CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-605

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 21-605

Clarinex D24
(desloratadine/pseudoephedrine sulfate)
Extended-release Tablet

Schering Corporation

Prasad Peri Ph.D.
Division of Pulmonary and Allergy Drug Products

Table of Contents

Appears This Way
On Original

Chemistry Review Data Sheet

1. NDA # **21-605**

2. REVIEW # 1

3. REVIEW DATE:. 2-Mar-2005

4. REVIEWER: Prasad Peri, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	4/30/2004
Stability Update	7/30/2004
Labeling Update	10/1/2004
Labeling Update	12/2/2004
Labeling Update	2/01/2005
Responses to Fax dated Feb, 3, 2005	2/10/2005
Responses to Fax dated Feb, 3, 2005	2/15/2005
Labeling Update	2/22/2005
Labeling Update	2/25/2005
Response to comments faxed Feb. 25, 2005	2/28/2005

7. NAME & ADDRESS OF APPLICANT:

Name: Schering Corporation

Chemistry Review Data Sheet

Address: 2000 Galloping Hill, Kenilworth, NJ 07033

Representative: Joseph Lamendola

Telephone: 201-458-7300

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: CLARINEX D-24™ Extended release tablets (proposed)
b) Non-Proprietary Name (USAN): desloratadine/pseudoephedrine sulfate
c) Code Name/# (ONDC only): SCH34117
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Desloratadine is an antihistamine (peripheral H_1-receptor antagonist) and pseudoephedrine sulfate is an adrenergic vasoconstrictor

11. DOSAGE FORM: Extended-release Tablet

12. STRENGTH/POTENCY: 5 mg desloratadine 240 mg pseudoephedrine sulfate

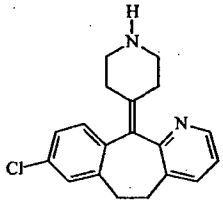
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

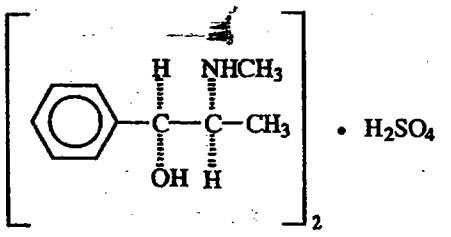
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____ SPOTS product – Form Completed

___X___ Not a SPOTS product

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



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: [redacted]

Pseudoephedrine H_2SO_4-(1S.2S)-2-methylamino-1-phenyl-1-propanol sulfate (2:1) salt
Molecular Formula: $(C_{10}H_{15}NO)_2 \bullet H_2SO_4$
Molecular Weight: [redacted]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
Drug Substance							
[redacted]	II	[redacted]	[redacted]	3	Adequate	Reviewed 1/15/2003	No changes since last review
	III			3	Adequate	11/25/1998	No changes since last review
	III			3	Adequate	Reviewed 10/15/2003	No changes since last review
	III			3	Adequate	3/24/2000	No changes since last review
	III			3	Adequate	Reviewed 2/7/2000	No changes since last review
	III			3	Adequate	Reviewed 9/14/2001	No changes since last review

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	III		3	Adequate	Reviewed 4/25/00	No changes since last review
	III		3	Adequate	Reviewed 5/23/00	No changes since last review

[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 #	DESCRIPTION
IND	58,545	Desloratadine SCH-483-QD and Pseudoephedrine
IND	59,109	Desloratadine Reditabs
IND	58,843	Desloratadine Tablets (atopic dermatitis)
IND	58,506	Desloratadine SCH-483-BID 5 mg desloratadfine and 120 mg Pseudoephedrine sulfate
IND	57,960	Desloratadine Syrup
IND	55,364	SCH 34117 Tablets
NDA	19-658	Claritin® (Loratadine) 10 mg Tablet
NDA	19-670	Claritin® D-12 Hour (5 mg Loratadine/ 120 mg pseudoephedrine sulfate)
NDA	21-165	Desloratadine 5 mg Tablets
NDA	21-297	Desloratadine 5 mg Tablets (alternate indication)
NDA	21-312	Clarinex Reditabs
NDA	21-300	Clarinex Syrup
NDA	21-506	Clarinex Syrup (pediatric indication)
NDA	21-313	Clarinex D-12

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE submitted	REVIEWER
Biometrics	N/A		No consults were sent due to full term shelf life data
EES	Acceptable on 2/15/2005	5/27/2004	All sites found adequate by the OC for this particular dosage form
Pharm/Tox	N/A		All acceptance criteria are within the proposed ICH Q3B guidelines
Biopharm	N/A		
LNC	N/A		
Methods Validation	Not validated		Will be submitted pending resolution of acceptance criteria. Impurities and release rate methods will be sent. Most other methods are compendial.
OPDRA	Acceptable		No issues identified.
EA	Exclusion Acceptable		Applicant has applied for a categorical exclusion/Certificate Provided
Microbiology	N/A		

The Chemistry Review for NDA 21-605

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval.

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

The applicant agreed to provide a prior approval supplement for the extension of shelf life of the drug product in blister packaging. This was communicated to us in their Feb. 10 2005 correspondence.

The applicant also agreed to provide a prior approval supplement within 6 months of approval of the application with the following information

II. Summary of Chemistry Assessments

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

Drug Substances

- The active ingredients used in the drug product are desloratadine and pseudoephedrine sulfate. Both actives have been used in other Schering products and a list is provided on page 10.
- Schering (Avondale, Ireland) makes desloratadine and makes the pseudoephedrine sulfate used in this product. Both sites have an acceptable EES recommendation from the Office of Compliance.

- Reference is made to the applicant's statement (v1.2, 4.A, p. 2) that "the active drug substance, desloratadine micronized (SCH 34117 micronized), is identical in all aspects to that used in the approved Clarinex® tablets, 5 mg (NDA 21-165)." All information regarding desloratadine drug substance is referenced to a submission dated June 27, 2003.
- Schering has provided copies of drug substance release and shelf life specifications for desloratadine which is identical to the specifications referenced in NDA 21-165.
- (+)-Pseudoephedrine sulfate obtained from —— is also used in several Schering's NDAs: Claritin-D and Claritin D-24, etc. Note that Schering has used pseudoephedrine sulfate from other manufacturers —— to manufacture Clarinex D-24 tablets and has demonstrated comparability of drug product from different sources of pseudoephedrine sulfate. However, the current proposed vendor is ——.
- All information related to the manufacturing and controls are referenced in —— Drug Master File (DMF —— . This DMF was reviewed (1/15/2003) and found adequate to support a NDA. No changes are reported for the DMF since the last review. In addition to USP compendial methods, Schering uses non compendial methods for description, assay and estimation of chromatographic impurities.

Drug Product

- The oval shaped light blue CLARINEX D-24 Extended release tablets contain an inner core of 240 mg pseudoephedrine sulfate (extended release portion), and the outer coating containing 5 mg desloratadine (immediate release portion). It is indicated for the treatment of seasonal allergic rhinitis. The total weight of the tablet is 842 mg and the proposed commercial batch size is —— tablets.
- The inactive ingredients are hypromellose USP, ethylcellulose NF, dibasic calcium phosphate dihydrate USP, magnesium stearate NF, povidone USP, silicone dioxide NF, talc USP, polyacrylate dispersion, polyethylene glycol NF, simethicone USP, Blue Lake Blend 50726 (FD&C Blue No. 2 Lake, titanium dioxide USP and edetate disodium USP) and ink (Opacode® S-1-17746 or Opacode® S-1-4159).
- The drug product is supplied in a —— HDPE white bottles (100 tablets count) —— Physician's sample tablets are supplied in —— blisters ——.
- The drug product manufacturing and testing facilities (Kenilworth, NJ and Union, NJ) have an acceptable recommendation (EES submitted) from the Office of compliance for the proposed dosage form.
- Several issues have been noted during the review of the manufacturing process of the drug product and are highlighted below. **However they were evaluated and found not to be approval issues.**
    - Lack of adequate in-process controls for the coating process leading to several instances of stage II testing for content uniformity/assay for desloratadine.

However, as with all other solid oral dosage forms the applicant uses USP <905> Content Uniformity acceptance criterion which is wide (85-115% LC).

- The desloratadine component of the tablet is heat sensitive

However, when stored at 25°C/60% RH conditions the drug product is stable in bottles for 2 years and in blisters for 12 months. Based on this observation, adequate warnings in terms of storage statement are recommended as illustrated in the next section.

- All issues regarding the specifications, methods and labeling have been resolved.
- Schering will provide a prior approval supplement within 6 months of the approval of the drug product with the following information:

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

The drug product is a coated tablet and is intended to be swallowed without crushing. It is intended for a once a day administration for the treatment of allergic rhinitis and congestion. The primary stability data generated on three commercial representative batches indicate that the drug product is stable at 25°C/60% for 24 months. Clarinex D-24 HOUR Extended-release tablets are supplied in bottles containing 100 tablets. These are typically for pharmacy distribution and are meant to be repackaged in smaller bottles. Unit use blisters (pack of 5) are for physician samples.

Since the drug product is labile to heat, the storage statement on the drug product is labeled "Heat Sensitive. Avoid exposure at or above 30°C (86°F)". With the warning as stated, and based on the data provided for NDA stability lots, a shelf life of 24 months is granted for the drug product stored in bottles and 12 months for physician samples packaged in blisters respectively

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendment ultimately provided adequate information on the chemistry, manufacturing and controls for the production of Clarinex-D 24 HOUR Extended release tablets.

The trade name was found acceptable by OPDRA and by the Division of Pulmonary and Allergy Drug Products.

The application is recommended for approval based on the data provided in the NDA and subsequent amendments to the CMC section.

III. Administrative

A. Reviewer's Signature

Chemist:
Prasad Peri, Ph.D. *{Signed electronically in DFS}*

B. Endorsement Block

Chemistry Team Leader:
Richard T Lostritto, Ph.D. {Signed electronically in DFS}

121 Page(s) Withheld

0 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Prasad Peri
3/2/05 04:04:23 PM
CHEMIST

Richard Lostritto
3/2/05 05:11:18 PM
CHEMIST