting	10 hours prior to dosing 4 hours post-dosing	10 hours prior to dosing 4 hours post-dosing

No. of Sequences	2	**Crossover**	Y
No. of Periods	4	**Replicate Design**	Y
No. of Treatments	4	**Balanced**	Y
No. of Groups (if appropriate)	N/A	**Washout Period**	21 days

Randomization Scheme
ABBA (A1B1B2A2): 1, 2, 5, 8, 11, 12, 13, 14, 15, 18, 19, 23, 24, 25, 26, 27, 32, 34, 36, 39, 41, 42, 45, 46, 48, 50, 52, 53, 58, 60
BAAB (B1A1A2B2): 3, 4, 6, 7, 9, 10, 16, 17, 20, 21, 22, 28, 29, 30, 31, 33, 35, 37, 38, 40, 43, 44, 47, 49, 51, 54, 55, 56, 57, 59

Blood Sampling Times 0 (pre-loratadine dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120 and 144 hours

Blood Volume Collected/Sample 7 mL

Blood Sample Processing/Storage EDTA plasma samples were protected from UV exposure and stored at -22^0C

IRB Approval Y
Informed Consent Y

No. Enrolled	60 (56 + 4 alternates)
No. Dosed	60
No. Completing	55
No. With Plasma Spls Analyzed	As indicated in the protocol samples from first 56 subjects were analyzed provided the subjects completed at least two periods. Additionally, for every subject who did not complete the full four periods, an alternate subject ideally matched on sequence was added.
Length of Confinement	From 10 hours pre-dosing to 36 hours post-dosing.
Restrictions	Along with the standard dietary, activity and drug restrictions, the exclusion criteria included hypersensitivity to loratadine or related drugs.
Safety Monitoring	Vital signs (blood pressure and pulse rate) were assessed and laboratory tests were conducted prior to dosing. Subjects were monitored by the medical personnel during confinement and were asked how they were feeling at the 36 hour and subsequent blood collections.
Sex(es) Included	All males (59 Caucasians, 1 Black).
Healthy Subjects Only	Y

B. Study Results

1. Clinical

Dropout Information

No. of Dropouts	5
Subjects No	20, 30, 39, 46 and 59.
Reason	All subjects discontinued due to personal reasons.
Period	Subject #39 after period I, subject #30 after period II and subjects #20, 46 and 59 after period III.
Adverse Events	Three possibly drug-related mild events occurred during treatment A. For additional information see pages 2018 and 2020, volume 1.6.
Protocol Deviations	Minor deviations with respect to blood sampling times, food and concomitant medication restrictions; unlikely to compromise the integrity of the study. Actual sampling times were used for all calculations.

Comments: None

2. Analytical Method Validation
NOT TO BE RELEASED UNDER FOI

Description

Analyte	Loratadine
Assay Method	HPLC with mass spectrometric detection
Matrix	Heparinized Plasma
Internal Standard	(b) (4)

Assay Validation – Pre-Study				
Analyte	Loratadine			
Calibration Standards				
Range (pg/mL)	19.9-9953.0			
Linearity (r^2)	0.9973			
Sensitivity (LOQ, pg/mL)	19.9			
Specificity	No interfering peaks			
Regression	Linear regression (1/concentration linear)			
Precision and accuracy				
QC Conc. (pg/mL)	19.9	60.1	1001.7	7512.6
Intra-day precision (%CV)	9.7	8.2	4.6	5.0
Intra-day accuracy (% of nominal)	105.5	86.8	89.1	87.5
Inter-day precision (%CV)	13.2	7.3	5.6	6.0
Inter-day accuracy (% of nominal)	100.9	84.2	89.5	90.0
Recovery				
% recovery of nominal	-	61.97	52.41	54.93
Stability				
QC Conc. (pg/mL)	60.0		7502.2	
Stability of plasma samples at room temperature for 8.8 hours (% of initial)	94.6		100.0	
QC Conc. (pg/mL)	62.5		7809.5	
5 freeze-thaw cycles (% of initial)	98.7		104.3	
QC Conc. (pg/mL)	60.1		7512.6	
Long-term stability at -22°C for 158 days (% of initial)	90.5		100.9	

Assay Validation – Within Study			
Analyte	Loratadine		
QC conc. (pg/mL)	60.0	1000.0	7500.0
Inter-day precision (%CV)	9.1	5.9	6.0
Inter-day accuracy (% of nominal)	94.8	94.8	97.8
Range (pg/mL)	20.0-10000.0		
Linearity (r^2)	0.9995		
Sensitivity (LOQ, pg/mL)	20.0		

Analytical Repeats: About 5.1% of all samples (286/5763) were repeated either due to loss during processing (2.25%), anomalous values, i.e. pharmacokinetic inconsistencies (1.8%), being above the curve limit (0.9%) or not reportable (0.2%). The pharmacokinetic repeats were analyzed in duplicate. Of the pharmacokinetic anomalies,

8/103 repeat analyses failed to corroborate with the original concentration, i.e. the difference between the original and repeat concentrations exceeded 30%. Therefore, these were designated "Not Reportable" as per SOPs AL-G-1520-10 and AL-G-1543-05.AO1.

Comments: Analytical method is acceptable.

3. Pharmacokinetic/Statistical Analysis

Loratadine

Mean Plasma Concentrations	Table #2, Figure #1	
Mean Pharmacokinetic Parameters	Table #4	
90% Confidence Intervals	lnAUCt: 97.1-111.0 lnAUCi: 96.6-108.1 lnCmax: 101.9-119.0 Details in Table #5	
AUCt/AUCi ratio	Test	Reference
Mean, %CV, range	0.93, 4.77, 0.69-0.98	0.93, 4.85, 0.74-0.99

Intra-subject variability, ln-transformed PK data		
Drug (parent)	Loratadine	
PK parameter	lnCmax	lnAUCt
Test	0.3878	0.2794
Reference	0.2895	0.2144

Comments: (on pharmacokinetic and statistical analyses)

1) For loratadine, the firm could not determine the Kel and AUCi values for subjects #13, during treatment B (B2, reference), period II. The reviewer agrees with the firm.

2) In the pharmacokinetic analysis of loratadine, subjects with

a) measurable drug concentrations at 0 hour: None
b) first scheduled post-dose sampling time as Tmax: None
c) first measurable concentration as Cmax: None

3) The firm considered the following data to be pharmacokinetic anomalies:

Subject	Period	Treatment	Sampling time	Plasma Concentration (pg/mL)
2	4	A2	24	424.2
2	4	A2	120	31.3
3	4	B2	144	27.2
45	4	A2	120	22.9

The plasma concentration value of subject #2 at 24 hours was 11.7 times the average of the two flanking concentration values. All other values reported above occurred at the end of the concentration time profiles and were preceded by at least three sampling time points which were measured to be below the limit of quantitation (BLQ). Therefore the firm set all the above data points to missing for pharmacokinetic and statistical analyses. The reviewer does not agree with these data adjustments.

4) The reviewer computed pharmacokinetic parameters by including the plasma concentrations listed above and calculated the 90% confidence intervals for loratadine using SAS® PROC MIXED. Following these calculations, the 90% confidence intervals for log transformed AUCt, AUCi and Cmax of loratadine remained within the acceptable limits of 80-125%.

5) ANOVA for loratadine showed no statistically significant period or sequence effect for parameters lnAUCt, lnAUCi and lnCmax.

6) The pharmacokinetic data on descarboethoxyloratadine submitted by the firm are acceptable. The 90% confidence intervals calculated by the firm for log transformed AUCt, AUCi and Cmax of descarboethoxyloratadine are within the acceptable limits of 80-125%. See Table 6 for details.

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

IV. Single-dose Post-Prandial Bioequivalence Study

A. Study Information

Study Number 001186
Medical Director Samuel Serfati, M.D.
Analytical Director (b) (4)
Clinical Site MDS Pharma Services Inc., Montreal Canada
Study Dates Period I: September 26-28, 2000
Period II: October 17-19, 2000
Period III: November 7-9, 2000
Analytical Site (b) (4)
Analysis Dates November 16-December 7, 2000
Sample Storage Period Up to 72 days

Treatment ID	A	B	C
Test or Reference	Test	Test	Reference
Product Name	Loratadine	Loratadine	Claritin®
Manufacturer	Ranbaxy Laboratories Ltd.	Ranbaxy Laboratories Ltd.	Schering Corporation
Lot No.	1074046	1074046	9RXF375
Dose Administered	10 mg	10 mg	10 mg

Route of Administration	Oral	Oral	Oral
Length of Fasting	10.5 hours pre-dosing 4 hours post-dosing	10 hours pre-dosing 4 hours post-dosing	10 hours pre-dosing 4 hours post-dosing
Food/Drug Interval	N/A	30 minutes	30 minutes
Standardized Breakfast	N	Y	Y
Breakfast Description	N/A	Standard high-fat	Standard high-fat

No. of Sequences	3	**Crossover**	Y
No. of Periods	3	**Replicate Design**	N
No. of Treatments	3	**Balanced**	Y
No. of Groups (if appropriate)	2	**Washout Period**	21 days

Randomization Scheme **ABC:**2, 11, 22, 23, **CBA:** 8, 14, 15, 21, **CAB:** 4, 5, 6, 12, **ACB:** 1, 3, 13, 17, **BCA:** 7, 9, 10, 16, **BAC:** 18, 19, 20, 24.

Blood Sampling Times 0 (pre-loratadine dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120 and 144 hours.

Blood Volume Collected/Sample 7 mL

Blood Sample Processing/Storage EDTA plasma samples were protected from UV exposure and stored at -22^0C.

IRB Approval	Y
Informed Consent	Y
No. Enrolled	24
No. Dosed	24
No. Completing	21
No. With Plasma Spls Analyzed	21
No. of Dropouts	3
Restrictions	Standard dietary, activity and drug restrictions.
Safety Monitoring	Vital signs (blood pressure and pulse rate) were assessed prior to dosing and at 1, 2, 4 and 8 hours post-dose. At the study exit, physical examination, laboratory tests and twelve-lead ECG were performed.
Sex(es) Included	All Caucasian males.
Healthy Subjects Only	Y

B. Study Results

1. Clinical

Dropout Information

Subject No	10, 11, 24
Reason	Personal reasons
Period	Subjects #10 and 24 after period I and subject #11 during period II.
Replacement	None

Adverse Events Two possibly and one remotely drug related mild events occurred during treatment C. For additional information see pages 298 and 300, volume 1.2.

Protocol Deviations Minor deviations with respect to blood sampling times; unlikely to compromise the integrity of the study. Actual sampling times were used for all calculations.

Comments: None

2. Analytical

Plasma samples were analyzed for loratadine by the same method as described above for the 10 mg fasting study protocol #001185.

Assay Validation – Within Study			
Analyte	Loratadine		
QC conc. (pg/mL)	60.0	1000.0	7500.0
Inter-day precision (%CV)	9.4	4.8	5.5
Inter-day accuracy (% of nominal)	95.2	95.3	97.9
Range (pg/mL)	20.0-10000.0		
Linearity (r^2)	0.9996		
Sensitivity (LOQ, pg/mL)	20.0		

Analytical Repeats: About 8.1% of all samples (132/1628) were repeated either due to loss during processing (3.1%), anomalous values, i.e. pharmacokinetic inconsistencies (2.9%), being above the curve limit (0.4%), missing H/L standards (1.4%) or not reportable (0.3%). The pharmacokinetic repeats were analyzed in duplicate. Of the pharmacokinetic repeats, 7/47 failed to corroborate with the original concentration, i.e. the difference between the original and repeat concentrations exceeded 30%. These were categorized as "Not Reportable" as per SOPs AL-G-1520-10 and AL-G-1543-05.AO1.

Comments: Analytical method is acceptable.

3. Pharmacokinetic/Statistical Analysis

Loratadine

Mean Plasma Concentrations	Table #3, Figure #2
Mean Pharmacokinetic Parameters	Table #7
Geometric Mean Ratio	lnAUCt 1.06
	lnAUCi 1.08
	lnCmax 1.05
	Details in Table #8

AUCt/AUCi ratio	Test (Fasted)	Test (Fed)	Reference (Fed)
Mean	0.93	0.94	0.94
%CV	3.64	4.48	3.67
Range	0.85-0.98	0.84-0.98	0.85-0.98

Total SD and within-subject error (root MSE): Values are shown below (for ln-transformed AUCt and Cmax only)

Total standard deviation and root mean square error, ln-transformed PK data		
Drug (parent)	Loratadine	
PK parameter	lnCmax	lnAUCt
Root MSE, test & ref combined	0.32388	0.24796

Comments: (on pharmacokinetic analysis)

1) For loratadine, the firm was not able to determine Kel and AUCi values for subject #1 during treatment B, period III and during treatment C, period II. The reviewer agrees with the firm.

2) In the pharmacokinetic analysis of loratadine, subjects with

a) measurable drug concentrations at 0 hour: None
b) first scheduled post-dose sampling time as Tmax: None
c) first measurable concentration as Cmax: None

3) The pharmacokinetic parameters for loratadine calculated by the reviewer are in good agreement with those determined by the firm.

4) ANOVA for loratadine showed no statistically significant period or sequence effect for parameters lnAUCt, lnAUCi and lnCmax.

5) The ratios of ln-transformed geometric means (Test fed/Reference fed) of AUCt, AUCi and Cmax (calculated by the reviewer and the firm) are within the acceptable limits of 0.8-1.25.

6) The pharmacokinetic data on descarboethoxyloratadine submitted by the firm are acceptable. The ratios of ln-transformed geometric means of AUCt, AUCi and Cmax of descarboethoxyloratadine calculated by the firm are within the acceptable limits of 0.8-1.25.

Conclusion: The single-dose post-prandial bioequivalence study is acceptable.

The CDER Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations posted on October 27, 2000 recommends the following:

- For BE studies, measurement of only the parent drug released from the dosage form, rather than the metabolite, is generally recommended.
- If the metabolite contributes meaningfully to safety and /or efficacy, the metabolite and the parent drug should be measured.

As recommended in the guidance, acceptability of bioequivalence studies for Loratadine Tablets is based on the parent compound, loratadine. Since descarboethoxyloratadine is the major active metabolite of loratadine, the summary statistics of its pharmacokinetic parameters submitted by the firm are included in the review (Tables 6 and 9).

V. Formulation(s)

Formulation information is provided in Table #1.

Comments: The formulation for the 10 mg strength of Ranbaxy's Loratadine tablets is acceptable.

V. Dissolution

A. Dissolution Method

There is no USP method for the dissolution testing of Loratadine Tablets. The firm has conducted dissolution testing of Loratadine Tablets, 10 mg according to the FDA-recommended method (cited from the biopharmaceutics review of NDA 19658 for Claritin® 10 mg tablets, dated 8/3/1989).

Analyte: Loratadine
Unit: 12 tablets
Dissolution Medium: 0.1N HCl
Temperature: 37^0C
Volume: 900 mL
Apparatus: Paddle (II)
Rpm: 50
Sampling Times: 5, 10, 15, 20, 30 and 45 minutes
Assay Method: e.g. UV at 265 nm
Proposed Dissolution Specifications: NLT (Q) (b)(4)% in 45 minutes.
FDA Dissolution Specification: NLT (Q) (b)(4)% in 60 minutes.

B. Results: The dissolution data are presented in Table #10.

C. Comments:

1) The lot numbers of the test and reference products used in the dissolution testing are the same as those used in the bio-study.

2) Table #16 indicates that dissolution profiles of the test and reference products are different at 5, 10, 15, 20 and 30 minutes but similar at 45 minutes.

3) Due to the rapid dissolution of Loratadine Tablets (Table #10) f2 comparison with the RLD is not relevant for this drug product.

4) The dissolution testing of Loratadine Tablets, 10 mg was conducted as specified in the FDA-recommended method.

5) The test product, Loratadine Tablets, 10 mg, Lot #R1GO718 meets the FDA dissolution specification of NLT (Q) (b)(4)% in 60 minutes.

Recommendations

1) The single-dose fasting bioequivalence study, protocol #001185, and the single dose fed bioequivalence study #001186 conducted by Ranbaxy Laboratories Ltd. on its Loratadine Tablets, 10 mg, Lot #1074046, comparing them to Claritin ® Tablets, 10 mg, Lot #9RXF375, manufactured by Schering Corporation have been found acceptable by the Division of Bioequivalence. These studies demonstrate that Loratadine Tablets, 10 mg, manufactured by Ranbaxy Laboratories Ltd. are bioequivalent to Claritin® Tablets, 10 mg, manufactured by Schering Corporation.

2) The in vitro dissolution testing conducted by Ranbaxy Laboratories Ltd. on its Loratadine Tablets, 10 mg, Lot #1074046 is acceptable.

3) The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. Dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 24 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

NLT (Q) (b)(4)% in 60 minutes.

The firm should be informed of the above recommendations.

Mamata S. Gokhale, Ph.D. Mamata Gokhale 5/31/01
Division of Bioequivalence

BMD 5/29/01

RD INITIALED BDAVIT
FT INITIALED BDAVIT Barbara M. Davit Date 5/31/01

Concur: N. Saluja Date 6/18/2001
for Dale P. Conner, Pharm.D. Director
Division of Bioequivalence

cc: ANDA# 76-134 (original, duplicate), Davit, HFD-658, Gokhale, HFD-658, Drug File, Division File

Table #1
Formulation of Loratadine Tablets, 10 mg by Ranbaxy Laboratories Ltd.

[1]Ingredient	mg/tablet	%
[2]Loratadine	10.00	10.00
[3]Lactose Monohydrate, NF		(b) (4)
Starch, NF (Corn) ((b) (4)		
Pregelatinized Starch, NF (b) (4)		
Pregelatinized Starch, NF (b) (4)		
Magnesium Stearate, NF		
(b) (4)		
Total weight	100.00	100.00

[1]All inactive ingredients are within approved safety limits (FDA Inactive Ingredient Guide, January, 1996).
[2]Active Ingredient, quantity is based on 100% assay on (b) (4).
(b) (4)

Table #2
Mean Plasma Concentrations of Loratadine
Following an Oral Dose of 10 mg (Fasting Study)
Treatment A (Test): Loratadine Tablets, 10 mg, Lot #1074046
Treatment B (Reference): Claritin® Tablets, 10 mg, Lot #9RXF375

Time (hours)	Mean (± SD) Plasma Concentrations (pg/mL)				
	Treatment A		Treatment B		Ratio B/A
0.00	0.00	0.00	0.00	0.00	0.00
0.25	18.82	50.58	12.55	60.51	1.50
0.50	430.38	694.33	354.14	723.88	1.22
0.75	1847.84	3211.45	1532.62	2835.64	1.21
1.00	2775.96	4023.68	2332.29	3602.46	1.19
1.50	2792.87	4018.28	2747.66	3973.34	1.02
2.00	2192.16	3116.37	2425.81	3538.90	0.90
2.50	1673.59	2356.51	1844.30	2560.93	0.91
3.00	1274.72	1933.56	1345.19	1863.28	0.95
3.50	1010.00	1557.02	1037.29	1468.62	0.97
4.00	810.93	1283.78	842.36	1228.81	0.96
4.50	622.75	1008.63	639.58	969.15	0.97
5.00	497.94	819.78	504.31	780.02	0.99
6.00	339.73	566.82	335.00	523.80	1.01
8.00	195.41	333.57	197.05	309.22	0.99
10.00	136.12	247.31	137.84	230.19	0.99
12.00	99.81	177.54	104.48	180.20	0.96
16.00	67.27	125.08	67.45	112.66	1.00
24.00	37.56	75.88	41.37	87.48	0.91
36.00	25.84	55.66	27.28	57.27	0.95
48.00	12.74	34.19	13.07	31.01	0.97
72.00	6.47	18.29	6.80	20.06	0.95
96.00	3.86	12.08	3.86	12.57	1.00
120.00	1.61	6.89	2.66	8.94	0.61
144.00	0.66	4.10	1.15	5.48	0.57

Table #3
Mean Plasma Concentrations of Loratadine
Following an Oral Dose of 10 mg (Fed Study)
Treatment A: Loratadine Tablets, 10 mg, Lot #1074046 (Fasted)
Treatment B: Loratadine Tablets, 10 mg, Lot #1074046 (Fed)
Treatment C: Claritin® Tablets, 10 mg, Lot #9RXF375 (Fed)

Time (hours)	Plasma Conc. (pg/ml), Mean, S.D.							
	Treatment A		Treatment B		Treatment C		Ratio B/C	Ratio B/A
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.25	30.43	74.72	13.21	22.93	3.95	13.79	3.34	0.43
0.50	491.07	833.26	340.85	487.09	171.51	225.94	1.99	0.69
0.75	1379.30	1607.74	1237.44	1696.99	732.05	1002.25	1.69	0.90
1.00	1882.42	1670.58	2098.30	2825.82	1588.14	2080.69	1.32	1.11
1.50	1873.17	2165.58	2704.14	2339.56	2254.91	2231.55	1.20	1.44
2.00	1472.70	1892.77	2701.26	2146.83	2511.09	2640.15	1.08	1.83
2.50	1095.69	1437.94	2456.42	2083.53	2620.69	2788.82	0.94	2.24
3.00	832.93	1190.78	1952.33	1819.81	2227.75	2620.18	0.88	2.34
3.50	591.06	772.02	1496.14	1333.58	1651.59	1905.29	0.91	2.53
4.00	442.41	546.29	1187.52	1082.46	1479.92	1910.22	0.80	2.68
4.50	329.27	410.72	1011.18	915.31	1093.85	1264.66	0.92	3.07
5.00	263.78	365.56	744.53	669.72	844.65	1045.63	0.88	2.82
5.50	220.92	301.36	588.26	514.58	629.80	712.45	0.93	2.66
6.00	184.72	251.85	442.47	344.37	488.66	548.40	0.91	2.40
8.00	110.72	125.73	245.07	203.34	252.82	236.73	0.97	2.21
10.00	84.56	147.87	162.97	126.44	169.22	160.54	0.96	1.93
12.00	49.64	60.46	123.42	92.21	112.49	110.31	1.10	2.49
16.00	33.10	45.24	89.22	72.78	82.12	75.45	1.09	2.70
24.00	16.73	25.51	41.77	37.72	42.85	43.00	0.97	2.50
36.00	8.72	23.70	36.40	38.90	38.36	41.54	0.95	4.17
48.00	3.22	9.99	14.19	18.69	14.98	24.52	0.95	4.41
72.00	1.32	5.90	4.94	12.19	8.78	16.45	0.56	3.74
96.00	0.00	0.00	1.10	4.90	4.15	10.69	0.27	0.00
120.00	0.00	0.00	0.00	0.00	2.42	7.71	0.00	0.00
144.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Table #4
Loratadine Pharmacokinetic Parameters
Single-Dose Fasting Study, 10 mg Dose
Treatment A (Test): Loratadine Tablets, 10 mg, Lot #1074046
Treatment B (Reference): Claritin® Tablets, 10 mg, Lot #9RXF375

Plasma Parameters	Cmax (pg/ml)		Tmax (hours)		Kel (1/hours)	
Treatment	A	B	A	B	A	B
MEAN	3320.30	3137.67	1.26	1.34	0.15	0.13
CV%	138.20	137.15	31.04	33.74	95.83	96.62

Plasma Parameters	T1/2 (hours)		AUCt (pg/ml-hours)		AUCi (pg/ml-hours)	
Treatment	A	B	A	B	A	B
MEAN	13.03	13.07	10167.5	10227.1	10684.2	10899.5
CV%	107.06	96.35	154.55	153.15	151.74	148.18

Table #5
Summary Statistics for Loratadine
Single-Dose Fasting Study, 10 mg Dose
Treatment A (Test): Loratadine Tablets, 10 mg, Lot #1074046
Treatment B (Reference): Claritin® Tablets, 10 mg, Lot #9RXF375

PK Parameter	Geometric Mean		Ratio	90% C.I.
(Treatment)	A	B	B/A	
lnAUCt (pg·hr/mL)	4889.75	4710.02	1.04	97.1-111.0
lnAUCi (pg·hr/mL)	5230.13	5116.03	1.02	96.6-108.1
lnCmax (pg·hr/mL)	1794.06	1629.11	1.10	101.9-119.0

Table #6
Summary Statistics for Descarboethoxyloratadine
Single-Dose Fasting Study, 10 mg Dose
Treatment A (Test): Loratadine Tablets, 10 mg, Lot #1074046
Treatment B (Reference): Claritin® Tablets, 10 mg, Lot #9RXF375

PK Parameter	Geometric Mean		Ratio	90% C.I.
(Treatment)	A	B	B/A	
lnAUCt (pg·hr/mL)	37826.06	37919.98	1.00	96.6-104.3
lnAUCi (pg·hr/mL)	39415.93	39568.20	1.00	96.6-104.2
lnCmax (pg·hr/mL)	2548.58	2450.28	1.04	98.6-108.9

Table #7
Loratadine Pharmacokinetic Parameters
Single-Dose Fed Study, 10 mg Dose
Treatment A: Loratadine Tablets, 10 mg, Lot #1074046 (Fasted)
Treatment B: Loratadine Tablets, 10 mg, Lot #1074046 (Fed)
Treatment C: Claritin® Tablets, 10 mg, Lot #9RXF375 (Fed)

Plasma Parameters	Cmax (pg/ml)			Tmax (hours)			Kel (1/hours)		
Treatment	A	B	C	A	B	C	A	B	C
MEAN	2202.97	3516.05	3507.35	1.07	1.86	1.86	0.15	0.07	0.06
CV%	106.90	83.31	85.70	24.63	44.36	38.21	82.55	67.07	72.50

Plasma Parameters	T1/2 (hours)			AUCt (pg/ml-hours)			AUCi (pg/ml-hours)		
Treatment	A	B	C	A	B	C	A	B	C
MEAN	8.61	14.97	19.20	5941.00	11903.3	12039.8	6282.81	12835.1	12978.4
CV%	74.33	53.73	75.64	121.90	81.30	99.22	118.94	77.76	96.65

Table #8
Summary Statistics for Loratadine
Single-Dose Fed Study, 10 mg Dose
Treatment B: Loratadine Tablets, 10 mg, Lot #1074046 (Fed)
Treatment C: Claritin® Tablets, 10 mg, Lot #9RXF375 (Fed)

PK Parameter	Geometric Mean		Ratio
(Treatment)	B	C	B/C
lnAUCt (pg·hr/mL)	9145.5	8633.6	1.06
lnAUCi (pg·hr/mL)	9744.8	9064.7	1.08
lnCmax (pg·hr/mL)	2711.5	2589.0	1.05

Table #9
Summary Statistics for Descarboethoxyloratadine
Single-Dose Fed Study, 10 mg Dose
Treatment B: Loratadine Tablets, 10 mg, Lot #1074046 (Fed)
Treatment C: Claritin® Tablets, 10 mg, Lot #9RXF375 (Fed)

PK Parameter	Geometric Mean		Ratio
(Treatment)	B	C	B/C
lnAUCt (pg·hr/mL)	41763.0	39448.9	1.06
lnAUCi (pg·hr/mL)	42903.6	41281.4	1.04
lnCmax (pg·hr/mL)	2865.8	2724.1	1.05

Table #10
Results of In Vitro Dissolution Testing
Reference Product: Claritin® Tablets by Schering Corporation
Test Product: Loratadine Tablets by Ranbaxy Laboratories Ltd.

RESULTS OF *IN VITRO* DISSOLUTION TESTING						
10 mg Strength						
Sampling Times (min.)	Test Product Lot #1074046			Reference Product Lot #9RXF375		
	Mean %	Range	% CV	Mean %	Range	% CV
5	79	62-102	13.9	28	24-31	9.0
10	97	89-101	3.8	41	37-46	6.3
15	101	99-103	1.1	52	46-66	9.8
20	102	100-104	1.3	72	55-82	12.4
30	103	101-104	1.0	90	69-97	10.6
45	103	99-104	1.5	103	96-109	3.9

Figure 1

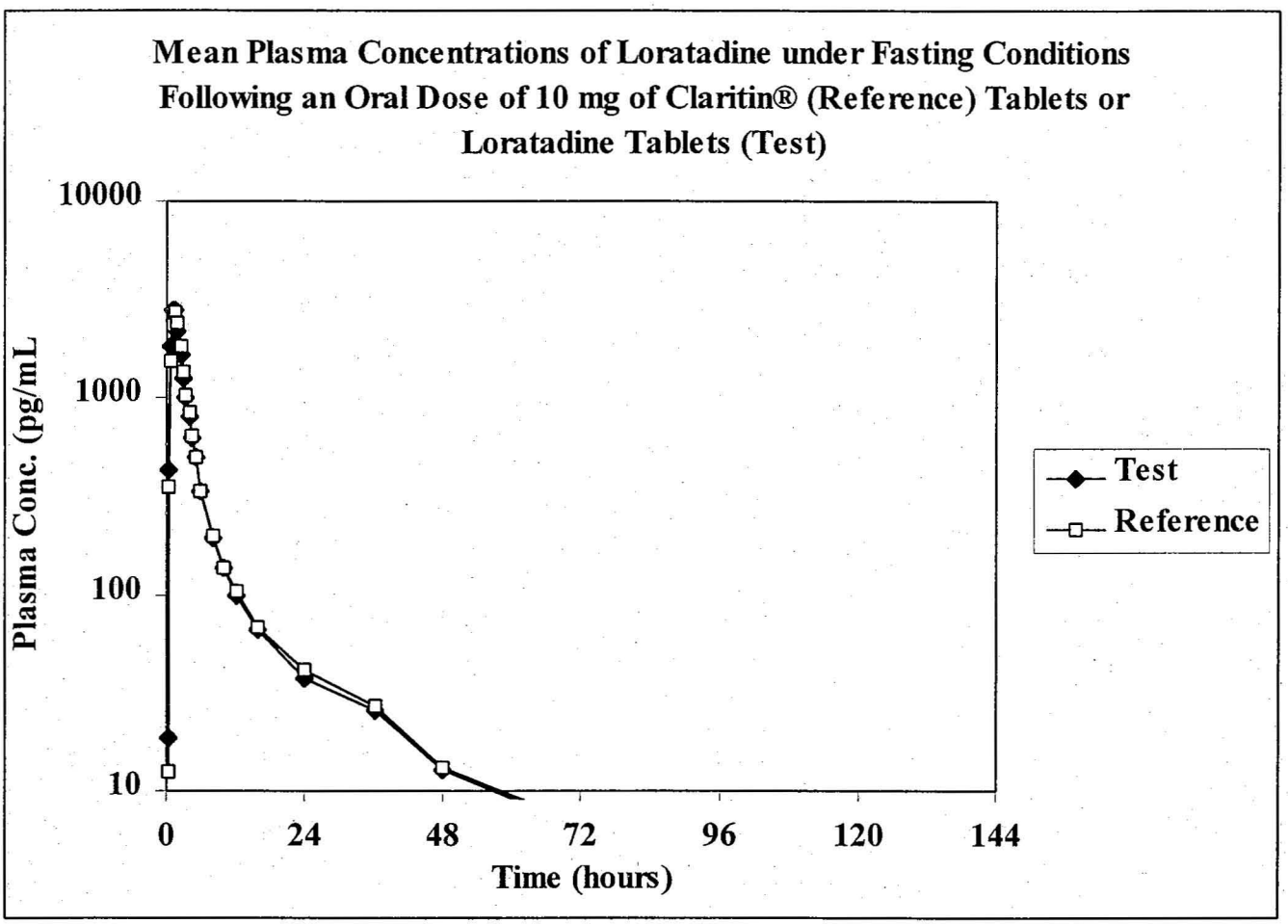
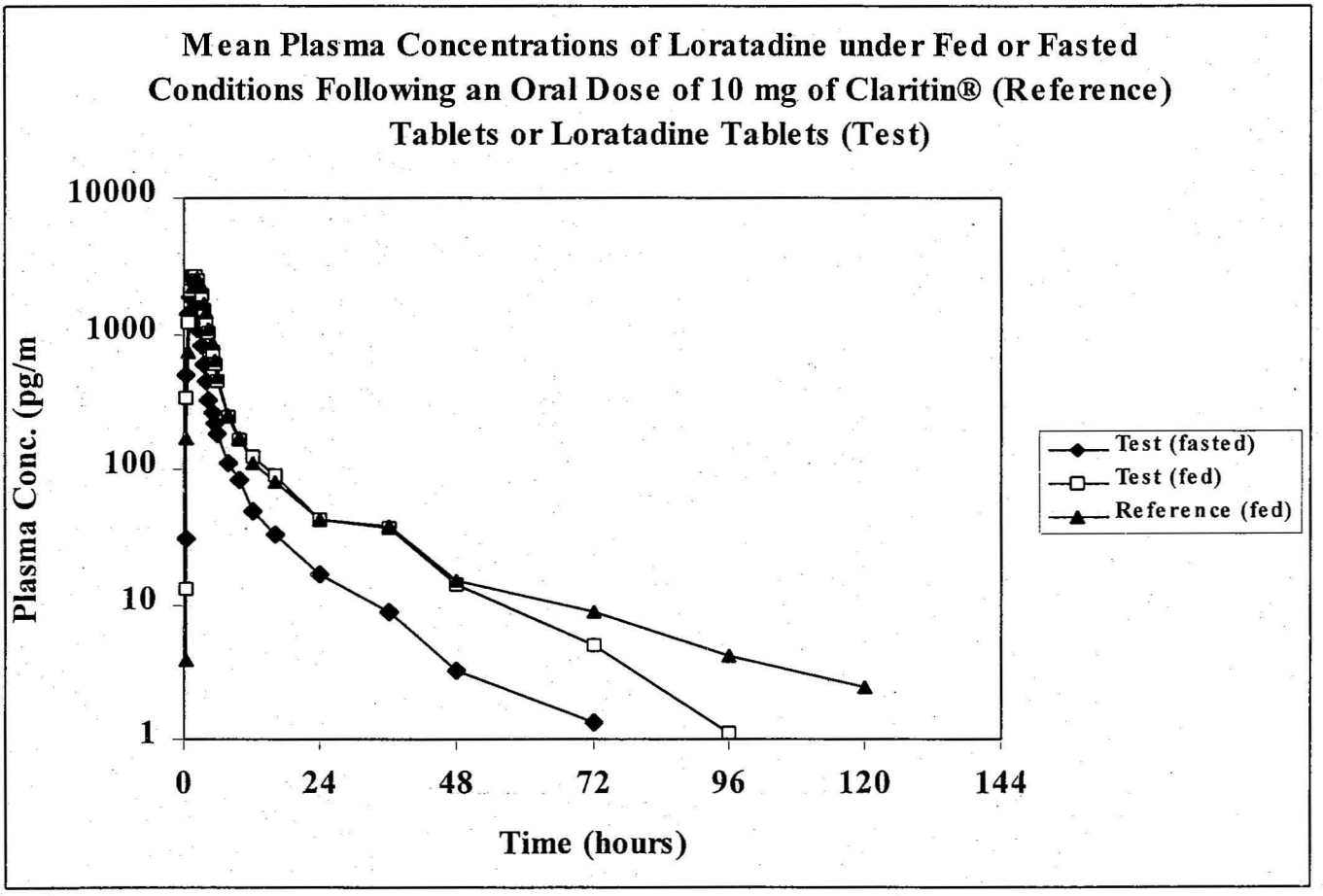

Mean Plasma Concentrations of Loratadine under Fasting Conditions Following an Oral Dose of 10 mg of Claritin® (Reference) Tablets or Loratadine Tablets (Test)
Plasma Conc. (pg/mL
10000
1000
100
10
0
24
48
72
96
120
144
Time (hours)
Test
Reference

Figure 2


Mean Plasma Concentrations of Loratadine under Fed or Fasted Conditions Following an Oral Dose of 10 mg of Claritin® (Reference) Tablets or Loratadine Tablets (Test)
Plasma Conc. (pg/m
10000
1000
100
10
1
0
24
48
72
96
120
144
Time (hours)
Test (fasted)
Test (fed)
Reference (fed)

CC: ANDA #76-134
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer: M. Gokhale
HFD-658/ TL: B. Davit

V:\FIRMSNZ\RANBAXY\LTRS&REV\76134SD.301.DOC
Printed in final on 5/31/2001

Endorsements: (Final with Dates)
HFD-658/ M. Gokhale MSG 5/31/01
HFD-658/ B. Davit BND 5/31/01
HFD-650/ D. Conner for Nuy 6/18/2001
HFD-617/ S. Mazzella

Bioequivalency- Acceptable Submission Date: ~~19~~ 15 March, 2001

OIC 1) Fasting Study (STF) Strength: 10 mg
Clinical: MDS Pharma Services Inc., Montreal Canada Outcome: AC
Analytical [redacted] (b) (4)

OIC 2) Food Study (~~STA~~ STP) Strength: 10 mg
Clinical: MDS Pharma Services Inc., Montreal Canada Outcome: AC
Analytical: [redacted] (b) (4)

Outcome Decisions: AC- Acceptable

Winbio comments: STF – Acceptable
STA– Acceptable

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OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-134 SPONSOR : Ranbaxy Laboratories Ltd.

DRUG AND DOSAGE FORM : Loratadine Tablets

STRENGTH(S) : 10 mg

TYPES OF STUDIES : [SD] [SDF] MULT [OTHER]

CLINICAL STUDY SITE(S) : MDS Pharma Services Inc., Montreal Canada

ANALYTICAL SITE(S) (b) (4)

STUDY SUMMARY : In single dose fasting and post-prandial bioequivalence studies, Loratadine tablets, 10 mg were shown to be bioequivalent to Claritin® tablets, 10 mg.

DISSOLUTION : Acceptable

DSI INSPECTION STATUS

Inspection needed: YES / [NO]	Inspection status:	Inspection results:
First Generic ____ New facility ____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : MAMATA S. GOKHALE, Ph.D. BRANCH : III

INITIAL : MSK DATE : 5/31/01

TEAM LEADER : BARBARA M. DAVIT, Ph.D. BRANCH : III

INITIAL : Barbara M. Davit DATE : 5/31/01

for

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

INITIAL : [signature] DATE : 6/18/2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076134

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

April 10, 2001

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 OVERNIGHT

ADDITIONAL INFORMATION TO A PENDING APPLICATION

NEW CORRES
NC

RE: Loratadine Tablets, 10 mg
ANDA 76-134
Additional Information – Updated exclusivity statement

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets, 10 mg. Reference is also made to the telephone contact of April 10, 2001 requesting a revision to the Exclusivity statement.

Attached is the updated page.

If you have any questions regarding this submission please contact me at 609-720-5617

Sincerely,

Patricia Strasser (for)

Patricia S. Strasser (for)
Shirley Ternyik
US Agent for Ranbaxy Laboratories Limited

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
APR 11 2001
OGD

ANDA 76-134

APR 12 2001

Ranbaxy Pharmaceuticals Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Shirley Ternyik
600 College Road East
Princeton, NJ 08540

Dear Madam:

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

Reference is made to the telephone conversation dated April 10, 2001 and to your correspondence dated April 10, 2001.

NAME OF DRUG: Loratadine Tablets, 10 mg

DATE OF APPLICATION: March 15, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 19, 2001

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

CONTENTS OF THE NOTICE

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

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

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

  1) Each owner of the patent or the representative

designated by the owner to receive the notice;

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

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

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

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

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

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

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

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

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

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

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we

ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

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

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

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

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

Should you have questions concerning this application, contact:

Ruby Yu
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S Davis for

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

cc: ANDA 76-134
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB date 11-APR-2001
HFD-615/PPatel, CSO date 4/11/01
Word File V:\Firmnz\Ranbaxy\ltrs&rev\76134.ACK
FT/ EEH 04/10/01
ANDA Acknowledgment Letter!

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

NC

May 16, 2001

NEW CORRESP

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

AMENDMENT TO A PENDING APPLICATION

Spoke w/ Pat Strasser & asked for new rr w/ dates. Also, information regarding potential litigation was Req 6/1/01 5/30/01

RE: **Loratadine Tablets, 10 mg**
ANDA 76-134
Amendment – Notice to Patent Holders

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets, 10 mg.

29-AUG-2001

Ranbaxy Laboratories Limited has complied with the requirements under 31 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 the application to certify that we have notified the appropriate holder. The letter sent to Schering Corporation was dated May 10, 2001 and sent on May 11, 2001. Attached is a copy of the certified receipt of the notice from the listed drug holder, Schering Corporation.

If you have any questions regarding this submission please contact me at 609-720-5617 or Shirley Ternyik at 609-720-5612. Thank you.

Sincerely,

Patricia S. Strasser (for)
Shirley Ternyik
US Agent for Ranbaxy Laboratories Limited

CENTER FOR DRUG EVALUATION AND RESEARCH
MAY 17 2001
OGD

5/31/01

Emily Thomas
NAI
9/18/01
30 month - 11/14

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

August 30, 2001

FAX AND
UPS OVERNIGHT

AMENDMENT TO A
PENDING APPLICATION

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

RE: Loratadine Tablets, 10 mg
ANDA 76-134
Notice of Civil Action

NEW CORRESP
NC

Dear Sir:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets, 10 mg. Reference is also made to the May 16, 2001 amendment and the FDA telephone contact of August 29, 2001.

The holder of the approved drug application for the listed drug, Schering Corporation was notified of Ranbaxy's ANDA 76-134 filing of Loratadine Tablets, 10 mg via certified mail sent on May 11, 2001. The certified return receipt did not have a date stamped when the Schering Corporation had received the notice.

Therefore, as was requested, we are including a copy of the Civil Action No. 01-CV-2990, filed on behalf of the Schering Corporation to the U.S District Court of NJ on 6/22/01. In this Civil Action the Schering Corporation states that they received written notification of ANDA 76-134 on May 14, 2001.

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

CENTER FOR DRUG
AUG 3 1 2001
EVALUATION AND RESEARCH

MINOR AMENDMENT

ANDA 76-134

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)

SEP - 6 2001

TO: APPLICANT: Ranbaxy Laboratories Limited TEL: 609-720-5612

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

FROM: Ruby Yu PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 15, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine Tablets, 10 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 and Bioequivalency comments provided. Labeling comments will be provided when the review is completed.

RY
9/6/01

SEP - 6 2006

38. **Chemistry Comments to be Provided to the Applicant:**

ANDA: 76-134 APPLICANT: Ranbaxy Laboratories, Limited

DRUG PRODUCT: Loratadine Tablets, 10 mg

A. The deficiencies presented below represent MINOR deficiencies.

1. The Drug Master File (DMF) #15251 for Loratadine has been found to be deficient. The deficiencies have been transmitted to the DMF holder. Please do not respond to this deficiency letter until you have received notification from the DMF holder that the deficiencies have been addressed. Please note that each of the deficiencies must be found to be satisfactory before the approval of this application.

2. Please provide the source, characterization data, and Certificate of Analysis for your in-house working standard (Lot #3LTN00499).

3. Please revise your Active Pharmaceutical Ingredient Specifications as follows:

   a) Please add a second specific identification test.

   b) Please add a test and limit for melting range.

   c) Please tighten your acceptance criteria for Assay.

   d) Please add a second specification for Particle Size for particles < (b) (4) µm.

4. Please develop a validated HPLC method for assay of Loratadine drug substance and add this test to your specifications.

5. Please add the Related Substances test to your (b) (4) retest procedure for the active pharmaceutical ingredient.

6. The inactive ingredient, Lactose Monohydrate NF, comprises (b) (4) of the tablet weight (b) (4) %). Please add a test and limit for Tapped Density and Particle Size into your raw material specifications for Lactose Monohydrate NF.

7. Please correct the value given for the total manufacturing loss of tablets to (b) (4) tablets (not (b) (4) tablets) in your executed Batch Reconciliation Data sheet.

8. Please account for the (b) (4) observed in the manufacturing procedure of the exhibit batch. Please provide a process deviation report and preventative action plan.

9. Please incorporate a second identification test into your finished product release specifications.

10. Please revise your finished product release and stability specification for dissolution to that recommended by the Division of Bioequivalence: NLT (b) (4)% (Q) in 60 minutes.

11. The stability study in the Simulated Bulk Packaging is not acceptable. Please submit stability data for the drug product in the Bulk Shipment Packaging.

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

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

2. A request for method validation testing of your drug substance and drug product methods has been sent to a FDA field laboratory. You will be contacted in the near future to submit samples to complete this testing.

3. Please submit all available room temperature stability data.

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

Sincerely yours,

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 76-134 APPLICANT: Ranbaxy Laboratories Ltd.
DRUG PRODUCT: Loratadine Tablets,
10 mg

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

We acknowledge that the following dissolution testing will be incorporated into your stability and quality control programs. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 24 apparatus 2 (paddle) at 50 rpm. The test product should meet the following dissolution specifications:

NLT (Q) (b) (4) in 60 minutes.

Please note that the Division of Bioequivalence does not accept pharmacokinetic data adjustment due to pharmacokinetic anomalies. The actual plasma concentration values determined by the analyst should be used in calculating pharmacokinetic parameters.

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

Sincerely yours,

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

Emily Mason
NAI
12/1/01

COVINGTON & BURLING

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

WASHINGTON, DC
NEW YORK
LONDON
BRUSSELS
SAN FRANCISCO

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

September 26, 2001

BY HAND DELIVERY

NC

NEW CORRESP

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

Re: ANDA No. 76-134
Notice of Filing of Legal Action for Patent Infringement

Ladies and Gentlemen:

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

(i) The ANDA number is 76-134;

(ii) The name of the ANDA applicant is Ranbaxy Laboratories, Ltd.;

(iii) The established name of the drug is loratadine, the strength is 10 milligrams, and the dosage form is tablets; and

(iv) Schering hereby certifies that an action for patent infringement, Civil Action No. 01-2990 (JAG), was filed in an appropriate court (the United States District Court for the District of New Jersey) on June 22, 2001. Copies of the Summons and Complaint in that action are enclosed.

Schering received notice of a Paragraph IV Certification alleging the noninfringement and/or invalidity of United States Patent Nos. 4,659,716 and 4,863,931 on May 14, 2001. Schering is the owner of these patents. Schering brought the above-described action for patent infringement within 45 days of the receipt of notice of the Paragraph IV Certification.

Accordingly, pursuant to Section 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act, ANDA No. 76-134 cannot be approved until the expiration of the thirty-month period beginning on May 14, 2001 and ending on November 14, 2003, or until such time as ordered by the Court.

Thank you for your attention to this matter.

Sincerely yours,

Michael S. Labson

Counsel for Schering Corporation

Enclosures

RANBAXY
LABORATORIES LIMITED

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

October 10, 2001

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

MINOR AMENDMENT

N/AM

ORIG AMENDMENT

Reference: **ANDA 76-134**
Loratadine Tablets 10 mg

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets 10 mg submitted March 15, 2001.

Reference is also made to the FDA's minor deficiency letter dated September 6, 2001.

Attached are the responses to the questions, they follow in the same order as they appear in the deficiency.

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 Office of Generic Drugs.

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

Sincerely,

Scott D. Tomsky(for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 12 2001

RANBAXY
LABORATORIES LIMITED

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

ORIG AMENDMENT
N/AF.

November 7, 2001

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

FAX & UPS

LABELING AMENDMENT

Reference: **ANDA 76-134**
Loratadine Tablets 10 mg

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets 10 mg submitted March 15, 2001.

Reference is also made to the telephone call and the labeling deficiency of November 5, 2001. Per FDA's telephone contact, the labels are acceptable as is. The package insert needs to be revised according to the innovator's package insert of 9/00 for Clartin®. In addition, the requirement for the side-by-side comparison is waived at this time.

Attached is a copy of Ranbaxy's revised package insert. Four copies of draft labeling are provided.

If you have any questions regarding this submission, please call me at (609)-720-5633 or Abha Pant at (609) 720-5666.

Sincerely,

Iris Feliciano

Iris Feliciano (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

CENTER FOR DRUG EVALUATION AND RESEARCH
NOV 0 8 2001

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-134 Applicant Ranbaxy Laboratories Limited

Drug Loratadine Tablets Strength 10mg

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

REVIEWER:

DRAFT RECEIPT

FINAL ACTION

1. Project Manager Ruby Wu Team 4
   Review Support Br
   Date 11/19/01
   Initials RWu
   Date RWu 11/20
   Initials

   Application Summary:

   Original Rec'd date 3/19/01

   EER Status Pending ☒ Acceptable ☐ OAI ☐

   P 5x2 Date Acceptable for Filing 3/19/01 J

   Date of EER Status

   733 III 12/14/02 Patent Certification (type) III and IV

   Date of Office Bio Review 6/13/01

   716 IV 10/21/04 Date Patent/Exclus.expires See side

   Date of Labeling Approv. Sum 11/15/01

   731 IV 3/15/09 Citizens Petition/Legal Case Yes ☐ No ☒

   Date of Sterility Assur. App. N/A

   (If YES, attach email from PM to CP coord)

   Methods Val. Samples Pending Yes ☒ No ☐

   30 month ends 11/14/03 First Generic Yes ☐ No ☒

   30 Day Clock Start End notify for TA

   (If YES, check PETS)

   Commitment Rcd. from Firm Yes ☐ No ☐

   Pediatric Exclusivity Tracking PETS)

   Modified-release dosage form: Yes ☐ No ☒

   Date checked NDA#

   Interim Dissol. Specs in AP Ltr: Yes ☐

   Nothing Submitted ☐

   Written request issued ☐

   Study Submitted ☐

   Previously reviewed and tentatively approved ☐ Date

   Previously reviewed and CGMP def./N/A Minor issued ☐ Date

   Comments:

2. Div. Dir./~~Deputy Dir.~~
   Chemistry Div. I ~~or II~~
   Date 11/20/01
   Initials RR
   Date 11/21/01
   Initials RR
   Comments:

   The CMC section is satisfactory. MUEER ~~or~~ pending.

3. Frank Holcombe
   Assoc. Dir. For Chemistry
   Date —
   Initials
   Date —
   Initials
   Comments: (First generic drug review)

   N/A

   three ANDAs are currently tentatively approved - Mylan, Geneva, and Teva.

4. Pat Beers Block
   Supv., Review Support Branch
   Date
   Initials
   Date
   Initials
   EER Status: Refer to the DAPS review below.

   Bioequivalence sites:

   Clinical site:

   Inspection needed: ☐ yes ☐ no

   Status: ☐acceptable ☐unacceptable ☐ pending

   Date of status:

   Reason:

   Analytical site:

   Inspection needed: ☐ yes ☐ no

   Status: ☐acceptable ☐unacceptable ☐pending

   Date of status:

   Reason:

   Bioequivalence office level sign off:

   Labeling Status:

   Microbiology status:

   Patent Certification:

   Controlled Correspondence/Cit.Pet:

   Comments: RLD =

REVIEWER:	DRAFT RECEIPT	FINAL ACTION
5. Greg Davis Supv., Reg. Support Branch	Date 12/20/2001 Initials RW	Date 12/20/01 for Initials RW

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked Reviewed/granted
If Para. IV Certification- did applicant ☐ III / ☒ IV 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 ☒ (Not is suit with ☐ III ☒ IV) RLD=Clarinex Tablets 10mg NDA 19658 Schering Corp.
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Comments: Ranbaxy made a "paragraph 3" certification to the '233 patent (12/19/02) and "paragraph 4" certifications to the '716 (10/21/14) and '931 (3/15/09) patents. There is no unexpired exclusivity.

6. Peter Rickman Acting Director, DLPS	Date 12/20/01 Initials RW	Date 12/20/01 Initials RW for

Comments: Acceptable EES dated 12/18/01 (verified 12/20/01). No OAI. Labels noted. Bioequivalence studies (fasting + fed) found acceptable. 3 lot dissolution studies also acceptable. (b) (4) the clinical (b) (4) studies were performed by Mds Pharma Services in Montreal, Canada. This facility has an acceptable OSI inspectional history. Office level to be updated 6/2/01. Labeling acceptable for NDA on 11/15/01. CMC acceptable 11/19/01. Methods validation - pending.

7. Robert L. West Acting Deputy Director, OGD	Date 12/20/01 Initials RW	Date 12/20/2001 Initials Robert L West

Para. IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☒ No ☐; Petition: Yes ☐ No ☒
Comments: This application is recommended for tentative approval. Patent litigation between Ranbaxy/Schering is ongoing.

8. Gary Buehler Director, OGD	Date 12/20/01 Initials GB	Date 12/20/01 Initials GB

Comments:

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

9. Project Manager Ruby Wu Review Support Branch	Date 12/20/01 Initials RWu	Date 12/20/01 Initials RWu

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

Applicant notification:
1:25 pm Time notified of approval by phone 1:30 Time approval letter faxed (left msg)

FDA Notification:
12/20/01 Date e-mail message sent to "OGD approvals" account
12/20/01 Date Approval letter copied to "//cder/drugapp" directory

eports\approval\approvrou

RANBAXY
LABORATORIES LIMITED

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

July 3, 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 20855-2773

UPS

Amendment to a Pending ANDA

N/AM

ORIG AMENDMENT

Reference: **ANDA 76-134**
Loratadine Tablets 10 mg

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets 10 mg submitted March 15, 2001.

This ammendment includes the following information to the above referenced ANDA:

RECEIVED
JUL 05 2002
OGD / CDER

1) An additional packaging configuration for blisters.
2) The addition of an outside firm for the packaging in the blister configuration.

To support this amendment the following information is being supplied:

1) DMF access letter and Certificate of Compliance and Data Sheet for [redacted] (b) (4). (Refer to **Attachment 1**).

2) cGMP and Debarment letter from [redacted] (b) (4) Last inspected July 2001. (Refer to **Attachment 2**).

3) Receiving records of the components used by [redacted] (b) (4) for packaging into the blister configuration as well as reconciliation and accountability. (Refer to **Attachment 3**)

4) Product release COA for Loratadine Tablets 10 mg, lot #1074046 and also Stability data after packaging in blisters. (Refer to **Attachment 4**).

5) Side-by-side comparison labeling, as well as 12 copies of final printed labels (Refer to **Attachment 5** [sections IV and V]).

We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this amendment has been provided to the Food and Drug Administration, International Operations Group.

If you have any questions or comments regarding this amendment, please call me at 609-720-5328, or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Alex Mironov

Alexander Mironov
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECORD OF TELEPHONE CONVERSATION

Reference is made to the ANDA dated March 15, 2001 and tentative approval letter dated December 20, 2001.

The following deficiencies/comments were communicated to the firm:

Deficiencies:

1. Please provide a blister diagram (including dimensions) and IR identification spectra of the blister components.

2. Please provide USP <661> and <671> testing documentation for the blister packaging.

3. Please perform leak testing (one-time or in-process) on the blister to demonstrate seal integrity.

4. Please update the stability tables for the blister packaging with the correct dissolution specification: NLT (b)(4)% (Q) in 60 min.

5. Please propose an expiration dating period for the product packaged in the blister pack.

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

1. Please provide all available room temperature stability data for the product in the proposed packaging systems.

2. The labeling portion of your amendment is under review. Deficiencies, if any, will be conveyed to you under separate cover.

The firm's response may be submitted as a telephone amendment.

DATE:
August 8, 2002

ANDA NUMBER
76-134

TELECON INITIATED BY
FDA

PRODUCT NAME:
Loratadine Tablets, 10mg

FIRM NAME:
Ranbaxy Laboratories Limited

FIRM REPRESENTATIVES:
Abha Pant (US Agent)
Scott Tomsky

TELEPHONE NUMBER:
609-720-5666

FDA REPRESENTATIVES
Neeru Takiar
John Franolic
Sarah Kim

SIGNATURES:
Neeru Takiar NT 8/8/02
John Franolic JF 8/8/02
Sarah Kim S. K 8/8/02

CC: ANDA 76-134
Chem. I Telecon Binder
V:\FIRMSNZ\RANBAXY\TELECONS\76134.tc.080802.doc

RANBAXY
LABORATORIES LIMITED

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

August 13, 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 20855-2773

UPS AND FAX

TELEPHONE Amendment

ORIG AMENDMENT
N/A m

Reference: **ANDA 76-134**
Loratadine Tablets 10 mg

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets 10 mg submitted March 15, 2001. Reference is also made to the telephone contact on August 8, 2002 between Ranbaxy and the Agency.

Attached are the responses to the questions discussed in the telephone conference.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this amendment has been provided to the Food and Drug Administration, International Operations Group.

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

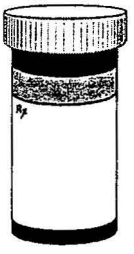
Sincerely,

Scott D. Tomsky (for)

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

RECEIVED
AUG 1 4 2002
OGD / CDER

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

To: Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited
Fax: 609-720-1155 **Phone:** 609-720-5609

From: Debra M. Catterson
Labeling Reviewer
Fax: 301-443-3847 **Phone:** 301-827-5846

Number of Pages (including cover sheet): 3 **Date:** October 7, 2002

Comments:

Dear Mr. Tomsky,

Attached is the labeling review of your July 3, 2002 submission for ANDA 76-134 for Loratadine Tablets, 10 mg.

Please feel free to call me if you have any questions.

Sincerely,

Debra M. Catterson

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

ANDA Number: 76-134

Date of Submission: July 3, 2002 (Amendment)

Applicant's Name: Ranbaxy Laboratories Limited

Established Name: Loratadine Tablets, 10 mg

Labeling Deficiencies:

1. **CONTAINER:**

   a. Bottles of 14 and 500: Satisfactory in draft as of the March 15, 2001 submission.

   b. Unit Dose Blister Card of 10 Tablets:

      Revise "Tablets" to read "Tablet" on each of the ten unit dose blister labels.

2. **CARTON** Label [For box of 100 (10 x 10) unit dose tablets]:

   a. Revise "100 Unit-Dose Capsules" to read "100 Unit-Dose Tablets" wherever it appears on your label.

   b. Revise "(10 Strips of 10 Unit-Dose Capsules)" to read "(10 Blister Strips of 10 Unit-Dose Tablets)" wherever it appears on your label.

   c. Insert the following text after the "This unit-dose package is not child resistant." statement:

      "This package is intended for institutional inpatient use. If dispensed for outpatient use, appropriate safety packaging must be provided."

3. **INSERT:**

   a. DESCRIPTION: Revise "monhydrate" to read "monohydrate".

   b. ADVERSE REACTIONS: Loratadine Syrup:

      Delete the entire paragraph that begins with the sentence: "(b) (4) (b) (4)". [The information should be deleted because this patient population is not referenced in the Dosage and Administration section.]

   c. HOW SUPPLIED

      i. Revise "Unit-dose package of 100" to read "Unit-dose package of 100 (10 blister strips of 10 tablets)".
      ii. Insert the following text immediately preceding the temperature storage statement:

      "Protect unit-dose packaging from excessive moisture."

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

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

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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

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

RANBAXY
LABORATORIES LIMITED

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

October 21, 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 20855-2773

FAX & UPS OVERNIGHT

ORIG AMENDMENT
N/Af

RECEIVED
OCT 22 2002
OGD / CDER

Reference: Loratadine Tablets, 10 mg ANDA 76-134

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets, 10 mg.

Reference is also made to the labeling facsimile deficiency, dated October 7, 2002, in which Ranbaxy was asked to further revise the labels and the package insert for the above referenced product.

Provided on the following pages are the Agency's deficiencies followed by Ranbaxy's response. The labels and the package insert have been revised as requested. Twelve sets of the final printed labels and package insert are included in **Attachment 1**. To facilitate review we have provided a side-by-side labeling comparison with Ranbaxy's revised labeling and the previously submitted labeling, with all differences explained and shown with the use of color, in **Attachment 2**. We have provided, for your reference, in **Attachment 3,** an actual blister pack which will illustrate that the blister pack does contain a child resistant closure.

Please contact the undersigned at 609-720-5633, or Abha Pant at 609-720-5666, if you have any questions regarding this labeling amendment.

Sincerely,

Iris Feliciano

Iris Feliciano
Regulatory Affairs Labeling Specialist (***for***)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RANBAXY
LABORATORIES LIMITED

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

October 30, 2002

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

FAX & UPS OVERNIGHT

Reference: Loratadine Tablets, 10 mg ANDA 76-134

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets, 10 mg.

Reference is also made to a telephone conversation with Debbie Catterson, OGD labeling reviewer, on October 29, 2002 in which Ranbaxy was asked to provide final printed labeling for the 10 mg, 14 and 500 tablet counts.

Twelve sets of the final printed labels are included in Attachment 1.

Sincerely,

Iris Feliciano

Iris Feliciano
Regulatory Affairs Labeling Specialist (***for***)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
OCT 31 2002
OGD / CDER

ANDA 76-134

DEC 3 2002

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

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 15, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine Tablets, 10 mg.

On November 27, 2002, the FDA approved Schering's supplemental new drug application providing for the over-the-counter (OTC) use of Claritin® (loratadine) Tablets, Syrup, and RediTabs®. With this approval, the approved indications for these products are "for the temporary relief of symptoms of hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat." Please note that the use of these products for the treatment of chronic idiopathic urticaria (CIU) is not included in the approved OTC labeling. The agency has been informed that with the introduction of products labeled for OTC use, these products will no longer be marketed with prescription (Rx) labeling. Thus, since your ANDA currently references the former product with prescription only labeling, your application cannot be approved.

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

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

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

Sincerely yours,

12/3/02

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

Enclosure:
Claritin Labeling

CC: ANDA 76-134
DUP/Division File

HFD-617/ P.Chen, PM Peter Chen 12/2/02

V:\FIRMSNZ\RANBAXY\LTRS&REV\76134.LoratadineOTC.doc

RECORD OF TELEPHONE CONVERSATION

The following message was left on the voicemail.

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

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

DATE: December 12, 2002
ANDA NUMBER 76-134
TELECON INITIATED BY FDA
PRODUCT NAME: Loratadine Tablets, 10mg
FIRM NAME: Ranbaxy Laboratories Limited
FIRM REPRESENTATIVES: Abha Pant (US Agent)
TELEPHONE NUMBER: 609-720-5666
FDA REPRESENTATIVES Sarah Kim
SIGNATURES: Sarah Kim S.K. 12/12/02

CC: ANDA 76-134
Chem. I Telecon Binder
V:\FIRMSNZ\RANBAXY\TELECONS\76134.tc.121202.doc

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

January 22, 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

ORIG AMENDMENT
N/AF

Reference: ANDA 76-134
Loratadine Tablets, 10 mg
Response to Letter Dated December 3, 2002

Dear Sir/Madam:

Reference is made to ANDA 76-134 for Loratadine Tablets, 10 mg in which Ranbaxy was requested to provide over-the-counter (OTC) labeling according to Schering's approved Claritin (loratadine) Tablets supplemental new drug application dated, November 27, 2002.

Reference is also to the FDA correspondence dated, December 3, 2002, in which Ranbaxy was asked to submit revised final printed labeling which is consistent in content and in "Drug Facts Format" which provides for the OTC use of the Reference Listed Drug.

Provided on the following pages is the agency's letter. Ranbaxy's Loratadine Tablets, 10 mg (OTC) labeling has been provided as requested. Six sets of the final printed OTC labeling are included in **Attachment 1** of this submission. To facilitate review we have provided a side-by-side labeling comparison of Ranbaxy's OTC labeling to Schering's approved OTC labeling, with all differences shown with the use of color, in **Attachment 2**.

Please contact the undersigned at 609-720-5633, or Abha Pant at 609-720-5666, if you have any questions regarding this labeling supplement.

Sincerely,

Iris Feliciano

Iris Feliciano
Regulatory Labeling Specialist (**for**)
U.S. Agent Abha Pant, Director of Regulatory Affairs

RECEIVED
JAN 23 2003
OGD / CDER

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

January 30, 2003

ORIG AMENDMENT
N/Am

TELEPHONE RESPONSE

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: **ANDA 76-134**
Loratadine Tablets, 10 mg

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets, 10 mg. Reference is also made to the FDA telephone contact of January 7, 2003 in which Ranbaxy was further asked to provide the agency with tamper evident methodology for the container closure systems referenced in the pending ANDA.

Ranbaxy had submitted information to the Agency dated December 13, 2002 referencing the relevant pages and volumes which provided information on the description of the tamper-evident packaging for the bottles and blister packs.

As per the Agency's request, we have enclosed a summary of the tamper-evident methodology.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this amendment has been provided to the Food and Drug Administration, International Operations Group.

Please contact the undersigned at 609-720-5609, or Abha Pant at 609-720-5666, if you have any questions regarding this response.

Sincerely,

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

RECEIVED
JAN 31 2003
OGD / CDER

RANBAXY
PHARMACEUTICALS INC.

February 26, 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 AND FAX

Amendment to Pending ANDA

ORIG AMENDMENT
N/AM

Reference: ANDA 76-134
Loratadine Tablets 10 mg

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets 10 mg submitted March 15, 2001. Reference is also made to the Amendment submitted to the Agency dated July 3, 2002.

By way of the July 3, 2002 Amendment Ranbaxy provided information for an additional packaging configuration for blisters and the addition of an outside firm [redacted] (b) (4) for the blister packaging operation. In addition, Ranbaxy provided additional information to the Agency on August 13, 2002 for diagrams of the blisters, IR data for the packaging components, permeation data as well as updated 12 month CRT stability data in the blister packs.

At this time Ranbaxy would like to make the following revision to the product specifications for the blister pack configuration:

- increase [redacted] (b) (4) specification for the Blister Packs ONLY from a limit of NMT [redacted] (b) (4)% to a limit of NMT [redacted] (b) (4)%.

Please see the attached Summary of information regarding this revision.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this amendment has been provided to the Food and Drug Administration, International Operations Group.

RECEIVED
FEB 27 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 response, please call me at 609-720-5609, or Abha Pant at 609-720-5666. Thank you.

Sincerely,

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

RANBAXY
PHARMACEUTICALS INC.

ORIGINAL

March 12, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Fax: 301-594-0183
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS & FAX
TELEPHONE
LABELING AMENDMENT

ORIG AMENDMENT
N/AF

Reference: **ANDA 76-134**
OTC Loratadine Tablets 10 mg

Dear Sir/Madam:

Reference is made to pending ANDA 76-134, for Loratadine Tablets 10 mg.

Reference is also made to the telephone contact of January 31, 2003 in which Ranbaxy was asked to further revise the container labeling for the above referenced product.

Provided on the following pages are the agencies telephone comments followed by Ranbaxy's response. The labels have been revised as requested. Twelve sets of the final printed revised labels are included in the **"original"** copy and an additional 6 sets of labeling are in the duplicate copy in **Attachment 1** of this submission. To facilitate review, we have provided a side-by-side labeling comparison with Ranbaxy's revised labeling and previously submitted, with all differences shown with the use of color, **Attachment 2.**

Please contact the undersigned at 609-720-5697, or Abha Pant at 609-720-5666, if you have any questions regarding this labeling amendment.

Sincerely,

RECEIVED
MAR 13 2003
OGD / CDER

Mary C. Goyette
Regulatory Labeling Coordinator (*for*)
Abha Pant, US Agent, Regulatory Affairs Director

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

RANBAXY
PHARMACEUTICALS INC.

March 27, 2003

FAX AND
UPS OVERNIGHT

AMENDMENT TO A
PENDING APPLICATION

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

NEW CORRESP
NC

RE: Loratadine Tablets, 10 mg
ANDA 76-134

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets, 10 mg. Reference is also made to the FDA telephone contact of March 26, 2003 in which the Agency requested a new correspondence regarding the status of the Civil Action suit regarding this ANDA.

Reference is made to our August 30, 2001 letter to the Agency (attached) in which Ranbaxy included a copy of Civil Action No. 01-CV-2990, filed on behalf of the Schering Corporation to the U.S. District Court of NJ on 6/22/01.

Ranbaxy hereby includes the most recent information pertaining to this patent and court case. Ranbaxy has recently been informed that the civil action has been administratively terminated by the US. District Court of NJ on February 28, 2003. (Please see attached letter).

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

RECEIVED
MAR 2 8 2003
OGD / CDER

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

MINOR AMENDMENT

APR - 3 2003

ANDA 76-134

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)

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

ATTN: Abha Pant, U.S. Agent FAX: 609-514-9797

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

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 15, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine Tablets, 10 mg.

Reference is also made to your amendment(s) dated: July 3, and August 13, 2002; and January 30, and February 26, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 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.

SGK
4/3/03

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-134

APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Loratadine Tablets, 10 mg

The deficiency presented below represents a Minor deficiency.

A. Deficiency:

A single out-of-limit result is not an adequate basis for a specification revision. Please provide full term stability data (24 months) to justify the increase in (b) (4) specification for the blister packs. Also please provide test data on tablet hardness and tablet friability for the blister packs at 24 months test interval along with data on other available stability samples.

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.

April 7, 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 AND FAX

Minor Amendment

ORIG AMENDMENT
N / AM

Reference: **ANDA 76-134**
Loratadine Tablets 10 mg

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets 10 mg submitted March 15, 2001. Reference is also made to the Minor Amendment received April 3, 2003.

The deficiency and our response are provided 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 amendment has been provided to the Food and Drug Administration, International Operations Group.

If you have any questions or comments regarding this response, 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
US Agent for Ranbaxy Laboratories Limited

RECEIVED
APR 09 2003
OGD / CDER

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

RANBAXY
PHARMACEUTICALS INC.

June 24, 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 AND FAX

Additional Information

ORIG AMENDMENT
N/Am

Reference: **ANDA 76-134**
Loratadine Tablets 10 mg

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets 10 mg submitted March 15, 2001. Reference is also made to the Minor Amendment response sent to the Agency on April 7, 2003 in which Ranbaxy submitted additional stability data on the 22 month time point to illustrate the results being observed for Loss on Drying.

Now that the full term stability data (24 months) is available, we hereby are submitting this data to supplement the application.

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

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this amendment has been provided to the Food and Drug Administration, International Operations Group.

Sincerely,

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

RECEIVED
JUN 25 2003
OGD / CDER

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

RANBAXY
PHARMACEUTICALS INC.

July 22, 2003

FAX AND
UPS OVERNIGHT

AMENDMENT TO A
PENDING APPLICATION

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

NEW CORRESP
NC

RE: Loratadine Tablets, 10 mg
ANDA 76-134

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets, 10 mg. Reference is also made to the FDA telephone contact of July 21, 2003 in which the Agency requested an update regarding the status of the Civil Action suit regarding this ANDA.

Reference is made to our August 30, 2001 letter to the Agency in which Ranbaxy included a copy of Civil Action No. 01-CV-2990, filed on behalf of the Schering Corporation to the U.S. District Court of New Jersey. The civil action as filed by Schering is included in **Attachment 1**.

As indicated in the attached complaint, Ranbaxy filed paragraph IV certifications against U.S. Patent Nos. 4,659,716 and 4,863,931. Schering Corporation filed an action for patent infringement under 35 USC 271(e)(2)(A) against Ranbaxy for alleged infringement only of the '716 patent. See paragraphs 2, 7 and 8 of **Attachment 1**.

The '716 patent, however, has been declared invalid 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 (see **Attachment 2**). This litigation consolidated civil action nos. 99-2237, 98-1259, 00-255, 99-2820, 00-1439, 00-1657, 00-2944, 01-9, 01-279, and 01-520. The result of the consolidated litigation is that the patent asserted against Ranbaxy has been declared invalid in a consolidated litigation over Loratadine.

As a consequence of the outcome of the consolidated litigation, the litigation between Schering and Ranbaxy has been administratively terminated in the attached Order from the District Court of New Jersey (see **Attachment 3**). Notice of this termination was provided to FDA in a letter from Ranbaxy dated March 27, 2003. Thus, although Ranbaxy was not a party to the consolidated litigation above, the patent holding in

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PHONE: (609) 720-9200 **FAX:** (609) 720-1155

that litigation is the same patent over which Schering sued Ranbaxy and for which the action has been administratively terminated.

If you have any questions regarding this submission please contact me at 609-720-5617 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Mike Yefimenko
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RANBAXY
PHARMACEUTICALS INC.

August 1, 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

AMENDMENT TO A
PENDING APPLICATION

RE: Loratadine Tablets, 10 mg
ANDA 76-134

NEW CORRESP
NC

Dear Sir/Madam:

Reference is made to the pending ANDA 76-134 for Loratadine Tablets, 10 mg. Reference is also made to the letter sent to the Agency on July 22, 2003 updating the Agency on the status of the Civil Action suit regarding this ANDA.

Today the United States Court of Appeals for the Federal Circuit has ruled that the District court did not err in their finding. The report is included in **Attachment 1**.

Based on the fact that the '716 patent has been declared invalid in the above mentioned consolidated litigation, Ranbaxy hereby requests for Final Approval of this ANDA.

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

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OGD APPROVAL ROUTING SUMMARY

NDA # 76-134 Applicant Ranbaxy Laboratories Limited
ug Loratadine Tablets, 10 mg Strength 10 mg

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

REVIEWER:	DRAFT Package	FINAL Package
1. Project Manager, Sarah Kim Review Support Br Team 4	Date _____ Initials _____	Date 8/8/03 Initials SK

Application Summary:

Original Rec'd date 3/19/01
Date Acceptable for Filing 3/19/01
Patent Certification (type) III, IV
Date Patent/Exclus.expires _____
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD =
Date checked _____ NDA# _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 7/16/02
Date of Office Bio Review 6/18/01
Date of Labeling Approv. Sum 3/25/03
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☒
Commitment Rcd. from Firm Yes ☐ No ☐
MV acceptable 11/30/02
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐ N/A

L
33 12/19/02
E
716 10/21/04
913 3/15/09

Previously reviewed and tentatively approved ☑ Date 12/20/01
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

2. ~~Gregg Davis~~ Martin Stoner
~~Deputy Director, DLPS~~ Branch Chief PPIII & IV ANDAs Only
Date 8/12/03 Initials MHS
Date 8/12/03 Initials MHS

Contains GDEA certification: Yes ☑ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☑ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☑ No ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐
Has case been settled: Yes ☑ No ☑ (see notes)
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☑ (Generic Pharmas PC exclusivity exp. 7/21/2003)
Comments: District court of NJ on 8/8/02 declared that claims 1 & 3 of the '716 patent are invalid.
- This District court decision was appealed by Schering
- on 2/28/03 the District Court of NJ stayed CA 01-2990 pending the resolution of consolidated appeals
- 8/1/03 the Appellate court affirmed the District courts decision that claims 1 & 3 of the '716 are invalid
- B/c the claims of the '716 patent were found invalid this decision applies to All ANDAs, not just those mentioned in the consolidated appeal

Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
Date Checked 12 August 2003
Nothing Submitted ☑
Written request issued ☐
Study Submitted ☐

3. Div. Dir./~~Deputy Dir.~~ O.K for final Approval
Chemistry Div. I
Date 8/14/03 Initials 12C
Date 8/15/03 Initials 12C
Comments:

The CMC section is satisfactory for AP.

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-134 Applicant Ranbaxy Laboratories Limited
dg Loratadine Tablets, 10 mg Strength 10 mg

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

REVIEWER:	DRAFT Package	FINAL Package
1. Project Manager, Sarah Kim Review Support Br Team 4	Date _____ Initials _____	Date 8/8/03 Initials SKim

Application Summary:

Original Rec'd date 3/19/01
Date Acceptable for Filing 3/19/01
Patent Certification (type) III, IV
Date Patent/Exclus.expires _____
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
(If YES, Pediatric Exclusivity Tracking System (PETS)

RLD =
Date checked _____ NDA# _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 7/16/02
Date of Office Bio Review 6/18/01
Date of Labeling Approv. Sum 3/25/03
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☒
Commitment Rcd. from Firm Yes ☐ No ☐
MV acceptable 11/30/02
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐ N/A

Previously reviewed and tentatively approved ☑ Date 12/20/01
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

83 12/9/02 I
716 10/21/04
913 3/15/09

2. Gregg Davis **PPIII & IV ANDAs Only** Deputy Director, DLPS	Date _____ Initials _____	Date 8/18/03 Initials for

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

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

RLD = Claritin Tablets 10mg
Schering Corp. NDA 19-658

Refer to M. Shimer's endorsement (attached). There is no unexpired exclusivity listed in the Orange Book for this drug product.

3. Div. Dir./Deputy Dir. Chemistry Div. I	Date _____ Initials _____	Date _____ Initials _____

Comments:

Please see the first page RLD

REVIEWER:	DRAFT Package	FINAL Package
4. Frank Holcombe Assoc. Dir. For Chemistry Comments: (First generic drug review)	Date Initials	Date Initials

N/A. This ANDA was previously tentatively approved on 12/20/01. Geneva's ANDA 75-209 for this drug product was approved on 1/21/03.

5. Peter Rickman Director, DLPS	Date 8/18/03 Initials RW	Date 8/18/03 Initials RW for

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

Comments: Acceptable, ES dated 7/16/02 (Verified 8/18/03). No OAE alerts noted. This ANDA was tentatively approved on 12/20/01 pending the outcome of litigation over the status of the '716 patent. Refer to the administrative sign-off form completed at that time. In the interim, Ranbaxy has made minor CMC changes and revised their PPL to conform to the proper content and format (Drug Facts Format). PPL found satisfactory for approval 3/25/03. CMC found acceptable 9/18/03. Methods validation was completed and found acceptable.

5. Robert L. West Deputy Director, OGD	Date 8/18/03 Initials RW	Date 8/18/2003 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 (3/15/09) and '716 (10/21/04) patents. Ranbaxy was sued by Schering over the '716 patent. On 8/8/02, a judgment was entered by the district court finding Schering's '716 patent to be invalid. This decision was appealed by Schering. On 8/1/03 the Federal Appeals Court affirmed the district court's decision.

180 day generic drug exclusivity previously granted to Geneva (ANDA 75-209 expired on 7/21/03.

This ANDA is recommended for approval.

6. Gary Buehler Director, OGD Comments:	Date 8/18/03 Initials GB	Date 8/18/03 Initials GB

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

7. Project Manager, Sarah Kim Review Support Br Team 4	Date 8/18/03 Initials SK	Date 8/18/03 Initials SK

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

Applicant notification:

10:45 AM Time notified of approval by phone 11:00 AM Time approval letter faxed

Left message for Abba Pant

FDA Notification:

8/18/03 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

8/18/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory..

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