CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-941

ADMINISTRATIVE DOCUMENTS

PATENT AND EXCLUSIVITY INFORMATION

Active Ingredient:	C-22 aliphatic alcohol (*n*-docosanol)
Strength:	10% by weight
Trade Name:	LIDAKOL®
Dosage Form:	Topical Formulation
Sponsor:	LIDAK PHARMACEUTICALS
NDA No.:	20-941

Applicable Patent Nos.:	Expiration Date:
U.S. Pat. No. 4,874,794	October 17, 2006
U.S. Pat. No. 5,071,879	October 17, 2006
U.S. Pat. No. 5,194,451	December 10, 2008
U.S. Pat. No. 5,166,219	December 3, 2008
U.S. Pat. No. 5,534,554	December 13, 2013
U.S. Pat. No. 5,098,896	March 24, 2009
U.S. Pat. No. 5,214,071	May 25, 2010
U.S. Pat. No. 5,296,514	March 22, 2011

Approval Dates:

Exclusivity: Five years from the date of approval as provided by the Drug Price Competition and Patent Term Restoration Act of 1984.

CAG-3640.2
121197

LIDAK PHARMACEUTICALS

LIDAKOL®, (*n*-Docosanol, Behenyl Alcohol) 10% Cream
NDA 20-941

In accordance with the Generic Drug Enforcement Act of 1992, we certify that LIDAK Pharmaceuticals did not and will not use in any capacity the services of any person or firm debarred under subsections (a) or (b) [Section 306 (a) or (b) of the Federal Food, Drug, and Cosmetics Act] in connection with NDA 20-941 for LIDAKOL®, (*n*-Docosanol, Behenyl Alcohol) 10% Cream.

LIDAK Pharmaceuticals verifies that all trials conducted in the United States which are used to support NDA 20-941, were conducted in compliance with Institutional Review Board regulations in 21 CFR Part 56 and the informed consent regulations 21 CFR Part 50. Non-US protocols used to support the claims in this application were reviewed by independent Ethics Committees/Review Boards and these trials were performed in accordance with the declaration of Helsinki and its subsequent revisions.

James E Berg

James E. Berg,
Vice President of Clinical Affairs

12/12/97

Date

007

11077 NORTH TORREY PINES ROAD · LA JOLLA, CALIFORNIA 92037 · (619) 558-0364, FAX: (619) 453-5845

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 3/28/00	**DUE DATE:** 5/3/00	**OPDRA CONSULT #:** 00-0092

TO:
Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH:
Kevin D. White
Project Manager
HFD-540

PRODUCT NAME: **Abreva** **(docosanol cream) 10%** **NDA #:** 20-941	**MANUFACTURER:** Avanir Pharmaceuticals

SAFETY EVALUATOR: Peter Tam, R.Ph.

OPDRA RECOMMENDATION:
OPDRA has no objections to the use of the proprietary name, Abreva. See the checked box below.

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

✓ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/S/ 5/5/00

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 5/5/00

Peter Honig
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 5/2/00

NDA#: 20-941

NAME OF DRUG: Abreva
(docosanol cream) 10%

NDA: Avania Pharmaceuticals

I. INTRODUCTION:

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540) on March 28, 2000, to review the proposed proprietary drug name, Abreva in regard to potential name confusion with existing proprietary/generic drug names.

The Division of OTC Drug Products (HFD-560) has reviewed this product under the proposed name, Abreve. The Labeling and Nomenclature Committee (LNC) on 11/19/98 approved it. LNC believed there was low risk of confusion between Abreve and Aleve due to different dosage forms (i.e.cream vs tablet). However, the Division believes that the possibility for confusion between these two products is high. A consult was forwarded to OPDRA on 1/24/00 for a quick turn around evaluation of this proposed trade name, Abreve. OPDRA expert panel has serious concerns about the similarity of Abreve with Aleve, even though these two products are available in two different dosage forms. OPDRA's preliminary conclusion was an objectionable concern and asked the firm to submit a new name for review. Jerry Phillips conveyed this opinion to the Division through an e-mail on 1/24/00.

The firm has submitted a new name, Abreva, for review with the Division of Dermatologic and Dental Drug Products (HFD-540).

PRODUCT INFORMATION

Abreva is the only non-prescription medication that treats the cause of cold sores. The product claims that when it is used early, it may help block the cold sore infection. Abreva is indicated for cold sores/fever blisters on the face or lips. It is recommended for adults and children 12 years or over. The cream should apply to affected area gently but completely. The usual dose is to apply 5 times a day until healed.

Abreva will be supplied in 2 gm tubes.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to Abreva to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

1. The panel discussed the following sound-alike drug name.

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
Abreva	10% cream, docosanol	Apply 5 times daily until healed	
Aleve	200 mg tablet, naproxen	200 mg every 8-12 hours	*SA/

*SA = Sound-alike
*LA = Look-alike

The panel concluded that the above listed drug and Abreva pose no significant safety risk, and therefore, the proprietary name, Abreva is not objectionable.

2. DDMAC – no objections

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[1] MICROMEDEX Healthcare Intranet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

[5] WWW location http://www.uspto.gov/tmdb/index.html.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

These studies were conducted by OPDRA and involved 94 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Abreva with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient order and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Abreva (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

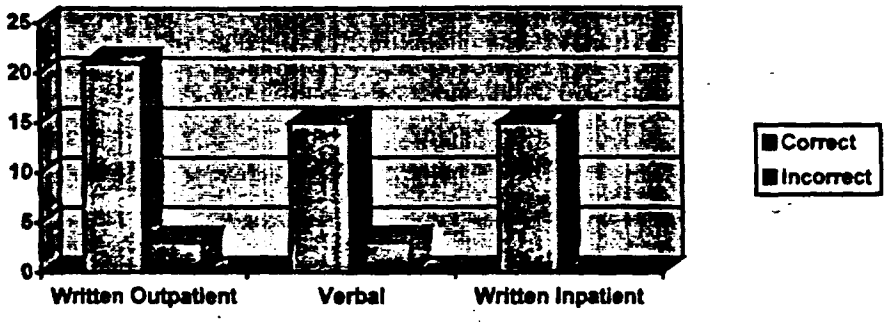
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Abreva #1 Sig: As directed	Abreva #1 Sig: As directed
Inpatient RX: Continue Abreva as directed	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Outpatient	31	24 (77%)	21	3
Verbal	32	18 (56%)	15	3
Written Inpatient	31	19 (61%)	15	4
Total	94	61(65%)	51 (84%)	10 (16%)



Eighty-four percent of the participants responded with the correct name, Abreva. The incorrect written and verbal responses are as follows in Table II.

Tablet II

	Incorrectly Interpreted
Written Outpatient	Avreva
	Avieva
	Aoreva
Written Inpatient	Abura (4)
Verbal	Aprewa
	Abrea
	Abreatha

C. SAFETY EVALUATOR RISK ASSESSMENT

One product name, Aleve, was identified in the expert panel discussion that were thought to be similar (sound-alike) to Abreva but was not considered to have potential for confusion. Aleve was not considered a safety risk, given the lack of convincing verbal/written similarities. Moreover, other dissimilarities between these 2 products include dosage forms, usual dosing, strength and dosing interval. Potential concerns regarding drug marketing and promotion in regard to the proposed name were also discussed and produced no objections by DDMAC.

In addition, the results of the verbal and written analysis studies demonstrate that fifty-one out of sixty-one (84%) participants correctly interpreted Abreva. We also did not uncover any overlapping existing approved drug product names in our studies. Because of the size of the study, this doesn't provide persuasive evidence that an error might not occur when exposed to the general population.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Abreva, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container labels and carton and insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1. We recommend increasing the letter size of established name at least half as large as the letters comprising the proprietary name in accord with CFR 201.10 (g) (2).

2. Delete the terminal zero when expressing the net weight (2 g).

B. CARTON LABELING

1. See comments under CONTAINER LABEL.

2. We recommend that the Inernet sit (www.Abreva .net) not be included on the labeling.

3. Include the temper-resistant warnings.

IV. RECOMMENDATIONS:

1. OPDRA has no objections to the use of the proprietary name, Abreva.

2. OPDRA recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Peter Tam at 301-827-3241

/S/ 5/2/00

Peter Tam, R.Ph.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 5/5/2000

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair, NLRC (HFD-530)

From: Division of Dermatologic and Dental Drug Products		HFD-540
Attention: Steve Hathaway, Ph.D.	**Phone:** 827-2069	
Date: October 15, 1998		
Subject: Request for assessment of a proposed trademark for Rx drug product		
Proposed Trademark: Abreve Cream, 10% Abreva Cream, 10%		**NDA 20-941**
Established name, including dosage form: Cream Behenyl alcohol, a.k.a. n-docosanol		
Other trademarks by the same firm for companion products: None approved.		
Indications for use (may be a summary if proposed statement is lengthy): For the treatment of herpes labialis (oral).		
Initial comments from the submitter (concerns, observations, etc.): The active ingredient, behenyl alcohol or n-docosanol, has been used as an ingredient in cosmetics and toiletries. A previously submitted proposal, LIDAKOL, was approved by the LNC on 14-APR-1998 (#975).		

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. August 95

975

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair, NLRC (HFD-530)

From: Division of Dermatologic and Dental Drug Products	HFD-540
Attention: Steve Hathaway, Ph.D.	**Phone:** 827-2069
Date: March 2, 1998 WA 3/2/98	
Subject: Request for assessment of a proposed trademark for Rx drug product	
Proposed Trademark: Lidakol Cream, 10%	**NDA** 20-941
Established name, including dosage form: Cream Behenyl alcohol, a.k.a. n-docosanol	
Other trademarks by the same firm for companion products: None approved.	
Indications for use (may be a summary if proposed statement is lengthy): For the treatment of herpes labialis (oral).	
Initial comments from the submitter (concerns, observations, etc.): The active ingredient, behenyl alcohol or n-docosanol, has been used as an ingredient in cosmetics and toiletries.	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. August 95

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1095a	HFD#	540	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	Steve Hathaway			ABREVE	behenyl alcohol, a.k.a. n-docosanol

A. Look-alike/Sound-alike

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

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

____ Satisfactory

XXX Unsatisfactory/Reason

A USAN must be applied for as the established name

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date /S/ 11/19/98

CDER LABELING AND NOMENCLATURE COMMITTEE

NSULT # 975	HFD# 540	PROPOSED PROPRIETARY NAME:
NTION: STEVE HATHAWAY		LIDAKOL CREAM, 10%

A. Look-alike/Sound-alike

	Potential for confusion:
IDOCAINE	___ Low XXX Medium ___ High
	___ Low ___ Medium ___ High
	___ Low ___ Medium ___ High
	___ Low ___ Medium ___ High
	___ Low ___ Medium ___ High

B. Misleading Aspects

C. Other Concerns

D. Established Name

XXX Satisfactory

___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations: XXX ACCEPTABLE ___ UNACCEPTABLE

F. Signature of Chair/Date /S/ 4/14/98

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 20941/000
Priority: 1S
Org Code: 540
Stamp: 22-DEC-1997 Regulatory Due: 22-DEC-1998
Action Goal:
District Goal: 22-AUG-1998
Applicant: LIDAK
11077 NORTH TORREY PINES RD
LA JOLLA, CA 92037
Brand Name: LIDAKOL(N-DOCOSANOL) TOP CREAM 10%
Established Name:
Generic Name: N-DOCOSANOL
Dosage Form: CRM (CREAM)
Strength: 10% W/W

FDA Contacts:

K. WHITE	(HFD-540)	301-827-2023	, Project Manager
J. HATHAWAY	(HFD-540)	301-827-2069	, Review Chemist
W. DECAMP II	(HFD-540)	301-827-2041	, Team Leader

Overall Recommendation:

Establishment: [redacted]
DMF No:
AADA No:

Profile: OIN
OAI Status: NONE
Responsibilities: FINISHED DOSAGE PACKAGER
Last Milestone: OC RECOMMENDATION
Milestone Date 09-FEB-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: [redacted]
DMF No:
AADA No:

Profile: CTL
OAI Status: NONE
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Last Milestone: OC RECOMMENDATION
Milestone Date 09-FEB-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: [redacted]
DMF No:
AADA No:

Profile: OIN
OAI Status: NONE
Responsibilities: FINISHED DOSAGE MANUFACTURER
Last Milestone: INSPECTION PERFORMED
Milestone Date 12-JUN-1998

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: SUBMITTED TO DO
Milestone Date 02-NOV-1998

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Establishment [redacted]

DMF No: [redacted]
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 15-SEP-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: SUBMITTED TO DO
Milestone Date 02-NOV-1998

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE

Responsibilities: DRUG SUBSTANCE OTHER TESTER

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
Milestone Date **30-OCT-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **09-FEB-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE RELEASE TESTER**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date **02-NOV-1998**

Responsibilities: **DRUG SUBSTANCE OTHER TESTER**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **09-FEB-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE STERILITY TESTER**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**

Responsibilities: **FINISHED DOSAGE OTHER TESTER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
Milestone Date **09-FEB-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DETAIL REPORT

HFD 540
K WHITE

Application: NDA 20941/000
Stamp: 22-DEC-1997
Regulatory Due: 03-JUN-2000
Applicant: LIDAK
11077 NORTH TORREY PINES RD
LA JOLLA, CA 92037
Priority: 1S
Org Code: 540

Action Goal:
District Goal: 22-AUG-1998
Brand Name: LIDAKOL (DOCOSANOL 10% CREAM)
Estab. Name:
Generic Name: DOCOSANOL

Dosage Form: (CREAM)
Strength: 10% W/W

Application Comment:
FDA Contacts: K. WHITE (HFD-540) 301-827-2023 , Project Manager
J. HATHAWAY (HFD-540) 301-827-2069 , Review Chemist
W. DECAMP II (HFD-540) 301-827-2041 , Team Leader

Overall Recommendation: ACCEPTABLE on 31-MAR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]

DMF No: AADA:
Responsibilities: FINISHED DOSAGE PACKAGER
Profile: OIN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-FEB-1998				HATHAWAYS
OC RECOMMENDATION	09-FEB-1998			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: [redacted]

DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-FEB-1998				HATHAWAYS
OC RECOMMENDATION	09-FEB-1998			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: [redacted]

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: OIN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-FEB-1998				HATHAWAYS
SUBMITTED TO DO	09-FEB-1998	PS			FERGUSONS
ASSIGNED INSPECTION	20-FEB-1998	PS			PNOISIN

INSPECTION PERFORMED 12-JUN-1998 15-MAY-1998 PNOISIN

[redacted]

DO RECOMMENDATION 30-DEC-1998 ACCEPTABLE ARHODES
INSPECTION

NO SIGNIFICANT DEFICIENCIES TO PRECLUDE APPROVAL OF THE APPLICATION. HOWEVER, THERE WERE SOME DEFICIENCIES CONCERNING THE APPLICATION HOLDER, PREVIOUSLY COMMUNICATED VIA EES. FIRM PROMISED CORRECTIONS IN A WRITTEN RESPONSE AND DURING A MEETING WITH [redacted] ON 6/16/98. MOST 483 ITEMS DEALT WITH POST-APPROVAL ISSUES.

OC RECOMMENDATION 30-DEC-1998 ACCEPTABLE DAMBROGIOJ
DISTRICT RECOMMENDATION

Establishment: [redacted]

DMF No: AADA:
Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-FEB-1998				HATHAWAYS
OC RECOMMENDATION	09-FEB-1998			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: [redacted]

DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-FEB-1998				HATHAWAYS
OC RECOMMENDATION	09-FEB-1998			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: [redacted]

DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Responsibilities: DRUG SUBSTANCE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment: TESTING OF DRUG SUBSTANCE STABILITY SAMPLES (on 30-OCT-1998 by J. HATHAWAY (HFD-540) 301-827-2069)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-OCT-1998				HATHAWAYS
SUBMITTED TO DO	02-NOV-1998	GMP			DAMBROGIOJ
DO RECOMMENDATION	31-MAR-1999			ACCEPTABLE BASED ON FILE REVIEW	MEDWARDS
OC RECOMMENDATION	31-MAR-1999			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: [redacted]
DMF No: [redacted] AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment: NO STREET ADDRESS LISTED IN APPLICATION. (on 09-FEB-1998 by M. EGAS (HFD-322) 301-594-0095)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-FEB-1998				HATHAWAYS
SUBMITTED TO DO	09-FEB-1998	GMP			EGASM
ASSIGNED INSPECTION	09-FEB-1998	GMP			EGASM
INSPECTION SCHEDULED	10-APR-1998		04-JUN-1998		EGASM
INSPECTION PERFORMED	25-JUN-1998		18-JUN-1998		EGASM
DO RECOMMENDATION	15-SEP-1998			ACCEPTABLE INSPECTION	DAMBROGIOJ
OC RECOMMENDATION	15-SEP-1998			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: [redacted]
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment: STORAGE AND TESTING OF DRUG SUBSTANCE STABILITY SAMPLES (on 30-OCT-1998 by J. HATHAWAY (HFD-540) 301-827-2069)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-OCT-1998				HATHAWAYS
SUBMITTED TO DO	02-NOV-1998	GMP			DAMBROGIOJ
DO RECOMMENDATION	31-MAR-1999			ACCEPTABLE BASED ON FILE REVIEW	MEDWARDS
OC RECOMMENDATION	31-MAR-1999			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: [redacted]
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE OTHER TESTER

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Profile: CTL OAI Status: NONE

Estab. Comment: THIS FACILITY WAS NOTED DURING THE INSPECTION OF THE DRUG PRODUCT SITE, AND WAS NOT LISTED IN THE NDA. ITS PURPOSE DURING DEVELOPMENT WAS FOR [redacted] ANALYSIS OF THE DRUG SUBSTANCE; UNCLEAR IF THIS WILL BE A CONTINUING FUNCTION AFTER APPROVAL. (on 15-OCT-1998 by J. HATHAWAY (HFD-540) 301-827-2069)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-OCT-1998				HATHAWAYS
OC RECOMMENDATION	30-OCT-1998			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: [redacted]

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: THIS FACILITY WAS NOTED DURING THE INSPECTION OF THE DRUG PRODUCT SITE, AND WAS NOT LISTED IN THE NDA. ITS PURPOSE DURING DEVELOPMENT WAS FOR [redacted] ANALYSIS OF THE DRUG SUBSTANCE; UNCLEAR IF THIS WILL BE A CONTINUING FUNCTION AFTER APPROVAL. (on 15-OCT-1998 by J. HATHAWAY (HFD-540) 301-827-2069)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-OCT-1998				HATHAWAYS
SUBMITTED TO DO	30-OCT-1998	GMP			FERGUSONS
ASSIGNED INSPECTION	02-NOV-1998	PS			AMEHL
INSPECTION PERFORMED	03-DEC-1998		02-DEC-1998		GDICKINS
NO DEFICIENCIES WERE NOTED DURING THE INSPECTION AND NO FDA-483 WAS ISSUED. THIS TESTING LABORATORY WAS RESPONSIBLE FOR METHOD VALIDATION ONLY. NO ROUTINE TESTING WILL BE PERFORMED AT THIS SITE.					
DO RECOMMENDATION	03-DEC-1998			ACCEPTABLE INSPECTION	GDICKINS
A PRE-APPROVAL INSPECTION WAS CONDUCTED 11/30-12/2/98. NO DEFICIENCIES WERE NOTED; NO FDA-483 WAS ISSUED. THIS TESTING LABORATORY WAS RESPONSIBLE FOR METHOD VALIDATION ONLY. THEY WILL NOT BE PERFORMING ANY ROUTINE TESTING FOR THIS PRODUCT.					
OC RECOMMENDATION	07-DEC-1998			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: [redacted]

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STERILITY TESTER

Profile: CTL OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-FEB-1998				HATHAWAYS
OC RECOMMENDATION	09-FEB-1998			ACCEPTABLE BASED ON PROFILE	FERGUSONS

July 13 response due

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

CENTER FOR DRUG EVALUATION & RESEARCH
REC'D
JUN 13 2000
MEGA DOC RM

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
AVANIR Pharmaceuticals	June 12, 2000
TELEPHONE NO. *(Include Area Code)* (858) 558-0364	**FACSIMILE (FAX) Number** *(Include Area Code)* (858) 424-5845
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 9393 Towne Centre Drive, Suite 200 San Diego CA 92121	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-941

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Docosanol	Abreva

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Behenyl alcohol	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Cream	10%	Topical

(PROPOSED) INDICATION(S) FOR USE:
Recurrent oral-facial herpes simplex infections

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ 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 ☒ 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 ☒ 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: Request for Formal Dispute Resolution -- Labeling

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ 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))
	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) Request for Formal Dispute Resolution -- Labeling

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 review 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
James E. Berg	James E. Berg, VP Clinical & Regulatory Affairs	6/12/00

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
9393 Towne Centre Dr., Suite 200, San Diego CA 92121	(858) 410-2598

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

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Please DO NOT RETURN this form to this address.

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)

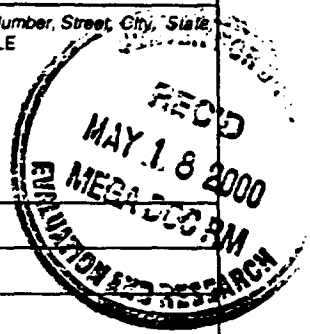
Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
AVANIR Pharmaceuticals	May 17, 2000
TELEPHONE NO. *(Include Area Code)* (858) 558-0364	**FACSIMILE (FAX) Number** *(Include Area Code)* (858) 453-5845
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 9393 Towne Centre Drive, Suite 200 San Diego CA 92121	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE



PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued): 20-941

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Docosanol	Abreva

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: Behenyl alcohol — CODE NAME *(If any)*:

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Cream	10%	Topical

(PROPOSED) INDICATION(S) FOR USE:
Recurrent oral-facial herpes simplex infections

APPLICATION INFORMATION

APPLICATION TYPE (check one): ☒ 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: ☒ 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 ☒ 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: Letter to Cmbudsman, data listing, and statistical report regarding patient diaries (92-LID-02)

PROPOSED MARKETING STATUS (check one): ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1 — THIS APPLICATION IS: ☒ 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)

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)

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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
AVANIR Pharmaceuticals	January 21, 2000
TELEPHONE NO. *(Include Area Code)* (619) 558-0364	**FACSIMILE (FAX) Number** *(Include Area Code)* (619) 453-5845
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 9393 Towne Centre Drive, Suite 200 San Diego CA 92121	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-941

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Docosanol	Abreve

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Behenyl alcohol — CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Cream	10%	Topical

(PROPOSED) INDICATION(S) FOR USE:
Recurrent Oral-facial Herpes Simplex

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ 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 ☒ 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 ☒ 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 audit of study 92-LID-02

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ 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)

Summary Table of Form FDA 483 Observations and Sponsor Responses

Protocol description	Purpose or use described by protocol	Protocol reference (Attachment 2)	Value of material (with respect to primary endpoint)	Comments
Patient diaries	Remind patient of study. Self-assessment data was confirmed each time by investigator and placed in CRF. Thus, CRF is primary source document	p. 16 "The patients self-assessments will be confirmed or corrected by regular clinical observations during the treatment episode."	Secondary Primary source data is CRF	Diaries lost during site relocation and sponsor takeover. Diaries were a tool for patients. Not key data source.
Patient photographs	Not defined in protocol	p. 7 "Photographs will be taken at every clinician's assessment."	Tertiary	Not taken. No provisions or descriptions on how to evaluate or enter photographic data. No provision for photographs on CRF
Tele-conferences	Patient contact	p. 15 for "compliance, safety and tolerability"	Tertiary	Not completed. Patients too difficult to contact. Parameters entered in CRF by investigator at patient's visit

OCT 29 1999

Division Director's Memorandum Re Medical Officer Review of Clinical Study 92-02: Statistical Addendum (signed by MO on 10/28/99) for NDA 20-941

In addition to the issues addressed in the cited MOR, there are two additional points to consider:

1. Study 92-02 is the smallest of five studies and the only one in which "success" was demonstrated against the stearic acid placebo.

Study 92-02 was the first of five studies comparing Lidakol against the stearic acid placebo. The subsequent four studies did not demonstrate superiority for Lidakol:

Study	Lidakol		Placebo	
	# of subjects/healing time		# of subjects/healing time	
92-04	35	7-8d	27	6-7d
94-04	159	4.9d	154	4.7d
94-05	270	7.0d	272	6.9d
95-10	168	5.7d	164	5.9d

2. The point estimate for the subset driving success in 92-02 is extreme.

The mean time to healing of 1.4 days for the 8 early treatment patients at the Netherlands site drove the "success" of Study 92-02. The times to healing for prodrome and erythema patients receiving Lidakol in 94-04 and 95-10 were 3.7 and 3.4 days, respectively. Early treatment was not studied in 94-05.

Regulatory recommendation:

If the results from 92-02 are to be considered critical to a determination of effectiveness, then at least the Netherlands site should be inspected.

/S/

Jonathan Wilkin, MD 10/29/99
Dir, Derm & Dental Drug Products

cc:
NDA 20-941

Via Telefacsimile

May 26, 2000

TO: Jim Berg
Avanir Pharmaceuticals
858-453-5845

FROM: Dr. Robert J. DeLap
Director, ODE V

RE: NDA 20-941 (Docosanol 10% Cream)

Dear Mr. Berg:

We have reviewed your submission dated May 25, 2000 regarding the suggested wording for the labeling and have the following comments:

We note your agreement on our items 1f, 1h, 1i and 1j.

The Division agrees to your proposals for items 1d, 1e, and 1g; we note your agreement to delete the sentence identified in item 1c; and we accept your plans regarding your web site and toll free number (item 1m).

We continue to have concerns regarding items 1a, 1b, 1k, 1l, and 2a. While we are clearly interested in having the salient features of the product clearly described in labeling, we are concerned about including any statements that may be misinterpreted. "Treatment" of cold sores is deemed an accurate descriptive term for a product that may speed the healing of a lesion, but has not been shown to provide a prompt symptomatic benefit apart from its effect on healing time (an external analgesic would be expected to provide a prompt symptomatic benefit, but might not be expected to affect healing time; we did not see evidence that this product was differentiated from placebo in this regard in the studies). Also, we have concerns regarding how the alternative labeling statement you have proposed for item 1k, and the labeling statement we identified in 1l, will be construed in comparisons among products in the marketplace. Finally, it is not clear how a claim of "non-greasy" is properly defined, and whether this product would qualify, considering the composition of the product and the use of docosanol as a lubricant in other settings.

We are continuing our review of those items, and we anticipate communicating further with you following an internal meeting on Tuesday, May 30. It is our intention to complete our action on that date. Please feel free to submit any additional comments or alternative proposals you may have. We are currently unable to identify any acceptable alternatives to our original requests regarding these items.

Please contact Mary Jane Walling at 301-827-2268 for follow-up.

MEMORANDUM OF A TELEPHONE CONVERSATION

DATE: 5/23/00

APPLICATION NUMBER: NDA 20-941; Abreva (docosanol) Cream, 10%

BETWEEN:

Name: Jim E. Berg, V.P., Clinical & Regulatory Affairs
Phone: 858 410-2598
Representing: Avanir Pharmaceuticals

AND

Name: Kevin Darryl White
Division of Dermatologic and Dental Drug Products, HFD-540

SUBJECT: Blank Diary Card for Study 92-LID-02

Mr. Berg was asked, per Dr. Bob DeLap, to submit a blank diary card from Study 92-LID-02 to the Agency for review. Mr. Berg indicated that no 92-LID-02 diary cards are available. However, the diary card template use for both studies (92-01 and 92-02) could be faxed for review (see attached).

This template is labeled Study 92-LID-01; that study was amended on October 7, 1992 in IND [redacted] to become study 92-LID-02. The change in study number was to reflect an original three-group study (comparing docosanol to placebo and acyclovir) to a two-group study comparing docosanol to placebo only. According to Mr. Berg, the other features of the above-mentioned study design remained the same.

/S/

Kevin Darryl White
Regulatory Health Project Manager

cc: Original NDA 20-941
HFD-540/Div. File
HFD-540/PM/White/5/31/00

TELECON