CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-312

CHEMISTRY REVIEW(S)

NDA 21-312

Clarinex®RediTabs® (desloratadine orally disintegrating tablets)

Schering Corporation

Craig M. Bertha, Ph.D.
Division of Pulmonary and Allergy Drug Products (HF-570)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21312

2. REVIEW #4:

3. REVIEW DATE: 29-MAY-2002

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Amendment	05-OCT-2001
Amendment	19-JUL-2001
Amendment	22-MAY-2001
Amendment	26-MAR-2001
Amendment	13-MAR-2001
Original NDA	21-DEC-2000

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	21-DEC-2001 (assigned 28-MAY-2002)

7. NAME & ADDRESS OF APPLICANT:

Name:	Schering Corporation
Address:	Galloping Hill Road Kenilworth, NJ 07033
Representative:	Dr. Joseph Lamendola
Telephone:	(908) 740-2628

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Clarinex® RediTabs®
b) Non-Proprietary Name (USAN): desloratadine orally disintegrating tablets
c) Code Name/# (ONDC only):N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: antihistamine (peripheral H_1-receptor antagonist) for treatment of seasonal allergic rhinitis (SAR) and for treatment of chronic idiopathic urticaria in patients 12 and older

11. DOSAGE FORM: orally disintegrating tablets

12. STRENGTH/POTENCY: 5 mg of desloratadine per dosage unit

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: X Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) [Note22]:

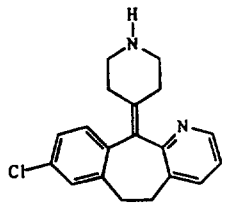
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Chemical Names: 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-benzo[5,6]cylcohepta[1,2-b]pyridine

Molecular Formula: $C_{19}H_{19}ClN_2$
Molecular Wt: 310.8
CAS Reg. No.:



Desloratadine

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	4	[redacted]	[redacted]	3	Adequate	09-MAR-2001	See p. 10 of CR#1
[redacted]	3	[redacted]	[redacted]	3	Adequate	08-MAR-2001	See p. 32 of CR#1
[redacted]	4	[redacted]	[redacted]	3	Adequate	25-SEP-1996	See p. 10 of CR#1

[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 are enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
NDA 21-165	Schering Corp.	Drug Substance	Adequate	See reviews for related approved NDA	DS information was referenced to the tablet NDA

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
Investigation New Drug Application	IND [redacted]	Schering Corp	Original IND for Clarinex RediTabs (desloratadine orally disintegrating tablets)

18. CONSULTS/CMC-RELATED REVIEWS:

Chemistry Review Data Sheet

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Expiration Dating Period Expiration Dating Period	30-JUL-2001 28-MAY-2002	-Final 19-OCT-2001/F. Zhou, Ph.D. -Final 29-May-2002/F. Zhou, Ph.D.	[redacted]
EES		28-MAY-2002	WITHHOLD as of 8/10/01	update request submitted
Pharm/Tox	N/A			See N21-165 and p. 26 of CR#1
Biopharm	N/A			
OPDRA	Trademark and imprint review	15-MAR-2001	-Final 23-APR-2001	Recommended unit-of-use labeling and distinct labeling coloring
Methods Validation	DP methods	15-Oct-2001	Pending from San Juan, Report from Philadelphia received on 28-DEC-2001	Review to be done when both reports available
EA	N/A			Categorical exclusion requested based on low environmental exposure (considers all dosage forms for desloratadine), see p. 42 of CR#1
Microbiology	N/A			See p. 31 of CR#1 regarding methods and p. 32 of CR#1 regarding microbial limits

APPEARS THIS WAY
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The Chemistry Review for NDA 21-312

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommended action for this application from the CMC perspective is **approvable (AE)** pending the recommendation of ACCEPTABLE from the Office of Compliance regarding all of the associated sites that will be used for the manufacture and control for preparation of this drug product. Note that an update request was submitted to the EES on 28-MAY-2002.

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)

The drug product is an orally disintegrating tablet containing 5 mg of the antihistamine desloratadine (SCH 34117) with a total tablet weight after ——— ——— The dosage form is unique in that it can be taken orally both with or without water. The orally disintegrating tablets are packaged in foil-foil——— blisters and it is noted that [ ] formulation. The drug substance desloratadine is a metabolite of loratadine but due to the loss of the ethyl carbamate moiety relative to loratadine, the molecule is more basic and has enhanced solubility under acidic conditions. The gelatin and mannitol included in the formulation are ——— ——— dosage form. The gelatin ——— and the mannitol the ——— The dosage unit is flavored ——— polacrilin potassium ——— the active. Aspartame is ——— and citric acid ——— ——— ——— ——— Due to the unique character of the formulation and dosage form, the applicant has incorporated a specification for dosage unit tensile strength, which is somewhat analogous to hardness testing for

tablets. Clinical batches, primary stability, and the proposed formulation are the same, thus no bridging studies were necessary.

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

Due to the nature of the dosage form, the drug product is only provided in unit-of-use blisters. After peeling off the foil blister backing, the orally disintegrating tablet can be pushed from the blister backing and can be taken orally either with or without water.

C. Basis for Approvability or Not-Approval Recommendation

From the CMC perspective, the application is approvable pending the resolution of GMP problems and an acceptable recommendation from OC.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D., Review Chemist
HFD-570/820

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C. CC Block

cc:
Orig. NDA 21-312
HFD-570/Division File
HFD-570/CBertha
HFD-570/GPoochikian
HFD-570/AZeccola
HFD-570/SBarnes

R/D Init. by: GPoochikian

Filename and Location: c:\data\mydocuments\reviews etc\NDA\21312\01-12-21.rev.doc

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/s/

Craig Bertha
6/3/02 06:57:40 AM
CHEMIST

Guiragos Poochikian
6/3/02 02:29:20 PM
CHEMIST

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

NDA #: 21-312 **CHEM. REVIEW #** 3 **REVIEW DATE:** 10/15/01

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12/21/00	12/21/00	3/05/01
CORRESPONDENCE[1]	3/13/01	3/15/01	3/16/01
AMENDMENT	3/26/01	3/28/01	4/3/01
AMENDMENT	5/22/01	5/23/01	5/29/01
AMENDMENT	7/19/01	7/20/01	7/25/01
AMENDMENT[2]	10/5/01	10/9/01	10/9/01

[1]DP samples; [2]Subjects of this review.

NAME & ADDRESS OF APPLICANT: Schering Corporation
Galloping Hill Road
Kenilworth, N.J.
07033

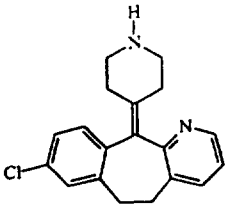
DRUG PRODUCT NAME

Proprietary:	Clarinex® Reditabs®
Nonproprietary/USAN:	desloratadine rapidly-disintegrating tablets
Code Name/#:	SCH 34117
Chem.Type/Ther.Class:	1S

PHARMACOL. CATEGORY/INDICATION: antihistamine (peripheral H_1-receptor antagonist) for treatment of seasonal allergic rhinitis (SAR) and for treatment of chronic idiopathic urticaria in patients 12 and older

DOSAGE FORM: tablet
DOSE: 5 mg once daily
STRENGTHS: 5 mg/tablet
ROUTE OF ADMINISTRATION: oral
DISPENSED: _X_ Rx ___ OTC
SPECIAL PRODUCTS: ___Yes _X_ No

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



Desloratadine

8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-benzo[5,6]cylcohepta[1,2-b]pyridine
Molecular Formula: $C_{19}H_{19}ClN_2$

Molecular Weight: 310.8

SUPPORTING DOCUMENTS:

DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 review
— Type IV	—	—	adequate	3/9/01 (C. Bertha, HFD-570)	See p. 10 of CR #1
— Type III	— —	—	adequate	3/8/01 (C. Bertha, HFD-570)	See p. 32 of CR #1
—	—	—	adequate	9/25/96 (A. Shaw, HFD-180)	See p. 10 of CR #1

RELATED DOCUMENTS (if applicable):

IND [ ] Desloratadine Tablets, Schering
IND
IND
IND [ ] Desloratadine Reditab Tablets, Schering
NDA 21-165 Clarinex Tablets, Schering
NDA 21-312 Clarinex Reditabs, Schering
NDA [ ]
NDA 21-297 Alternate indication for DP of NDA 21-165

CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	3/8/01	WITHHOLD	OC recommendation of 8/10/01
Microbiology	N/A	-	See p. 31 of CR#1 regarding methods and p. 32 of CR#1 regarding microbial limits.
Biometrics	7/30/01	Pending	Updated (18 months) stability data provided with applicant proposed 24 month expiry.
Pharmacology	N/A		See N21-165 and p. 26 of CR#1.
Methods Validation	10/15/01	Pending	
Environmental Assessment	Not forwarded.		Categorical exclusion requested based on low environmental exposure and considers all dosage forms for desloratadine (see p. 42 of CR#1)
Labeling & Nomenclature, OPDRA	3/15/01	Review received	See N21-165 reviews on drug trademark, N20-704 for dosage form trademark. 3/15/01 consult on "C" imprint, dosage form descriptor see remark (p. 5)

REMARKS/COMMENTS: See review notes, p. 5.

CONCLUSIONS & RECOMMENDATIONS: The application as submitted is approvable pending the recommendation of ACCEPTABLE from the Office of Compliance regarding all of the associated sites that will be used for the manufacture and control for preparation of this drug product. Until such time, it is recommended that any action letter should indicate the current unacceptable compliance status. Comment 6 should be forwarded to the applicant again since the biometrics consult is pending.

cc:
Org. NDA 21-312
HFD-570/Division File
HFD-570/CBertha/10/15/01
HFD-570/DHilfiker
HFD-570/GPoochikian

R/D Init by: _____

filename: 01-10-05.rev.doc

_____
Craig M. Bertha, Ph.D.
Review Chemist (HFD-570/820)

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/s/

Craig Bertha
10/17/01 12:04:47 PM
CHEMIST

Guiragos Poochikian
10/17/01 02:16:54 PM
CHEMIST

SUPPORTING DOCUMENTS:

DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 review
Type IV	[redacted]	[redacted]	adequate	3/9/01 (C. Bertha, HFD-570)	See p. 10 of CR #1
Type III	[redacted]	[redacted]	adequate	3/8/01 (C. Bertha, HFD-570)	See p. 32 of CR #1
[redacted]	[redacted]	[redacted]	adequate	9/25/96 (A. Shaw, HFD-180)	See p. 10 of CR #1

RELATED DOCUMENTS (if applicable):

IND [redacted] Desloratadine Tablets, Schering
IND [redacted]
IND [redacted]
IND [redacted] Desloratadine Reditab Tablets, Schering
NDA 21-165 Clarinex Tablets, Schering
NDA 21-312 Clarinex Reditabs. Schering
NDA [redacted]
NDA 21-297 Alternate indication for DP of NDA 21-165

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CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	3/8/01	Pending	
Microbiology	N/A	-	See p. 31 of CR#1 regarding methods and p. 32 of CR#1 regarding microbial limits.
Biometrics	7/30/01	Pending	Updated (18 months) stability data provided with applicant proposed 24 month expiry.
Pharmacology	N/A		See N21-165 and p. 26 of CR#1.
Methods Validation	Not forwarded.		Once copies of the MV package are received they will be forwarded to Agency laboratories (see draft letter).
Environmental Assessment	Not forwarded.		Categorical exclusion requested based on low environmental exposure and considers all dosage forms for desloratadine (see p. 42 of CR#1)
Labeling & Nomenclature, OPDRA	3/15/01	Review received	See N21-165 reviews on drug trademark, N20-704 for dosage form trademark. 3/15/01 consult on "C" imprint, dosage form descriptor see remark (p. 4)

REMARKS/COMMENTS: See review notes, p. 5.

CONCLUSIONS & RECOMMENDATIONS: **The application as submitted is approvable** from the standpoint of chemistry, manufacturing, and controls. A deficiency and comment are included in the attached draft letter to the applicant, chemistry portion, to be forwarded to the applicant by the PM.

cc:
Org. NDA 21-312
HFD-570/Division File
HFD-570/CBertha/7/30/01
HFD-570/DHilfiker
HFD-570/GPoochikian

R/D Init by: _____

filename: 01-07-19.rev.doc

_____
Craig M. Bertha, Ph.D.
Review Chemist (HFD-570/820)

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/s/

Craig Bertha
8/1/01 09:43:37 AM
CHEMIST

Guiragos Poochikian
8/1/01 03:46:51 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

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

NDA #: 21-312	CHEM. REVIEW # 1	REVIEW DATE: 4/2/01

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12/21/00	12/21/00	3/05/01
CORRESPONDENCE[1]	3/13/01	3/15/01	3/16/01
AMENDMENT	3/26/01	3/26/01	3/26/01[2]

[1]DP samples. [2]Via telephone facsimile only as of 3/26/01.

NAME & ADDRESS OF APPLICANT: Schering Corporation
Galloping Hill Road
Kenilworth, N.J.
07033

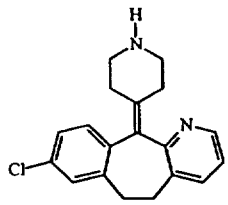
DRUG PRODUCT NAME

Proprietary:	Clarinex™ Reditabs
Nonproprietary/USAN:	desloratadine rapidly disintegrating tablets
Code Name/#:	SCH 34117
Chem.Type/Ther.Class:	1S

PHARMACOL. CATEGORY/INDICATION: antihistamine (peripheral H_1-receptor antagonist) for treatment of seasonal allergic rhinitis (SAR) and for treatment of chronic idiopathic urticaria in patients 12 and older

DOSAGE FORM: tablet
DOSE: 5 mg once daily
STRENGTHS: 5 mg/tablet
ROUTE OF ADMINISTRATION: oral
DISPENSED: _X_ Rx ___ OTC
SPECIAL PRODUCTS: ___Yes _X_ No

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



Desloratadine

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

SUPPORTING DOCUMENTS:

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DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 review
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Type III			adequate	3/8/01 (C. Bertha, HFD-570)	See p. 31 of CR #1
			adequate	9/25/96 (A. Shaw, HFD-180)	See p. 9 of CR #1

RELATED DOCUMENTS (if applicable):

IND — Desloratadine Tablets, Schering
IND
IND
IND — Desloratadine Reditab Tablets, Schering
NDA 21-165 Clarinex Tablets, Schering
NDA 21-312 Clarinex Reditabs, Schering
NDA
NDA 21-297 Alternate indication for NDA 21-165

CONSULTS:

Consult	Date Forwarded	Status	Comments
EER	3/8/01	Pending	
Microbiology	N/A	-	See p. 30 regarding methods and p. 30 regarding microbial limits.
Biometrics	Not forwarded.		Pending updated stability data submission.
Pharmacology	N/A		See N21-165 and p. 25.
Methods Validation	Not forwarded.		Once methods and acceptance criteria finalized packages will be requested.
Environmental Assessment	Not forwarded.		Categorical exclusion requested based on low environmental exposure..
Labeling & Nomenclature, OPDRA	3/15/01	Pending	See N21-165 reviews on drug trademark, N20-704 for dosage form trademark. 3/15/01 consult on "C" imprint, dosage form descriptor see remark (p. 5)

REMARKS/COMMENTS: See review notes, p. 5.

CONCLUSIONS & 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. The PM should forward the deficiencies to the applicant.

cc:
Org. NDA 21-312
HFD-570/Division File
HFD-570/CBertha/4/2/01
HFD-570/GTrout
HFD-570/GPoochikian

R/D Init by: _____

filename: 00-12-21.rev.doc

Craig M. Bertha, Ph.D.
Review Chemist (HFD-570/820)

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/s/

Craig Bertha
4/2/01 02:03:40 PM
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Guiragos Poochikian
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CHEMIST

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