CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-989

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: January 11, 2000. Number of Pages (including ~~cover~~ sheet) - 17

TO: William C. Govier, M.D., Ph.D., President and CEO
COMPANY: SnowBrand Pharmaceuticals, Inc.
FAX #: 734-665-8672

MESSAGE: **NDA 20-989 EVOXAC Caps., 30 mg**

Please find approval letter for NDA 20-989.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

FOOD AND DRUG ADMINISTRATION
DIVISION OF DERMATOLOGIC AND
DENTAL DRUG PRODUCTS
HFD-540
9201 CORPORATE BLVD.
ROCKVILLE, MARYLAND 20850

DATE: 8/26/99

TO:

Name

Fax No.

Phone No.

Location

FROM:

Name MARY JEAN KOZMA-FORNARO
Fax No. 301 827-2075/2091
Phone No. 301 827-2020

Comments: NDA 20989
Cicimelle labeling

**APPEARS THIS WAY
ON ORIGINAL**

14 Page(s) Redacted

Draft

Labeling

FOOD AND DRUG ADMINISTRATION
DIVISION OF DERMATOLOGIC AND
DENTAL DRUG PRODUCTS
HFD-540
9201 CORPORATE BLVD.
ROCKVILLE, MARYLAND 20850

DATE: 8/26/99

TO:

Name _____

Fax No. _____

Phone No. _____

Location _____

FROM:

Name MARY JEAN KOZMA-FORNARO
Fax No. 301 827-2075/2091
Phone No. 301 827-2020

Comments: NDA 20589

23 Page(s) Redacted

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Labeling

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secret and/or

confidential

commercial

information

SU ORIGINAL

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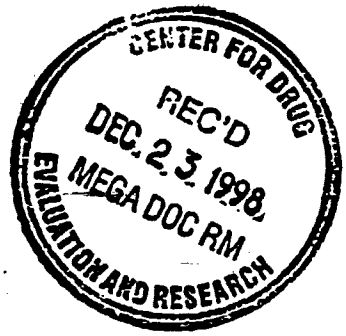
[redacted]

22 December 1998

RETURN RECEIPT REQUESTED

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Attn: Document Control Room
Food and Drug Administration, CDER, ODE V
9201 Corporate Blvd, HFD-540
Rockville, MD 20850



RE: Cevimeline Hydrochloride Capsules
4 Month-Safety Update
NDA 20-989

Dear Dr. Wilkin:

Pursuant to section 505(i) of the Federal Food, Drug and Cosmetic Act and section 314.50 of Title 21 of the Code of Federal Regulations, SnowBrand Pharmaceuticals, Inc. submits this 4-month safety update to NDA 20-989. The New Drug Application for cevimeline hydrochloride capsules [redacted] 30 mg is for the treatment of symptoms of dry mouth, [redacted] in patients with Sjögren's Syndrome.

The information provided in this 120-day safety update is intended to supplement the data provided in the NDA. The two main components are:

- An updated integrated safety summary with data for more than 300 patients exposed to cevimeline for a minimum of 6 months and more than 100 patients exposed to cevimeline for a minimum of 1 year, as discussed in the End-of-Phase II meeting
- The final report for study SB97US05 presenting a comparison of safety data collected from patients receiving cevimeline manufactured using the alternate process (AP) with those collected from patients receiving cevimeline manufactured using the existing process (EP), as discussed at the pre-NDA meeting.

Please contact me should you need any further assistance [redacted]

Sincerely,

[redacted]

Manager, Regulatory and Product Development

cy: Dr. Govier
Mr. Inoke

Memorandum

June 25, 1999

JUN 25 1999

To: Jonathan Wilkin, M.D.
Director, DDDDP, HFD-540

Through: Dennis Bashaw, Pharm.D. /S/ 6/24/99
Team Leader, Pharmacokinetics, HFD-880

From: Assad Noory /S/ 6/25/99
Reviewer, Pharmacokinetics, HFD-880

Subject: Formulations of cevimeline HCl capsules of phase II and phase III clinical trials.

During the review of NDA 20-989, cevimeline HCl capsules, only one of the two phase III clinical trials were successful. The second phase III trial was a failure due to high placebo response rate. The clinical division (DDDDP) explored the possibility of using a phase II clinical trial to replace the failed phase III clinical trial in support of the approval of NDA 20-989. The phase II clinical trial was, however performed with a different formulation of cevimeline HCl capsules than the phase III trial. In the phase II trial lot number 400802K was used, whereas, in the phase III trial lot number H6K02 was used. The Director of DDDDP, Dr. Wilkin requested that DPE III provide its opinion regarding the comparability of the two different capsule formulations used in the phase II and phase III clinical trials.

The formulations of the two capsules are listed below.

	Phase II, (Lot # 400802K) (mg/capsule)	Phase III, (Lot # H6K02) (mg/capsule)
Cevimeline HCl		
Lactose Monohydrate, NF,		
Hydroxypropyl Cellulose, NF		
Magnesium Stearate		
TOTAL		

The Phase II formulation consists of a The phase III formulation, in addition to lactose, contains , cellulose, which is soluble in water of below 40 °C and magnesium stearate, that is not soluble in water.

The dissolution test for phase II formulation (Lot # 40080K) was done whereas the phase III formulation (Lot # H6K02) was tested . Both tests used as the dissolution media. The mean results along with the ranges are shown bellow.

	Lot # 40080K	Lot # H6K02
Paddle Speed		
Sampling Time		
Dissolution [Mean (range)]		

If we consider the minimum dissolution of the capsules, the value of is not appreciably different from Therefore, both formulations can be considered as rapidly dissolving products in water.

Additionally, it is reported in the DMF [redacted] that cevimeline HCl is highly soluble in buffers of pH 2, 4, 6, 8, 10, 12, and 14. This means that cevimeline HCl capsules would most likely show rapid dissolution in buffers of pH 2-8 as well.

In the bioequivalence study (study # SB97US01), submitted with the NDA, a capsule with the phase III formulation, was evaluated against a reference solution of cevimeline . The results of this study show that the capsules were bioequivalent to the solution. The time to reach the maximum plasma concentration (Tmax) for the capsule was 5.5% longer than the reference solution (1.72 hr. versus 1.63 hr). The adjusted Cmax (observed Cmax divided by dose) was 4.4% less for the capsule formulation than the reference solution. This indicates that the capsule formulation is indistinguishable from a reference solution.

Recommendation:
It is the opinion of the 540/550 Combined PK Review Team that the two capsule formulations used in the Phase II and Phase III trials are essentially equivalent. This finding is based on the following:
1. Cevimeline HCl is a highly soluble drug substance.
2. Cevimeline capsules are rapidly dissolving products [redacted]
3. The in vivo performance of the phase III capsule formulation is indistinguishable from a solution.

CC:
CC: NDA 20-989
HFD-540/DIV. File
HFD-540/Prj. Mgr./Cintron
HFD-880 (Noory)
HFD-880 (Bashaw)
HFD-880 (Lazor)
(CDR. Attn: Barbara. Murphy)

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 11/17/99 10:24:43 AM
From: Olga Cintron (CINTRONO)
To: See Below
Subject: NDA 20-989 Cevimeline HCl 30 mg capsules - Resubmission

A complete response to the August 27, 1999, approvable letter, was received on November 12, 1999. The resubmission includes revised draft labeling and a safety update which are the only two issues that the sponsor needed to respond.

The revised draft labeling is very close to the labeling that was sent with the 8/27/99 AE letter with suggested revisions from the sponsor on several sections of the labeling.

Snow Brand has agreed with the Agency's recommendations with respect to the indication and the dose. The [redacted] has been officially withdrawn from the NDA.

This resubmission is regarded as a class 1 and the User Fee Goal date is January 12, 2000.

An electronic copy of the revised labeling is attached to this e-mail, should be getting a hardcopy of the submission shortly. Please let now when you anticipate that your review will be compeleted.

Thanks, Olga

To:	Fred Hyman	(HYMANF)
To:	James Vidra	(VIDRAJ)
To:	Norman See	(SEEN)
To:	Assadollah Noory	(NOORYA)
Cc:	Jonathan Wilkin	(WILKINJ)
Cc:	John Kelsey	(KELSEYJ)
Cc:	Wilson DeCamp	(DECAMP)
Cc:	Abby Jacobs	(JACOBSA)
Cc:	Dennis Bashaw	(BASHAW)
Cc:	Rajagopalan Srinivasan	(SRINIVASAN)
Cc:	Mary Jean Kozma-Fornaro	(KOZMAFORNARO)

14 PAGE(S) REDACTED

Draft

Labeling

Executive CAC
Date of Meeting 18-MAY-1999

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Alternate Member: Paul Andrews, Ph.D., HFD-150
Team Leader: Abby Jacobs, Ph.D., HFD-540
Presenting Reviewer: Norman See, Ph.D., HFD-540

Author of Minutes: Norman See

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA 20-989
Drug Name: Cevimeline HCl
Sponsor Snow Brand Pharmaceuticals, Inc.

Mouse Carcinogenicity Study: The committee agreed with the division that no evidence of carcinogenicity was obtained in the mouse bioassay. This is in contrast to the position of the sponsor, who had proposed that the label of the product mention that [redacted] Statistical analysis by the agency indicated that these findings were not significant, and did not represent a biological signal of concern to humans. This decision also considered historical control comparisons for this common mouse tumor.

Rat Carcinogenicity Study: The committee agreed with the division that the small (but statistically significant) increase in the incidence of uterine adenocarcinomas in female rats that received 100mg/kg/day should be mentioned in the label of the product. The sponsor's draft label stated that no [redacted] therefore, the division's position on uterine adenocarcinomas in the rat is in contrast to the sponsor's position.

Executive CAC Recommendations and Conclusions:
Both carcinogenicity bioassays were adequately designed and executed and are suitable for regulatory purposes.

No evidence of carcinogenicity was obtained in the mouse bioassay.

An increase in the incidence of uterine adenocarcinomas observed in female rats that received 100mg/kg/day should be mentioned in the label of the product.

/S/ 5/28/99
Joseph J DeGeorge, Chair, Executive CAC

APPEARS THIS WAY
ON ORIGINAL

cc:\
/Division File, HFD-540
/JACOBS, HFD-540
/SEE, HFD-540
/CINTRON, HFD-540
/SEIFRIED, HFD-024

/S/ 11/6/00

Printed by Olga Cintron

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 06-Jul-1999 03:15pm
From: Carol-Anne Currier
CURRIER
Dept: HFD-344 MPN1 125
Tel No: 301-827-7397 FAX 301-594-1204

TO: Olga Cintron (CINTRONO)

CC: Jose Carreras (CARRERASJ)
Subject: Re: NDA 20-989 Cevimeline HCl Caps.

Olga-

Please see attached final summary for this NDA sent June 22, 1999. Copies of the letters sent to the investigators were sent to your division. Please contact Dr. Carreras if you need any further details of the inspections.

Carolanne

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER
FOR DRUG EVALUATION AND RESEARCH

DATE: June 22, 1999

FROM: Jose Carreras, M.D.
Good Clinical Practice 2
Division of Scientific Investigations, HFD-344

SUBJECT: Final evaluation of clinical investigator inspections.

NDA 20-989
Cevimeline HCL Capsules
SnowBrand Pharmaceuticals, Inc.

TO: Project Manager: Olga Cintron
Medical Officer: Dr. Frederick Hyman
HFD-550

NAME	CITY	Protocol	CL
John J. Condemi, M.D.	New York	#SB96US02	VAI
Francis J. Dega, M.D.	Boise, Idaho	#SB96US04	VAI
nne L. Petrone, M.D.	Dallas, Texas	#SB96US02	NAI
Daniel Small, M.D.	Sarasota, Florida	#SB96US04	NAI

No objectionable conditions were found in the above sites which would preclude the use of their data submitted in support of pending NDA.

Jose A. Carreras, M.D.

Key to Classifications
NAI = No deviation from regulations
VAI = Minor Deviation(s) from regulations

APPEARS THIS WAY
ON ORIGINAL

/S/

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 18 1999

John J. Condemi, M.D.
Allergy and Asthma Immunology
of Rochester Research Center
919 Westfall Building B
Rochester, New York 14618

Dear Dr. Condemi:

Between April 5 - 9, 1999, Mr. John A. Podsadowski, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of the clinical study (protocol #SB96US02) of the investigational drug Cevimeline (SNI-2011), performed for SnowBrand Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we find that, except for non-reporting of an adverse drug event for subject #0309 (vertigo) and minor record-keeping deficiencies, you conducted the study in basic compliance with federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations. We acknowledge your response and your promise to make corrections/changes in your procedures to assure that the finding noted above will not be repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Podsadowski during the inspection.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-344
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research

CFN - 1316169

Field classification: B

Headquarters classification:
_____1) NAI
__X__2) VAI-no response required
_____3) VAI-response requested

Deficiencies noted:
_____ inadequate consent form
_____ inadequate drug accountability
_____ failure to adhere to protocol
__X__ inadequate records
__X__ failure to report ADRS in the case report form
_____ Other (specify)

cc:
HFA-224
HFD-540 Doc. Rm. NDA 20-989
HFD-540 Review Div.Dir.
HFD-540 MO/Hyman
HFD-540/PM/Cintron
HFD-340/Reading File
HFD-344/Chron File
HFD-344/CIB File/2100
HFD-344/Carreras
HFD-344/Currier
HFR-NE350/Thomas
HFR-NE350/Podsadowski

Note to Reviewer:
No objectionable conditions noted. Data appear acceptable.

r/d:JACarreras: 5/5/99
r/d:nlp:5/6/99
Final:nlp:5/13/99

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 18 1999

Dianne L. Petrone, M.D.
Research Associates of North Texas
Division of Arthritis Centers
712 N. Washington #200
Dallas, Texas 75246

Dear Dr. Petrone:

Between April 13 - 19, 1999, Ms. Kelly J. Pegg, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of the clinical study (protocol #SB96US02) of the investigational drug Cevimeline (SNI-2011), performed for SnowBrand Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to the pertinent federal regulations and/or good clinical practices governing your conduct of clinical investigations.

We appreciate the cooperation shown Investigator Pegg during the inspection.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-344
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research

CFN - N/A

Field classification: NAI

Headquarters classification:
___X___1)NAI
_____2)VAI-no response required
_____3)VAI-response requested

cc:
HFA-224
HFD-540 Doc. Rm. NDA 20-989
HFD-540 Review Div.Dir.
HFD-540 MO/Hyman
HFD-590/PM/Cintron
HFD-340/Reading File
HFD-344/Chron File
HFD-344/CIB File/2100
HFD-344/Carreras
HFD-344/Currier
HFR-SW150/Thornburg
HFR-SW1540/Martinez
HFR-SW1540/Pegg

Note to Reviewer: ✔
No objectionable conditions noted. Data appear acceptable.

r/d:JACarreras: 5/6/99
final:nlp:5/13/99

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

/S/
HFD 540

Food and Drug Administration
Rockville MD 20857

JUN 24 1999

Francis J. Dega, M.D., F.A.C.P.
Medical Arts Building, Suite 512
999 North Curtis Road
Boise, Idaho 83706

Dear Dr. Dega:

Between April 26 and 29, 1999, Ms. Astrida Mattson, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #SB96US04) of the investigational drug Cevimeline (SNI-2011), performed for SnowBrand Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we find that, except for non-reporting of an adverse drug event for subject #1702 (parotid swelling and tenderness) and non reporting a concomitant medication (Doxepine) for subject #1103, you conducted the study in basic compliance with federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations. We note that at the conclusion of the inspection, Ms. Mattson discussed these observations with you. We acknowledge your response and your promise to make corrections/changes in your procedures to assure that the findings noted above will not be repeated in any ongoing or future studies.

We appreciate the cooperation shown Ms. Mattson during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-344
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

CFN - N/A

Field classification: VAI
Headquarters classification:
___1)NAI
_X_2)VAI-no response required
___3)VAI-response requested

Deficiencies noted:
____ inadequate consent form
____ inadequate drug accountability
_X_failure to adhere to protocol
____ inadequate records
_X_ failure to report ADRS in the case report form
____ Other (specify)

cc:
HFA-224
HFD-540 Doc. Rm. NDA 20-989
HFD-540 Review Div.Dir.
HFD-540 MO/Hyman
HFD-540/PM/Cintron
HFD-340/Reading File
HFD-344/Chron File
HFD-344/CIB File/9793
HFD-344/Carreras
HFD-344/Currier
HFR-PA350/Wiskerchen
HFR-PA3540/Mattson

Note to Reviewer:
No objectionable conditions noted. Data appear acceptable.

r/d:JACarreras: 6/15/99
redrafted:nlp:6/17/99
final:nlp:6/22/99

[redacted]

11 January 2000 RETURN RECEIPT REQUESTED

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Acceptance of the label as provided on January 10, 2000

Dear Dr. Wilkin:

This letter serves as our acceptance of the labeling as provided by FDA on January 10, 2000.

Should you need any additional information, please feel free to contact me at [redacted] or by fax [redacted]

Sincerely,

[redacted]

Manager, Regulatory and Product Development

cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

[redacted]

[redacted]

NDA Drug Amendment
BM

28 December 1999 RETURN RECEIPT REQUESTED

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Request of Dr. Hyman of December 23, 1999

Dear Dr. Wilkin:

This submission is in response to Dr. Hyman's request of December 23, 1999.

Enclosed please find the laboratory test results for the five patients who were rollover patients from SB96US02 and SB96US04 who did not have SB96US03 data at the four month safety update but did have SB96US03 data at the final safety update.

Should you need any additional information, please feel free to contact me at [redacted] or by fax [redacted]

Sincerely,

[redacted]

[redacted]

Manager, Regulatory and Product Development

cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

[redacted]

ORIGINAL

[redacted]

20 December 1999 RETURN RECEIPT REQUESTED

NDA ORIG AMENDMENT

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Question and request of Drs. Hyman and Kelsey from 16 December 1999

Dear Dr. Wilkin:

This submission is in response to Drs. Hyman and Kelsey's question and request of December 16, 1999.

1. Dr. Hyman inquired why on page 16 (section 1.5) of volume 2 of our submission of 11 November 1999, it is stated that "no patients with Sjogren's syndrome died during participation in a study" whereas there are 4 deaths narratives included in the same volume.

Answer:
Our statement is correct. A full explanation is provided:
The 4 deaths narratives are as follow:

a. Patient 2007 was in SB96US02 (Sjogren's study). The patient was withdrawn from the study on 10 December 1997 and died 7 February 1998 (almost 2 months later).
b. Patient 3004 was in SB96US03 (Sjogren's study). The patient discontinued from the study and the last dose was taken on 30 September 1997. Four months after discontinuing the study, the patient died.
c. Patient 053 was in ———————
d. Patient 02314326 was in ———————

Patients a and b were no longer participants in a study. They had withdrawn from the study and their deaths did not happen until 2 and 4 months after their last dose. We have included their narratives for completeness sake as our internal rules require that we inform FDA of all information that we receive.

Patient c was in an ——— and not a Sjogren's study.

DUPLICATE

Patient d was in a Japanese Sjogren's study. This study was not in the integrated statistical database and page 16 (section 1.5) only addresses the patients in the integrated statistical database.

2. Dr. Hyman requested that we only provide serious adverse event narratives that were new and had not been submitted in the original NDA or the 4 months safety update. He stated that since we have already submitted everything to that point, there was no need to resubmit.

In response to this request, we are including behind the tab labeled **SAE NARRATIVES** only the new narratives for serious adverse events that have not been submitted in the original NDA or the 4 months safety update. None of these events were considered to be related to drug by the investigator.

3. As requested in our conversation, a concise statement of the changes that occurred after the 4 month safety update cut-off is provided here:

At the cut off date of the 4 month safety update (5 October 1998), study SB96US03 was still ongoing. There were **five** patients **(see ATTACHMENT)** who were rollover patients from SB96US02 and SB96US04 who did not have SB96US03 data at the four month safety update but did have SB96US03 data at the final safety update. One of these was a placebo patient in SB96US02, who then received active drug in SB96US03. Thus, this latter patient was the only additional active patient in the final safety update.

Patients who were still ongoing in SB96US03 at the 4 month safety update cutoff completed the open label study. The final data for these patients does not change in anyway the safety conclusions of the NDA or those of the 4 months safety update as will be seen in the following table.

For ease of comparison, we are including a side by side comparison of the "incidence of adverse events occurring in ≥3% of patients in the all active group" from the data of the 4 months safety data and the final safety data **(TABLE 1)**.

We have included, in the comparison tables, data for the ——— for completeness, even though we have withdrawn that dose from our label.

Should you need any additional information, please feel free to contact me at [redacted] or by fax [redacted]

Sincerely,

[redacted]

Manager, Regulatory and Product Development

cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

[redacted]

NDA CHG AMENDMENT

BL

14 December 1999

RETURN RECEIPT REQUESTED

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research. ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville. MD 20850

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Request of Dr. Hyman from 13 December 1999

Dear Dr. Wilkin:

This submission is in response to Dr. Hyman's request of December 13. 1999. We are providing herein a brief narrative explaining our rational for the changes in labeling from the version you provided us in the approvable letter dated August 27. 1999.

Attached for reference is a copy of our submission of 16 November 1999 in which we have highlighted in yellow the changes in the package insert we have made from the version you provided us in the approvable letter dated August 27. 1999.
The changes that we requested in that submission are indicated as follow:

- The crossed-out sentences are to be deleted.
- The underlined sentences are to be added.

Section: Pharmacokinetics (p.2)
After 24 hours — of the dose was recovered as cis and trans-sulfoxide
Rational:
We believe the use of —— in your version of the label was a typo. The actual compounds are the "cis and trans-sulfoxide".

Section: Clinical Studies (p.2)

Rational:
Since 30 mg tid is the only dose being pursued in the label and for which data from clinical studies are being presented. this sentence is no longer relevant and thus we deleted it from the label.

ORIGINAL

[redacted]

Section: Clinical Studies (p.3)

Rational:
Again, the only dose being reviewed is 30 mg tid. and efficacy data on the in the clinical studies is not relevant.

Section: Clinical Studies (p.3)

Rational:
We have consolidated the two sentences you provided (No statistically significant differences were noted in the patient global evaluations. There was a higher placebo response rate in this study compared to the aforementioned studies) into one sentence.

Section: Warnings (p.3)
Patients with significant cardiovascular disease may potentially be unable to compensate for transient changes in hemodynamics or rhythm induced by EVOXAC TM.
Rational:
We have strengthened the cardiovascular warning because there is the possibility that some patients may demonstrate cardiovascular effects, although we did not see them in the studies.

Sections: Carcinogesis, Mutagenesis and Impairment of Fertility and Pregnancy Category C (p.5 and 6)
We have requested a review by Dr. See of the dose multiple calculation in our submission of 13 December 1999. We are suggesting that the label read under the carcinogenicity, mutagenicity and impairment of fertility and under pregnancy:

"45mg/kg/day (approximately 5 times the maximum recommended dose for a 60kg human when compared on the basis of body surface area estimates)."

Section: Pregnancy Category C (p.6)
the maximum recommended dose for a 60kg human when compared on the basis of body surface area estimates).
Rational:
We believe the use of —— in your version of the label was a minor typo.

APPEARS THIS WAY
ON ORIGINAL

Section: Geriatric Use (p.6)

Rational:
We deleted this sentence since we have the following numbers of subjects aged 65 or over:

Patients exposed to cevimeline included in the integrated statistical database	<65 years (%)	>=65 (%)
885	568 (64.2%)	317 (35.8%)

The studies done specifically in elderly subjects younger subjects.

Section: Management of overdose (p.11)
general supportive measures should be instituted

Rational:
Following your comments. we have indicated that general supportive measures should be instituted initially. We have also changed the tone of the remainder of the paragraph to say "may also be of value". We believe that it may be helpful to the physician to provide some guidance.

Section: Dosage and Administration (p. 12)

Rational:

Section: How Supplied (p. 12)
Store at 25°C (77°F) excursion permitted to 15°–30°C (59°-86° F)
Rational:
The wording in the container label for the storage conditions is correct. We are modifying the wording in the package insert to be consistent.

If you have any questions, please feel free to contact me at [redacted] or by fax [redacted]

Sincerely,

[redacted]

Manager, Regulatory and Product Development

cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

[redacted]

DRUG AMENDMENT

BP

13 December 1999

RETURN RECEIPT REQUESTED

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Dose multiple calculation

Dear Dr. Wilkin:

Thank you for your facsimile of December 6, 1999.
We reviewed the calculation of your pharmacologist and we have the following remark:

Since the recommended dosage for cevimeline will be 30 mg three times daily (90mg/day) or 1.5mg/kg/day in a 60kg individual, and not [redacted] three times daily, we suggest that the dose multiple calculation should be:

Dose Multiple = Animal Dose x Animal Km/Human Dose x Human Km
= 45mg/kg/day x 6/1.5mg/kg/day x 37
= 4.8 which rounds up to 5

Based on this calculation, we propose the following changes to the label (changes bolded and underlined):

In the section Carcinogenesis, Mutagenesis and Impairment of Fertility:

Cevimeline did not adversely affect the reproductive performance or fertility of male Sprague-Dawley rats when administered for 63 days prior to mating and throughout the period of mating at dosages up to 45mg/kg/day (approximately **5** times the maximum recommended dose for a 60kg human following normalization of the data on the basis of body surface area estimates).

In the section Pregnancy Category C:

Cevimeline was associated with a reduction in the mean number of implantations when

[redacted]

given to pregnant Sprague-Dawley rats from 14 days prior to mating through day seven of gestation at a dosage of 45mg/kg/day (approximately 5 times the maximum recommended dose for a 60kg human when compared on the basis of body surface area estimates).

If you have any questions, please feel free to contact me at [redacted] or by fax [redacted]

Sincerely,

[redacted]

Manager, Regulatory and Product Development

cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

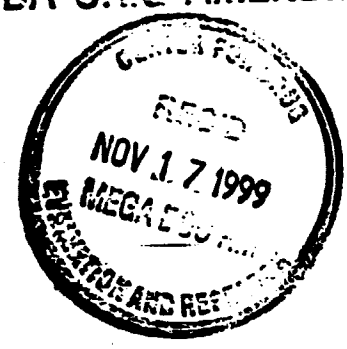
ORIGINAL

BL

16 November 1999

RETURN RECEIPT REQUESTED

NDA ONE AMENDMENT



Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Ms. Cintron's request of reformatted package insert

Dear Dr. Wilkin:

As per Ms. Cintron's request, enclosed please find a copy of the reformatted package insert. This package insert is the exact same one presented in our submission of 11 November 1999 (Complete response to the approvable letter of August 27, 1999).

As you requested, I have highlighted the sections where we have made changes (highlighted in yellow) from the version you provided us in the approvable letter dated August 27, 1999.

I have also underlined the sentences we have added and crossed-out the sentences we have deleted from the version you provided us on August 27, 1999.

If you need further assistance, please contact me at ——— or by fax ———

Sincerely yours,

———

Manager, Regulatory Affairs

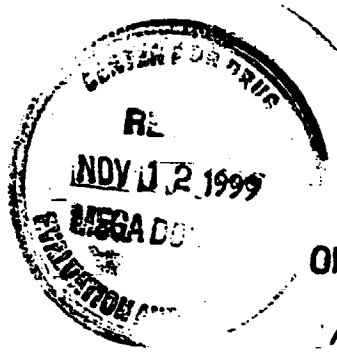
Cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

11 November 1999

RETURN RECEIPT REQUESTED

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850



ORIG AMENDME
AZ

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Complete response to the approvable letter of August 27, 1999

Please refer to the letter of August 27, 1999 issued by Dr. Robert DeLap, Director, Office of Drug Evaluation V, indicating that NDA 20-989 for EVOXAC™ (cevimeline HCL) was approvable.

Enclosed in this submission is a complete response to the above referenced letter:

1. Revised draft labeling for EVOXAC™ based on our meeting of November 3 with your Division.

2. Final safety update.

   We have attempted to follow as closely as possible the same format as the one in the 4 month safety update for ease of your review. As you can see, no new safety issues are raised.

3. Case report forms for patients who died or discontinued due to an adverse event.

In addition, as requested, we hereby officially withdraw the ——— from the NDA.

We believe this provides a complete response to the approvable letter of August 27, 1999. Should you have any questions, please feel free to contact me at ———

Sincerely yours,

———

———

Manager, Regulatory Affairs

Cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

ORIGINAL

ORIGINAL

NC

NEW CORRESP

11/8/99
See meeting minutes for meeting of 11/3/99 which is a complete record of the discussion of the items approvable action for this NDA

18 October 1999 RETURN RECEIPT REQUESTED

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Pre-Meeting Package for the FDA Meeting on November 3, 1999

Dear Dr. Wilkin:

Enclosed please find a pre-meeting package for our meeting with your Division on November 3, 1999.

In this package, we have summarized the pertinent information from the NDA regarding the dosing schedule and the indications of EVOXAC™. At the meeting, we would like to discuss the expansion of the dose range ——— and the indications ——— ——— beyond those already accepted in the Approvable letter dated August 27, 1999. In addition, we would like to discuss the wording of several specific sections of the package insert.

The list of participants representing the Sponsor and our proposed agenda are also attached.

We look forward to our meeting with your Division.

NAI for Chemistry.
12-2-99

Sincerely,

———

———

Manager. Regulatory Affairs

Cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

Redacted 6

pages of trade

secret and/or

confidential

commercial

information

ORIGINAL

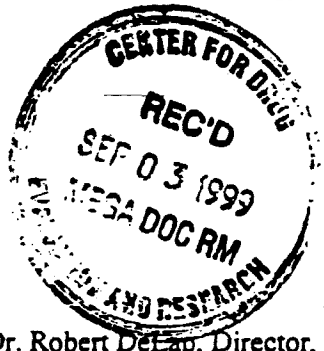
NEW CORRESP

NC

1 September 1999

RETURN RECEIPT REQUESTED

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850



Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Intent to file amendment

Dear Dr. Wilkin:

Please refer to the letter of August 27, 1999 issued by Dr. Robert DeLap, Director, Office of Drug Evaluation V, indicating that NDA 20-989 for EVOXAC™ (cevimeline HCl) was approvable.

As requested in that letter, we are notifying you of our intent to file an amendment to this NDA to provide the information requested in the letter.

We would also at this time like to request a formal meeting with the Division to discuss the draft labeling. We realize that there was not enough time available for us to be able to discuss the labeling before receiving the approvable letter. Below is a list of topics from the labeling which we would like to further discuss with you. We plan to submit an information and discussion package to the Division prior to the meeting and will present the existing data to support our positions as clearly as possible. We would appreciate it if you could suggest possible dates for a meeting, preferably in early October.

Our proposed agenda for the meeting is as follows:

I. Revision of the draft package insert.

A. Possible inclusion of ———— as a synonym in parentheses following "Sjögrens Syndrome".

B. Flexibility in the recommended dosing.

1.

2. [redacted]

C. Indications.

1. We would like to discuss the inclusion of [redacted] as an indication. The data are quite strong as to the significance of the results for this indication.

2. We would like to discuss the inclusion of [redacted] as an indication. [redacted]

II. Any other items that the Division would like to discuss.

We look forward to our meeting with your Division.

Sincerely yours,

[redacted]

Manager, Regulatory Affairs

Cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

copy for file

27 August 1999

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
920 . Corporate Boulevard
Rockville, MD 20850

Re Cevimeline Hydrochloride Capsules
NDA 20-989
Follow up to teleconference with Dr. Wilkin and Dr. Kozma-Fornaro of August 26, 1999

Dear Dr. Wilkin:

I am writing to follow-up ~~on our conversation of yesterday, August 26, 1999.~~

We certainly understand the time constraints currently imposed on the review process. We also appreciate the innovative and creative approach to this situation shown in the choices that were presented to us.

We believe a little more time for us to discuss the final wording in the package insert would be beneficial. On some points, we in fact prefer your wording. On others, we believe that the patient's best interests could be better served with some discussion.

We request that you issue an approvable letter, as offered, and that you provide us with the opportunity to have direct discussions ~~regarding the package insert. We also~~ would like to request that a meeting be scheduled as soon as mutually convenient so that we may bring the review process to a conclusion.

Sincerely,

Manager, Regulatory Affairs

Cy Dr. Govier (Snow Brand Pharmaceuticals, Inc)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

ORIG AMENDMENT
BM

3 August 1999

RETURN RECEIPT REQUESTED

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Response to Dr. Kozma-Fornaro's facsimile of July 30-Out of range labs

Dear Dr. Wilkin:

This submission is made in response to Dr. Kozma-Fornaro's facsimile of July 30, 1999. For ease of review, her question is repeated in bold letters followed by our answer.

Why is the sample size from which the out-of-normal laboratory values are reported different between the table entitled "Incidence of Treatment Emergent Out-of-Range Laboratory Values: Sjogren's All Active"(on page 7 of volume 1 of the 7/22/99 submission) and Table 12.3.2 (entitled "Laboratory Normality Shifts from Baseline to Endpoint: Sjogren's All Active") from the Safety Update.

The table "Incidence of Treatment Emergent Out-of-Range Laboratory Values: Sjogren's All Active"(on page 7 of volume 1 of the 7/22/99 submission) was generated in response to Drs. Kelsey and Hyman's requests. They requested that we regenerate table 40 page 112 volume 130 of the original NDA with number of patients with lab values outside normal range. This table was based on data from the original NDA.

However, Table 12.3.2 (entitled "Laboratory Normality Shifts from Baseline to Endpoint: Sjogren's All Active") found in the four month safety update was generated using the updated database and thus the sample size is larger than in the original NDA. Tables from the 4 month safety update can only be compared with other tables from the 4 month safety update, and not with tables from the original NDA, and vice-versa.

In this submission the following summary table, based on data from the 4 month safety update, is being provided:

- No. Pts With Lab Values Outside Normal Range-Sjogren's All Active

Please note that the N in "Incidence of Treatment Emergent Out-of-Range Laboratory Values: Sjogren's All Active" table is based on all post-baseline assessments. That is if the patient had post-baseline assessments at 15, 30, and 60mg , the patient will be counted at all three dose levels.

On the other hand, the N in "Laboratory Normality Shifts from Baseline to Endpoint: Sjogren's All Active" table is based on the endpoint assessment. That is if the patient had post-baseline assessments at 15, 30 and 60mg and was on 60mg at endpoint, he will be counted only once at the 60mg dose level.

Therefore, only the overall N can be compared for All Active groups. As an example, ALAT (SGPT) has an N=655 in both tables for All Active groups.

In addition, as you requested, we are including the patient numbers for all patients with PCS high in the four month safety update for Sjogren's placebo controlled (SPC) and Sjogren's all active (SAA).

- PCS high-Sjogren's placebo controlled-4 month safety update (SA) under the TAB: **PCS high-SPC-4 month SA**
- PCS high-Sjogren's all active-4 month safety update under the TAB: **PCS high-SAA-4 month SA**

For completeness, we are also including the patient numbers for all patients with PCS high in the original NDA submission under TABS: **PCS high-SPC-original submission and PCS high-SAA-original submission**

Also, should you wish to review the line listings of the actual laboratory results for all patients who had an abnormal laboratory result from the **four month safety update** (approx. 10 volumes), we will be happy to send them to you.

The case report forms for patient #3004 are included per your request. This patient had a normal ALAT value at week 22 following the 17 week elevated value, as seen on page 238 volume 10 of 21 July 1999 submission.

Should you need further clarification, please contact me at [redacted]

Sincerely,

[redacted]

[redacted]

Manager, Regulatory Affairs

Cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

[redacted]

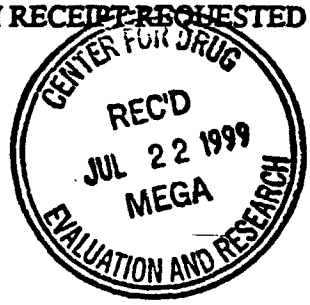
APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

BM

21 July 1999

RETURN RECEIPT REQUESTED



Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

ORIG AMENDMENT

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Request of Drs. Kelsey and Hyman of 14 July 1999-Out of range lab values

Dear Dr. Wilkin:

This submission is made in response to requests 1, 2 and 3 of July 14, 1999 from Drs. Kelsey and Hyman regarding out-of-range lab values.

This submission includes the following:

Volume 1:

1. Normal ranges for the various laboratory tests **(TAB: Lab normal ranges)**

2. The information contained in condensed form in table 40, page 112, volume 130 of the NDA has been amplified to show the numbers of patients having any abnormal lab value in any test. **(TAB: No. pts w/lab outside normal range).** This information is provided in two parts. The first section includes patients in placebo controlled studies, and therefore also shows the number of placebo patients who had abnormal lab values in any test. The incidence of abnormal tests is almost identical in the placebo group and the test groups. **(TAB: Sjogrens placebo controlled).** The second section shows the numbers of all of the patients who received active drug, whether in placebo controlled studies or other studies, who had an abnormal laboratory value. **(TAB: Sjogrens all active).**

3. This section consists of the line listings of the actual laboratory results for all patients who had an abnormal laboratory result. **(TAB: Pts with lab outside normal range)**

Volumes 2-11:

For completeness, these volumes contain line listings for all of the laboratory tests results for all patients who had one or more abnormal laboratory result. This is presented in order to provide an overall picture of the findings in a particular patient for a particular laboratory test. This is to show the prevalence of one-time, idiosyncratic findings with no pattern of abnormality. **(TAB: All data for pts. with lab outside normal range)**

Should you need further clarification, please contact me at

Sincerely,

Manager, Regulatory Affairs

Cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

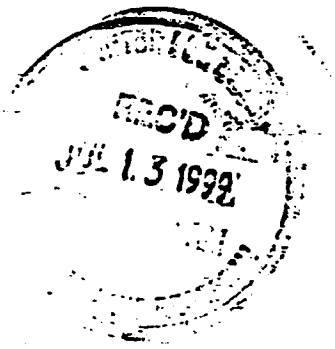
ORIG AMENDMENT

BM

13 July 1999

RETURN RECEIPT REQUESTED

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850



Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Request of Dr. Kelsey of 9 July 1999 regarding labeling

Dear Dr. Wilkin,

Below please find responses to Dr. Kelsey's request of 9 July 1999:

1) In the draft package insert (NDA amendment dated 21 June 1999), on page 9, the statement "the following events were reported in treated Sjogren's patients (<1%): Causal relation is unknown [redacted] " captures adverse events observed for patients on drug. No adverse events observed for patients on placebo are captured here.

2) We concur with you that [redacted] should be deleted from Special Senses Disorders" on page 11.

3) Increased "Npn" under Urogenital Disorders on page 11 stands for "increased nonprotein nitrogen"

If you have any question or require additional information, please contact me at [redacted]

Sincerely,

[redacted]

Manager, Regulatory Affairs

Cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338.
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
SnowBrand Pharmaceuticals, Inc.	July 13, 1999
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
619-350-4495	619-350-9965
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
12636 High Bluff Drive, Suite 300 San Diego, CA 92130	

JUL 13 1999

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 20-989

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Cevimeline Hydrochloride	EVOXAC™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)* SNI-2011

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
capsule	30 mg	oral

(PROPOSED) INDICATION(S) FOR USE:
Xerostomia in Sjögren's patients

APPLICATION INFORMATION

APPLICATION TYPE (check one)
[X] NEW DRUG APPLICATION (21 CFR 314.50) [ ] ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
[ ] BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE [X] 505 (b) (1) [ ] 505 (b) (2) [ ] 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
[ ] ORIGINAL APPLICATION [X] AMENDMENT TO A PENDING APPLICATION [ ] RESUBMISSION
[ ] PRESUBMISSION [ ] ANNUAL REPORT [ ] ESTABLISHMENT DESCRIPTION SUPPLEMENT [ ] SUPAC SUPPLEMENT
[ ] EFFICACY SUPPLEMENT [ ] LABELING SUPPLEMENT [ ] CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT [ ] OTHER

REASON FOR SUBMISSION
Response to FDA request

PROPOSED MARKETING STATUS (check one) [X] PRESCRIPTION PRODUCT (Rx) [ ] OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS [X] PAPER [ ] PAPER AND ELECTRONIC [ ] ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
x	2. Labeling (check one) [x] Draft Labeling [ ] Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[redacted]	[redacted] Manager, PhD, Manager Regulator and Product Development	July 13, 1999

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
[redacted]	[redacted]

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

ORIG AMENDMENT

BM

12 July 1999

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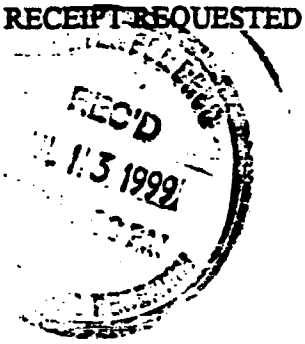


Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Request of Dr. Hyman of 8 July 1999

Dear Dr. Wilkin,

Enclosed please find a table illustrating the criteria for identifying laboratory values as potentially clinically significant. This is in response to Dr. Hyman's request of 8 July 1999.

If you have any question or require additional information, please contact me at [redacted]

Sincerely,

[redacted]

Manager, Regulatory Affairs

Cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

Criteria for Identifying Laboratory Values as Potentially Clinically Significant

Chemistry		Hematology	
Analyte	PCS Criteria	Analyte	PCS Criteria
Glucose	≤ 50, ≥ 180 mg/dL	White Cell Count	≤ 2.8, ≥ 16 x 10^3/mm^3
Sodium	≤ 115, ≥ 155 mEq/L	Neutrophils	≤ 15%, ≥ 90%
Potassium	≤ 3.0, ≥ 5.8 mEq/L	Lymphocytes	≤ 10%, ≥ 80%
Chloride	≤ 90, ≥ 115 mEq/L	Monocytes	≥ 20%
Urea Nitrogen	≥ 30 mg/dL	Eosinophils	≥ 10%
Creatinine	≥ 2.0 mg/dL	Basophils	≥ 5%
Uric Acid			
Male	≥ 10.5 mg/dL	Red Cell Count	≤ 3.5 x 10^6/mm^3
Female	≥ 8.5 mg/dL	Hemoglobin	
Phosphorus, Inorganic	≤ 1.5, ≥ 6.0 mg/dL	Male	≤ 11.5 g/dL
Calcium	≤ 7, ≥ 15.5 mg/dL	Female	≤ 9.5 g/dL
		Hematocrit	
Cholesterol, Total	≥ 300 mg/dL	Male	≤ 37%
Triglycerides	≥ 250 mg/dL	Female	≤ 32%
Protein, Total	≤ 4.5, ≥ 9.0 g/dL	Platelet Count	≤ 75, ≥ 700 x 10^3/mm^3
Albumin	≤ 2.5, ≥ 6.5 g/dL		
Alkaline Phosphatase	≥ 3 x ULN		
AST (SGOT)	≥ 3 x ULN		
ALT (SGPT)	≥ 3 x ULN		
GGT	≥ 3 x ULN		
Total Bilirubin	≥ 2.0 mg/dL		
Lactate Dehydrogenase	≥ 3 x ULN		
Creatine Kinase	≥ 3 x ULN		
Serum Amylase	≥ 3 x ULN		

ULN=Upper Limits of Normal

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338.
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
SnowBrand Pharmaceuticals, Inc.	July 12, 1999
TELEPHONE NO. (*Include Area Code*)	**FACSIMILE (FAX) Number (*Include Area Code*)**
619-350-4495	619-350-8965
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued*):	**AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE**
12636 High Bluff Drive, Suite 300 San Diego, CA 92130	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) NDA 20-989

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
Cevimeline Hydrochloride	EVOXAC™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*if any*)

CODE NAME (*if any*)
SNI-2011

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
capsule	30 mg	oral

(PROPOSED) INDICATION(S) FOR USE:
Xerostomia in Sjögren's patients

APPLICATION INFORMATION

APPLICATION TYPE (check one)
[X] NEW DRUG APPLICATION (21 CFR 314.50) [ ] ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
[ ] BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE [X] 505 (b) (1) [ ] 505 (b) (2) [ ] 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
[ ] ORIGINAL APPLICATION [X] AMENDMENT TO A PENDING APPLICATION [ ] RESUBMISSION
[ ] PRESUBMISSION [ ] ANNUAL REPORT [ ] ESTABLISHMENT DESCRIPTION SUPPLEMENT [ ] SUPAC SUPPLEMENT
[ ] EFFICACY SUPPLEMENT [ ] LABELING SUPPLEMENT [ ] CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT [ ] OTHER

REASON FOR SUBMISSION
Response to FDA request

PROPOSED MARKETING STATUS (check one) [X] PRESCRIPTION PRODUCT (Rx) [ ] OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS [X] PAPER [ ] PAPER AND ELECTRONIC [ ] ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
x	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[redacted]	Manager, PhD, Manager Regulator and Product Development	July 12, 1999

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
[redacted]	[redacted]

NEW CORRESP

NEW CORRESP

NC

8 July 1999

RETURN RECEIPT REQUESTED

Ms. Olga Cintron
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
HFD-540, Room N248
9201 Corporate Boulevard
Rockville, MD 20850

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Request for point of contact for future correspondence for NDA 20-989

Dear Ms. Cintron:

In response to your request for a point of contact for future correspondence for NDA 20-989, please forward future official correspondence (action letter...) to:

William C. Govier, M.D., Ph.D.
President and CEO
SnowBrand Pharmaceuticals, Inc.
2001 Commonwealth Blvd., Suite 205
Ann Arbor, MI 48105
Phone (734-665-9070); Fax (734-665-8672)

For day to day requests for further information on the NDA, please contact me at _____ or by facsimile _____ as you have done in the past and I will be happy to promptly provide you any additional information you request.

Sincerely,

_____

_____

Manager, Regulatory and Product Development

cy: Dr. Govier (SnowBrand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

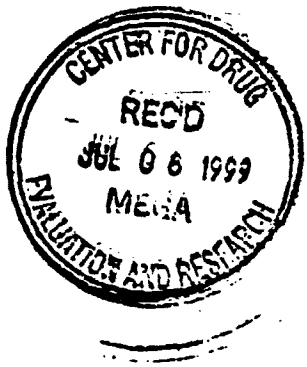
BM

7 July 1999

RETURN RECEIPT REQUESTED

Ms. Olga Cintron
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
HFD-540, Room N248
9201 Corporate Boulevard
Rockville, MD 20850

ORIG AMENDMENT



Total: 4 pages

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Response to Drs. Hyman's Request of 2 July 1999

Dear Ms. Cintron:

Hope you had a nice holiday!
Enclosed please find the response to Dr. Hyman's request of 2 July 1999.

In the package insert for cevimeline hydrochloride, the following statements (in bold and underlined) are made under "Geriatric Use":

[redacted]

The following tables document this statement. The adverse events selected for presentation in the tables are the ten most prevalent in Sjogren's placebo-controlled studies at the dose of 30mg.

APPEARS THIS WAY
ON ORIGINAL

Sjogren's placebo-controlled studies; dose=15mg

Adverse events	≤60 years; Total n=81		>60 years; Total n=59	
	n	%	n	%
Nausea	6	7.4	6	10.1
Increased sweating	3	3.7	4	6.7
Headache	15	18.5	3	5.0
Diarrhea	10	12.3	6	10.1
Upper respiratory tract infection	4	4.9	7	11.8
Rhinitis	7	8.6	2	3.3
Abdominal pain	6	7.4	7	11.8
Urinary tract infection	5	6.1	3	5.0
Increased saliva	1	1.2	-	-
Vomiting	0	0	2	3.3

This table is derived from end of text table 7.10.1 volume 132 of the NDA

Sjogren's placebo-controlled studies; dose=30mg

Adverse events	≤60 years; Total n=104		>60 years; Total n=49	
	n	%	n	%
Nausea	26	25.0	9	18.3
Increased sweating	23	22.1	8	16.3
Headache	22	21.1	10	20.4
Diarrhea	13	12.5	6	12.2
Upper respiratory tract infection	13	12.5	4	8.1
Rhinitis	12	11.5	2	4.0
Abdominal pain	9	8.6	2	4.0
Urinary tract infection	7	6.7	3	6.1
Increased saliva	6	5.7	-	-
Vomiting	6	5.7	1	2.0

This table is derived from end of text table 7.10.1 volume 132 of the NDA

Sjogren's placebo-controlled studies; dose=60mg

Adverse events	≤60 years; Total n=23		>60 years; Total n=4	
	n	%	n	%
Nausea	12	52.1	2	50.0
Increased sweating	16	69.5	4	100
Headache	7	30.4	1	25.0
Diarrhea	5	21.7	1	25.0
Upper respiratory tract infection	2	8.7	0	0
Rhinitis	0	0	0	0
Abdominal pain	3	13.0	1	25.0
Urinary tract infection	1	4.3	0	0
Increased saliva	3	13.0	-	-
Vomiting	3	13.0	1	25.0

This table is derived from end of text table 7.10.1 volume 132 of the NDA

Dose related trends in adverse events by age were observed with rigors, dizziness, nausea, abdominal pain, diarrhea, increased saliva and increased sweating in patients ≤ 60 years of age, and with increased sweating in patients > 60 years of age.

The following tables document this statement:

Sjogren's placebo-controlled studies; ≤60 years

Adverse events	Dose 15mg Total n=81		Dose 30mg; Total n=104		Dose 60mg; Total n=23	
	n	%	n	%	n	%
Rigors	0	0	2	1.9	8	34.7
Dizziness	4	4.9	5	4.8	4	17.3
Nausea	6	7.4	26	25.0	12	52.1
Abdominal pain	6	7.4	9	8.6	3	13.0
Diarrhea	10	12.3	13	12.5	5	21.7
Increased saliva	1	1.2	6	5.7	3	13.0
Increased sweating	3	3.7	23	22.1	16	69.5

This table is derived from end of text table 7.10.1 volume 132 of the NDA

Sjogren's placebo-controlled studies; >60 years

Adverse events	Dose 15mg Total n=59		Dose 30mg; Total n=49		Dose 60mg; Total n=4	
	n	%	n	%	n	%
Increased sweating	4	6.7	8	16.3	4	100

This table is derived from end of text table 7.10.1 volume 132 of the NDA

If you need further assistance, please contact me at ——— or by fax ———

Sincerely,

———

———

Manager, Regulatory and Product Development

APPEARS THIS WAY
ON ORIGINAL

cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

ORIGINAL

NEW CORRESP

6 July 1999

RETURN RECEIPT REQUESTED

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Request of Drs. DeCamp and Dr. Vidra of 6 July 1999

Dear Dr. Wilkin,

The purpose of this submission is to withdraw the CMC amendment we submitted on June 25, 1999.

Enclosed, please find a new CMC amendment which consists of mock-ups of printed commercial capsules. These are provided for your review in Attachment I. Capsules are opaque white and printed in black ink.

If you have any question or require additional information, please contact me at

Sincerely,

Manager, Regulatory Affairs

Cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

BC

25 June 1999

RETURN RECEIPT REQUESTED

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

CMC AMENDMENT

Re: EVOXAC ™-Cevimeline Hydrochloride Capsules
NDA 20-989

Dear Dr. Wilkin,

The purpose of this submission is to provide you with the following CMC information on EVOXAC capsules.

1. Mock-up of printed commercial capsules are provided for your review in Attachment I. Capsules are opaque white and printed in black ink.

2. A copy of the process validation protocol and the proposed schedule for conducting validation are provided in Attachment II. In addition, packing validation protocols for 9 count, 100 count and 500 count bottles are also provided.

3. Attachment III contains the following:

   - Stability Protocol and 3-month stability data from the physician's sample packages.

   - Samples of nine count capsules in HDPE bottles were placed on stability at 25°C/60%RH, 30°C/60%RH and 40°C/75%RH. They were tested according to schedule.

     The stability data show that there were no failures for samples stored at 25°C/60%RH or 40°C/75%RH. The only change seen in the study to date has been a decrease in dissolution at 40°C/75%RH.

- A mock up of immediate container label and carton label for the physician samples.
- Packaging Protocol, Master Production Record and Finished Goods Specification for the physician samples.

4. Three other interim stability reports of Cevimeline Hydrochloride Capsules are included in Attachment IV for your review.

If you have any question or require additional information, please contact me at [redacted]

Sincerely,

[redacted]

[redacted]

Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

JC

NEW CORRESP

22 June 1999

RETURN RECEIPT REQUESTED

Ms. Olga Cintron
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
HFD-540, Room N248
9201 Corporate Boulevard
Rockville, MD 20850

Via facsimile

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Response to Drs. Hyman and Vidra's Requests of 21 June 1999

Dear Ms. Cintron:

Enclosed please find responses to Dr. Hyman and Vidra's requests of 21 June 1999.

1. Patient exposure for 6 months and 1 year:

The number of patients indicated as having been exposed for 6 months or 1 year in the original ISS represents the number of those patients at the indicated cut-off date. The large open label study (SB96US03) was still ongoing at that time. Therefore, additional patients would constantly be reaching the 6 month and 1 year time points. Thus, by the time of the 4 month update, many additional patients had reached 6 months and 1 year. There is no correlation with the number of new patients entered into the study during that time period. The increase is strictly a function of patients who had already been in the study and reached the milestones.

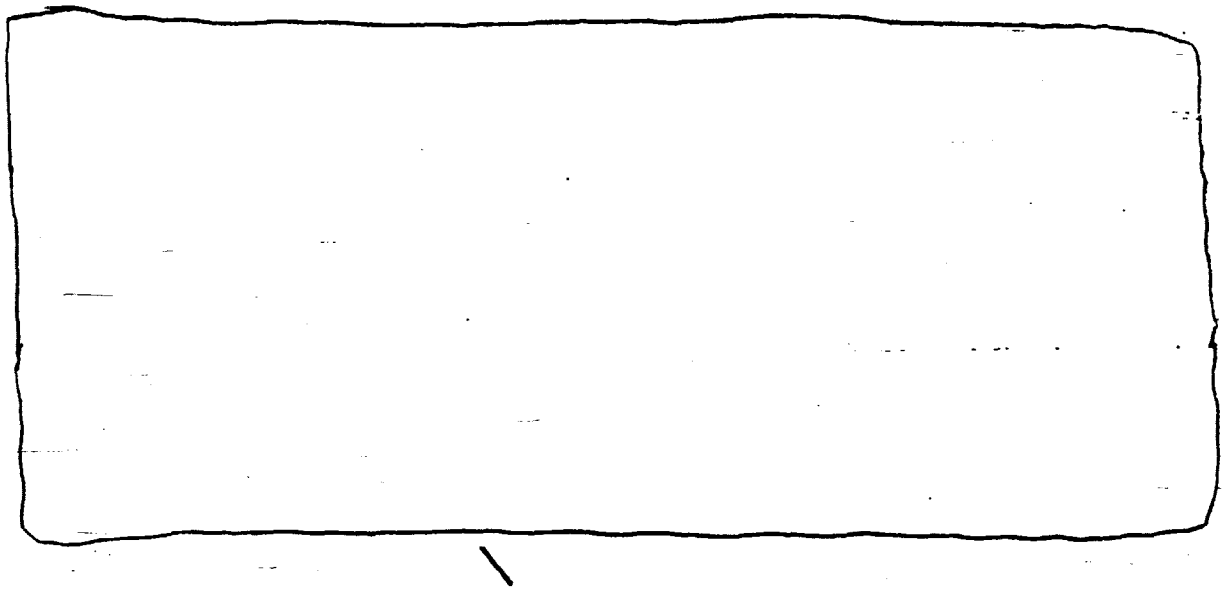
2. Primary versus secondary Sjogren's:

The diagnosis of Sjogren's syndrome (Sicca Syndrome) has a number of facets. While it is a little difficult to set down all of the factors absolutely clearly, we are confident that the investigators knew the difference between Primary Sjogren's and Secondary Sjogren's, as they were all active in the field and made that distinction every day. In addition, at preliminary investigator's meetings, we had experts such as _____ in attendance to clarify any questions.

The primary distinction to be made between Primary and Secondary is the presence in Secondary Sjogren's of evidence of accompanying rheumatoid arthritis or other connective tissue diseases. All of the other factors mentioned, such as anti-Ro/SS-A and anti-LA/SS-B antibodies, as well as Rheumatoid Factor can and do occur in both Primary and Secondary Sjogren's. Actually, Rheumatoid Factor occurs in up to 40% of normal individuals, but it is almost always present in both Primary and Secondary Sjogren's.

The paragraph in the protocol amendment was trying to make the point that for Secondary Sjogren's, the patients had to have evidence of rheumatoid arthritis or some other connective tissue disease, in addition to the other factors. It probably was not written in the best possible way, but we are certain that the investigators, especially after the investigator's meetings, understood the meaning.

3. Company Logo:
Below, please find the mock-up of the container label for cevimeline. I have marked with an arrow the logo for Snow Brand Pharmaceuticals.



If you need further assistance, please contact me at ——— or by fax ———

Sincerely,

———

———

Manager, Regulatory and Product Development

cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

ORIGINAL

21 June 1999

RETURN RECEIPT REQUESTED

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

DRUG AMENDMENT
BC

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Response to Dr. Hyman's request of June 10, 1999 and June 17, 1999

Dear Dr. Wilkin,

Enclosed please find the revised package insert for Cevimeline Hydrochloride capsules per recommendations offered by Dr. Hyman, medical officer on June 10, 1999 (by facsimile) and on June 17, 1999 (by teleconference).

As recommended by Dr. Hyman, we have examined the Salagen package insert as a model. However, we noted that the Salagen insert mentions 376 patients receiving Salagen, whereas the two adverse events tables presented account for 255 patients.

We would like to include all of our patients in the adverse events disclosure section. Therefore, we have tabulated all placebo patients, and all patients who received 15, 30 or 60mg doses of cevimeline. We feel that this provides a clear picture of the expected adverse event profile.

If you have any additional questions or need further clarification, please do not hesitate to contact me at [redacted] (or fax [redacted].

Sincerely,

[redacted]

Manager, Regulatory and Product Development

cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

6 hard copies received 6/22/99 Lilli in mail ISP

ORIGINAL

16 June 1999

RETURN RECEIPT REQUESTED

Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

ORIG AMENDMENT

BC

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Response to Dr. Vidra's request of 11 June 1999

Dear Dr. Wilkin,

Reference is made to a teleconference on 11 June 1999 that I had with Dr. Vidra, reviewing chemist and Ms. Cintron, project manager of your Division. During the above teleconference, Dr. Vidra asked that we revise immediate container labels for EVOXAC™, with the physical address of Yamanouchi Shaklee Pharma (the manufacturing facility).

The purpose of this submission is to provide you with revised immediate container labels per Dr. Vidra's request.

If you have any additional questions or need further clarification, please do not hesitate to contact me at ——— (or fax ———).

Sincerely,

———

Manager, Regulatory and Product Development

cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

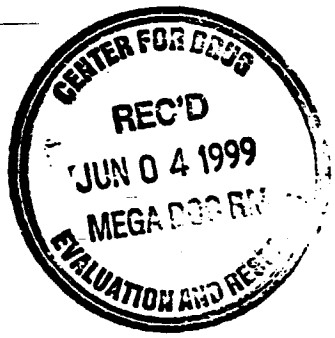
APPEARS THIS WAY
ON ORIGINAL

4th copy
B2

3 June 1999

RETURN RECEIPT REQUESTED

ORIG AMENDMENT



Dr. Jonathan Wilkin
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
Document Control Room HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Response to FDA Request of May 26, 1999

Dear Dr. Wilkin,

Reference is made to a teleconference that I had on May 26, 1999 with Ms. Cintron, and Drs. DeCamp, Vidra of your Division regarding the CMC section of the cevimeline NDA. The purpose of this submission is to provide answers to their questions. For ease of review, the questions and points raised by the FDA are repeated here in bold letters followed by our response to them.

1. **Trade name of the product.**

   We have selected EVOXAC™ as the trade name of the product.

2. **Samples of immediate container labels and carton labels.**

   Full size color proofs of immediate container labels are provided in Attachment-1. Also included in Attachment-1 are black and white copies of carton labels. Please note that only black and white labels will be used in shipping cartons.

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

[redacted]

If you have any additional questions or need further clarification, please do not hesitate to contact me at [redacted] (or fax [redacted]).

Sincerely,

[redacted]

Manager, Regulatory and Product Development

cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

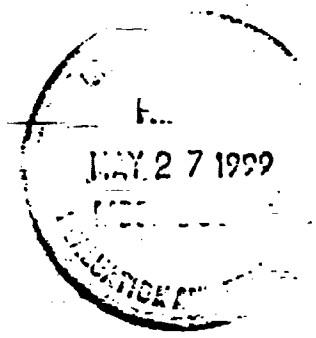
BM

26 May 1999

RETURN RECEIPT REQUESTED

ORIG AMENDMENT

Ms. Olga Cintron
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
HFD-540, Room N248
9201 Corporate Boulevard
Rockville, MD 20850



Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Response to FDA Request of May 25, 1999
Clarification of primary vs. secondary Sjogren's

Dear Ms. Cintron:

It was a pleasure talking to you and Dr. Hyman yesterday.

I have enclosed some reference articles to provide an explanation of the definition of primary vs. secondary Sjogren's syndrome that we used in the study protocols (attachment 1: relevant section of protocol and amendment 1).

Primary Sjogren's syndrome is when lacrimal glands and parotid and other salivary glands are infiltrated and dysfunctional. This occurs without the presence of other autoimmune, connective tissue disease (e.g., lupus, rheumatoid arthritis, etc.)

Secondary Sjogren's syndrome is when Sjogren's symptoms (keratoconjunctivitis sicca and xerostomia) are present and accompanied by a disease affecting the body's connective tissue.

The "Sjogren's syndrome" chapter of "Diagnosis and Management of Rheumatic Diseases" (attachment 2) explains the distinction between primary and secondary Sjogren's and provides a nice overview of the laboratory tests. This chapter also speaks to other parts of the body that are affected by Sjogren's Syndrome, such as the skin, respiratory tract and vagina. These other affected areas are the basis for our question to the patients and the data collection regarding "overall dryness", and are the basis for our overall dryness statement in the proposed indication.

Table 2 of chapter 1 of "The new Sjogren's Syndrome handbook" (attachment 3) also classifies primary vs. secondary syndrome.

I have also attached the American Rheumatism Association Diagnostic Criteria (attachment 4) used in the case of secondary Sjogren's patients.

If you need further assistance, please contact me at [redacted] or by fax [redacted]

Sincerely,

[redacted]

Manager, Regulatory and Product Development

cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

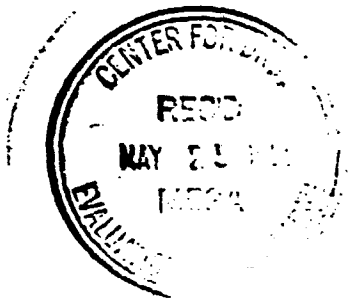
APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

24 May 1999 — [redacted] RETURN RECEIPT REQUESTED

BB

Ms. Olga Cintron
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
HFD-540, Room N248
9201 Corporate Boulevard
Rockville, MD 20850



Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Response to FDA Request of May 14, 1999
Assay validation for pharmacokinetic studies

Dear Ms. Cintron:

Enclosed please find the assay validation reports for the following studies:

- II-2
- CS89-1
- R/4800/0002
- SB97US01

If you need any additional documents or information, please let me know (phone: ——— or fax ———) and I will be happy to provide it to you.

Sincerely,

———

———

Manager, Regulatory and Product Development

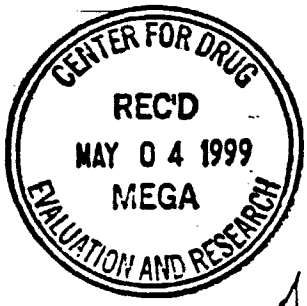
cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

3 May 1999

RETURN RECEIPT REQUESTED



Noted; see review (Orig. Pharm. summary)
1 NDA 20-989
1ST
5/12/99

Ms. Olga Cintron
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
HFD-540, Room N248
9201 Corporate Boulevard
Rockville, MD 20850

[redacted]

BP

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Response to FDA Request of April 14, 1999
Historical Data Concerning the Incidence of Spontaneous Tumors in CD-1 Mice and Fisher 344 Rats

Dear Ms. Cintron:

Enclosed please find an additional copy of the historical control data concerning the incidence of spontaneous tumors in CD-1 mice and Fisher 344 rats. This data is in connection with the carcinogenicity studies —— '007 and —— '006 submitted in NDA 20-989.

If you need any additional documents or information, please let me know (phone: ———— or fax ————) and I will provide it to you promptly.

Sincerely,

———

————————

Manager, Regulatory and Product Development

cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

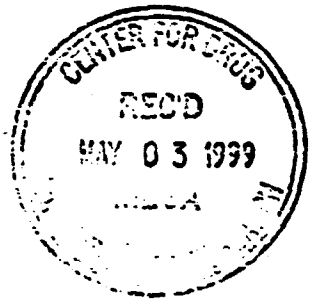
ORIGINAL

Tel:

30 April 1999

RETURN RECEIPT REQUESTED

Ms. Olga Cintron
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
HFD-540, Room N248
9201 Corporate Boulevard
Rockville, MD 20850



Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Response to FDA Request of April 27, 1999
CMC Information requested

BA

Dear Ms. Cintron:

Thank you for your facsimile of April 27, 1999.

Enclosed please find the chemistry information you have requested:

1. Your District Laboratories can request their samples for Method Validation from:

	Name	Address	Phone	Fax
Drug Substance Manufacturer	Senior Managing Director			
Drug Product Manufacturer (Yamanouchi Shaklee Pharma)	Mr. Bill Schaber Manager Quality Assurance	Yamanouchi Shaklee Pharma 1050 Arastradero Road Palo Alto, CA 94304	650-849-8525	650-849-8622

2. Enclosed please find two additional sets of volumes 1.4 and 1.5 of the NDA. These are the Method Validation volumes.

APPEARS THIS WAY
ON ORIGINAL

If you need any additional documents or information, please let me know (phone: [redacted]; or fax [redacted]) and I will provide it to you promptly.

Sincerely,

[redacted]

Manager, Regulatory and Product Development

cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

21 April 1999

RETURN RECEIPT REQUESTED

NDA ORIG AMENDMENT

BP

Dr. Olga Cintron
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, ODE V
HFD-540, Room N248
9201 Corporate Boulevard
Rockville, MD 20850

Re: Cevimeline Hydrochloride Capsules
NDA 20-989
Response to FDA Request of April 14, 1999
Historical Data Concerning the Incidence of Spontaneous Tumors in CD-1 Mice and Fisher 344 Rats

Dear Dr. Cintron:

As promised in my facsimile of 16 April 1999 to Dr. Blay, enclosed please find the historical control data concerning the incidence of spontaneous tumors in CD-1 mice and Fisher 344 rats. This data is in connection with the carcinogenicity studies — '007 and — .006 submitted in NDA 20-989.

This document is being provided in response to your request of April 14, 1999. This information was faxed to us by ——— As soon as we receive a hard copy of this document from ——— we will also provide you with a copy.

If you need any additional documents or information, please let me know (phone: ——— or fax ———) and I will provide it to you promptly.

Sincerely,

———

———

Manager, Regulatory and Product Development

cy: Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

ORIGINAL

ORIGINAL

7 January 1999 NDA ORIG AMENDMENT RETURN RECEIPT REQUESTED

BB

Jonathan K. Wilkin, M.D., Director
Food and Drug Administration, CDER
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd, Building 2
Document Control Room, N115
Rockville, MD 20850

RE: Cevimeline Hydrochloride Capsules
Pharmacokinetics Amendment
NDA 20-989

Dear Dr. Wilkin:

The purpose of this letter is to submit an amendment to the pharmacokinetics report SNI-2011-001. The changes are summarized in the errata pages found on pages 9 and 212.

Please note that the original report for this study was submitted in the NDA volume 34.

If you have any questions regarding this submission, please do not hesitate to contact me at

Sincerely,

Manager, Regulatory and Product Development

cy: Dr. Govier
Mr. Inoke

APPEARS THIS WAY
ON ORIGINAL

BC

DRUG AMENDMENT

28 December 1998

RETURN RECEIPT REQUESTED

Jonathan K. Wilkin, M.D., Director
Food and Drug Administration, CDER
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd, Building 2
Document Control Room, N115
Rockville, MD 20850

NAI
JV 320A
cov ltr
NDA 1/7/99
151

RE: Cevimeline Hydrochloride Capsules
CMC Amendment
NDA 20-989

Dear Dr. Wilkin:

We hereby amend NDA 20-989 by submitting the second part of the table for the "Specifications of SNI-2011 Reference Standard" which was inadvertently omitted in the original NDA (page should be page 7A volume 5 of the NDA).

This page was also submitted as an amendment to the DMF no. —— on September 17, 1998 by —— drug substance manufacturer.

Please contact me should you need any further assistance ——

Sincerely,

——

Manager, Regulatory and Product Development

cy: Dr. Govier
Mr. Inoke

APPEARS THIS WAY
ON ORIGINAL

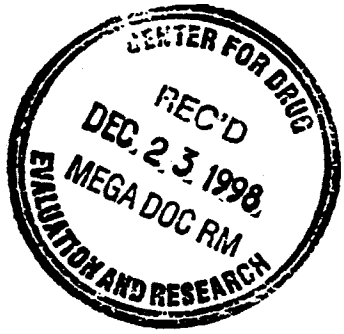
ORIGINAL

SU ORIGINAL

22 December 1998

RETURN RECEIPT REQUESTED

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Attn: Document Control Room
Food and Drug Administration, CDER, ODE V
9201 Corporate Blvd, HFD-540
Rockville, MD 20850



RE: Cevimeline Hydrochloride Capsules
4 Month-Safety Update
NDA 20-989

Dear Dr. Wilkin:

Pursuant to section 505(i) of the Federal Food, Drug and Cosmetic Act and section 314.50 of Title 21 of the Code of Federal Regulations, SnowBrand Pharmaceuticals, Inc. submits this 4-month safety update to NDA 20-989. The New Drug Application for cevimeline hydrochloride capsules ——— ' 30 mg is for the treatment of symptoms of dry mouth, ——— in patients with Sjögren's Syndrome.

The information provided in this 120-day safety update is intended to supplement the data provided in the NDA. The two main components are:

- An updated integrated safety summary with data for more than 300 patients exposed to cevimeline for a minimum of 6 months and more than 100 patients exposed to cevimeline for a minimum of 1 year, as discussed in the End-of-Phase II meeting

- The final report for study SB97US05 presenting a comparison of safety data collected from patients receiving cevimeline manufactured using the alternate process (AP) with those collected from patients receiving cevimeline manufactured using the existing process (EP), as discussed at the pre-NDA meeting.

Please contact me should you need any further assistance ———

Sincerely,

———

Manager, Regulatory and Product Development

APPEARS THIS WAY
ON ORIGINAL

cy: Dr. Govier
Mr. Inoke

ORIGINAL

15 October 1998

Dr. Roy Blay
Project Manager
Division of Dermatologic and Dental Drug Products HFD-540
Food and Drug Administration, CDER, ODE
9201 Corporate Blvd. HFD-540, Room #N255
Rockville, MD 20850

Via Federal Express for delivery on October 16

RE: Cevimeline Hydrochloride Capsules
Response to your requests on 14 October 1998
NDA 20-989

Dear Dr. Blay:

Thank you for the teleconference this morning.

Enclosed please find the documents you requested yesterday:

1) Dr. Gao's request (statistics):
SAS data version 12 for windows provided by our statisticians and programmers.
An explanation is attached to the disks.
Should Dr. Gao need additional information or data, please let us know and we will be happy to provide it to him.

2) Dr. See's request (pre-clinical):
Study [redacted] -319-2628, teratology of [redacted] -5008 in rabbits, was conducted by [redacted] in accordance with GLP.

3) Dr. Chambers' request (clinical):
Enclosed please find replacement disks B and D for Dr. Chambers' review. A list of the documents on these disks is attached.

If you need any additional documents or information, please let me know (phone: [redacted] or fax [redacted] and I will provide it to you promptly.

Sincerely,

[redacted]

Manager, Regulatory and Product Development

cy: Dr. Carman (Snow Brand Pharmaceuticals, Inc.)
Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

30 September 1998

Mr. Roy Blay
Project Manager
Food and Drug Administration
Division of Dermatologic and Dental Drug Products, HFD-540
Food and Drug Administration, CDER, ODE
5600 Fishers Lane
Rockville, MD 20857

Via Federal Express for delivery on October 1

RE: Cevimeline Hydrochloride Capsules
Response to your requests on 29 September 1998
NDA 20-989

Dear Mr. Blay:

Thank you for your facsimile of yesterday.

Enclosed please find the electronic copies of the documents requested by Drs. Chambers and Dr. Hyman. The documents are provided on 3.5" disks in Microsoft Word 6.0 format. Should you wish these on CDs, we will gladly provide them to you.

Also, should you need any additional copies electronically or hard copy for your review, please let me know and I will provide it to you promptly.

Sincerely,

Manager, Regulatory and Product Development

cy. Dr. Carman (Snow Brand Pharmaceuticals, Inc.)
Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

ORIGINAL

26 August 1998

NEW CORRESP
NC

Mr. Roy Blay
Project Manager
Food and Drug Administration
Division of Dermatologic and Dental Drug Products, HFD-540
Attn: Document Control Room
Food and Drug Administration, CDER, ODE
5600 Fishers Lane
Rockville, MD 20857

RE: Cevimeline Hydrochloride Capsules
Desk copies of NDA summary volume
NDA 20-989

NIFE 9/1/98 /S/

Dear Mr. Blay:

Enclosed please find 12 desk copies of the summary volume for the cevimeline NDA.

I look forward to working with you during the review process. Should you need any additional information, please do not hesitate to contact me at _____ (fax: _____

Sincerely,

_____

Manager, Regulatory and Product Development

cy: Dr. Carman (Snow Brand Pharmaceuticals, Inc.)
Dr. Govier (Snow Brand Pharmaceuticals, Inc.)
Mr. Inoke (Snow Brand Milk Products Co., Ltd.)

APPEARS THIS WAY
ON ORIGINAL

SNOWBRAND PHARMACEUTICALS, INC.

26 August 1998

RETURN RECEIPT REQUESTED

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkens Ave.
Rockville, MD 20852

RE: Cevimeline Hydrochloride Capsules
Original New Drug Application
NDA 20-989

Dear Dr. Wilkin:

Pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act and section 314.50 of Title 21 of the Code of Federal Regulations, SnowBrand Pharmaceuticals, Inc. submits a New Drug Application for cevimeline hydrochloride capsules, 30 mg, for the treatment of symptoms of dry mouth, in patients with Sjögren's Syndrome.

The safety and efficacy of cevimeline hydrochloride has been evaluated based on data from 1646 patients with Sjögren's Syndrome, and in healthy volunteers, from which we conclude that cevimeline is safe and effective in the treatment of Sjogren's patients at the recommended doses.

United States patents 4,855,290; 5,340,821 and 5,580,880 have been issued to cover the composition of derivatives and method of use of cevimeline for Sjögren's Syndrome and xerostomia.

In compliance with the requirements set forth in 21 CFR 315.50(d)(1), SnowBrand Pharmaceuticals, Inc. certifies that a field copy of the Chemistry, Manufacturing and Controls section of this application prepared in accordance with the regulations set forth under 21 CRF 314.50(d)(1), along with a copy of the FDA form 356h and the Overall NDA Summary volume is also being provided to Mr. Jose Martinez at the FDA Dallas District Office under separate cover at the following address:

3550 General Atomics Court
Diego, CA 92121
619-455-2463
619-455-2464 Fax

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
10127 Morocco Street, Suite 119
San Antonio, TX 78216

This application was compiled by a team of scientists at Snow Brand Pharmaceuticals, Inc., Snow Brand Milk Products Co. Ltd. and [redacted] who are available to answer your questions or to assist you during the review of this application. Please contact [redacted], Manager of Regulatory and Product Development at [redacted], if you need further assistance [redacted]

Sincerely,

Mark D Carman

Mark D. Carman, PhD
President & CEO
SnowBrand Pharmaceuticals, Inc.

APPEARS THIS WAY
ON ORIGINAL

45 Day Meeting Checklist
NDA 20-989 Cevimeline

OCT 19 1998

Clinical:

1. Clinical section is organized in a manner to allow substantive review to begin.

2. Clinical section is indexed and paginated in a manner to allow substantive review to begin.

3. Clinical section is legible.

4. Dose-ranging studies were appropriately designed.

5. Two adequate and well-controlled studies were submitted.

6. The pivotal efficacy studies are of appropriate design to meet basic requirements for approvability based on proposed draft labeling.

6b. The data sets for the pivotal studies are complete for the requested indications.

7. The pivotal efficacy studies appear to be adequate and well-controlled.

8. Line listings are adequate for data submitted.

9. Both of the pivotal trials were conducted in the United States. The drug is currently [redacted] On the surface, it appears as though the data from Japan is submitted for completeness. If, during the more thorough review of the data, the sponsor uses the Japanese data to support safety or efficacy, more information may be requested to support a rationale for the application of foreign data.

10. The applicant has submitted all required case record forms.

11. The safety data is presented in a satisfactory manner.

12. Cevimeline is not marketed in any country. In addition to the drug development program in the United States, [redacted] The applicant has presented safety assessment data based on all current world-wide knowledge regarding the product.

13. The applicant has submitted draft labeling consistent with 201.56 and 201.57.

14. There were no special studies requested by the Division during pre-submission discussions with the sponsor. During the Pre-NDA meeting, the FDA agreed that data from SB97US05 (open label study) could be submitted with the 120 day safety update if these data are required to bridge the EP and AP synthesis of Cevimeline.

15. The NDA is fileable

/S/ 10/6/98
Reviewing Dental Officer

/S/ 10/19/98
Dental Team Leader

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: December 6 , 1999. Number of Pages (including cover sheet)1

TO: ——— , Manager, Regulatory Affairs
COMPANY: ———
NUMBER: ———
MESSAGE: **RE: NDA 20-989 Cevimeline HCl Caps.**

The dose multiples calculation per the pharmacologist follow:

Dose multiples that are based on body surface area estimates are calculated from mg/kg dosages through use of a species-specific conversion factor, or Km. For rats a Km of 6 is typically used. A Km of 37 is used for a 60kg human. The maximum human dose of cevimeline is — mg/day — mg three times daily), or — ng/Kg/day in a 60Kg individual. The dose multiple calculation is:

Dose Multiple = Animal Dose x Animal Km/Human Dose x Human Km

= 45mg/kg/day x — mg/kg/day x 37

= — which rounds down to —

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

cc: NDA 20-989
HFD-540/Div File
HFD-540/Sec

FOOD AND DRUG ADMINISTRATION
DIVISION OF DERMATOLOGIC AND
DENTAL DRUG PRODUCTS
HFD-540
9201 CORPORATE BLVD.
ROCKVILLE, MARYLAND 20850

DATE: 7/30/99

TO:

Name _____

Fax No. _____

Phone No. _____

Location _____

FROM:

Name MARY JEAN KOZMA-FORNARO
Fax No. 301 827-2075/2091
Phone No. 301 827-2020

Comments: Re: NDA 20989 -

My question + 2 requests from Clinical Reviewer.

/S/

T. Frolga

I have one question and two requests for [redacted] about the new materials that came in this week to NDA 20-989. They are as follows:

Question:

Regarding the table entitled, "Incidence of Treatment Emergent Out-of-Range Laboratory Values: Sjogren's All Active" (on page 7 of Volume 1 of the 7/22/99 submission) and Table 12.3.2 (entitled "Laboratory Normality Shifts from Baseline to Endpoint: Sjogren's All Active") from the Safety Update. - Why is the sample size from which the out-of-normal laboratory values are reported different between the two tables? It is particularly noticeable in the 15mg and 30 mg group totals.

Requests:

A. For each of the subjects with laboratory values defined as PCS high in the safety update, could you provide us their patient number, so that we can look up the pattern of laboratory values in the line listing already provided in this most recent submission?

B. Please provide the Case Report Forms for Patient #3004. Unless I am reading the line listings incorrectly, she had an extremely high ALAT value at Week 17, and then no more reports of further values after this time.

Thanks.

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 7/30/99 12:36:03 PM
From: Fred Hyman (HYMANF)
To: Mary Jean Kozma-Fornaro (KOZMAFORNARO)
Cc: John Kelsey (KELSEYJ)
Subject: Question for [redacted] for NDA 20-989, Cevimeline

MaryJean,

I have one question and two requests for [redacted] about the new materials that came in this week to NDA 20-989. They are as follows:

Question:

Regarding the table entitled, "Incidence of Treatment Emergent Out-of-Range Laboratory Values: Sjogren's All Active" (on page 7 of Volume 1 of the 7/22/99 submission) and Table 12.3.2 (entitled "Laboratory Normality Shifts from Baseline to Endpoint: Sjogren's All Active") from the Safety Update. - Why is the sample size from which the out-of-normal laboratory values are reported different between the two tables? It is particularly noticeable in the 15mg and 30 mg group totals.

quests:

A. For each of the subjects with laboratory values defined as PCS high in the safety update, could you provide us their patient number, so that we can look up the pattern of laboratory values in the line listing already provided in this most recent submission?

B. Please provide the Case Report Forms for Patient #3004. Unless I am reading the line listings incorrectly, she had an extremely high ALAT value at Week 17, and then no more reports of further values after this time.

Thanks.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELEPHONE CONVERSATION

Date: July 14, 1999.

JUL 14 1999

NDA: 20-989

Drug: Cevimeline HCl Capsules

Sponsor attendees: [redacted] Manager, Regulatory and Product Development

FDA attendees: John Kelsey, DDS, MBA, Dental Team Leader, HFD-540
Fred Hyman, DDS, Dental Officer, HFD-540
Olga Cintron, R.Ph., Project manager, HFD-540

The Agency indicated the review of the submission dated July 12, 1999, containing the table illustrating the criteria used for identifying values as potentially clinically significant was completed. Review of this information indicated that the criteria used to determine if a laboratory value was potentially clinically significant are unacceptable. In light of this, the following information was requested from the Sponsor:

1. To submit the normal range limits for all the laboratory values.
2. To submit a revised table illustrating the number of subjects with laboratory values outside the normal range.
3. To submit the line listings for all the subjects who presented values outside the normal range.
4. To submit case report forms for those subjects who were included in the "PCS" table originally submitted by Snow Brand.

The Agency indicated that this information was critical to determine an action for the application, and that it was extremely important to expedite submission of the aforementioned information. [redacted] indicated that she will call the Agency and let us know when this information will be submitted.

The conversation ended cordially.

Signature, minutes preparer: [redacted] 7/14/99

cc:
Original NDA 20-989
HFD-540/Div File
HFD-540/Kelsey 7/14/99.
HFD-540/Hyman
HFD-540/Cintron

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 10, 1999. Number of Pages (including cover sheet) 2
TO: [redacted], Manager, Regulatory and Product Development
COMPANY: [redacted]
NUMBER: [redacted]

MESSAGE: **RE: NDA 20-989 Cevimeline HCl Caps.**

Please find medical officer's request for information.

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

cc: NDA 20-989
HFD-540/DIV FILES
HFD-540/ 151

APPEARS THIS WAY
ON ORIGINAL

Please submit new versions of the Adverse Events tables, which currently appear in the proposed label for EVOXAC ™ , using the following format:

List all Adverse Events (not just related to Drug) by preferred term in descending order of incidence for those events occurring with and incidence of ≥ 3%.

List those events that have been reported at an incidence of between 1% and 3% in a narrative form (as has already been done for the adverse events in less than 1% of subjects).

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

BEST POSSIBLE COPY

Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: May 14, 1999. Number of Pages (including cover sheet) 1
TO: [redacted]
COMPANY: [redacted]
NUMBER: [redacted]

MESSAGE: **RE: NDA 20-989**

Please submit the assay validation data for studies: II-2, CS89-1, and R/4800/0002. In addition, please submit the assay validation data for the [redacted] portion of Study SB97US01.

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

CC: NDA 20-989
HFD-540/Div Files
HFD-580/Nguyen

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 27, 1999. Number of Pages (including cover sheet)
TO: ———
COMPANY: ———
NUMBER: ———

MESSAGE: **RE: NDA 20-989**

Please submit the following chemistry information to NDA 20-989:

1. The name, address, telephone# and fax# of the specific individual to whom our two FDA District Laboratories can request their samples from for Method Validation.

2. Two additional sets of volumes for Method Validation, e.g. Volumes 1.4 and 1.5, are required. A total of three sets should have been submitted with the NDA. The chemist is assuming that Volumes 1.4 and 1.5 were the two Method Validation volumes.

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

cc: NDA 20-989
HFD-540/DIV FILES
HFD-540/Vidra

APPEARS THIS WAY
ON ORIGINAL

Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD. 20857

FACSIMILE TRANSMISSION RECORD

DATE: April 14, 1999 Pages (including cover) 1
TO: [redacted]
COMPANY: [redacted]
FAX #: [redacted]
PHONE #: [redacted]

MESSAGE: Please submit recent historical data concerning the incidence of spontaneous tumors in CD-1 mice and Fisher 344 rats. These data should be obtainable from the contract laboratory that performed the bioassays [redacted] This request is made in connection with the carcinogenicity studies submitted to NDA 20-989 (mouse study No. [redacted]007/982285, and rat study No. [redacted]006/982306). The data should be from recently conducted studies and utilize animals from the same source and strain, fed the same diet, etc., as the studies submitted to NDA 20-989.

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Roy Blay, Ph.D.
TITLE: Project Manager
TELEPHONE: (301) 827-2020 Fax # (301) 827- 2075 or 827-2091

HFD-540 Blay

RECORD OF TELEPHONE CONVERSATION	DATE: October 14, 1998, 2:10 PM
I called ——— and requested the following items: 1. SAS data set in Version 12 for Windows including the data for the pivotal studies and the ISE and ISS. 2. A statement regarding the GLP status of the rabbit teratology study (Report # ——-5-319-262B) or a statement regarding its deviation(s) from GLP. 3. New copies of disks B and D for Dr. Chambers' review (previous copies damaged in shipping). 4. The sponsor's availability from 10:00 AM to 11:00 AM on 10/15/98 to discuss the wording of the proposed indication for this drug. ——— said that Dr. Govier, the clinical study director from SnowBrands, would also be present. cc: NDA 20-989 Division File HFD-540\Blay\Gao\See\Kelsey\Chambers	NDA NUMBER 20-989 IND NUMBER xxxxxxxxxxx TELECON INITIATED BY APPLICANT/ SPONSOR (FDA) MADE (BY TELEPHONE) IN PERSON PRODUCT NAME Cevimiline FIRM NAME ——— NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD ——— TELEPHONE ———
SIGNATURE (51) 10/14/98 Roy A. Blay	DIVISION HFD-540, DDDDP