CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-989

CHEMISTRY REVIEW(S)

DEC 15 1999

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-989 **CHEM.REVIEW #**: 4 **REVIEW DATE**: 07-Dec-99

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
NDA 20-989/000	26-Aug-98	28-Aug-98	Review 1
NDA 20-989(Addendum)			Review 2
Desk Copy	25-Jun-99	28-Jun-99	Review 3
NDA 20-989/AZ	11-Nov-99	12-Nov-99	20-Nov-99

NAME & ADDRESS OF APPLICANT:

Snow Brand Pharmaceuticals, Ltd.
3550 General Atomics Court
San Diego, California 92121
ATTN: Mark D. Carman, Ph.D.
President & CEO
Telephone: (619) 455-2463
Fax: (619) 455-2464

DRUG PRODUCT NAME

Proprietary:	Cevimeline Hydrochloride
Nonproprietary/USAN:	None established
Code Names/#'s:	SNI-2011, AF102B, SND-5008, FKS-508
Chemical Type/ Therapeutic Classes:	1s

ANDA Suitability Petition/DESI/Patent Status: U.S. Patent 4,855,290, dated: 8/8/89

PHARMACOLOGICAL CATEGORY/INDICATION: M_1 Muscarinic receptor agonist/ treatment of xerostomia [redacted] in Sjogren's Syndrome.

DOSAGE FORM: Hard gelatin capsule
STRENGTHS: 30mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
(±)*Cis*-2'-methylspiro(1-azabicyclo[2.2.2]octane-3,5'-[1,3]oxathiolane) hydrochloride hydrate (2:1)

Molecular Formula:	$C_{10}H_{17}NOS.HCl.1/2H_2O$
Molecular Weight:	244.79 (salt) 199.32 (free base)
CAS No.:	153504-70-2

SUPPORTING DOCUMENTS: NDA 20-989/000

REMARKS/COMMENTS:
NDA 20-989/AZ provides for labeling changes stemming from the applicant's August 27, 1999 Approvable Rating. The CMC portion of the "corrected" labeling changes were reviewed. Two minor deficiencies previously mentioned still require correction. The two CMC labeling deficiencies remain as:

1. In the DESCRIPTION portion of this labeling, cevimeline's chemical name of (±)*Cis*-2'-methylspiro(1-azabicyclo[2.2.2]octane-3,5'-[1,3]oxathiolane) hydrochloride, hydrate (2:1), should be modified by adding the dash (-) in front of the 3,5'.
2. In the HOW SUPPLIED section of this labeling, the [redacted] cevimeline hydrochloride [redacted] should be deleted as previously requested.

CONCLUSIONS & RECOMMENDATIONS:
This NDA is APPROVABLE with respect to chemistry concerns. However, it is recommended that modificiations to the labeling be incorporated as outlined above.

/S/ 12/7/99
James D. Vidra, Ph.D.
Review Chemist, HFD-830/HFD-540

cc: Orig. NDA#20-989/000
HFD-540/Division File
HFD-540/ProjMan/Cintron
HFD-540/Chem/Vidra
HFD-540/TeamLdr/DeCamp
filename:

/S/ 12/17/99

/S/ 12/28/99

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DIVISION OF DERMATOLOGY AND DENTAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-989 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 07-Jul-99

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
NDA 20-989/000	26-Aug-98	28-Aug-98	See Chm Rev #1
BC	28-Dec-98	29-Dec-98	See Chm Rev #1
BC	30-Apr-99	03-May-99	See Chm Rev #1
BZ	03-Jun-99	04-Jun-99	See Chm Rev #1
ADDENDUM	10-Jun-99	NA	See Chm Rev #1
DESK COPY	16-Jun-99	NA	See Chm Rev #1
DESK COPY	25-Jun-99	28-Jun-99	08-Jul-99

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STRENGTHS: 30mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: X Rx __ OTC

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Molecular Formula: $C_{10}H_{17}NOS.HCl.1/2H_20$

Molecular Weight: 244.79 (salt)
199.32 (free-base)

CAS No.: 153504-70-2

SUPPORTING DOCUMENTS: NDA 20-989/000

CONSULTS: Not Applicable

REMARKS / COMMENTS:

DRUG SUBSTANCE: Unchanged. See Chemistry Review #1.

DRUG PRODUCT: Unchanged. See Chemistry Review #1.

LABELING: As per 21 CFR 206.10(a), the code imprint for the EVOXAC Capsule in the attachment was previously requested and reviewed as a means of identification of this drug product. The code imprint consisted of both the drug product's name, EVOXAC, and its strength, ——— 30 mg, on this opaque white, '———— ———— imprinted capsule.

CONCLUSIONS & RECOMMENDATIONS:
The second chemistry review of NDA 20-989/000 continues to recommend APPROVAL.

/S/ 7/7/99
James D. Vidra, Ph.D.
Review Chemist

Attachment

cc: Orig. NDA 20-989/000
HFD-540/Division File
HFD-540/ProjMan/Cintron
HFD-540/DenOff/Hyman
HFD-540/Chem/Vidra
HFD-540/ChemTL/DeCamp /S/ 7/8/99
HFD-830/DivDir/Chen
Filename: N20989Rev2

/S/ 7/9/99 Note: only the 30mg is recommended for approval from the clinical team

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1 PAGE(S) REDACTED

Draft

Labeling

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-989 **CHEM.REVIEW #**: 1 **REVIEW DATE**: 27-Apr-99

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
NDA 20-989/000	26-Aug-98	28-Aug-98	04-Sep-98
BC	28-Dec-98	29-Dec-98	21-Jan-99
BC	30-Apr-99	03-May-99	12-May-99
BZ	03-Jun-99	04-Jun-99	09-Jun-99
ADDENDUM	10-Jun-99	NA	NA
DESK COPY	16-Jun-99	NA	NA

JUN 22 1999

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Code Names/#'s:	SNI-2011, AF102B, SND-5008, FKS-508
Chemical Type/ Therapeutic Classes:	1s

ANDA Suitability Petition/DESI/Patent Status: U.S. Patent 4,855,290,

PHARMACOLOGICAL CATEGORY/INDICATION: M_1 Muscarinic receptor agonist/treatment of xerostomia [redacted] in Sjogren's Syndrome.

DOSAGE FORM: Hard gelatin capsule

STRENGTHS: [redacted] 30mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: X Rx _____ OTC

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(+)Cis-2-methylspiro(1-azabicyclo[2.2.2]octane-3,5'-[1,3]oxathiolane) hydrochloride hydrate (2:1)

Molecular Formula: $C_{10}H_{17}NOS.HCl.1/2H_2O$

Molecular Weight: 244.79 (salt)
199.32 (free base)

CAS No.: 153504-70-2

SUPPORTING DOCUMENTS:

IND [redacted] (Original)
DMF [redacted]
DMF [redacted]
DMF [redacted]
IND [redacted]

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

CONSULTS: Establishment Inspection Summary Report (APPENDIX #1)
Labeling & Nomenclature Committee

REMARKS/COMMENTS:

Cevimeline Hydrochloride is a new molecular entity formulated into [redacted] 30 mg cevimeline HCl hard gelatin capsules for the treatment of xerostomia [redacted] in patients with Sjogren's Syndrom Cevimeline HCL is synthesized by [redacted] with details provided in the Type II DMF [redacted] Two synthetic processes, the Existing Process (EP) and Alternate Process (AP), for the manufacture of cevimeline HCl were compared and found equivalent. The EP processed cevimeline HCl, or drug substance (DS), was used in all preclinical studies, pivotal Phase 2 and 3 clinical trials and primary stability studies. The AP process will be used for the marketed product.

NDA 20-989
Cevimeline Capsules, ——— 30 mg

The drug product (DP) or cevimeline HCL ——— 30 mg capsules contain lactose monohydrate, NF; hydroxypropyl cellulose, NF; magnesium stearate, NF; and the empty gelatin capsule. The DP will be manufactured and packaged at the ——— location. All clinical and stability studies were conducted on batch sizes of ——— capsules with the commercial batch size being ——— capsules. The container/closure system for ——— 30 mg capsules will be in 100cc (containing 100 capsules) and 400cc HDPE (containing 500 capsules) bottles using ——— child-resistant screwcaps respectively. The submitted stability data indicates the acceptability of an 24 month expiration date with extensions likely as additional positive stability data is submitted. The only detectable impurity was the ——— which is adequately controlled.

An Addendum was attached (ATTACHMENT #2) which supported the use of the Phase 2 clinical in replacing one of the Phase 3 clinicals. This CMC review included a favorable comparison of the Phase 2 and Phase 3 formulations, the Phase 2 and 3 drug substance and drug product specifications, their dissolution rates and their drug product stability data. Although their formulations differed, all other comparisons were comparable and acceptable.

CONCLUSIONS & RECOMMENDATIONS:
The original NDA 20-989/000 for Cevimeline Hydrochloride Capsules is RECOMMENDED FOR APPROVAL.

/S/ 4/27/99
James D. Vidra, Ph.D.
Review Chemist

Attachments

cc: Orig. NDA#20-989/000
HFD-540/Division File
HFD-540/ProjMan/Cintron
HFD-540/Pharm/See
HFD-540/MedOff/Hyman
HFD-540/Chem/Vidra
HFD-540/TeamLdr/DeCamp /S/ 5/27/99
HFD-830/DivDir/Chen

filename: ———

/S/ 7/9/99

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DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-989 **CHEM.REVIEW #**: 1 (Addendum) **REVIEW DATE**: 10-Jun-99

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Addendum to NDA 20-989/000			

NAME & ADDRESS OF APPLICANT:

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Molecular Weight:	244.79 (salt)
	199.32 (free base)
CAS No.:	153504-70-2

SUPPORTING DOCUMENTS: NDA 20-989/000

CONSULTS: Not Applicable

REMARKS/COMMENTS:
The Phase 2 Clinical Study #SB95US01 is being considered as a possible replacement for one of the two failed Phase 3 Pivotal Trial clinicals (Studies #SB96US02 and #SB96US04) in NDA 20-989. In making a proper decision, chemistry was requested to compare the formulations used in both Phase 2 and 3 clinicals and aid in determining their equivalence. Therefore the following five number of comparisons were made: 1) Drug product formulations; 2) Bulk drug substance specifications; 3) Drug product dissolution rates; 4) Drug product stabilities; and 5) Drug product specifications.

Although the drug product formulations were significantly different in the Phase 2 and 3 clinicals, their bulk drug and drug product specifications were similar, their dissolution rates were equivalent, and their stabilities were deemed comparable.

NDA 20-989
Cevimeline Capsules, — 30 mg

Once it was determined the two formulations were significantly different, the Biopharmaceutical team member was contacted and all of the compiled chemistry data in this report plus additional information was given to him for his bioequivalence review. A meeting was held on on 6/10/99 with Biopharm to discuss their decision. The decision was delayed until a new Biopharm policy could be discussed.

CONCLUSIONS & RECOMMENDATIONS:

The specific drug product formulations used in the Phase 2 and 3 clinical studies were reviewed and found significantly different although other aspects of the two formulations were similar. This information was relayed and discussed with the Biopharm team member for additional bioequivalency review.

/S/ 6/11/99
James D. Vidra, Ph.D.
Review Chemist

/S/ 7/9/99 Note: subsequent Biopharm review addressed this issue.

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