

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
21-297**

Chemistry Review(s)

**MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC
HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

REC
2/15/02
9:29AM

DATE: January 24, 2002

TO: N21-297 File
N21-363 File



THROUGH: Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary Drug Products (HFD-570)

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
Division of Pulmonary Drug Products (HFD-570)

SUBJECT: Submissions of January 22, 2002 for both applications referenced above.

BACKGROUND:

Because of compliance problems associated with various manufacturing and testing sites for the Clarinex Tablets (desloratadine tablets) application N21-165, the applicant withdrew the Kenilworth, NJ site (January 10, 2001 submission) as a manufacturing site, the Singapore site as a manufacturing site (May 22, 2001 submission), and the Union, NJ site as a testing site (August 15, 2001 submission).

CONTENT:

The related applications N21-297 and N21-363 are for additional indications (chronic idiopathic urticaria and allergic rhinitis, respectively). The submission of January 22, 2002 refers to the past withdrawal of the above mentioned sites for the parent application N21-165 and states that these site withdrawals also apply to N21-297 and N21-363. Since the action dates for these two applications are approaching in the near future, the chemist requested through EES that the Office of Compliance update their overall recommendation for the sites associated with these applications on January 22, 2002. The EES lists the overall recommendation for the N21-297 and N21-363 applications as both WITHHOLD as of July 30, 2001 and August 10, 2001, respectively, as of the date of this memorandum. The CMC team can not recommend the approval of the applications until the OC makes a favorable recommendation.

/S/

Craig M. Bertha, Ph.D.
Chemistry Reviewer

cc:

Post memo note: Once the sites with compliance problems (listed in "BACKGROUND" above) were removed from the EES for N21-297 and N21-363, OC made overall recommendation of ACCEPTABLE on 1/31/02.

Orig. NDA 21-297
Orig. NDA 21-363
HFD-570/Div. Files
HFD-570/CBertha 1/24/02
HFD-570/GPoochikian
HFD-570/AZeccola

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

/s/

Craig Bertha
1/24/02 12:36:29 PM
CHEMIST

Guiragos Poochikian
1/25/02 10:53:47 AM
CHEMIST

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

NDA #: 21-297 **CHEM. REVIEW #:** 2 **REVIEW DATE:** 9/20/01

RECOMMENDED ACTION: APPROVABLE

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	8/30/00	8/31/00	9/11/00
BC Amendment	10/19/00	10/20/00	10/20/00
AZ Amendment*	9/7/01	9/10/01	9/12/01

*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 H₁-receptor antagonist for
Chronic Idiopathic Urticaria

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

STRENGTHS: 5 mg. (Total daily dose: 5 mg)

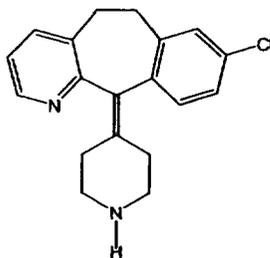
ROUTE OF ADMINISTRATION: Oral

DISPENSED: Rx OTC

SPECIAL PRODUCTS: YES 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-piperidinylidene)-5H-benzo-
[5,6]cyclohepta[1,2-b]pyridine
Molecular Formula: C₁₉H₁₉ClN₂
Molecular Weight: 310.8

REMARKS/COMMENTS:

Drug Substance and Drug Product
(Please see review page 4)

CONCLUSIONS AND RECOMMENDATIONS:

Currently, considering that the Office of Compliance recommends a WITHHOLD for the application, an **approvable (AE)** recommendation can be made from the standpoint of chemistry, manufacturing and controls. The comment in the draft letter should be forwarded to the applicant in the action letter. Note that all pertinent CMC information for N21-297 is referenced to the earlier N21-165. N21-297 is an application that is for a different indication, i.e., chronic idiopathic urticaria (CIU).

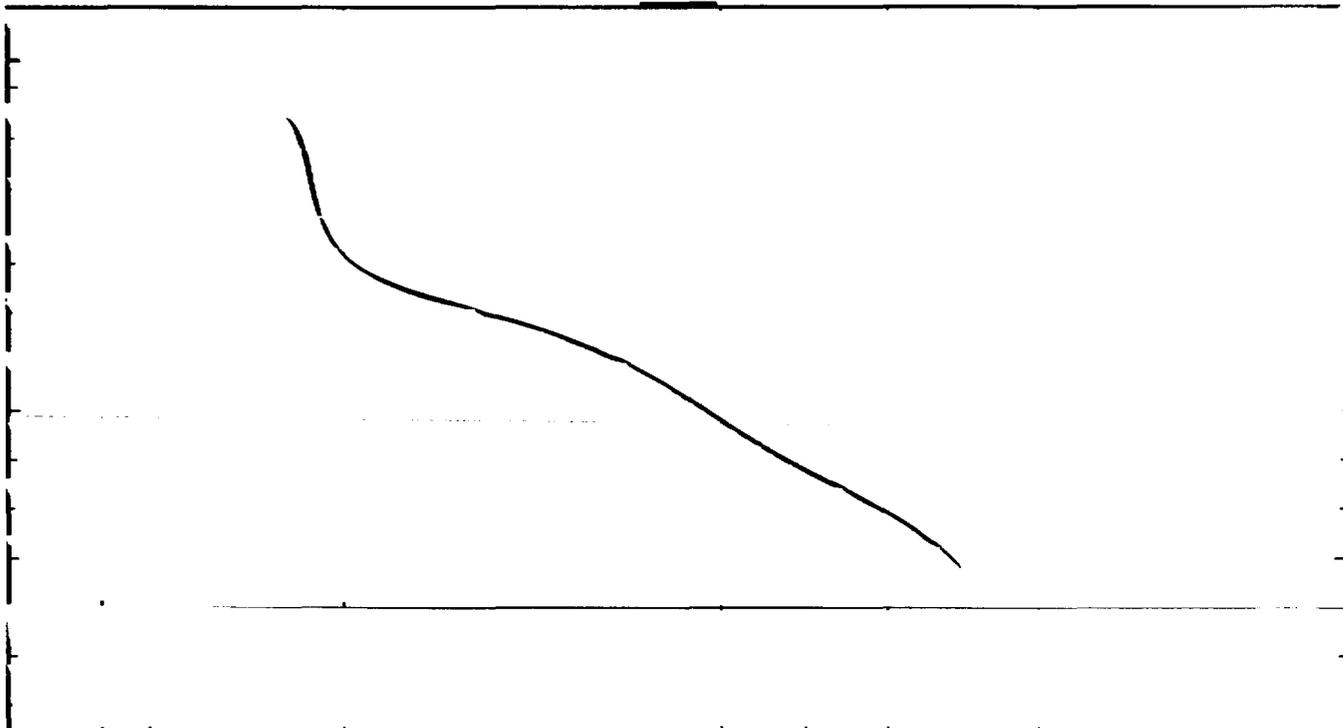
cc:
Orig. NDA 21-297
HFD-570/Division File N21-297
HFD-570/CBertha/9/20/01
HFD-570/DHilfiker
HFD-570/GPoochikian
HFD-820/EDuffy
HFD-800/CHoiberg
R/D Init. by: _____
filename: 01-09-10.rev.doc



Craig M. Bertha, Ph.D. Review Chemist

SUPPORTING DOCUMENTS:

DMFs



RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
IND	█	Schering Corp.	S
IND		Schering Corp.	
IND		Schering Plough	
IND		Schering Plough	
IND		Schering Corp.	
IND		Schering Plough	
NDA	19-658	Schering Corp.	SCH 34117 Tablets Claritin® (Loratadine) 10 mg Tablet
NDA	21-165	Schering Plough	Desloratadine Tablets

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	9/19/00	Pending	Pending inspection
Environmental Assessment	Not applicable	Adequate	Applicant has applied for a categorical exclusion under 21 CFR 25.31(b) in the BC Amendment dated 10/19/00.
Methods Validation	11/1/00 for N21-165	Sent, Results are Pending, See p. 5 of CR#2.	MV for drug substance (assay, assay related compounds, polymorph content, PSD) and drug product (dissolution rate, moisture, assay, degradation products, uniformity of dosage units)

REMARKS/COMMENTS:

In the CMC section of this NDA vol. 1.2, sec. 4, page 1, for both drug substance and drug product has been referenced to NDA 21-165. This application is for the treatment indication of chronic idiopathic urticaria (CIU).

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secret and/or

confidential

commercial

information

**CHEMISTRY REVIEW # 1
ADDENDUM**

June 25, 2001

REMARKS/COMMENTS:

Drug Substance and Drug Product
(Please see review page 4)

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 pertaining to N21-165. An EER has been forwarded to OC dated 9/19/00 for this application N21-297 with the same sites as N21-165. When an acceptable EER for all sites is provided for N21-297 this application may be approved, but not before the approval of N21-165. Note that a method validation comment has been generated by the FDA field labs regarding one of the test methods. This comment has been forwarded to the applicant in an approvable letter for this application N21-297.

cc:

Orig. NDA 21-297

HFD-570/Division File N21-297

HFD-570/KSwiss/6/25/01

HFD-570/GTrout

HFD-570/GPoochikian

HFD-800CHOiberg

R/D Init. by: _____

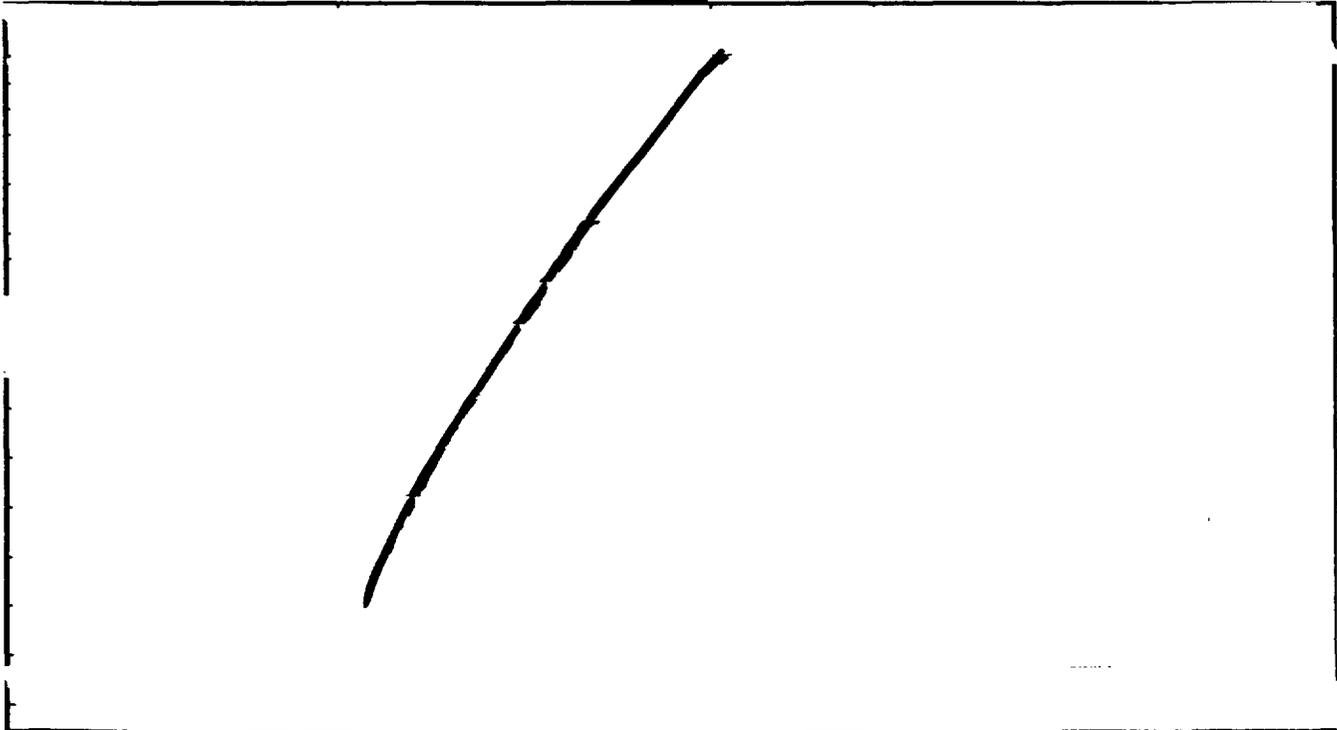
filename: N21297.CR1.DOC

151

Kevin A. Swiss, Ph.D. Review Chemist

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.	SCH 34117 Tablets
NDA	21-165	Schering Plough	Claritin® (Loratadine) 10 mg Tablet Desloratadine Tablets

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	9/19/00	Pending	Pending inspection
Environmental Assessment	Not applicable	Adequate	Applicant has applied for a categorical exclusion under 21 CFR 25.31(b) in the BC Amendment dated 10/19/00.
Methods Validation	11/1/00 for N21-165	Sent, Results are Pending	MV for drug substance (assay, assay related compounds, polymorph content, PSD) and drug product (dissolution rate, moisture, assay, degradation products, uniformity of dosage units)

REMARKS/COMMENTS:

The _____ manufacturing site provided in this and NDA 21-165 is now only Schering Avondale (DMF _____). In amendment dated May 22, 2001, Schering provides that the Singapore site has been withdrawn for _____ manufacture. To re-implement _____ manufacture at this site, an approved prior-approval supplement is needed.

The following pertains to the Amendment C or BC dated March 26, 2001.
 Schering provides that the PM, Ms. G. Trout, requested clarification regarding the Categorical Exclusion provided by Schering for this NDA. Schering provides that the Categorical exclusion encompasses all dosage forms and total usage at the 5th approval year.

Evaluation: Satisfactory. Categorical exclusion is adequate.

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ON ORIGINAL

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

/s/

Kevin Swiss
6/25/01 03:55:34 PM
CHEMIST

Guiragos Poochikian
6/25/01 04:37:52 PM
CHEMIST

CHEMISTRY MEMO

June 8, 2001

•



Food & Drug Administration

Memorandum

Date : June 8, 2001

From: Kevin Swiss, Ph.D., HFD-570

Subject: Withdrawal of Schering-Plough Ltd. Singapore Branch as a Desloratadine Drug Substance Manufacturing Site.

Memo to Files: NDAs N21-165, N21-297, _____, N21-363

Schering Plough has informed the division in an amendment dated May 22, 2001, to the above NDAs, that the Schering Plough Singapore desloratadine drug substance manufacturing site has been withdrawn from the Clarinex 5 mg Tablets NDAs N21-165, N21-297, N21-363 and the _____ . The appropriate NDA EES's have been changed to include the withdrawal of the Singapore site.

In the future after these NDAs are approved, Schering needs an approved "prior-approval supplement" for _____ ' manufacture _____ at Singapore.

Org. NDAs 21-165, 21-297, _____ 21-363
HFD-570/Division File
HFD-570/KSwiss/6/8/01
HFD-570/COstroff
HFD-570/GPoochikian
HFD-570/GTrout
HFD-800/CHoiberg
R/D Init by: GPoochikian _____
filename: N21165.memo.doc

151

Kevin A. Swiss, Ph.D.
Review Chemist (Drug Product)

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/s/

Kevin Swiss
6/8/01 05:55:56 PM
CHEMIST

Guiragos Poochikian
6/8/01 05:58:52 PM
CHEMIST

CHEMISTRY REVIEW #1

January 2001

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

NDA #: 21-297 **CHEM. REVIEW #:** 1 **REVIEW DATE:** 1/24/01

RECOMMEND ACTION: APPROVABLE

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL*	8/30/00	8/31/00	9/11/00
BC Amendment*	10/19/00	10/20/00	10/20/00

*Subject of this review

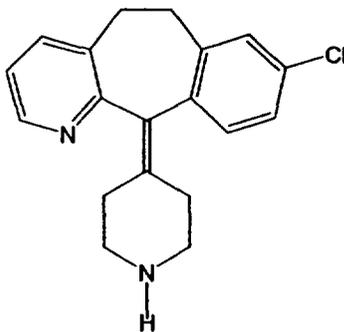
NAME & ADDRESS OF APPLICANT: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

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 H₁-receptor antagonist for Chronic Idiopathic Urticaria
DOSAGE FORM: Solid oral dosage form (tablet, film coated)
STRENGTHS: 5 mg. (Total daily dose: 5 mg)
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx OTC
 YES NO

SPECIAL PRODUCTS:
(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-piperidinylidene)-5H-benzo-
[5,6]cyclohepta[1,2-b]pyridine
Molecular Formula: C₁₉H₁₉ClN₂
Molecular Weight: 310.8

REMARKS/COMMENTS:

Drug Substance and Drug Product
(Please see review page 4)

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 pertaining to N21-165. An EER has been forwarded to OC dated 9/19/00 for this application N21-297 with the same sites as N21-165. When an acceptable EER for all sites is provided for N21-297 this application may be approved, but not before the approval of N21-165.

cc:

Orig. NDA 21-297

HFD-570/Division File N21-297

HFD-570/KSwiss/1/24/01

HFD-570/GTrout

HFD-570/GPoochikian

HFD-820/SKoepe

HFD-800CHOiberg

R/D Init. by: _____

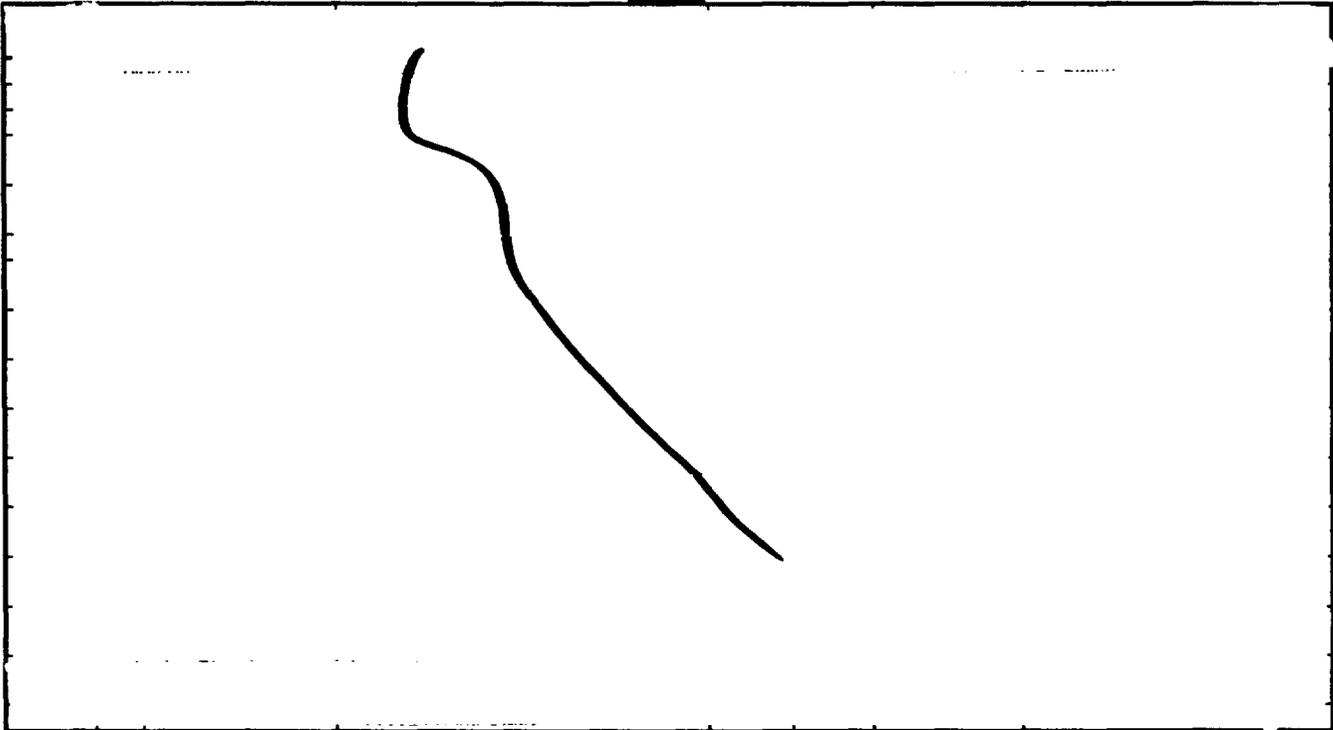
filename: N21297.CR1.DOC

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Kevin A. Swiss, Ph.D. Review Chemist

SUPPORTING DOCUMENTS:

DMFs



RELATED DOCUMENTS (if applicable)

Type	Number	Owner	Subject
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IND		Schering Plough	
IND		Schering Corp.	
IND		Schering Plough	SCH 34117 Tablets
NDA	19-658	Schering Corp.	Claritin® (Loratadine) 10 mg Tablet
NDA	21-165	Schering Plough	Desloratadine Tablets

CONSULTS:

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EER	9/19/00	Pending	Pending inspection
Environmental Assessment	Not applicable	Adequate	Applicant has applied for a categorical exclusion under 21 CFR 25.31(b) in the BC Amendment dated 10/19/00.
Methods Validation	11/1/00 for N21-165	Sent, Results are Pending	MV for drug substance (assay, assay related compounds, polymorph content, PSD) and drug product (dissolution rate, moisture, assay, degradation products, uniformity of dosage units)

REMARKS/COMMENTS:

In the CMC section of this NDA vol. 1.2, sec. 4, page 1, for both drug substance and drug product has been referenced to NDA 21-165.

APPEARS THIS WAY
ON ORIGINAL

/s/

Kevin Swiss
1/26/01 06:00:02 PM
CHEMIST

Guiragos Poochikian
1/30/01 02:31:41 PM
CHEMIST

The request for a categorical exemption from the environmental assessment has been granted. See page four of Chemistry Review # 1.

**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 21297/000	Priority: 1S	Org Code: 570
Stamp: 31-AUG-2000 Regulatory Due: 10-MAR-2002	Action Goal:	District Goal: 09-JAN-2002
Applicant: SCHERING 2000 GALLOPING HILL RD KENILWORTH, NJ 070335030	Brand Name: CLARINEX (DESLORATADINE) 5MG TABLET	
	Established Name:	
	Generic Name: DESLORATADINE	
	Dosage Form: TAB (TABLET)	
	Strength: 5 MG	
FDA Contacts: C. OSTROFF (HFD-570)	301-827-1050	, Project Manager
R. NISHIKAWA (HFZ-017)		, Review Chemist
G. POOCHIKIAN (HFD-570)	301-827-1050	, Team Leader

Overall Recommendation:

ACCEPTABLE on 31-JAN-2002 by P. LEFLER (HFD-324) 301-827-0062
WITHHOLD on 30-JUL-2001 by LABRADORW
WITHHOLD on 05-JUN-2001 by P. LEFLER (HFD-324) 301-827-0062

Establishment: 2650155 SCHERING CORP PRIDCO INDUSTRIAL PARK SR 83 LAS PIEDRAS, PR 00671	DMF No: AADA No:
Profile: TCM OAI Status: OAI ALERT	Responsibilities: ---
Last Milestone: OC RECOMMENDATION	
Milestone Date: 30-JAN-2002	
Decision: ACCEPTABLE	
Reason: BASED ON FILE REVIEW FIRM RESPONSE TO DEFIC. ADEQ	

Establishment: 9612726 SCHERING PLOUGH (AVONDALE) / COUNTY WICKLOW, , EI	DMF No: ██████████ AADA No:
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Profile: CSN OAI Status: NONE	Responsibilities:
Last Milestone: OC RECOMMENDATION	
Milestone Date: 22-JAN-2002	
Decision: ACCEPTABLE	
Reason: BASED ON PROFILE	

**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

June 15, 2001

**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 21297/000	Priority: 1S	Org Code: 570
Stamp: 31-AUG-2000 Regulatory Due: 30-JUN-2001	Action Goal:	District Goal: 01-MAY-2001
Applicant: SCHERING 2000 GALLOPING HILL RD KENILWORTH, NJ 070335030	Brand Name: CLARINEX (DESLORATADINE) 5MG TABLET	
	Established Name:	
	Generic Name: DESLORATADINE	
	Dosage Form: TAB (TABLET)	
	Strength: 5 MG	
<hr/>		
FDA Contacts: C. OSTROFF (HFD-570)	301-827-1050	, Project Manager
K. SWISS		, Review Chemist
G. POOCHIKIAN (HFD-570)	301-827-1050	, Team Leader

Overall Recommendation:

WITHHOLD on 05-JUN-2001 by P. ALCOCK (HFD-324) 301-827-0062

Establishment: 2210048 SCHERING CORP 2000 GALLOPING HILL RD KENILWORTH, NJ 07033	DMF No: AADA No:
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Profile: **TCM** OAI Status: **POTENTIAL OAI** Responsibilities:

Last Milestone: **OC RECOMMENDATION**

Milestone Date: **05-JUN-2001**

Decision: **WITHHOLD**

Reason: **DISTRICT RECOMMENDATION**

Establishment: 2211256 SCHERING CORP 1011 MORRIS AVE UNION, NJ 07083	DMF No: AADA No:
---	---------------------

Profile: **CTL** OAI Status: **POTENTIAL OAI** Responsibilities:

Last Milestone: **OC RECOMMENDATION**

Milestone Date: **05-JUN-2001**

Decision: **WITHHOLD**

Reason: **DISTRICT RECOMMENDATION**

Establishment: 2650155 SCHERING CORP PRIDCO INDUSTRIAL PARK SR 83 LAS PIEDRAS, PR 00671	DMF No: AADA No:
--	---------------------

Profile: **TCM** OAI Status: **OAI ALERT** Responsibilities:

Last Milestone: **OC RECOMMENDATION**

Milestone Date: **05-JUN-2001**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **WITHHOLD**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9612726** DMF No: **—**
SCHERING PLOUGH (AVONDALE) / 1 AADA No:
COUNTY WICKLOW, , EI

Profile: **CSN** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **19-SEP-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

**APPEARS THIS WAY
ON ORIGINAL**

**ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

June 15, 2001

Profile: CTL

OAI Status: POTENTIAL OAI

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-SEP-2000				SWISSK
SUBMITTED TO DO	19-SEP-2000	GMP			DAMBROGIOJ
DO RECOMMENDATION	30-JAN-2001			WITHHOLD	RBROWN4
OC RECOMMENDATION	05-JUN-2001			WITHHOLD	ALCOCKP

Establishment: 2650155

SCHERING CORP

PRIDCO INDUSTRIAL PARK SR 83

LAS PIEDRAS, PR 00671

DMF No:

AADA:

Responsibilities:

Profile: TCM

OAI Status: OAI ALERT

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-SEP-2000				SWISSK
SUBMITTED TO DO	19-SEP-2000	10D			DAMBROGIOJ
ASSIGNED INSPECTION	11-OCT-2000	PS			MTORRES
INSPECTION SCHEDULED	27-NOV-2000		27-DEC-2000		MTORRES
DO RECOMMENDATION	26-FEB-2001			WITHHOLD	MTORRES
OC RECOMMENDATION	05-JUN-2001			WITHHOLD	ALCOCKP

Establishment: 9612726

SCHERING PLOUGH (AVONDALE) / LOFTUS BRYAN

COUNTY WICKLOW, , EI

DMF No:

AADA:

Responsibilities:

Profile: CSN

OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-SEP-2000				SWISSK
OC RECOMMENDATION	19-SEP-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

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