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. 5,166,219 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.
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,
Vice President of Clinical Affairs

12/12/97
Date
CONSULTATION RESPONSE  
Office of Post-Marketing Drug Risk Assessment (OPDRA; HFD-400)

<table>
<thead>
<tr>
<th>DATE RECEIVED: 3/28/00</th>
<th>DUE DATE: 5/3/00</th>
<th>OPDRA CONSULT #: 00-0092</th>
</tr>
</thead>
</table>

**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.

/Signature/  
5/5/00

/Signature/  
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

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, Abreva. The Labeling and Nomenclature Committee (LNC) on 11/19/98 approved it. LNC believed there was low risk of confusion between Abreva 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, Abreva. OPDRA expert panel has serious concerns about the similarity of Abreva 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\textsuperscript{1,2,3} as well as several FDA databases\textsuperscript{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\textsuperscript{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.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dose Form</th>
<th>Generic Name</th>
<th>Usual Dose</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abreva</td>
<td>10% Cream</td>
<td>Acyclovir</td>
<td>Apply 5 times daily until healed</td>
<td></td>
</tr>
<tr>
<td>Aleve</td>
<td>200 mg tablet, naproxen</td>
<td>200 mg every 8-12 hours</td>
<td>*SA/</td>
<td></td>
</tr>
</tbody>
</table>

*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


\textsuperscript{2} American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

\textsuperscript{3} Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

\textsuperscript{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.

\textsuperscript{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.

<table>
<thead>
<tr>
<th>HANDWRITTEN PRESCRIPTION</th>
<th>VERBAL PRESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient RX:</strong></td>
<td></td>
</tr>
<tr>
<td>Abreva #1</td>
<td>Abreva #1</td>
</tr>
<tr>
<td>Sig: As directed</td>
<td>Sig: As directed</td>
</tr>
<tr>
<td><strong>Inpatient RX:</strong></td>
<td></td>
</tr>
<tr>
<td>Continue Abreva as directed</td>
<td></td>
</tr>
</tbody>
</table>

2. Results:

The results are summarized in Table I.

<table>
<thead>
<tr>
<th>Study</th>
<th># of Participants</th>
<th># of Responses (%)</th>
<th>Correctly Interpreted</th>
<th>Incorrectly Interpreted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Written Outpatient</td>
<td>31</td>
<td>24 (77%)</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>Verbal</td>
<td>32</td>
<td>18 (56%)</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Written Inpatient</td>
<td>31</td>
<td>19 (61%)</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>61 (65%)</td>
<td>51 (84%)</td>
<td>10 (16%)</td>
</tr>
</tbody>
</table>
Eighty-four percent of the participants responded with the correct name, Abreva. The incorrect written and verbal responses are as follows in Table II.

<table>
<thead>
<tr>
<th></th>
<th>Incorrectly Interpreted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Written Outpatient</td>
<td>Abreva</td>
</tr>
<tr>
<td></td>
<td>Avieva</td>
</tr>
<tr>
<td></td>
<td>Aoreva</td>
</tr>
<tr>
<td>Written Inpatient</td>
<td>Abura (4)</td>
</tr>
<tr>
<td>Verbal</td>
<td>Aprewa</td>
</tr>
<tr>
<td></td>
<td>Abrea</td>
</tr>
<tr>
<td></td>
<td>Abreatha</td>
</tr>
</tbody>
</table>

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 Internet sit (www.Abrevat.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, Abrevat.

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)

<table>
<thead>
<tr>
<th>From:</th>
<th>Division of Dermatologic and Dental Drug Products</th>
<th>HFD-540</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention:</td>
<td>Steve Hathaway, Ph.D.</td>
<td>Phone: 827-2069</td>
</tr>
<tr>
<td>Date:</td>
<td>October 15, 1998</td>
<td></td>
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<tr>
<td>Subject:</td>
<td>Request for assessment of a proposed trademark for Rx drug product</td>
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</tr>
<tr>
<td>Proposed Trademark:</td>
<td>Abreve Cream, 10%</td>
<td></td>
</tr>
<tr>
<td>Abreve Cream, 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDA 20-941</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Established name, including dosage form:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cream</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behenyl alcohol, a.k.a. n-docosanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other trademarks by the same firm for companion products:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None approved.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
REQUEST FOR TRADEMARK REVIEW

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

<table>
<thead>
<tr>
<th>From: Division of Dermatologic and Dental Drug Products</th>
<th>HFD-540</th>
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<tbody>
<tr>
<td>Attention: Steve Hathaway, Ph.D.</td>
<td>Phone: 827-2069</td>
</tr>
<tr>
<td>Date: March 2, 1998</td>
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<tr>
<td>Subject: Request for assessment of a proposed trademark for Rx drug product</td>
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<tr>
<td>Proposed Trademark: Lidakol Cream, 10%</td>
<td>NDA 20-941</td>
</tr>
</tbody>
</table>

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: ABREVE  PROPOSED ESTABLISHED NAME: behenyl alcohol, a.k.a. n-docosanol
ATTENTION: Steve Hathaway

A. Look-alike/Sound-alike

<table>
<thead>
<tr>
<th>Aisle</th>
<th>Potential for confusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXX</td>
<td>Low</td>
</tr>
<tr>
<td>XXX</td>
<td>Low</td>
</tr>
<tr>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>Low</td>
<td>Medium</td>
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</table>

B. Misleading Aspects:  

C. Other Concerns:  

D. Established Name

<table>
<thead>
<tr>
<th>Satisfactory</th>
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<tbody>
<tr>
<td>XXX Unsatisfactory/Reason</td>
</tr>
<tr>
<td>A USAN must be applied for as the established name</td>
</tr>
</tbody>
</table>

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:  LIDAKOL CREAM, 10%

NTION:  STEVE HATHAWAY

A. Look-alike/Sound-alike

<table>
<thead>
<tr>
<th>Potential for confusion:</th>
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<tbody>
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<tr>
<td>Low</td>
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<td>High</td>
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<tr>
<td>Low</td>
<td>Low</td>
<td>High</td>
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</table>

3. Misleading Aspects

C. Other Concerns

3. Established Name

<table>
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<th>XXX</th>
<th>Satisfactory</th>
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<tbody>
<tr>
<td>Un satisfactory/Reason</td>
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</tbody>
</table>

Recommended Established Name

- Proprietary Name Recommendations:  XXX ACCEPTABLE  UNACCEPTABLE

- Signature of Chair/Date  /S/  4/14/98
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<th>Application:</th>
<th>NDA 20941/000</th>
<th>Priority: 1S</th>
<th>Org Code: 540</th>
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<tbody>
<tr>
<td>Regulatory Due:</td>
<td>22-DEC-1998</td>
<td>Brand Name:</td>
<td>LIDAKOL (N-DOCOSANOL) TOP</td>
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<tr>
<td>Applicant:</td>
<td>LIDAK</td>
<td>CREAM 10%</td>
<td></td>
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<tr>
<td></td>
<td>11077 NORTH TORREY PINES RD</td>
<td>Established Name:</td>
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<td>LA JOLLA, CA 92037</td>
<td>Generic Name:</td>
<td>N-DOCOSANOL</td>
</tr>
<tr>
<td>FDA Contacts:</td>
<td>K. WHITE (HFD-540)</td>
<td>Dosage Form:</td>
<td>CRM (CREAM)</td>
</tr>
<tr>
<td></td>
<td>J. HATHAWAY (HFD-540)</td>
<td>Strength:</td>
<td>10% W/W</td>
</tr>
<tr>
<td></td>
<td>W. DECAMP II (HFD-540)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| FDA Contacts: | K. WHITE (HFD-540) | Responsibilities: FINISHED DOSAGE PACKAGER |
|              | 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:**

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<th>DMF No:</th>
<th>AADA No:</th>
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<tbody>
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<tbody>
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<td>Milestone Date: 09-FEB-1998</td>
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<th>AADA No:</th>
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<td>Responsibilities: FINISHED DOSAGE MANUFACTURER</td>
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<td>Last Milestone: INSPECTION PERFORMED</td>
<td>Milestone Date: 12-JUN-1998</td>
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Profile: CTL | OAI Status: NONE | Responsibilities: DRUG SUBSTANCE STABILITY TESTER
Last Milestone: SUBMITTED TO DO
Milestone Date: 02-NOV-1998

Establishment: | DMF No: | AADA No:
---|---|---
Profile: CSN | OAI Status: NONE | Responsibilities: DRUG SUBSTANCE MANUFACTURER
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-SEP-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: | DMF No: | AADA No:
---|---|---
Profile: CTL | OAI Status: NONE | Responsibilities: DRUG SUBSTANCE STABILITY TESTER
Last Milestone: SUBMITTED TO DO
Milestone Date: 02-NOV-1998

Establishment: | DMF No: | AADA No:
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Profile: CTL | OAI Status: NONE | Responsibilities: DRUG SUBSTANCE OTHER TESTER
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**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 30-DEC-1998

**Decision:** ACCEPTABLE

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

**Acceptable on 31-Mar-1999 by J. D. Ambrogio** (HFD-324) 301-827-0062

### Establishment

#### Responsibilities: Finished Dosage Packager

**Profile:** OIN  
**OAI Status:** NONE

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### Establishment

#### Responsibilities: Finished Dosage Release Tester

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

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### Establishment

#### Responsibilities: Finished Dosage Manufacturer

**Profile:** OIN  
**OAI Status:** NONE

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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.

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

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Establishment:

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

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Establishment:

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

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Establishment:

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE OTHER TESTER
**Profile:** CTL  
**OAI Status:** NONE

**Establishment 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 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)

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**Establishment:**

**DMF No:**

**Responsibilities:** DRUG SUBSTANCE OTHER TESTER

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

**Establishment 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 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)

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<td>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.</td>
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**Establishment:**

**DMF No:**

**Responsibilities:** FINISHED DOSAGE STERILITY TESTER

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

**Establishment Comment:**

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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)

APPLICANT INFORMATION

NAME OF APPLICANT
AVANIR Pharmaceuticals

DATE OF SUBMISSION
June 12, 2000

TELEPHONE NO. (Include Area Code) (858) 558-0364

FACSIMILE (FAX) Number (Include Area Code)

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/NF name)
Docosanol

PROPRIETARY NAME (trade name) IF ANY
Abreva

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)
Beheryl alcohol

CODE NAME (If any)

DOSEAGE FORM
Cream

STRENGTHS
10%

ROUTE OF ADMINISTRATION
Topical

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

APPLICATION INFORMATION

APPLICATION TYPE
(check one)
X NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

BILOGICS 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

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)
X PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMESSubmitted
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, BIMFs, and DMFs referenced in the current application)

FORM FDA 356h (7/97)
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.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
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
James E. Berg, VP Clinical & Regulatory Affairs

TYPED NAME AND TITLE  
Telephone Number
(858) 410-2598

DATE 6/12/00

ADDRESS 9893 Towne Centre Dr., Suite 200, San Diego CA 92121

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.
APPLICATION INFORMATION

NAME OF APPLICANT: AVANIR Pharmaceuticals

DATE OF SUBMISSION: May 17, 2000

TELEPHONE NO.: (858) 558-0364

FACSIMILE (FAX) Number: (858) 453-5845

APPLICANT ADDRESS: 9393 Towne Centre Drive, Suite 200
San Diego CA 92121

AUTHORIZED U.S. AGENT NAME & ADDRESS: Abreva

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/LA Salvage): Docosanol

PROPRIETARY NAME (trade name) IF ANY: Behenyl alcohol

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any): Abreva

COVERAGE FORM: Cream

STRENGTH: 10%

ROUTE OF ADMINISTRATION: Topical

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

APPLICATION INFORMATION

APPLICATION TYPE: NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

BILOGICS 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: AMENDMENT TO A PENDING APPLICATION

ORIGINAL APPLICATION

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 patent diaries (92-LID-02)

PROPOSED MARKETING STATUS: PRESCRIPTION PRODUCT - Rx

OVER THE COUNTER PRODUCT - OTC

NUMBER OF VOLUMESSubmitted: 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 (CFR), DMF number, and manufacturing steps and/or type of testing (e.g., chemical testing, 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)

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
AVANIR Pharmaceuticals

DATE OF SUBMISSION
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)
Docosanol

PROPRIETARY NAME (trade name) IF ANY
Abrevo

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

CODE NAME (If any)

DOSAGE FORM:
Cream

STRENGTHS:
10%

ROUTE OF ADMINISTRATION:
Topical

APPLICATION INFORMATION

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

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)
☐ 307

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-LIO-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 (CFR), 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, PMA, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
## Summary Table of Form FDA 483 Observations and Sponsor Responses

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

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

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.

cc: NDA 20-941

/S/
Jonathan Wilkin, MD
Dr. Derm & Dental Drug Products

10/29/99
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 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