CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75706

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMISTRY REVIEW NO.# 1 (First Generic)

2. ANDA # 75-706

3. NAME AND ADDRESS OF APPLICANT:
Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4001 SW 47th Avenue
Ft. Lauderdale, FL 33314

4. LEGAL BASIS FOR SUBMISSION:
Reference listed drug: Claritin-D® 24 Hour
NDA Nos: N20470 001 (August 23, 1996)
Manufacturer: Schering

Patents: #4,282,233 expires: July 19, 2002
Note: Firm certified that it will not market the product prior to the expiration of this patent.

#4,659,716 expires: April 21, 2004
#4,863,931 expires: September 15, 2008
#5,314,697 expires: October 23, 2012
Note: Firm certified that it will comply with the requirements per section 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with requirements under section 314.95(c) with respect to content of the notices.

Exclusivity: Expired

Debarment Certification: Included (v1.2, page 703)

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Loratadine and Pseudoephedrine Sulfate, USP

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

9. AMENDMENTS AND OTHER DATES:
Firm:

09-21-1999	Date of Application
12-14-1999	Amendment - Response to refuse to file letter dated 11/22/99.
02-11-2000	New correspondence - Change in ownership
02-28-2000	New correspondence - Patent Amendment

FDA:
11-22-1999 Refuse to file letter
02-07-2000 ANDA Acceptance letter

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

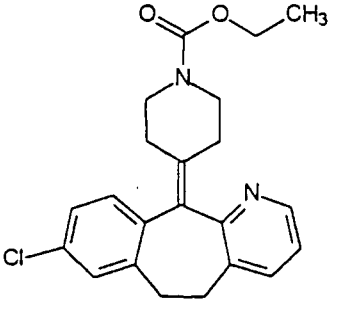
11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s):
DMF . See section #37 of this application for details.

13. DOSAGE FORM: Tablets, Extended-release

14. POTENCY: 10 mg/240 mg

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



Pseudoephedrine Sulfate. Benzenemethanol,α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate (2:1) (salt). $(C_{10}H_{15}NO)_2.H_2SO_4$. 428.54. [7460-121-0]. USP 24, page 1441.

16. RECORDS AND REPORTS: N/A

17. COMMENTS:
The following sections are *NOT SATISFACTORY:*
22. Synthesis
23. Raw material
26. Manufacturing and processing
27. Container
29. Laboratory Controls
30. Stability
The following sections are *PENDING*
33. EER

18. CONCLUSIONS AND RECOMMENDATIONS: Not approvable (MAJOR - NA)

19. REVIEWER: Neeru B. Takiar DATE COMPLETED: 04/06/00
Endorsed by D. Gill, Ph.D. Revised: 04/27/00; 7/18/00

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Chem Review #1

JUL 31 2000

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

NDA: 75-706 **APPLICANT:** Andrx Pharmaceuticals, Inc.

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

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. The following pertains to the chipping and imprinting of the tablets:

   a. On page 000245 of the application, you specify "ANDA test batch tablets were not imprinted with the product code, however, all production batches will be imprinted". Please explain why the bio batch tablets were not imprinted and how this bio batch is equivalent to production batch or listed drug product. Also, there was a significant loss of yield due to chipping of tablets (page 397).

   b. Please manufacture a new batch reflecting the manufacture of a tablet with proper imprinting and provide a complete certificate of analysis for the batch. In addition, please provide comparative content uniformity data on one hundred tablets for both batches, i.e. batch #605R004 and new batch with imprinted tablets.

   c. Please provide friability data on the coated tablets to show stability of tablets.

   d. Since weight variation is affected by both the core tablets and active ingredient, content uniformity assay of coated tablet should be established as an in-process control.

2. Both DMFs, for Loratadine and for Pseudoephedrine Sulfate USP, have been found deficient and the holders have been notified. Please provide the notification in your response that the DMF holders have responded to the deficiencies.

3. Please separate residual solvents from organic volatile impurities and provide a statement from the manufacturer indicating that per USP 24 <467>, no organic impurities other than are used in the manufacturing of drug substance, Loratadine.

4. Please develop a more accurate and precise method for the analysis of Loratadine to replace titration assay and include a specification for the identification of Loratadine by method on the certificate of analysis.

5. Please identify each known impurity for Loratadine by its chemical name and tighten the impurities limits (individual known and total) based on the actual observed values and provide them on the revised certificate of analysis for Loratadine drug substance.

6. Please establish and include bulk loose and bulk tapped density specification for drug substance, Loratadine.

7. Please justify the need to test Loratadine for sulfate and report the result in actual numerical value.

8. Please revise the Pseudoephedrine Sulfate specifications for ordinary impurities to as specified in the manufacturer's specifications (known, secondary and total). A method may be used for the identification and analysis of impurities. Actual numerical values should be reported on the certificate of analysis.

9. Please revise your re-testing schedule for active ingredients, Loratadine and Pseudoephedrine Sulfate, USP to state that the drug substance should be tested prior to its use, either one year after its original release date or its retest date and testing shall include all the analysis.

10. Please revise your re-testing schedule for inactive ingredients to state that the microbial testing for the inactives, where appropriate, should be conducted every year.

11. You submitted the master and exhibit packaging record for tablets and capsules. Please provide the revised intended and exhibit batch packaging record for tablets only, which is the subject of this ANDA, packaged in 100's and 1000's.

12. Please provide the multiple internal reflectance data for 1500 HDPE bottle to meet the USP <661> requirements.

13. Please establish a specification for tablet thickness based on the observed values and include it in the in-process controls.

14. testing should be performed as a routine in-process control for all production batches for this product. Between six to ten samples should be tested from each Samples should be between 1 to 3 equivalent of tablet weight. The specifications for assay should be revised to be between % with an RSD of NMT %. Please modify your Master Batch Records to include this test as a routine in-process control.

15. In-process specification for individual tablet weight is high. Please tighten to % of the theoretical tablet weight.

16. You submitted a copy of the blank batch record for the production size batches on December 14, 1999 in response to agency's comment, specifying the same in-process specification for hardness as listed for the ANDA batch . However, in-process specification for hardness submitted in the original application for post-approval production batches is Please provide the revised in-process controls for the post-approval production batches reflecting the correct specification for hardness.

17. Please revise your related compound specifications for the drug product release and stability to include limits for individual known, individual unknown and total impurities. Specifications reported for individual and total impurities are high. Please revise the impurity specifications to be closer to the actual observed values.

18. Please establish a specification for moisture content in the stability controls.

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

1. Please update your specifications for all excipients and provide the revised certificate of analysis to refer to USP 24.

2. A satisfactory cGMP compliance evaluation of the firms referenced in the ANDA is required for approval.

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

4. Acceptance of your dissolution method and specifications for release and stability are contingent upon the results of the bio-equivalence review.

5. Your response must also address the labeling deficiencies.

6. If the chipping issue is not resolved, we may not accept the previous batch 605R004 as the bio batch.

Sincerely yours,

/S/

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

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMISTRY REVIEW NO.#** 2

2. **ANDA #** 75-706

3. **NAME AND ADDRESS OF APPLICANT:**
Andrx Pharmaceuticals, Inc.
U.S. Agent for: Andrx Pharmaceuticals, L.L.C.
Attention: Diane Servello
4001 SW 47th Avenue
Ft. Lauderdale, FL 33314

4. **LEGAL BASIS FOR SUBMISSION:**
Reference listed drug: Claritin-D® 24 Hour
NDA Nos: N20470 001 (August 23, 1996)
Manufacturer: Schering

Patents: #4,282,233 expires: July 19, 2002
Note: Firm certified that it will not market the product prior to the expiration of this patent.

#4,659,716 expires: April 21, 2004
#4,863,931 expires: September 15, 2008
#5,314,697 expires: October 23, 2012
Note: Firm certified that it will comply with the requirements per section 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with requirements under section 314.95(c) with respect to content of the notices.

Exclusivity: Expired

Debarment Certification: Included (v1.2, page 703)

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

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

7. **NONPROPRIETARY NAME:** Loratadine and Pseudoephedrine Sulfate

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

9. **AMENDMENTS AND OTHER DATES:**

09-21-1999	Date of Application
12-14-2000	Major amendment - Response to deficiency letter dated 7/31/2000
12-15-2000	General correspondence-New address for future contact
03-12-2001	Amendment - Bioequivalence

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

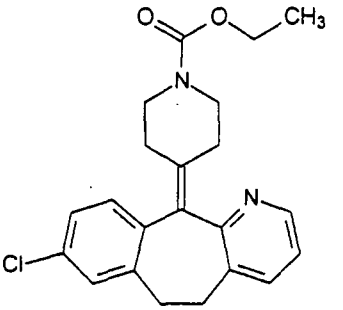
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
DMF . See section #37 of this application for details.

13. **DOSAGE FORM**: Tablets, Extended-release

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

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



Pseudoephedrine Sulfate. Benzenemethanol,α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate (2:1) (salt). $(C_{10}H_{15}NO)_2.H_2SO_4$. 428.54. [7460-121-0]. USP 24, page 1441.

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

17. **COMMENTS**:
The following sections are *NOT SATISFACTORY:*
22. Synthesis
23. Raw material
29. Laboratory Controls
30. Stability
The following sections are *PENDING*
32. Labeling

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

19. **REVIEWER:** Neeru B. Takiar **DATE COMPLETED:** 05/11/01
Endorsed by D. Gill, Ph.D.

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Chem. Review #2

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-706 **APPLICANT**: Andrx Pharmaceuticals, Inc.

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

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please note that the DMF for Pseudoephedrine sulfate, USP has been found deficient and the holder, has been notified of the DMF deficiencies. Please do not respond to this MINOR amendment until you have been informed by the DMF holder stating that a satisfactory response to the Agency's deficiency letter has been submitted.

2. Your response to deficiency 5 in the amendment dated December 14, 2000 regarding impurities specification is not satisfactory. The proposed impurity specifications for the loratadine drug substance are high. Please lower the acceptance criteria for individual known and total impurities for loratadine to be closer to the actual observed values.

3. Please reduce the specification for heavy metals for loratadine drug substance to NMT ppm.

4. Your response to deficiency 10 in the amendment dated December 14, 2000 regarding microbial test for inactive is not satisfactory. Please revise your re-testing schedule for inactive ingredients to specify that the microbial test should be performed every year for the inactive ingredients requiring microbial testing.

5. Your response to deficiency 14 in the amendment dated December 14, 2000 regarding testing is not satisfactory. It is recommended that testing for pseudoephedrine sulfate must be performed as a routine in-process control for all production batches for this product. Please modify the in-process controls in your Master Batch Records accordingly.

6. Your response to deficiency 17 in the amendment dated December 14, 2000 regarding impurity specification for drug product release and stability is not satisfactory. The proposed specifications for known, unknown and total impurities for drug product release and stability are high. Please lower the limit for impurities close to the actual observed values.

7. The dissolution testing should be incorporated into your stability and quality control program as recommended by the Division of Bio-equivalence:

Please provide the revised specifications accordingly.

8. Your response to deficiency 18 in the amendment dated December 14, 2000 regarding moisture testing for drug product stability is not satisfactory. Please revise the stability protocol to state that moisture content for the drug product packaged in the marketed container will be monitored for the first three production batches and establish a specification for moisture content in the stability controls.

9. Please provide the full term (24 months) controlled room temperature stability data for both lots #605R004 (previous) and #605R005 (new) packaged in marketed container/closure systems for the approval of this drug product.

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

1. Request to perform the methods validation for the new drug substance, Loratadine and the finished dosage form has been submitted to the FDA district office. Please submit samples promptly when requested.

2. Your response to the labeling deficiencies is pending review. Any comment, if found will be communicated in a separate letter.

Sincerely yours,

/S/ for 6-12-01

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

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMISTRY REVIEW NO.#** 3

2. **ANDA #** 75-706

3. **NAME AND ADDRESS OF APPLICANT:**
Andrx Pharmaceuticals, Inc.
U.S. Agent for: Andrx Pharmaceuticals, L.L.C.
Attention: Diane Servello
4001 SW 47th Avenue
Ft. Lauderdale, FL 33314

4. **LEGAL BASIS FOR SUBMISSION:**
Reference listed drug: Claritin-D® 24 Hour
NDA Nos: N20470 001 (August 23, 1996)
Manufacturer: Schering

Patents: #4,282,233 expires: July 19, 2002
Note: Firm certified that it will not market the product prior to the expiration of this patent.

#4,659,716 expires: April 21, 2004
#4,863,931 expires: September 15, 2008
#5,314,697 expires: October 23, 2012
Note: Firm certified that it will comply with the requirements per section 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with requirements under section 314.95(c) with respect to content of the notices.

Exclusivity: Expired

Debarment Certification: Included (v1.2, page 703)

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

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

7. **NONPROPRIETARY NAME:** Loratadine and Pseudoephedrine Sulfate

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

9. **AMENDMENTS AND OTHER DATES:**
09-21-1999 Date of Application
07-17-2001 Minor amendment - Response to deficiency letter dated 6/13/2001

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

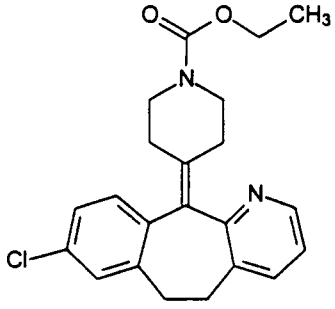
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
DMF . See section #37 of this application for details.

13. **DOSAGE FORM**: Tablets, Extended-release

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

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



Pseudoephedrine Sulfate. Benzenemethanol,α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate (2:1) (salt). $(C_{10}H_{15}NO)_2.H_2SO_4$. 428.54. [7460-121-0]. USP 24, page 1441.

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

17. **COMMENTS**:
The following sections are *NOT SATISFACTORY:*
23. Raw material
29. Laboratory Controls
30. Stability
The following sections are *PENDING*
32. Labeling

18. **CONCLUSIONS AND RECOMMENDATIONS**: Not approvable (NA - FAX)

19. **REVIEWER**: Neeru B. Takiar **DATE COMPLETED**: 08/31/01
Endorsed by D. Gill, Ph.D.

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Chem. Review #3

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-706 **APPLICANT:** Andrx Pharmaceuticals, Inc.

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

The deficiencies presented below represent FAX deficiencies.

A. Deficiencies:

1. Your response to deficiency 2 in the amendment dated July 17, 2001 is not satisfactory. Please lower the acceptance limit for total impurities for loratadine drug substance or provide justification for the proposed limit %).

2. Please correct the assay specification for loratadine drug substance, tab 2, amendment dated July 17, 2001 and provide the revised specifications.

3. Your response to deficiency 6 in the amendment dated July 17, 2001 is not satisfactory. Please lower the acceptance limit for total impurities for drug product release and stability or provide justification for the proposed limit %).

4. It is noted that there is a significant drop in the stability assay value for loratadine at 24 months test point time, lot #605R004, page 0111. Up and down trend is also observed for loratadine assay for room temperature and accelerated stability studies, lot #605R005, pages 0121, 0123, and 0125. However, no increase in degradation of the drug product is observed. Please provide explanation and justify that the analytical method for determining the assay and degradation for this drug product is stability indicating.

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

1. Review of your response to deficiency 7 in amendment dated July 17, 2001 will not be completed until the issues on dissolution specifications are resolved with the Division of Bio-equivalence. Please submit the final dissolution specifications after the issues are resolved toward drug product release and stability in order to complete the chemistry review.

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

Sincerely yours,

/S/ 9/17/01

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

cc: ANDA 75-706
Field Copy
Division File

Endorsements:

HFD-623/N.Takiar/08-31-01 09-05-01 N. Takiar 9/17/01
HFD-623/J.Franolic for D.Gill, Ph.D./09-14-01 John Franolic (for) 9/17/01
HFD-617/R.Yu, PM/09-14-01 9/17/01

F/T by: gp/09-17-01

FAX

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMISTRY REVIEW NO.#** 4

2. **ANDA #** 75-706

3. **NAME AND ADDRESS OF APPLICANT:**
Andrx Pharmaceuticals, Inc.
U.S. Agent for: Andrx Pharmaceuticals, L.L.C.
Attention: Diane Servello
4001 SW 47th Avenue
Ft. Lauderdale, FL 33314

4. **LEGAL BASIS FOR SUBMISSION:**
Reference listed drug: Claritin-D® 24 Hour
NDA Nos: N20470 001 (August 23, 1996)
Manufacturer: Schering

Patents: #4,282,233 expires: July 19, 2002
Note: Firm certified that it will not market the product prior to the expiration of this patent.

#4,659,716 expires: April 21, 2004
#4,863,931 expires: September 15, 2008
#5,314,697 expires: October 23, 2012
Note: Firm certified that it will comply with the requirements per section 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with requirements under section 314.95(c) with respect to content of the notices.

Exclusivity: None

Debarment Certification: Included (v1.2, page 703)

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

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

7. **NONPROPRIETARY NAME:** Loratadine and Pseudoephedrine Sulfate

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

9. **AMENDMENTS AND OTHER DATES:**
09-21-1999 Date of Application
10-16-2001 Fax amendment - Response to deficiency letter dated 9/18/2001

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

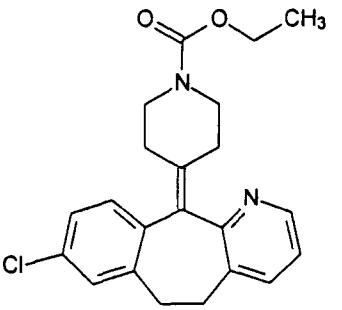
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
DMF . See section #37 of this application for details.

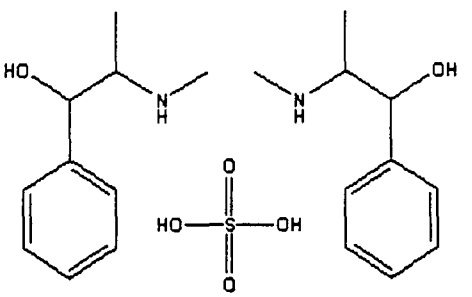
13. **DOSAGE FORM**: Tablets, Extended-release

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

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



Pseudoephedrine Sulfate. Benzenemethanol,α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate (2:1) (salt). $(C_{10}H_{15}NO)_2.H_2SO_4$. 428.54. [7460-121-0]. USP 24, page 1441.



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

17. **COMMENTS**:
The following sections are *Deficient*:
22. Synthesis
23. Drug Substance
29. Laboratory Controls
30. Stability
The following section is *Pending*:
32. Labeling

18. **CONCLUSIONS AND RECOMMENDATIONS**: NOT Approvable - NA MINOR

REVIEWER: Neeru B. Takiar **DATE COMPLETED**: 12/06/01
Endorsed by D. Gill, Ph.D.

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Chem Review #4

DEC 1 9

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-706 **APPLICANT:** Andrx Pharmaceuticals, L.L.C.

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

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. DMF for loratadine drug substance has been found inadequate and the DMF holder, has been informed. Please provide notification in your response that the DMF holder has responded to the Agency's deficiency letter.

2. You have been requested twice previously to tighten the acceptance limit for total impurities for drug substance, drug product release, and stability to reflect the actual observed test values obtained for the ANDA batch. However, your revised specification in the amendment dated October 16, 2001 (deficiency 1 & 3) is still high. Please lower the specification further to more accurately reflect the results obtained for the ANDA batch.

3. Please revise and provide the final dissolution acceptance criteria for Loratadine/Pseudoephedrine Sulfate Extended Release Tablets according to as recommended by the Division of Bio-equivalence for release and stability. Please provide the room temperature stability data and if possible, accelerated stability data to support the revised dissolution specifications.

4. Please provide data to justify that the three other synthetic impurities found in the loratadine drug substance are not degradants of the drug product.

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

1. Labeling comments, if any, will be sent to you under separate cover.

Sincerely yours,

/S/

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

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMISTRY REVIEW NO.#** 5

2. **ANDA #** 75-706

3. **NAME AND ADDRESS OF APPLICANT:**
Andrx Pharmaceuticals, Inc.
U.S. Agent for: Andrx Pharmaceuticals, L.L.C.
Attention: Diane Servello
4001 SW 47th Avenue
Ft. Lauderdale, FL 33314

4. **LEGAL BASIS FOR SUBMISSION:**
Reference listed drug: Claritin-D® 24 Hour
NDA Nos: N20470 001 (August 23, 1996)
Manufacturer: Schering

Patents: #4,282,233 expires: July 19, 2002
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Note: Firm certified that it will comply with the requirements per section 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with requirements under section 314.95(c) with respect to content of the notices.

Exclusivity: None

Debarment Certification: Included (v1.2, page 703)

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

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

7. **NONPROPRIETARY NAME:** Loratadine and Pseudoephedrine Sulfate

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

9. **AMENDMENTS AND OTHER DATES:**
09-21-1999 Date of Application
01-23-2002 Minor amendment-Response to deficiency letter of 12/13/01

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

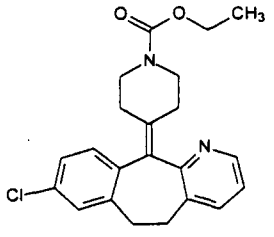
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
DMF See section #37 of this application for details.

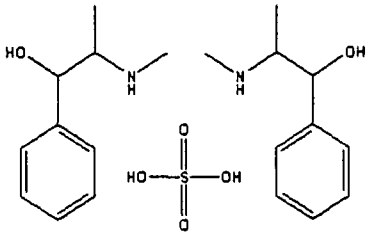
13. **DOSAGE FORM**: Tablets, Extended-release

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

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



Pseudoephedrine Sulfate. Benzenemethanol,α-[1-(methylamino)ethyl]-; [*S*-(*R**,*R**)]-, sulfate (2:1) (salt). $(C_{10}H_{15}NO)_2.H_2SO_4$. 428.54. [7460-121-0]. USP 24, page 1441.



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

17. **COMMENTS**: N/A

18. **CONCLUSIONS AND RECOMMENDATIONS**: Approvable

19. **REVIEWER**: Neeru B. Takiar **DATE COMPLETED**: 06/27/02

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Chem. Review #5

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMISTRY REVIEW NO.#** 6

2. **ANDA #** 75-706

3. **NAME AND ADDRESS OF APPLICANT:**
Andrx Pharmaceuticals, LLC
Attention: Janet Vaughn
4955 Orange Avenue
Ft. Lauderdale, FL 33314

4. **LEGAL BASIS FOR SUBMISSION:**
Reference listed drug: Claritin-D® 24 Hour
NDA Nos: N20470 001 (August 23, 1996)
Manufacturer: Schering

Patents: #4,282,233 expires: December 19, 2002
Note: Firm certified that it will not market the product prior to the expiration of this patent.

#4,659,716 expires: October 21, 2004
#4,863,931 expires: March 15, 2009
#5,314,697 expires: April 23, 2013
Note: Firm certified that it will comply with the requirements per section 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with requirements under section 314.95(c) with respect to content of the notices.

Exclusivity: None

Debarment Certification: Included (v1.2, page 703)

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

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

7. **NONPROPRIETARY NAME:** Loratadine and Pseudoephedrine Sulfate

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

9. **AMENDMENTS AND OTHER DATES:**

09-21-1999	Date of Application
09-30-2002	Minor amendment-Final Approval Request (Tentatively approved on July 9, 2002
01-06-2003	Response to T-con dated 12/12/02 regarding TAMPER-EVIDENT PACKAGING

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

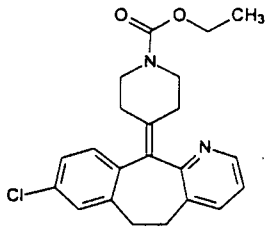
11. **Rx or OTC**: OTC

12. **RELATED IND/NDA/DMF(s)**:
DMF . See section #37 of this application for details.

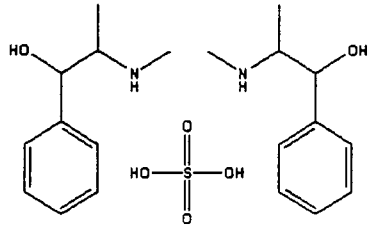
13. **DOSAGE FORM**: Tablets, Extended-release

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

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



Pseudoephedrine Sulfate. Benzenemethanol,α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate (2:1) (salt). $(C_{10}H_{15}NO)_2.H_2SO_4$. 428.54. [7460-121-0]. USP 26.



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

17. **COMMENTS**: N/A

18. **CONCLUSIONS AND RECOMMENDATIONS**: Approvable

19. **REVIEWER:** Neeru B. Takiar **DATE COMPLETED:** 01/30/03

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Chem. Review #6