CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75706

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY

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

ANDA Number: 75-706

Dates of Submission: January 29, 2003; December 26, 2002; and September 30, 2002

Applicant's Name: Andrx Pharmaceuticals, L.L.C.

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

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

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

CONTAINER Labels – Bottles of 100 and 1000:
Satisfactory as of the January 29, 2003 submission. [Vol. 6.1]

Revisions needed post-approval: None.

Patent Data – NDA 20-470

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

Exclusivity Data– NDA 20-470

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

BASIS OF APPROVAL:

Was this approval based upon a petition? No.

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

NDA Number: 20-470

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

NDA Firm: Schering Corporation

Date of Approval of NDA Insert and supplement: Nov. 27, 2002; NDA 20-470/SE6-016 (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-D® 24 HOUR (loratadine and pseudoephedrine sulfate, USP) Extended Release Tablets by Schering Corporation; NDA 20-470/SE6-016 (Rx to OTC switch); approved November 27, 2002.

This is the first generic for the loratadine/pseudoephedrine sulfate extended release 10 mg/240 mg OTC product.

2. PATENT/EXCLUSIVITIES

Patent Data – NDA 20-470

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

Exclusivity Data– NDA 20-470

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

3. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

NDA - Store between 15° and 25°C (59° and 77°F). Protect from light and store in a dry place.
ANDA - Store between 2° and 25°C (36° and 77°F). Protect from light and store in a dry place

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 Components and Composition statement.
[Vol. A1.1 pg. 80 of 9-21-99 submission.]

5. CONTAINER/CLOSURE SYSTEM

100 count: 150 cc white round HDPE bottle with 38mm white CRC with HS035 heat induction liner.
1000 count: 1500 cc white round HDPE bottle with 53mm white polypropylene cap with HS035 heat induction liner.
[Vol. A2.1, page 3 of 12-14-99 submission.]

Date of Review: 2/07/03 Dates of Submission: 1/29/03; 12/26/02; and 9/30/02

Primary Reviewer: Debra Catterson Date: /S/ 2/7/03

Team Leader: John Grace Date: /S/ 2/10/2003

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cc:

ANDA: 75-706
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)

Review

TENTATIVE APPROVAL SUMMARY

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

ANDA Number: 75-706

Date of Submission: December 14, 2000 (Amendment)

Applicant's Name: Andrx Pharmaceuticals, L.L.C.

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

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

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

CONTAINER Labels – [Bottles of 100's and 1000's]:
Satisfactory in **draft** as of the December 14, 2000 submission.

Professional Package INSERT:
Satisfactory in **draft** as of the December 14, 2000 submission.

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

1. CONTAINER (100's):

   Revise the last two digits of the NDC number to read "01" instead of "10".

2. INSERT:

   ADVERSE REACTIONS: First paragraph after "Urinary System:" section: Revise the first sentence to read: "Additional adverse events reported with the combination of loratadine and pseudoephedrine include abnormal hepatic function, aggressive reaction, anxiety, apathy,...".

I communicated these revisions to Diane Servello, of Andrx Pharmaceuticals, L.L.C., by telephone and by facsimile on January 4, 2002.

Patent Data – NDA 20-470

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

4659716*PED	October 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4863931	September 15, 2008	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
4863931*PED	March 15, 2009	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
5314697	April 23, 2013	n/a	Stable extended release oral dosage composition comprising loratadine and pseudoephedrine (http://www.uspto.gov/patft/index.html)	IV	None
5314697*PED	April 23, 2013	n/a	Stable extended release oral dosage composition comprising loratadine and pseudoephedrine (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 20-470

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

BASIS OF APPROVAL:

Was this approval based upon a petition? No.

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

NDA Number: 20-470

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

NDA Firm: Schering Corporation

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

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

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

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

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?		x	

– Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	

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

FOR THE RECORD:

1. MODEL LABELING

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

This is the first generic for the loratadine/pseudoephedrine sulfate extended release 10 mg/240 mg product.

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 20-470

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

Exclusivity Data– NDA 20-470

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

[Vol. A1.1 pg. 12 of 9-21-99 submission.]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Andrx Pharmaceuticals, L.L.C.
4001 SW 47th Avenue
Fort Lauderdale, FL 33314 [Vol. A1.1 pg. 233.]

4. CONTAINER/CLOSURE

100 count: 150 cc white round HDPE bottle with 38mm white CRC with HS035 heat induction liner.
1000 count: 1500 cc white round HDPE bottle with 53mm white polypropylene cap with HS035 heat induction liner.
[Vol. A2.1, page 3 of 12-14-99 submission.]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the components/composition statement.
[Vol. A1.1 pg. 80 of 9-21-99 submission.]

6. PACKAGING CONFIGURATIONS

RLD: Bottles of 100, and blister packages of 10 x 10 tablet Unit Dose-Hospital Pack.
ANDA: Bottles of 100 and 1000.
[Vol. A1.1 pg. 57]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None.
RLD: Store between 15° and 25°C (59° and 77°F).
ANDA: Same as RLD
[Vol. A1.1 pg.57]

8. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: Dispense in a tight container as defined in USP/NF (Container label only)
ANDA: Same as RLD.
[Vol. A1.1 pg. 58]

9. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on November 15, 2001, that the application is acceptable.
[Vol. A5.1]

Date of Review: 1/03/02 Date of Submission: 12/14/00

Primary Reviewer: Debra Catterson Date:
/S/ 1/4/02

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

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cc:

ANDA: 75-706
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)

Review

FIRST GENERIC

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

ANDA Number: 75-706

Date of Submission: December 14, 1999 (original draft labeling)

Applicant's Name: Andrx Pharmaceuticals, Inc.

Established Name: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets 10 mg/240 mg

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Labeling Deficiencies:

1. **CONTAINER** (Bottles of 100 and 1000); and
2. **INSERT:**

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

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

/S/

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

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