CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-300

CHEMISTRY REVIEW(S)

NDA 21-300
Chem. Rev. 3

Clarinex Syrup

Schering Corporation

Prasad Peri
Division of New Drug Chemistry II
Office of New Drug Chemistry

Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-300

2. REVIEW #: 3

3. REVIEW DATE: June 6, 2004

4. REVIEWER: Prasad Peri, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	Dec. 8, 2000
Chemistry Review # 1 (Dr. Kevin Swiss)	Jan. 26, 2001
Chemistry Review # 2 (Dr. Prasad Peri)	Oct. 16, 2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment BC (resubmission) Response to AE Letter dated Nov. 9, 2001	Feb. 27, 2004
Amendment BC (Response to Fax dated Aug. 6, 2004)	Aug. 13, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Schering Corporation
Address:	2000 Galloping Hill Road, Kenilworth, NJ 07033
Representative:	Nicholas J. Pellicione, Vice President CMC Global Regulatory Affairs
Telephone:	908-740-4355

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Clarinex™ (desloratadine) Syrup.
b) Non-Proprietary Name (USAN): desloratadine syrup (0.5 mg/mL)
c) Code Name/# (ONDC only): SCH 483
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(1) of the FD&C Act

10. PHARMACOL. CATEGORY:
Peripheral H_1-receptor antagonist for Allergic Rhinitis/Chronic Idiopathic Urticaria

11. DOSAGE FORM:
Syrup

12. STRENGTH/POTENCY:

0.5 mg/mL

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

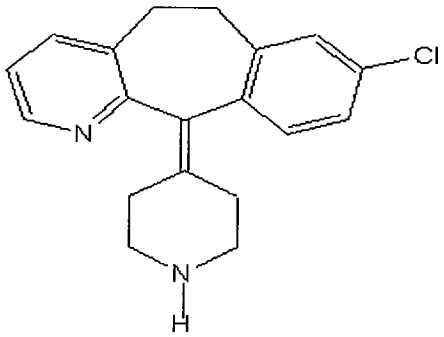
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

8-Chloro-6,11-dihydro-11-(4-piperdinylidene)-5*H*-benzo-[5,6]cyclohepta[1,2-b]pyridine

Molecular Formula: $C_{19}H_{19}ClN_2$

Molecular Weight: 310.8

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
				1	Adequate	11/5/99	
				3	Adequate	11/5/98	
				3	Adequate	4/30/96	
				3	Adequate	1/11/01	
				3	Adequate	4/16/04	See review by Bart Ho
				1	Adequate	1/23/01	
				1	Adequate	7/27/04	
				1	Adequate	1/11/01	
				N/A	Withdrawn from NDA on 5/22/01	N/A	

[1] Action codes for DMF Table:

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION/INDICATION
IND	**59,109**	Desloratadine Reditabs
[redacted]	[redacted]	[redacted]
IND	**58,545**	Desloratadine and Pseudoephedrine Tablets (SCH 483-QD)
IND	**58,506**	Desloratadine and Pseudoephedrine Tablets (SCH 483-BID)
IND	**57,960**	Desloratadine Syrup
IND	**55,364**	SCH 34117 Tablets
NDA	**21-165**	Clarinex Tablets
NDA	**21-297**	Clarinex Tablets (Chronic Idiopathic Urticaria)
NDA	**21-312**	Clarinex Orally Disintegrating Tablets

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Necessary		
EES	Sent	March 16, 2004	Adequate
Pharm/Tox	Not Necessary		
Biopharm	N/A		
LNC	Pending		Schering updated the name of the drug product to Aerius Syrup. A OPDRA consult has been forwarded by the project manager. The evaluation is pending
Methods Validation	To be sent		Will be sent pending resolution of acceptance criteria for drug product
OPDRA	To be sent		New name has been forwarded to the OPDRA for their evaluation.
EA	Acceptable		
Microbiology	N/A		

The Chemistry Review for NDA 21-300

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA may be approved from a CMC perspective. Note that NDA 21-563 (Clarinex Syrup for pediatric use in patients 6 months to <2 years) is supported by NDA 21-300. The drug products are identical. Since all the CMC related issues (pending Aerius name change evaluation from OPDRA) in NDA 21-300 are resolved, in this review, NDA 21-563 may be approved as well. A separate cover form and executive summary is not being made. This review essentially supports both the NDAs.

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

The Agency acknowledges your agreement to re-evaluate the proposed shelf life acceptance criteria for impurities [redacted] based on stability data for the [redacted] marketed batches and [redacted] ubsequent stability batches.

The Agency also acknowledges your agreement to revise the acceptance criteria for all impurities at release and shelf life to [redacted] of the NDA approval.

The Agency also acknowledges your agreement to report with six months (6) months the status report on your good faith effort at developing and validating a direct test method for quantificating the impurities in [redacted] Further if an appropriate method is developed and validated, appropriate acceptance criteria will be established.

II. Summary of Chemistry Assessments

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

Drug Substance

Schering references an approved NDA 21-165 in total for desloratadine drug substance. This NDA was approved Dec. 21, 2001. The drug substance manufacturing sites provided in NDA 21-165 are Schering Avondale ([redacted]). This DMF was last reviewed in April 2004 and found acceptable.

Drug Product

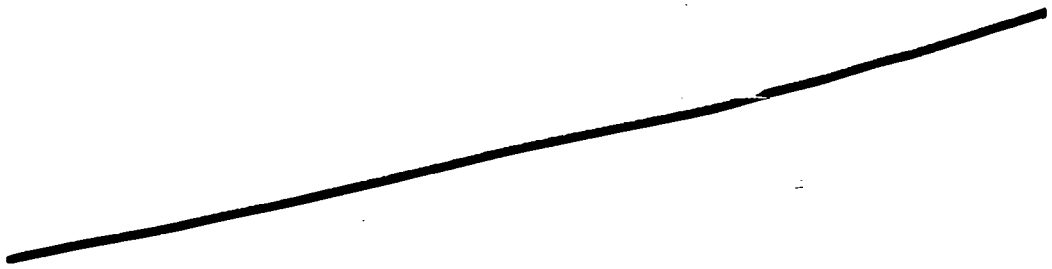
Drug product is an aqueous syrup dosage form, clear orange in color, presented in three container-closures: ¾-ounce amber [redacted] glass bottle, 4-ounce amber [redacted] glass bottle, and a 16-ounce amber [redacted] glass bottle.

The excipients of the drug product are propylene glycol USP, Sorbitol Solution USP, Citric Acid Anhydrous USP, Sodium Citrate Dihydrate USP, Sodium Benzoate NF, Edetate Sodium USP, Sucrose NF, Natural and Artificial Flavor for Bubble Gum ([redacted]), Dye FD&C Yellow No. 6, Water Purified USP.

The applicant has provided 36 months of long term stability data for 3 pilot scale batches and 3 commercial scale batches [redacted] The stability data and the statistical analyses support the proposed shelf life of 24 months for the drug product.

Initial indications suggested that at the one month time point the 3/4 ounce bottle exhibited significantly higher amount of impurities compared to the 4 oz and 16 ounce bottles. However this trend evened out at the late stages in stability for all the bottles. This data is provided and evaluated in this review.

The proposed acceptance criteria for the degradants are supported by the data provided. However, the applicant is being asked to revise the acceptance criteria for degradants and impurities to [redacted] to be consistent with other products. The applicant has agreed to revise the acceptance criteria for all degradants to [redacted] of the approval of the NDA.



The Agency suggested that Schering also agree to perform a good faith effort at developing a direct test method for quantificating these low level impurities in [redacted] Schering agreed to this in their amendmend dated August 13, 2004. Schering will provide to the Agency a status report on their efforts within six months of the approval of the NDA.

A biometric consult is not being requested to evaluate the shelf life since the proposed acceptance limits for the drug product will be easily met by the drug product at release and stability.

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

The drug product is oral solution to be administered by a calibrated dropper or other suitable device.

C. Basis for Approvability or Not-Approval Recommendation

The drug product may be approved from a Chemistry Manufacturing and Controls perspective with a 24 month shelf life.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Prasad Peri
Chemistry Team Leader Name/Date: Rik Lostritto
Project Manager Name/Date: Zeccola, Antony

C. CC Block

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- 1

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/s/

Prasad Peri
8/16/04 03:54:49 PM
CHEMIST

Richard Lostritto
8/17/04 05:20:43 PM
CHEMIST

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-300 **CHEM. REVIEW #:** 1 ADDENDUM **REVIEW DATE:** 6/25/01

RECOMMEND ACTION: NOT APPROVABLE

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12/8/00	12/8/00	1/9/00
AMENDMENT C/BC*	3/26/01*	3/28/01*	3/28/01*

NAME & ADDRESS OF APPLICANT: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

DRUG PRODUCT NAME:

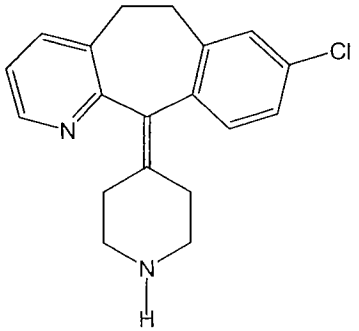
Proprietary: Clarinex™ (desloratadine) Syrup

Nonproprietary/USAN: desloratadine syrup (0.50 mg/mL)

Code Name/#: SCH 34117
Chem. Type/Ther. Class: 3S

PHARMACOL. CATEGORY/INDICATION: Peripheral H_1-receptor antagonist for Allergic Rhinitis/Chronic Idiopathic Urticaria
DOSAGE FORM: Aqueous Syrup (solution)
STRENGTHS: 0.50 mg/mL (Total Daily Dose: 5 mg)
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx _ OTC
SPECIAL PRODUCTS: _ YES X NO
(If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)

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



8-Chloro-6,11-dihydro-11-(4-piperdinylidene)-5*H*-benzo-[5,6]cyclohepta[1,2-b]pyridine
Molecular Formula: $C_{19}H_{19}ClN_2$
Molecular Weight: 310.8

CONCLUSIONS AND RECOMMENDATIONS:

The application is still not approvable from the standpoint of chemistry, manufacturing and controls. Deficiencies were detailed in the accompanying review notes in CR#1 and were forwarded to the applicant in a discipline review letter dated February 8, 2001.

cc:
Orig. NDA 21-300
HFD-570/Division File N21-300
HFD-570/KSwiss/6/25/01
HFD-570/GTrout
HFD-570/GPoochikian
HFD-820/CHoiberg
R/D Init. by: _____
filename: N21300.CR1AD.DOC

_____
Kevin A. Swiss, Ph.D. Review Chemist

3 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- 2

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/s/

Kevin Swiss
6/25/01 04:28:10 PM
CHEMIST

Guiragos Poochikian
6/25/01 04:44:16 PM
CHEMIST

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-300 **CHEM. REVIEW #:** 1 **REVIEW DATE:** 1/26/01

RECOMMEND ACTION: NOT APPROVABLE

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12/8/00	12/8/00	1/9/00

NAME & ADDRESS OF APPLICANT: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

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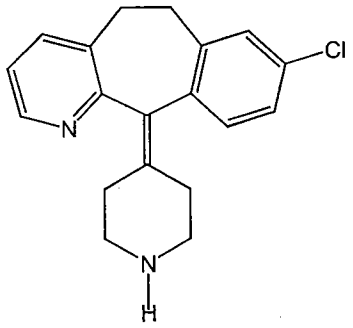

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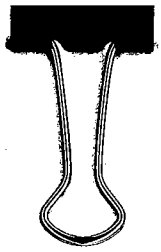
Molecular Formula: $C_{19}H_{19}ClN_2$
Molecular Weight: 310.8

CONCLUSIONS AND RECOMMENDATIONS:

The application as submitted is not approvable from the standpoint of chemistry, manufacturing and controls. Deficiencies are detailed in the accompanying review notes and summarized in the attached draft letter to the applicant, chemistry portion. These deficiencies should be promptly forwarded to the applicant.

cc:
Orig. NDA 21-300
HFD-570/Division File N21-300
HFD-570/KSwiss/1/26/01
HFD-570/GTrout
HFD-570/GPoochikian
HFD-820/SKoepke
R/D Init. by: _____
filename: N21300.CR1.DOC

_____
Kevin A. Swiss, Ph.D. Review Chemist



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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- 3

/s/

Kevin Swiss
1/30/01 10:04:11 AM
CHEMIST

Guiragos Poochikian
1/30/01 02:35:59 PM
CHEMIST