CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-989

ADMINISTRATIVE DOCUMENTS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20989/000
Stamp: 27-AUG-1998 Regulatory Due: 27-AUG-1999
Applicant: SNOWBRAND

Priority: 1S Org Code: 540
Action Goal: District Goal: 28-JUN-1999
Brand Name: CEVIMELINE HCL 30MG CAPS
Established Name:
Generic Name: CEVIMELINE HCL
Dosage Form: CAP (CAPSULE)
Strength: 30 MG

FDA Contacts:			
	O. CINTRON	(HFD-540)	301-827-2023 , Project Manager
	J. VIDRA	(HFD-540)	301-827-2065 , Review Chemist
	W. DECAMP II	(HFD-540)	301-827-2041 , Team Leader

Overall Recommendation:

ACCEPTABLE on 26-MAR-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: [redacted]
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date 31-MAR-1999

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: [redacted]
DMF No:
AADA No:

Profile: CSG OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date 31-MAR-1999

Responsibilities: FINISHED DOSAGE MANUFACTURER

APPEARS THIS WAY
ON ORIGINAL

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1209	HFD#	540	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	Jim Vidra			Evoxac	cevimeline HCl
RE:	NDA/IND #	20-999			

A. Look-alike/Sound-alike

	Potential for confusion:
	XXX Low ____ Medium ____ High
	XXX Low ____ Medium ____ High
	XXX Low ____ Medium ____ High
	XXX Low ____ Medium ____ High
	____ Low ____ Medium ____ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

____ Satisfactory
____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date /ST 8/11/99

SnowBrand Pharmaceuticals, Inc.

Debarment Certificate

SnowBrand Pharmaceuticals, Inc. certifies that the applicant did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) of 21 United States Code §335a, in connection with the new drug application for cevimeline.

SnowBrand Pharmaceuticals, Inc.

By: Mark D Carman
Name: Mark D. Carman
Title: President and CEO

APPEARS THIS WAY
ON ORIGINAL

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

SnowBrand Pharmaceuticals, Inc.

Patent Certification

SnowBrand Pharmaceuticals, Inc. certifies that United States Patent No. 4,855,290 covers the composition of cevimeline ; United States Patent No. 5,340,821 covers the composition and method of use of cevimeline for treating Sjoegren Syndrome and that United States Patent No. 5,580,880 covers the method of use of cevimeline for the treatment of Xerostomia. The drug cevimeline is the subject of this application for which approval is sought.

SnowBrand Pharmaceuticals, Inc.

By: Mark D Carman
Name: Mark D. Carman
Title: President and CEO

APPEARS THIS WAY
ON ORIGINAL

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

SNOWBRAND PHARMACEUTICALS, INC.

Patent Information and Declaration

U.S. Patent Number:	4,855,290
Name:	Derivatives of Quinuclidine
Expiration Date:	August 8, 2006
Type of Patent:	Drug Product
Owner:	Israel Institute for Biological Research
Agent:	Cushman, Darby & Cushman

U.S. Patent Number:	5,340,821
Name:	Composition and Method of Treating Sjoegren Syndrome Disease
Expiration Date:	August 23, 2011
Type of Patent:	Drug Product and Method
Owner:	Snow Brand Milk Products Co. Ltd.
Agent:	Snow Brand America, Inc.

U.S. Patent Number:	5,580,880
Name:	Method for the Treatment of Xerostomia
Expiration Date:	June 6, 2015
Type of Patent:	Method of Use
Owner:	Snow Brand Milk Products Co. Ltd.
Agent:	Snow Brand America, Inc.

The undersigned declares that (i) U.S. Patent No. 4,885,290 covers the composition of derivatives of cevimeline; (ii) U.S. Patent No. 5,340,821 covers the composition and method of use of cevimeline for treating Sjoegren Syndrome; and (iii) U.S. Patent No. 5,580,880 covers the method of use of cevimeline for the treatment of Xerostomia. The product cevimeline is the subject of this application for which approval is sought.

SnowBrand Pharmaceuticals, Inc.

By: Mark D Carman

Name: Mark D. Carman

Title: President and CEO

APPEARS THIS WAY
ON ORIGINAL

3550 General Atomics Court

San Diego, CA 92121

619-455-2463

EXCLUSIVITY SUMMARY FOR NDA # 20-989 SUPPL #__N/A_____

Trade Name: EVOXAC™ (cevimeline HCl) Capsules

Generic Name: cevimeline HCl

Applicant Name: SnowBrand, Pharmaceuticals, Inc. HFD # 540

Approval Date If Known:_____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES/_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X__/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

____

e) Has pediatric exclusivity been granted for this Active Moiety? No.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/ N/A

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/ 7/6/99.

Signature:Date:Title:

Signature of ~~Office~~/Division Director

Signature:Date /S/ 8/18/99

cc: Original NDA 20-989; HFD-540 Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

A # 20-989 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-550 Trade and generic names/dosage form: Evoxac (cevimeline HCl) caps Action: (AP) AE NA

Applicant Snow Brand Pharmaceutical Therapeutic Class 15

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Proposed indication in this application treatment of dry mouth in patients with Sjögren's syndrome

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__c. The applicant has committed to doing such studies as will be required.

- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

__d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. Insufficient number of patients in pediatric age group with the indication.

__5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ✓No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from medical officer (e.g., medical review, medical officer, team leader)

/S/ 1/3/00
Signature of Preparer and Title

1/3/00
Date

/S/ 1/3/00

/S/ 2/6/00

Orig NDA/BLA # 20-989
HFD-550/Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

BEST POSSIBLE COPY

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-989 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade and generic names/dosage form: EVOXAC (cevimeline HCl) Capsules Action: AP (AE) NA

Applicant Snow Brand Pharmaceuticals Therapeutic Class 1S

* Note: An approvable action was issued for this application. Pediatric study requirements will be addressed when approval letter is issued

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate __ inadequate __

Proposed indication in this application treatment of dry mouth in patients with Sjogren's syndrome

/S1 4/2/99

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

✓ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

Action letter describes the pediatric study requirement.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

/S1 8/20/99

See NOTE ABOVE.

__ c. The applicant has committed to doing such studies as will be required.

- __ (1) Studies are ongoing,
- __ (2) Protocols were submitted and approved.
- __ (3) Protocols were submitted and are under review.
- __ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ✓No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Concur /S1 8/16/99

This page was completed based on information from medical officer (e.g., medical review, medical officer, team leader)

/S1 Project Manager 7/6/99

Signature of Preparer and Title Date

/S1 8/20/99

Orig NDA/BLA #_____
HF_____/Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)