

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-941

CHEMISTRY REVIEW(S)

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS

HFD-540

Review of Chemistry, Manufacturing, and Controls

MAY 12 2000

NDA #: 20-941 **CHEM. REVIEW #:** 2 **REVIEW DATE:** 10-MAY-2000

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	19-DEC-1997	22-DEC-1997	Chem. Rev. #1
CORRESPONDENCE	11-SEP-1998	14-SEP-1998	Chem. Rev. #1
AMENDMENT	06-OCT-1998	07-OCT-1998	Chem. Rev. #1
AMENDMENT/BC	06-OCT-1998	07-OCT-1998	N/A
AMENDMENT/BZ	02-DEC-1999	03-DEC-1999	N/A
AMENDMENT/BL	25-FEB-2000	28-FEB-2000	N/A
AMENDMENT/XR	07-APR-2000	10-APR-2000	N/A
AMENDMENT/BL	05-MAY-2000	08-MAY-2000	12-MAY-2000

NAME & ADDRESS OF APPLICANT:

AVANIR Pharmaceuticals
9393 Towne Center Drive
San Diego, CA 92121

DRUG PRODUCT NAME

<u>Proprietary:</u>	ABREVA®
<u>Nonproprietary/USAN:</u>	Docosanol
<u>Code Names/ #'s:</u>	Behenyl alcohol
<u>Chemical Type/</u>	aliphatic alcohol
<u>Therapeutic Class:</u>	1 S

ANDA Suitability Petition/DESI/Patent Status:

N/A

PHARMACOLOGICAL CATEGORY/INDICATION:

Topical treatment of cold sores and fever blisters

DOSAGE FORM:

Cream

STRENGTHS:

10%

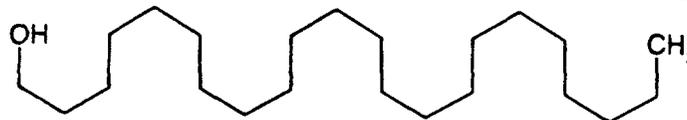
ROUTE OF ADMINISTRATION:

Topical

DISPENSED:

_____ Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:



Chemical Name: behenyl alcohol; n-docosanol; 1-docosanol
Mol. Formula: C₂₂H₄₆O
Mol. Weight: 326.61
CAS No. [661-19-8]

SUPPORTING DOCUMENTS: NONE

RELATED DOCUMENTS:

The following UPDATED patents protect various claims for the drug or methods of use of the drug, and replace those listed in the original application of 11-DEC-1997:

U.S. Patent No. 4,874,794, expiration date 28-APR-2009, for any composition containing 0.1% to 25% n-docosanol for topical treatment of virus-induced or inflammatory diseases.

U.S. Patent No. 5,071,879, expiration date 28-APR-2009, for treatment or prevention methods for human disease or virus infection by transmucous membranal or transdermal penetration of a composition of C22 aliphatic alcohol in a physiologically compatible carrier.

U.S. Patent No. 5,194,451, expiration date 28-APR-2009, for treatment or prevention methods for human inflammatory disease by transmucous membranal or transdermal penetration of a composition of C22 aliphatic alcohol in a physiologically compatible carrier.

U.S. Patent No. 5,166,219, expiration date 02-NOV-2009, for treatment methods for human inflammatory disease or arthritis by transmucous membranal or transdermal penetration of a composition of C22 aliphatic alcohol in a physiologically compatible carrier.

U.S. Patent No. 5,534,554, expiration date 13-DEC-2013, for therapeutic creams containing n-docosanol at greater than 5% by weight to topical application.

U.S. Patent No. 5,098,896, expiration date 23-APR-2011, for methods of corneal treatment by topically applied n-docosanol to promote epithelial healing.

U.S. Patent No. 5,214,071, expiration date 23-APR-2011, for methods of corneal treatment by topically applied n-docosanol to promote corneal healing.

U.S. Patent No. 5,296,514, expiration date 23-APR-2011, for methods of corneal healing by topically applied n-docosanol to promote corneal healing.

CONSULTS: NONE

REMARKS/COMMENTS:

The applicant addressed the requests for additional CMC information listed in the FDA letter of 22-NOV-1999. The additions of regulatory specifications for impurities in drug substance and drug product appear acceptable. The applicant will be asked to submit revised specification pages and stability protocols to reflect these changes.

The applicant also revised the preservative effectiveness test schedule for stability test protocol to include testing at 0, 18 and 36 months for the first three production batches of product. This conforms to usual practice, and is acceptable.

The draft final labeling submitted requires editorial changes; these were incorporated into the label during the labeling meeting on 12-MAY-2000.

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AVANIR Pharmaceuticals
ABREVA® Cream, 10%

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CONCLUSIONS & RECOMMENDATIONS:

APPROVAL

The applicant has adequately addressed all CMC information requests and requested revisions. Pending the submission of acceptable final printed labeling, the chemistry, manufacturing and controls portion of this application is approved.

/S/

S/12/2000
Joel S. Hathaway, Ph.D.
Review Chemist

cc: Orig. NDA 20-941
HFD-540/DivisionFile
HFD-540/Chem/JSHathaway
HFD-540/ChemTeamLdr/WHDeCamp
HFD-540/DivDir/JWilkin
HFD-830/DivDir/CWChen
HFD-540/MedOffr/MOkun
HFD-540/PharmTox/LReidd
HFD-540/ProjMgr/KDWhite
HFD-160/Micro/Sweeney

/S/5/12/00

Recommended for APPROVAL

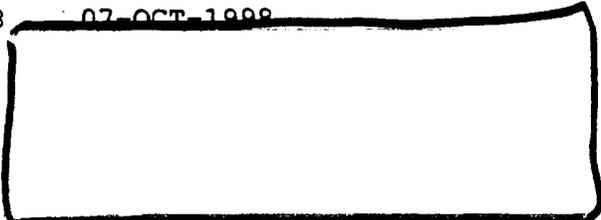
NOV 18 1998

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
HFD-540
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-941 CHEM. REVIEW #: 1 REVIEW DATE: 10-NOV-1998

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	19-DEC-1997	22-DEC-1997	09-JAN-1998
CORRESPONDENCE	11-SEP-1998	14-SEP-1998	
AMENDMENT	06-OCT-1998	07-OCT-1998	

NAME & ADDRESS OF APPLICANT:

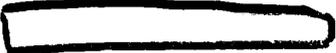


DRUG PRODUCT NAME

Proprietary:

LIDAKOL®

Nonproprietary/USAN:

n-Docosanol, 

Code Names/ #'s:

Chemical Type/

Therapeutic Class:

1 S

ANDA Suitability Petition/DESI/Patent Status:

N/A

PHARMACOLOGICAL CATEGORY/INDICATION:

Topical antiviral treatment of oral herpes lesions.

DOSAGE FORM:

Cream

STRENGTHS:

10%

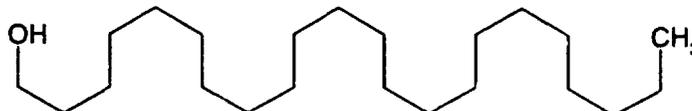
ROUTE OF ADMINISTRATION:

Topical

DISPENSED:

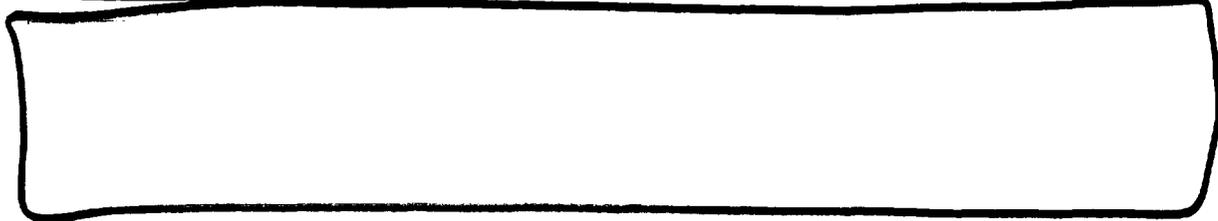
Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:



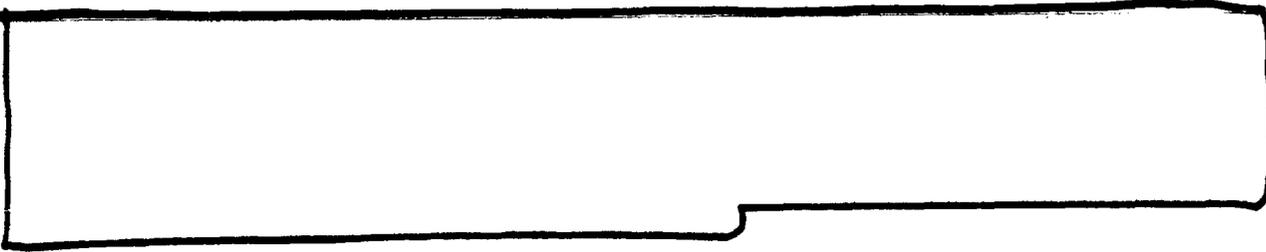
Chemical Name: behenyl alcohol; n-docosanol; 1-docosanol
Mol. Formula: C₂₂H₄₆O
Mol. Weight: 326.61
CAS No. [661-19-8]
Melting Pt.: 70-72°C
Partition Coefficient: logP_{o/w} = 12.1

SUPPORTING DOCUMENTS:





RELATED DOCUMENTS:



The following patents are claimed for the drug or method of use of the drug:



U.S. Patent No. 5,071,879, expiration date 17-OCT-2006, for treatment or prevention methods for human disease or virus infection by transmucous membranal or transdermal penetration of a composition of C22 aliphatic alcohol in a physiologically compatible carrier.

U.S. Patent No. 5,194,451, expiration date 10-DEC-2008, for treatment or prevention methods for human inflammatory disease by transmucous membranal or transdermal penetration of a composition of C22 aliphatic alcohol in a physiologically compatible carrier.

U.S. Patent No. 5,166,219, expiration date 03-DEC-2008, for treatment methods for human inflammatory disease or arthritis by transmucous membranal or transdermal penetration of a composition of C22 aliphatic alcohol in a physiologically compatible carrier.

U.S. Patent No. 5,534,554, expiration date 13-DEC-2013, for therapeutic creams containing n-docosanol at greater than 5% by weight to topical application.

U.S. Patent No. 5,098,896, expiration date 24-MAR-2009, for methods of corneal treatment by topically applied n-docosanol to promote epithelial healing.

U.S. Patent No. 5,214,071, expiration date 25-MAY-2010, for methods of corneal treatment by topically applied n-docosanol to promote corneal healing.

U.S. Patent No. 5,296,514, expiration date 22-MAY-2011, for methods of corneal healing by topically applied n-docosanol to promote corneal healing.

CONSULTS:

The proposed trade name "Lidakol," was submitted to the Labeling and Nomenclature Committee (LNC) through Chairman Dan Boring, Ph.D. (HFD-530). The LNC determined that the proposed trade name had only a medium potential for look-alike/sound-alike confusion with the drug name "lidocaine", and was acceptable, as shown in the attached communication (#975) dated 18-APR-1998.

Two newly proposed trade names, "Abreve" and "Abreva," were provided in correspondence dated 11-SEP-1998, and sent to the LNC on 15-OCT-1998. The LNC determined that these proposed trade names were acceptable, with "Abreve" having a potential look-alike/sound-alike confusion with the drug name "Aleve". The differences in the dosage form and indication serve to differentiate these products.

REMARKS/COMMENTS:

Final determination of the acceptability of this application by the Office of Compliance has not yet been received. Late notification by the sponsor regarding testing facilities caused the EER to return to pending status. Prior to this, all facilities except the drug product manufacturing site were acceptable.

CONCLUSIONS & RECOMMENDATIONS:

APPROVABLE

Based on the review of the chemistry, manufacturing and controls information presented in the NDA, a recommendation of "Approvable" is made. The following concerns are the issues which should be addressed by the sponsor before approval will be given:

1. Container labeling for the drug product should be provided for review, and should incorporate the appropriate trade name and US Adopted Name (USAN). Mock-ups of the primary package label, secondary packaging, if any (outer box, etc.) and physician's package insert should be provided.

2. Information should be provided to document the change control procedures to which the drug substance manufacturer will adhere for the manufacturing process of the drug substance. This requirement might be satisfied by a commitment from the drug substance manufacturer not to modify the process used to produce the n-docosanol (beyond the parameters described in the application) without prior notification to the NDA holder. Any future changes to the manufacturing process could be qualified via supplement to the NDA.
3. The sponsor should provide a commitment to perform the in-process tests on bulk lots at the site where filling of the physician's samples occurs, and an identity test on the incoming bulk lot. Please provide information for the holding time between formulation of the bulk batches and corresponding validation data.
4. To more closely reflect the actual levels of impurities seen in practice, the sponsor should revise the following regulatory specifications for drug substance : Total Related Substances, Individual Related Substances: n-tetracosanol, Identified Related Substances, and Unidentified Related Substances. The limits on these impurities should be reduced, with the proposed limits being based on the observed quantities of impurities as determined by analysis of the lots of drug substance used during development.
5. The applicant should propose a drug product regulatory specification for specified and unspecified impurities, or provide justification for the exclusion of this specification.

/S/

11/17/98

Joel S. Hathaway, Ph.D.
Review Chemist