CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-082

CHEMISTRY REVIEW(S)

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

NDA #: 21-082 **CHEM. REVIEW #:** 4 **REVIEW DATE:** 2/23/01

RECOMMEND ACTION: APPROVAL with a phase 4 commitment

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE (Reviewer)
ORIGINAL	10/7/99	10/8/99	10/20/99 (Khorshidi) 3/2/00 (Swiss)
Amendment BC	5/8/00	5/12/00	5/12/00 (Swiss)
Amendment BC	5/18/00	5/22/00	5/22/00 (Swiss)
Amendment AZ	9/7/00	9/8/00	9/11/00 (Swiss)
Amendment BC*	1/2/01	1/4/01	1/4/01 (Swiss)
Amendment BC*	1/15/01	1/17/01	1/17/01 (Swiss)
Amendment BC*	2/1/01	2/5/01	2/5/01 (Swiss)
Amendment BC*	2/14/01	2/14/01	2/14/01 (Swiss)
Amendment BC*	2/22/01	2/23/01	2/23/01 (Swiss)

*Subject of this review

NAME & ADDRESS OF APPLICANT: Novartis Consumer Health
560 Morris Avenue
Summit, NJ 07901-1312

DRUG PRODUCT NAME:

Proprietary: Tavist Allergy/Sinus/Headache Tablet

Nonproprietary/USAN: Clemastine Fumarate, Acetaminophen, and Pseudoephedrine Hydrochloride Tablet

Code Name/#: (unknown)

Chem. Type/Ther. Class: 4 S

PHARMACOL. CATEGORY/INDICATION: Allergic rhinitis

DOSAGE FORM: Immediate release solid oral dosage form (tablet)

STRENGTHS:

Clemastine Fumarate:	0.335 mg per tablet
Acetaminophen:	500 mg per tablet
Pseudoephedrine HCl:	30.0 mg per tablet

Total daily dose: 2 tablets QID, NMT 8 tablets daily.

ROUTE OF ADMINISTRATION: Oral

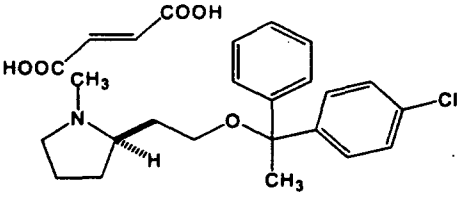
DISPENSED: X Rx _ OTC

SPECIAL PRODUCTS: _ YES X NO

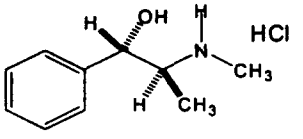
(If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)

APPEARS THIS WAY
ON ORIGINAL

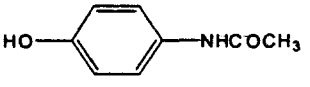
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Clemastine Fumarate
Molecular Formula: $C_{25}H_{30}ClNO_5$
Molecular Weight: 459.96



Pseudoephedrine HCl
Molecular Formula: $C_{10}H_{16}ClNO$
Molecular Weight: 201.70



Acetaminophen
Molecular Formula: $C_8H_9NO_2$
Molecular Weight: 151.17

SUPPORTING DOCUMENTS:

DMF's:

DMF No.	Holder Name	Subject	Status	Date Reviewed
			Adequate	K. Swiss (5/19/00)
			Adequate	K. Swiss (5/18/00) in support of DMF
			Adequate	B. Rogers (8/1/97) L. L. Huang (11/12/98)
			Adequate	A. Shaw (7/16/96) in support of DMF
			Adequate	H. Khorshidi (3/1/99)
			Adequate	J. Boal (12/17/99)
			Adequate	S.Basaran (1/28/99)

RELATED DOCUMENTS (if applicable):

Type	Number	Owner	Subject
IND		Novartis	
IND		Novartis	
IND		Novartis	
NDA	17-661	Novartis	Tavist (clemastine fumarate tablets, USP, 2.68 mg)
NDA	20-925	Novartis	Tavist-1 (clemastine fumarate tablets, USP, 1.34 mg)
NDA		Novartis	Tavist syrup (clemastine fumarate syrup)
NDA	20-640	Novartis	Tavist-D tablet
NDA	18-298	Novartis	Tavist-D tablets

CONSULTS:

Consult	Date forwarded	Status	Comments
EER	2/4/00 3/7/00 11/1/00	Acceptable on 1/2/01	EER for all manufacturing sites was initiated on 2/4/00 and 3/7/00 and then 11/1/00, results from 1/2/01 are listed below: [redacted] is acceptable. [redacted]) is acceptable. Novartis Basel (clemastine fumarate) is acceptable. Novartis Lincoln (drug product manufacturer.) is acceptable.
Environmental Assessment	N/A	See Comments	Novartis provides a categorical exclusion based on 21CFR25.31(b) in Vol. 1.6, D p 234.
Statistical analysis, HFD-570	1/10/01	Pending	Biostat reviewer Dr. Zhao provides expiry dating not to exceed 34 months for [redacted] and 37 months for [redacted]
Method Validation	Pending	Pending	Will be initiated on receipt of MV package.

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is approved from the standpoint of chemistry, manufacturing and controls. The phase 4 commitment in the comment to applicant section should be forwarded to the applicant by the PM in the approval letter.

Kevin A. Swiss, Ph.D. Review Chemist

cc:
Org. NDA 21-082
HFD-570/Division File
HFD-570/KSwiss/2/23/01
HFD-570/GPoochikian
HFD-570/DHilfiker
HFD-570/CLee

R/D Init by: _____

filename: N21082.CR4.1.doc

APPEARS THIS WAY
ON ORIGINAL

/s/

Kevin Swiss
2/23/01 03:13:25 PM
CHEMIST

Guiragos Poochikian
2/23/01 03:57:21 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

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

NDA #: 21-082 **CHEM. REVIEW #:** 3 **REVIEW DATE:** 12/17/00

RECOMMEND ACTION: NOT APPROVABLE

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	10/7/99	10/8/99	10/20/99 (Khorshidi) 3/2/00 (Swiss)
Amendment BC	5/8/00	5/12/00	5/12/00 (Swiss)
Amendment BC	5/18/00	5/22/00	5/22/00 (Swiss)
Amendment AZ*	9/7/00	9/8/00	9/11/00 (Swiss)

*Subject of this review

NAME & ADDRESS OF APPLICANT: Novartis Consumer Health
560 Morris Avenue
Summit, NJ 07901-1312

DRUG PRODUCT NAME:

Proprietary: Tavist Allergy/Sinus/Headache Tablet

Nonproprietary/USAN: Clemastine Fumarate, Acetaminophen, and Pseudoephedrine Hydrochloride Tablet

Code Name/#: (unknown)

Chem. Type/Ther. Class: 4 S

PHARMACOL. CATEGORY/INDICATION: Allergic rhinitis

DOSAGE FORM: Immediate release solid oral dosage form (tablet)

STRENGTHS:

Clemastine Fumarate:	0.335 mg per tablet
Acetaminophen:	500 mg per tablet
Pseudoephedrine HCl:	30.0 mg per tablet

Total daily dose: 2 tablets QID, NMT 8 tablets daily.

ROUTE OF ADMINISTRATION: Oral

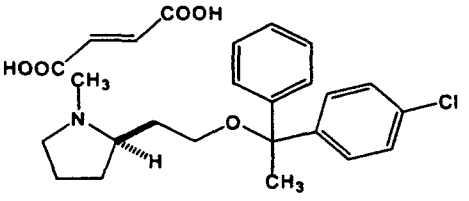
DISPENSED: X Rx _ OTC

SPECIAL PRODUCTS: _ YES X NO

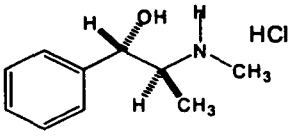
(If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)

APPEARS THIS WAY
ON ORIGINAL

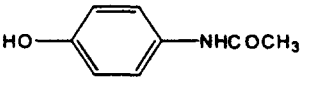
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Clemastine Fumarate
Molecular Formula: $C_{25}H_{30}ClNO_5$
Molecular Weight: 459.96



Pseudoephedrine HCl
Molecular Formula: $C_{10}H_{16}ClNO$
Molecular Weight: 201.70



Acetaminophen
Molecular Formula: $C_8H_9NO_2$
Molecular Weight: 151.17

SUPPORTING DOCUMENTS:

DMF's:

DMF No.	Holder Name	Subject	Status	Date Reviewed
			Adequate	K. Swiss (5/19/00)
			Adequate	K. Swiss (5/18/00) in support of DMF —
			Adequate	B. Rogers (8/1/97) L. L. Huang (11/12/98)
			Adequate	A. Shaw (7/16/96) in support of DMF —
			Adequate	H. Khorshidi (3/1/99)
			Adequate	J. Boal (12/17/99)
			Adequate	S.Basaran (1/28/99)

RELATED DOCUMENTS (if applicable):

Type	Number	Owner	Subject
IND	—	Novartis	—
IND	—	Novartis	—
IND	—	Novartis	—
NDA	17-661	Novartis	Tavist (clemastine fumarate tablets, USP, 2.68 mg)
NDA	20-925	Novartis	Tavist-1 (clemastine fumarate tablets, USP, 1.34 mg)
NDA	—	Novartis	Tavist syrup (clemastine fumarate syrup)
NDA	20-640	Novartis	Tavist-D — tablet
NDA	18-298	Novartis	Tavist-D tablets

CONSULTS:

Consult	Date forwarded	Status	Comments
EER	2/4/00 3/7/00 11/1/00	See Comments	EER for all manufacturing sites was initiated on 2/4/00 and 3/7/00 and then 11/1/00, results are below: [redacted] is on OAI Alert status. [redacted] is acceptable. Novartis Basel (clemastine fumarate) is acceptable. Novartis Lincoln (drug product manufacturer.) is acceptable.
Environmental Assessment	N/A	See Comments	Novartis provides a categorical exclusion based on 21CFR25.31(b) in Vol. 1.6, D p 234.
Statistical analysis, HFD-570	Pending	Pending	Pending specification resolution
Method Validation			To be initiated upon completion of the deficiencies.

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 chemistry list of deficiencies and comments letter. These deficiencies and comments should be forwarded to the applicant by the PM.

This NDA cannot be approved until a satisfactory EER is provided from OC.

Kevin A. Swiss, Ph.D. Review Chemist

cc:
Org. NDA 21-082
HFD-570/Division File
HFD-570/KSwiss
HFD-570/GPoochikian
HFD-570/DHilfiker
HFD-570/CLee
HFD-570/MWakelkamp-Barnes

R/D Init by: _____

filename: N21082.CR3.doc

APPEARS THIS WAY
ON ORIGINAL

/s/

Kevin Swiss
12/17/00 02:32:08 PM
CHEMIST

Guiragos Poochikian
12/18/00 09:57:46 AM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

Hilfiker

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

JUN 13 2000

NDA #: 21-082 **CHEM. REVIEW #:** 2 **REVIEW DATE:** 6/12/00

RECOMMEND ACTION: NOT APPROVABLE

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	10/7/99	10/8/99	10/20/99 (Khorshidi) 3/2/00 (Swiss)
Amendment BC*	5/8/00	5/12/00	5/12/00 (Swiss)
Amendment BC*	5/18/00	5/22/00	5/22/00 (Swiss)

*Subject of this review

NAME & ADDRESS OF APPLICANT: Novartis
560 Morris Avenue
Summit, NJ 07901-1312

DRUG PRODUCT NAME:

Proprietary: Tavist Allergy/Sinus/Headache

Nonproprietary/USAN: Clemastine Fumarate, Acetaminophen, and Pseudoephedrine Hydrochloride

Code Name/#: (unknown)

Chem. Type/Ther. Class: 4 S

PHARMACOL. CATEGORY/INDICATION: Allergic rhinitis

DOSAGE FORM: Immediate release solid oral dosage form (tablet)

STRENGTHS:

Clemastine Fumarate:	0.335 mg per tablet
Acetaminophen:	500 mg per tablet
Pseudoephedrine HCl:	30.0 mg per tablet

ROUTE OF ADMINISTRATION: Oral

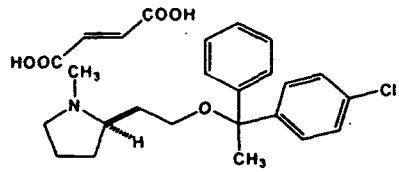
DISPENSED: X Rx _ OTC

SPECIAL PRODUCTS: _ YES X NO

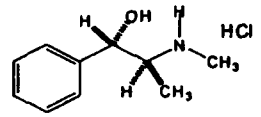
(If yes, fill out the form for special products and deliver to the TIA through the team leader for data entry)

APPEARS THIS WAY
ON ORIGINAL

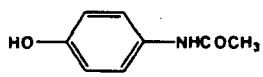
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Clemastine Fumarate
Molecular Formula: $C_{25}H_{30}ClNO_5$
Molecular Weight: 459.96



Pseudoephedrine HCl
Molecular Formula: $C_{10}H_{16}ClNO$
Molecular Weight: 201.70



Acetaminophen
Molecular Formula: $C_8H_9NO_2$
Molecular Weight: 151.17

APPEARS THIS WAY
ON ORIGINAL

SUPPORTING DOCUMENTS:

DMF's:

DMF No.	Holder Name	Subject	Status	Date Reviewed
			Adequate	K. Swiss (5/19/00)
			Adequate	K. Swiss (5/18/00) in support of DMF
			Adequate	B. Rogers (8/1/97) L. L. Huang (11/12/98)
			Adequate	A. Shaw (7/16/96) in support of DMF
			Adequate	H. Khorshidi (3/1/99)
			Adequate	J. Boal (12/17/99)
			Adequate	S.Basaran (1/28/99)

RELATED DOCUMENTS (if applicable):

Type	Number	Owner	Subject
IND		Novartis	
IND		Novartis	
IND		Novartis	
NDA	17-661	Novartis	Tavist (clemastine fumarate tablets, USP, 2.68 mg)
NDA	20-925	Novartis	Tavist-1 (clemastine fumar. tablets, USP, 1.34 mg)
NDA		Novartis	Tavist syrup (clemastine fumarate syrup)
NDA	20-640	Novartis	Tavist-D tablet
NDA	18-298	Novartis	Tavist-D tablets

CONSULTS:

Consult	Date forwarded	Status	Comments
EER	2/4/00 3/7/00	See Comments	EER for all manufacturing sites was initiated on 2/4/2000 and 3/7/00. results are below: is on OAI Alert status. is acceptable. Novartis Basel (clemastine fumarate) is acceptable. Novartis Lincoln (drug product manufacturer.) is acceptable.
Bio-pharm HFD-570			Pending
Statistical analysis, HFD-570			To be initiated upon completion of the deficiencies.

REMARKS/COMMENTS:

Drug Substance

1). There are three actives provided in this NDA, acetaminophen (APAP), pseudoephedrine hydrochloride (PSE) and clemastine fumarate (CF).

2).

clemastine fumarate is manufactured by Novartis in Basel, Switzerland.

3). An EER was sent on February 4, 2000 and updated March 7, 2000.

Novartis in Basel, Switzerland, manufacturer of clemastine fumarate is found acceptable on profile by OC.

4). It is anticipated that this NDA will be transferred to OTC after it is approved.

Drug Product

1). Comments pertaining to the drug product dissolution specifications and bioequivalence will be forthcoming to Novartis from Biopharmaceutics. Dissolution specifications have been cursory reviewed herein.

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

3). The biobatch is batch numbers clemastine fumarate 90016, acetaminophen 009389P304 and pseudoephedrine hydrochloride 222-67-46 for the drug substances and batch number 690-1999.35 drug product. The BA/BE batch is 690-2015.34C.

4). Novartis provides ——— packaging presentations, which are — blister types. The first blister is ——— (——— For the ——— blister, two drug product batches (1/10 scale) with 2 year stability data and 3 batches (full production scale) with 1 year long term and 6 months accelerated stability data. For the — blister, 3 batches (full production scale) are provided with 1 year long term and 6 months accelerated stability data.

5). Novartis seeks a — month expiry period for the ——— blister presentation. However, Novartis seeks a — month expiry period for the — blister presentation. Novartis provides that the accelerated stability data shows differences between the — presentations. After the regulatory deficiencies are addressed (see deficiency comments), a single expiry period for — blister presentations will be determined using the less-protective blister (e.g. —

6). It is anticipated that this NDA will be transferred to OTC after it is approved.

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 chemistry list of deficiencies and comments letter. These deficiencies and comments should be forwarded to the applicant by the PM.

/S/

Kevin A. Swiss, Ph.D. Review Chemist

cc:
Org. NDA 21-082
HFD-570/Division File
HFD-550/HKhorshidi
HFD-570/KSwiss
HFD-570/GPoochikian
HFD-570/DHilfiker

R/D Init by: /S/ 6/13/00

filename: N21082.CR2.doc

APPEARS THIS WAY
ON ORIGINAL

Hilfiker
APR - 1 2000

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

NDA #: 21-082 **CHEM. REVIEW #:** 1 **REVIEW DATE:** 3/31/00

RECOMMEND ACTION: NOT APPROVABLE

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	10/7/99	10/8/99	10/20/99 (Khorshidi) 3/2/00 (Swiss)

NAME & ADDRESS OF APPLICANT: Novartis
560 Morris Avenue
Summit, NJ 07901-1312

DRUG PRODUCT NAME:

Proprietary: Tavist Allergy/Sinus/Headache

Nonproprietary/USAN: Clemastine Fumarate/Acetaminophen/Pseudoephedrine Hydrochloride

Code Name/#: (unknown)
Chem. Type/Ther. Class: 4 S

PHARMACOL. CATEGORY/INDICATION: Allergic rhinitis

DOSAGE FORM: Immediate release solid oral dosage form (tablet)

STRENGTHS:

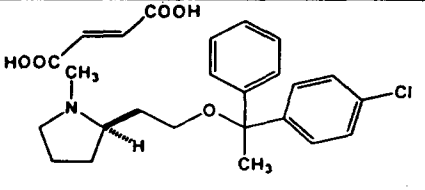
Clemastine Fumarate:	0.335 mg per tablet
Acetaminophen:	500 mg per tablet
Pseudoephedrine HCl:	30.0 mg per tablet

ROUTE OF ADMINISTRATION: Oral

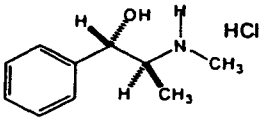
DISPENSED: X Rx _ OTC_

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)

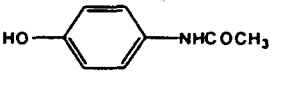
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Clemastine Fumarate
Molecular Formula: $C_{25}H_{30}ClNO_5$
Molecular Weight: 459.96



Pseudoephedrine HCl
Molecular Formula: $C_{10}H_{16}ClNO$
Molecular Weight: 201.70



Acetaminophen
Molecular Formula: $C_8H_9NO_2$
Molecular Weight: 151.17

SUPPORTING DOCUMENTS:

DMF's:

DMF No.	Holder Name	Subject	Status	Date Reviewed
[redacted]			Inadequate	K. Swiss (3/20/00)
			Inadequate	K. Swiss (2/16/00) in support of DMF [redacted]
			Adequate	B. Rogers (8/1/97) L. L. Huang (11/12/98)
			Adequate	A. Shaw (7/16/96) in support of DMF [redacted]
			Adequate	H. Khorshidi (3/1/99)
			Adequate	J. Boal (12/17/99)
			Adequate	S.Basaran (1/28/99)

RELATED DOCUMENTS (if applicable):

Type	Number	Owner	Subject
IND	[redacted]	Novartis	[redacted]
IND	[redacted]	Novartis	[redacted]
IND	[redacted]	Novartis	[redacted]
NDA	17-661	Novartis	Tavist (clemastine fumarate tablets, USP, 2.68 mg)
NDA	20-925	Novartis	Tavist-1 (clemastine fumar. tablets, USP, 1.34 mg)
NDA	[redacted]	Novartis	Tavist syrup (clemastine fumarate syrup)
NDA	20-640	Novartis	Tavist-D [redacted] tablet
NDA	18-298	Novartis	Tavist-D tablets

CONSULTS:

Consult	Date forwarded	Status	Comments
EER	2/4/00 3/7/00	Pending	EER for all manufacturing sites was initiated on 2/4/2000 and 3/7/00, results are below: [redacted] is on OAI Alert status. [redacted] is acceptable. Novartis Basel (clemastine fumarate) is acceptable. Novartis Lincoln (drug product man.) is pending.
Bio-pharm HFD-570			Pending
Statistical analysis, HFD-570			To be initiated upon completion of the deficiencies.

REMARKS/COMMENTS:

Drug Substance

1). There are three actives provided in this NDA, acetaminophen (APAP), pseudoephedrine hydrochloride (PSE) and clemastine fumarate (CF).

2). [ ] clemastine fumarate is manufactured by Novartis in Basel, Switzerland.

3). An EER was sent on February 4, 2000 and updated March 7, 2000. [ ] Novartis in Basel, Switzerland, manufacturer of clemastine fumarate is found acceptable on profile by OC.

4). It is anticipated that this NDA will be transferred to OTC after it is approved.

APPEARS THIS WAY
ON ORIGINAL

Drug Product

1). Comments pertaining to the drug product dissolution specifications and bioequivalence will be forthcoming to Novartis from Biopharmaceutics. Dissolution specifications have been cursory reviewed herein.

1). The EER for Novartis in Lincoln, Nebraska manufacturer of the drug product is currently pending inspection by DO and decision by OC.

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

3). The biobatch is batch numbers clemastine fumarate 90016, acetaminophen 009389P304 and pseudoephedrine hydrochloride 222-67-46 for the drug substances and batch number 690-1999.35 drug product. The BA/BE batch is 690-2015.34C.

4). Novartis provides [redacted] packaging presentations, which are [redacted] blister types. The first blister is [redacted] For the [redacted] blister, two drug product batches (1/10 scale) with 2 year stability data and 3 batches (full production scale) with 1 year long term and 6 months accelerated stability data. For the [redacted] blister, 3 batches (full production scale) are provided with 1 year long term and 6 months accelerated stability data.

5). Novartis seeks a [redacted] month expiry period for the [redacted] blister presentation. However, Novartis seeks a [redacted] month expiry period for the [redacted] blister presentation. Novartis provides that the accelerated stability data shows differences between the [redacted] presentations. After the regulatory deficiencies are addressed (see deficiency comments), a single expiry period for [redacted] blister presentations will be determined using the less-protective blister (e.g. [redacted]

6). It is anticipated that this NDA will be transferred to OTC after it is approved.

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 chemistry list of deficiencies and comments letter. These deficiencies and comments should be forwarded to the applicant by the PM.

/S/ for

Hossein S. Khorshidi, Ph.D. Review Chemist
Drug substance reviewer

/S/

Kevin A. Swiss, Ph.D. Review Chemist
Drug product reviewer

cc:
Org. NDA 21-082
HFD-570/Division File
HFD-550/HKhorshidi
HFD-570/KSwiss
HFD-570/GPoochikian
HFD-570/DHilfiker

R/D Init by: /S/ 4/1/00

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