CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-165

Chemistry Review(s)

NDA 21-345

CLARINEX (desloratadine) Tablets 5 mg

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Schering Plough LLC

\Indication: Relief of nasal and non-nasal symptoms of seasonal allergic rhinitis

Presentations: Light blue round film coated tablets, 5 mg, in HDPE bolttles of 30 and 500, and blisters of 30 and 100 tablets.

EER Status: Acceptable 12/20/2001

Consults: OPDRA – Acceptable 10/19/00 – update is pending

This NDA had previously been found acceptable pending a satisfactory inspectional status (see review dated 1/18/01 by SKoepke). Per the recent agreement with Schering, the [redacted] will be limited to Avondale, County Wicklow Ireland for [redacted] and Las Piedras, Puerto Rico for [redacted]

Issues related to technology transfer of manufacturing and principally, testing methodologies have been resolved by ORA. Updated stability data have been provided to the NDA for 3 lots of 100 count bottles and 1 in blisters. An expiry of [redacted] months will be granted. The firm has committed to investigate the impurities methodology and improve as warranted, and well as address peak identity and stability trend analysis.

FPL has been submitted and is acceptable pending OPDRA confirmation of the acceptablity of the trade name.

Over-All Conclusion
From a CMC perspective the application is recomended for approval.

/S/ 12/21/01

Eric P Duffy, PhD
Director, DNDC II/ONDC

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

NDA #: 21-165 **CHEM. REVIEW #:** 4 Addendum B **REVIEW DATE:** 1/19/01

RECOMMEND ACTION: APPROVABLE.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	10/20/99	10/22/99	11/4/99
Amendment BC	3/31/00	4/3/00	4/3/00
Amendment BC	4/19/00	4/20/00	4/20/00
Amendment BZ	5/18/00	5/19/00	5/19/00
Amendment BC	6/29/00	6/30/00	6/30/00
Amendment AC	8/2/00	8/3/00	8/3/00
Amendment BC	7/28/00	7/31/00	7/31/00
Amendment BC	9/14/00	9/15/00	9/15/00
Amendment BC	9/29/00	10/2/00	10/2/00
Amendment BC	10/3/00	10/4/00	10/4/00
Amendment BC	10/9/00	10/10/00	10/10/00
Amendment BC	10/13/00	10/16/00	10/16/00
Amendment BC	10/20/00	10/23/00	10/23/00
Amendment BC	10/27/00	10/30/00	10/30/00
Amendment BC	11/1/00	11/2/00	11/2/00
Amendment AF	11/2/00	11/3/00	11/3/00
Amendment BL	11/10/00	11/13/00	11/13/00
Amendment C*	1/10/01	1/11/01	1/11/01

*Subject of this review.

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

DRUG PRODUCT NAME:

Proprietary: CLARINEX Tablets

Nonproprietary/USAN: desloratadine 5 mg Tablet (film coated)
Code Name/#: SCH 34117
Chem. Type/Ther. Class: 1S

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

DOSAGE FORM: Solid oral dosage form (tablet, film coated)

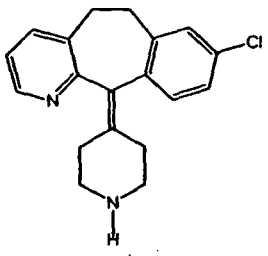
STRENGTHS: 5 mg.

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)-~~5H~~-benzo[5,6]cyclohepta[1,2-b]pyridine

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

SUPPORTING DOCUMENTS:

DMFs

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
IND		Schering Corp.	
IND		Schering Corp.	
IND		Schering Plough	
IND		Schering Plough	
IND		Schering Corp	
IND		Schering Plough	
NDA	19-658	Schering Corp.	Claritin® (Loratadine) 10 mg Tablet

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	12/7/99 and was acceptable, the EER was re-forwarded on 10/25/00.		
Biometrics, HFD-710	9/18/00	Adequate (See review CR#4)	Evaluation of expiry dating. See review CR#4
Pharm-Tox, HFD-570	12/14/99	Adequate On 8/14/00	Qualification of impurities in the drug substance
Pharm-Tox, HFD-570	8/7/00	Adequate On 10/17/00	Comments on degradant acceptance criteria of The degradant is below limit and is not a structure alert.
Environmental Assessment	Not applicable	Adequate	Applicant has been advised to apply for a categorical exclusion.
OPDRA	See summary and review notes	Adequate On 10/19/00	Discussion of desloratadine and Clarinex as a suitable name. See OPDRA comments from Mr. Jerry Phillips.
Methods Validation MV Package is the 10/27/00 Amendment BC	11/1/00 MV Package is the 10/27/00 Amendment BC	Sent, Results are Pending	

REMARKS/COMMENTS:

Drug Substance and Drug Product
(Please see Review Notes, pp. 4 – 6)

CONCLUSIONS AND RECOMMENDATIONS:
The application is approvable from the standpoint of chemistry, manufacturing and controls since a withhold EER was generated dated January 19, 2001. When an acceptable EER for all sites is provided this application may then be approved.

cc:
Orig. NDA 21-165
HFD-570/Division File N21-165
HFD-570/KSwiss/1/19/01
HFD-570/GTrout
HFD-570/VBorders
HFD-570/GPoochikian
HFD-820/SKoepke
HFD-800/CHoiberg
R/D Init. by: _____

/S/

Kevin A. Swiss, Ph.D. Review Chemist

Redacted 8

pages of trade secret and/or confidential commercial information

NOV - 8 2000

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

NDA #: 21-165 **CHEM. REVIEW #:** 4 **REVIEW DATE:** 11/8/00

RECOMMEND ACTION: APPROVAL (Pending acceptable EER and label comments)

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	10/20/99	10/22/99	11/4/99
Amendment BC	3/31/00	4/3/00	4/3/00
Amendment BC	4/19/00	4/20/00	4/20/00
Amendment BZ	5/18/00	5/19/00	5/19/00
Amendment BC	6/29/00	6/30/00	6/30/00
Amendment AC	8/2/00	8/3/00	8/3/00
Amendment BC*	7/28/00	7/31/00	7/31/00
Amendment BC*	9/14/00	9/15/00	9/15/00
Amendment BC*	9/29/00	10/2/00	10/2/00
Amendment BC*	10/3/00	10/4/00	10/4/00
Amendment BC*	10/9/00	10/10/00	10/10/00
Amendment BC*	10/13/00	10/13/00	10/13/00
Amendment BC*	10/20/00	10/23/00	10/23/00
Amendment BC*	10/27/00	10/30/00	10/30/00
Amendment BC*	11/1/00	11/2/00	11/2/00
Amendment AF*	11/2/00	11/3/00	11/3/00

*Subject of this review.

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

DRUG PRODUCT NAME:

Proprietary: CLARINEX Tablets

Nonproprietary/USAN: Desloratadine 5 mg Tablet (film coated)
Code Name/#: SCH 34117
Chem. Type/Ther. Class: 1S

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

DOSAGE FORM: Solid oral dosage form (tablet, film coated)

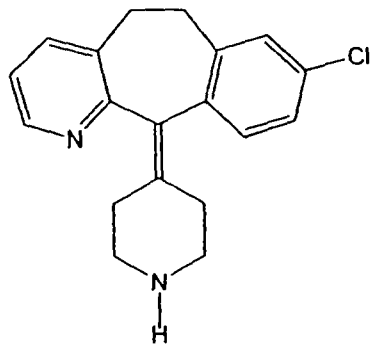
STRENGTHS: 5 mg.

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

SUPPORTING DOCUMENTS:

DMF's

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
IND		Schering Corp.	
IND		Schering Corp.	
IND		Schering Plough	
IND		Schering Plough	
IND		Schering Corp	
IND		Schering Plough	
NDA	19-658	Schering Corp.	Claritin® (Loratadine) 10 mg Tablet

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	12/7/99 and found acceptable on 7/10/00. The EER was re-forwarded on 10/25/00.	Pending on 10/31/00	
Biometrics, HFD-710	9/18/00	Adequate (See review)	Evaluation of expiry dating. See this review.
Pharm-Tox, HFD-570	12/14/99	Adequate On 8/14/00	Qualification of impurities in the drug substance
Pharm-Tox, HFD-570	8/7/00	Adequate On 10/17/00	Comments on degradant acceptance criteria of NMT The degradant is below limit and is not a structure alert.
Environmental Assessment	Not applicable	Adequate	Applicant has been advised to apply for a categorical exclusion.
OPDRA	See summary and review notes	Adequate On 10/19/00	Discussion of desloratadine and Clarinex as a suitable name. See OPDRA comments from Mr. Jerry Phillips.
Methods Validation MV Package is the 10/27/00 Amendment BC	11/1/00 MV Package is the 10/27/00 Amendment BC	Sent, Results are ~~Pending~~	

REMARKS/COMMENTS:

Drug Substance and Drug Product
(Please see Review Notes, pp. 4 – 5)

CONCLUSIONS AND RECOMMENDATIONS:
The application may be approved from the standpoint of chemistry, manufacturing and controls after label comments are addressed, and a satisfactory cGMP inspection is provided prior to the goal date. If an acceptable cGMP inspection is not provided by the goal date of this application, then this application may not be approved.

cc:
Orig. NDA 21-165
HFD-570/Division File N21-165
HFD-570/KSwiss/11/8/00
HFD-570/GTrout
HFD-570/YBorders
HFD-570/GPoochikian
HFD-820/SKoepke
R/D Init. by: CK 11/8/00

/S/
Kevin A. Swiss, Ph.D. Review Chemist

Redacted 28

pages of trade

secret and/or

confidential

commercial

information

TVOLL+

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

AUG 17 20

NDA #: 21-165 **CHEM. REVIEW #:** 3 **REVIEW DATE:** 8/15/00

RECOMMEND ACTION: NOT APPROVED

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	10/20/99	10/22/99	11/4/99
Amendment BC	3/31/00	4/3/00	4/3/00
Amendment BC	4/19/00	4/20/00	4/20/00
Amendment BZ	5/18/00	5/19/00	5/19/00
Amendment BC	6/29/00	6/30/00	6/30/00
Amendment AC*	8/2/00	8/3/00	8/3/00

*Subject of this review.

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

DRUG PRODUCT NAME:

Proprietary: CLARINEX

Nonproprietary/USAN: Desloratadine 5 mg Tablet (film coated)
Code Name/#: SCH 34117
Chem. Type/Ther. Class: 1S

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

DOSAGE FORM: Solid oral dosage form (tablet, film coated)

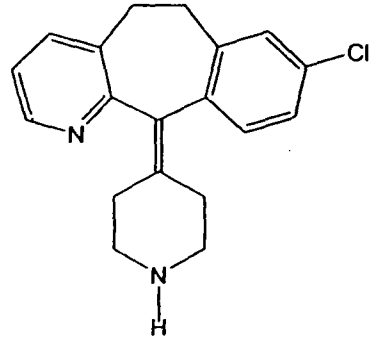
STRENGTHS: 5 mg.

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

SUPPORTING DOCUMENTS:

DMF's

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
IND	[redacted]	Schering Corp.	
IND		Schering Corp.	
IND		Schering Plough	
IND		Schering Plough	
IND		Schering Corp	
IND	[redacted]	Schering Plough	
NDA	19-658	Schering Corp.	Claritin® (Loratadine) 10 mg Tablet

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	12/7/99	Acceptable On 7/10/00	– Acceptable - Acceptable - Acceptable – Acceptable
Biometrics, HFD-710	Pending	Pending	Expiry dating. pending submission of data set provided by Schering.
Pharm-Tox, HFD-570	12/14/99	Adequate On 8/14/00	Qualification of impurities in the drug substance
Pharm-Tox, HFD-570	8/7/00	Pending	Comments on degradant acceptance criteria of NMT
Environmental Assessment	Not applicable	Adequate	Applicant has been advised to apply for a categorical exclusion.
Labeling & Nomenclature Committee	See comments	Pending	Discussion of desloratadine and Clarinex as a suitable name.

REMARKS/COMMENTS:

Drug Substance and Drug Product
(Please see Review Notes, pp. 4 – 5)

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.

Comments regarding the qualification of ' ' (drug substance impurities) are pending with Pharm-Tox. Comments pertaining to the USAN and trade names are still pending.

cc:
Orig. NDA 21-165
HFD-570/Division File N21-165
HFD-570/KSwiss/8/15/00
HFD-570/GTrout
HFD-570/GPoochikian
HFD-820/SKoepke
R/D Init. by: 8/16/00

/S/

Kevin A. Swiss, Ph.D. Review Chemist

Redacted 19

pages of trade

secret and/or

confidential

commercial

information

TRUST

JUL 13 2000

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

NDA #: 21-165 **CHEM. REVIEW #:** 2* **REVIEW DATE:** 7/13/00
*addendum

RECOMMEND ACTION: NOT APPROVED

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	10/20/99	10/22/99	11/4/99
Amendment BC	3/31/00	4/3/00	4/3/00
Amendment BC	4/19/00	4/20/00	4/20/00
Amendment BZ	5/18/00	5/19/00	5/19/00
Amendment BC*	6/29/00	6/30/00	6/30/00

*Subject of this review.

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

DRUG PRODUCT NAME:

Proprietary: "None proposed at this time"

Nonproprietary/USAN: Desloratadine Tablet
Desloratadine 5 mg

Code Name/#: SCH 34117

Chem. Type/Ther. Class: 1S

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

DOSAGE FORM: Solid oral dosage form (tablet)

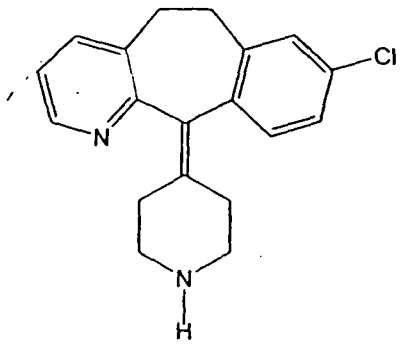
STRENGTHS: 5 mg.

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

SUPPORTING DOCUMENTS:

DMF's

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
IND		Schering Corp.	
IND		Schering Corp.	
IND		Schering Plough	
IND		Schering Plough	
IND		Schering Corp	
IND		Schering Plough	
NDA	19-658	Schering Corp.	Claritin® (Loratadine) 10 mg Tablet

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	12/7/99	Acceptable	Acceptable Acceptable Acceptable – Acceptable
Biometrics, HFD-710	Pending	Pending	Expiry dating, awaiting resolution of specifications related to regulatory specifications.
Pharm-Tox HFD-570	12/14/99	Pending	Qualification of impurities in the drug substance
Environmental Assessment	Not applicable	Adequate	Applicant has been advised to apply for a categorical exclusion.
Labeling & Nomenclature Committee	See comments	Pending	Discussion of desloratadine as a suitable name.

REMARKS/COMMENTS:

Drug Substance and Drug Product
(Please see Review Notes, pp. 4 – 5)

CONCLUSIONS AND RECOMMENDATIONS:

The application as submitted is not approved from the standpoint of chemistry, manufacturing and controls. A Deficiency is detailed in the accompanying review notes and summarized in the attached draft letter to the applicant, chemistry portion. The comment should be promptly forwarded to the applicant.

Comments pertaining to polymorphic forms in the drug substance/product are pending with Biopharm. Comments pertaining to the USAN name are still pending.

cc:
Orig. NDA 21-165
HFD-570/Division File N21-165
HFD-570/KSwiss/7/13/00
HFD-570/GTrout
HFD-570/GPoochikian
HFD-820/SKoepke
R/D Init. by: 7/13/00

/S/

Kevin A. Swiss, Ph.D. Review Chemist

Redacted 9

pages of trade

secret and/or

confidential

commercial

information

Trout
570

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

NDA #: 21-165 **CHEM. REVIEW #:** 2 **REVIEW DATE:** 6/16/00 JUN 18 2000

RECOMMEND ACTION: NOT APPROVABLE

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	10/20/99	10/22/99	11/4/99
Amendment BC*	3/31/00	4/3/00	4/3/00
Amendment BC*	4/19/00	4/20/00	4/20/00
Amendment BZ*	5/18/00	5/19/00	5/19/00

*Subject of this review.

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

DRUG PRODUCT NAME:

Proprietary: "None proposed at this time"

Nonproprietary/USAN: Desloratadine Tablet
~~Desloratadine 5 mg~~

Code Name/#: SCH 34117

Chem. Type/Ther. Class: 1S

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

DOSAGE FORM: Solid oral dosage form (tablet)

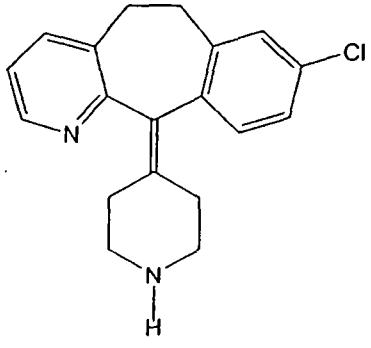
STRENGTHS: 5 mg.

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

SUPPORTING DOCUMENTS:

DMF's

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
IND		Schering Corp.	
IND		Schering Corp.	
IND		Schering Plough	
IND		Schering Plough	
IND		Schering Corp	
IND		Schering Plough	
NDA	19-658	Schering Corp.	Claritin® (Loratadine) 10 mg Tablet

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	12/7/99	Pending	– Acceptable Acceptable VAI – Acceptable
Biometrics, HFD-710	Pending	Pending	Expiry dating, awaiting resolution of specifications related to regulatory specifications.
Pharm-Tox HFD-570	12/14/99	Pending	Qualification of impurities in the drug substance
Environmental Assessment	Not applicable	Adequate	Applicant has been advised to apply for a categorical exclusion.
Labeling & Nomenclature Committee	See comments	Pending	Discussion of desloratadine as a suitable name.

REMARKS/COMMENTS:

Drug Substance and Drug Product
(Please see Review Notes, pp. 4 – 5)

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.

Comments pertaining to polymorphic forms in the drug substance/product are pending with Biopharm. Comments regarding the qualification of drug substance impurities) are pending with Pharm-Tox. Comments pertaining to the USAN name are still pending.

cc:
Orig. NDA 21-165
HFD-570/Division File N21-165
HFD-570/KSwiss/6/16/00
HFD-570/GTrout
HFD-570/GPoochikian
HFD-820/JGibbs
HFD-820/SKoepke
R/D Init. by:

/S/

Kevin A. Swiss, Ph.D. Review Chemist

Redacted 39

pages of trade

secret and/or

confidential

commercial

information

Trout

MAR - 9 2000

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

NDA #: 21-165 **CHEM. REVIEW #:** 1 **REVIEW DATE:** 3/7/00

RECOMMEND ACTION: NOT APPROVABLE

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	10/20/99	10/22/99	11/4/99

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

DRUG PRODUCT NAME:

Proprietary: "None proposed at this time"

Nonproprietary/USAN: Desloratadine Tablet
Desloratadine 5 mg

Code Name/#: SCH 34117

Chem. Type/Ther. Class: 1S

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

DOSAGE FORM: Solid oral dosage form (tablet)

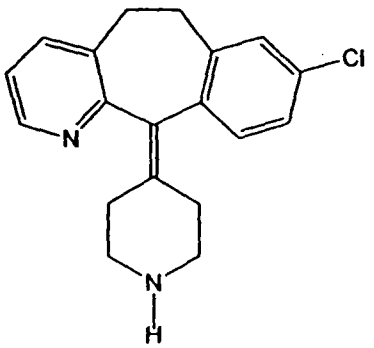
STRENGTHS: 5 mg.

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

SUPPORTING DOCUMENTS:

DMF's

RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
IND		Schering Corp.	
IND		Schering Corp.	
IND		Schering Plough	
IND		Schering Plough	
IND		Schering Corp	
IND		Schering Plough	
NDA	19-658	Schering Corp.	Claritin® (Loratadine) 10 mg Tablet

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	12/7/99	Pending	Acceptable
Biometrics, HFD-710	Pending	Pending	Expiry dating, awaiting resolution of specifications related to regulatory specifications.
Pharm-Tox HFD-570	12/14/99	Pending	Qualification of impurities in the drug substance
Environmental Assessment	Not applicable	Adequate	Applicant has been advised to apply for a categorical exclusion.
Labeling & Nomenclature Committee	See comments	Pending	Discussion of desloratadine as a suitable name.

REMARKS/COMMENTS:

Drug Substance

1). Two polymorphic forms are provided for desloratadine (see v1.2, 4.A.1.2 pp. 7 – 108). The two forms differ by 0.23 kcal/mol. Schering provides that Form I is most stable but has the poorer solubility.

2). DMF (Schering Avondale Ireland) and DMF (Schering Singapore) provide for the and were both reviewed dated November 23, 1999 and were found to be adequate in support of the application.

3). Avondale site produces than the Singapore site.

4). An EER was sent on December 7, 1999 and is currently pending.

5). A consult was forwarded to Dan Boring (Labeling and Nomenclature Committee and USAN representative) on 11/4/99 for evaluation of the established name (desloratadine) for the drug substance.

6). Two impurities in the drug substance are provided above the ICH Q3A guidelines. A consult has been sent to pharm tox regarding . Also note that 1 is flagged as a potential mutagen since it is a .

7). During the May 11, 1999 pre-NDA meeting for this application, Dr. H. Khorshidi informed Schering regarding these issues for drug substance, (synopsis included here).

- 1 year stability data on 3 batches at same site and commitments for future study.
- Quantitative color test.
- Tightened acceptance specifications for drug substance impurities and OVI's.
- PSD should be provided.
- Polymorph test method and specification.

Drug Product

1). The EER for the Union and Kenilworth NJ sites are withheld pending regulatory action dated January 19, 2000. Both sites have status, OC recommendations are withheld pending further action.

2). Drug product is a coated prompt-release solid-oral dosage form blue in color.

3). Schering provides two drug product batches with 1 year stability data and one product batch with 1 year data from another site. The third drug product batch has only release data, stability data will be sent in a future amendment. (*vide infra*)

4). The biobatch is batch number IRQ-98-9M1 drug substance and batch number 38833-142 drug product.

5). Drug product for which we have stability and release data has only been produced from Avondale site, although this NDA does provide data from Singapore.

6). The 1 year stability data for drug product batches was provided for two batches made at Kenilworth NJ and an additional batch provided from Las Piedras Puerto Rico. A third drug product batch has been provided in the NDA but only release data is provided. Schering provides an amendment ~~will follow with additional stability data.~~

7). Email correspondence has been sent to biopharmacology concerning polymorphic forms affecting dissolution and dissolution media.

8). During the May 11, 1999 pre-NDA meeting for this application, Dr. H. Khorshidi informed Schering regarding these issues for drug product (B.6.B) [NDA vol. 1.4, sec. 4.B.9.2]:

- ICH guidelines for impurities.
- Specification for hardness and friability.
- Suitable dissolution test method and specification.
- Manufacture should target
- Suitable stability data should be provided and commitment for future study.

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 21-165
HFD-570/Division File N21-165
HFD-570/KSwiss/3/7/00
HFD-570/GTrout
HFD-570/GPoochikian
HFD-820/JGibbs
HFD-820/SKoepke
R/D Init. by: 3/9/00

S

Kevin A. Swiss, Ph.D. Review Chemist

Redacted 82

pages of trade

secret and/or

confidential

commercial

information

Trout

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Addendum to Chemistry Consult

NDA No. 21-165 **Date of Consult:** 20 OCT 1999

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 14 AUG 2000

Information to be Conveyed to Sponsor: Yes ( ), No (✓)

Sponsor: Schering Plough Corp., Kenilworth, NJ

Drug Name: *Generic:* Descarboethoxyloratadine (DCL)
Code Name: SCH 34117
Commercial: Undetermined

Chemical name: 5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-(4-piperidinyllidene)

Formula: $C_{182}H_{310}N_{40}O_{35}$

Molecular Weight: 310.82

Drug Class: Anti-histamine

~~**Proposed Clinical Dose:** 5 mg/day, tablet~~

Review:

In the original Chemistry Consult (June 12, 2000), it was recommended that the sponsor limit the levels of( )to NMT( )in the drug substance or provide further qualification for the drug substance impurities (3 month toxicity study using appropriate levels of impurities). These comments were forwarded to the sponsor in a letter dated June 26, 2000. A teleconference was held with the sponsor on July 18, 2000 to discuss the above issue (see minutes). The sponsor indicated that the synthesis impurities were present in the 3-month rat and monkey toxicity studies at levels adequate to support the proposed levels in the drug substance. The sponsor submitted data to support their position in a package dated July 19, 2000. This addendum reviews the submission and proposed levels of( )(NMT( )% and( )%, respectively).

Sponsor's Submission: The sponsor submitted the levels of drug substance impurities in drug lots used for preclinical testing. In the longest duration toxicity study performed with SCH 34117, a 3-month oral study in monkeys (P-6976), levels of( )%( )and( )% were observed in SCH 34117 Batch 97-34117-X-03-RA at the time of batch release.

Evaluation of Sponsor's response: The Sponsor's response to the Division comment is acceptable since 48-fold and 88-fold safety margins are present for( ) respectively, when comparing levels of the drug substance impurities in the preclinical batches used in a 3-month oral monkey study at the NOAEL dose and the maximum expected human exposure at the proposed impurity levels. Table 1 summarizes the pertinent information. The Chemistry Reviewer, Dr. Kevin Swiss, indicated that the levels reported by the Sponsor are representative of levels present in the formulation at the time that the preclinical studies were performed.

Table 1:

Impurity	Proposed Limit %	Proposed Limit max µg/kg	Preclinical Dose %*	Preclinical Dose µg/kg	Species	Duration	Route	Safety Margin
		0.2		9.6	Monkey	3 mos	Oral	48
		0.3		26.4	Monkey	3 mos	Oral	88

* Levels determined at batch release.

Calculations:

Maximum Clinical Dose – ___:

Preclinical Dose:

Safety margin = Preclinical dose ÷ Clinical dose
= 9.6 µg/kg/day ÷ 0.2 µg/kg/day
= 48

Maximum Clinical Dose - ____

Preclinical Dose:

Safety margin = Preclinical dose ÷ Clinical dose
= 26.4 µg/kg/day ÷ 0.3 µg/kg/day
= 88

Overall Summary and Evaluation: The sponsor proposes specifications of NMT [redacted]% and [redacted]% for [redacted] respectively, for the drug product. A safety assessment was performed for two drug substance impurities [redacted] based upon the impurity levels reported in the preclinical batch used in a 3 month oral monkey study. Safety margins of 48 for [redacted] and 88 for [redacted] were demonstrated based upon levels observed at the NOAEL dose in the 3-month monkey study and expected human exposure levels. Thus, the specifications proposed by the sponsor are acceptable.

RECOMMENDATION

The sponsor's proposed specification limits of NMT [redacted]% for [redacted] and NMT [redacted]% for [redacted] are acceptable.

/S/ 8/14/00

Timothy J. McGovern, Ph.D., Pharmacologist

Aug 14, 2000

/S/

CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/K. Swiss
HFD-570/G. Trout
HFD-570/T. McGovern
HFD-540/B. Hill

NDA 21-165

Tertiary CMC Review for Clarinex (desloratidine) Tablets, 5 mg

Clarinex is a light blue round film coated tablet containing 5 mg of desloratidine. There are two morphic forms of desloratidine, but these have been determined to be bioequivalent. The in either Rathdrum, Ireland or Singapore. In the original application, was either in Schering's facilities in Kenilworth, NJ or in Las Piedras, PR.

The application was considered to be acceptable from a CMC point of view in Review #4 dated Nov. 8, 2000 pending a satisfactory GMP status of all facilities. The Kenilworth, NJ site was
In CMC review #4 Addendum B which includes of the Kenilworth site, the application is still recommended for approval pending an adequate GMP status of all facilities.

The Division concurs with this recommendation for approval pending adequate GMP status of all facilities with a minor labeling comment.

EA: Categorical Exclusion accepted in Chemistry Review #1 dated March 9, 2000.

EER: PENDING

Microbiology: N/A

OPDRA and Trade Name: The Tradename was accepted by the Agency on Oct 19, 2000.

Labeling : The dosage strength should be of equal prominence to the established name on the immediate carton label as it is on the blister backing.

/S/

Steven R. Koepke
Deputy Director, DNDC II