CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-941

APPROVAL LETTER

JUL 25 2000

NDA 20-941

Avanir Pharmaceuticals
Attention: James E. Berg
Vice President of Clinical Affairs and Product Development
9393 Towne Centre Drive
Suite 200
San Diego, CA. 92121

Dear Mr. Berg:

Please refer to your new drug application (NDA) dated December 19, 1997, received December 22, 1997, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abreva (docosanol) Cream, 10% .

We acknowledge receipt of your submissions dated June 6, 12, July 21, and 25, 2000. Your submission of June 6, 2000 constituted a complete response to our May 30, 2000 action letter.

This new drug application provides for the use of Abreva Cream, 10% (docosanol) for cold sore/fever blister treatment.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (immediate container and carton labels submitted July 21, 2000 and amended by your July 25 fax) and must be formatted in accordance with the requirements of 21 CFR 201.66. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternately, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 20-941." Approval of this submission by FDA is not required before the labeling is used.

You are cautioned not to promote the product as an antiviral or as providing symptomatic relief of cold sores. Promotion of symptomatic benefit should be limited to the information provided in labeling, that the product shortens healing time and duration of symptoms.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Babette Merritt, Project Manager, at (301) 827-2222.

Sincerely.

/S/ 7/25/00

Robert J. DeLap, M.D., Ph.D.
Director Office of Drug Evaluation V
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-941

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-941

Avanir Pharmaceuticals
Attention: James E. Berg
Vice President of Clinical Affairs and Product Development
9393 Towne Centre Drive
Suite 200
San Diego, CA, 92121

MAY 30 2000

Dear Mr. Berg:

Please refer to your new drug application (NDA) dated December 19, 1997, received December 22, 1997, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Abreva (docosanol) Cream, 10% .

We acknowledge receipt of your submissions dated December 22, 1998; January 8, 11, 13 and 15, February 26, March 18, 24, and 29, April 30, May 5, 14, and 24, June 25, August 3, and December 2, 1999; January 21, February 25, April 7 and May 5, 17 (two), 25, 30, 2000. Your submission of December 2, 1999 constituted a complete response to our December 22, 1998 action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (immediate container and carton labels).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Kevin Darryl White, Project Manager, at (301) 827-2020.

Sincerely,

/S/

Robert J. DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-941

NOT APPROVABLE LETTER

DF

DEC 22 1998

NDA 20-941

Avanir Pharmaceuticals
Attention: James E. Berg
Vice President of Clinical Affairs and Product Development
9393 Towne Centre Drive
Suite 200
San Diego, CA 92121

Dear Mr. Berg:

Please refer to your new drug application (NDA) dated December 19, 1997, received December 22, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LIDAKOL (*n*-docosanol cream) CREAM, 10%.

We acknowledge receipt of your submissions dated January 21 and 27, March 18, April 23, June 11, July 2, September 10 and 11, October 6 and 20, 1998. In addition, we also acknowledge receipt of your pre-submissions dated November 25, and December 10, 1997. The User Fee goal date for this application is December 22, 1998.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

1. The effectiveness of LIDAKOL (*n*-docosanol cream) CREAM, 10% in the treatment of recurrent oral-facial herpes simplex has not been adequately established.

   Two clinical studies (96-06 and 96-07), analyzed separately and together (as study 96-06/07), have been submitted as the primary evidence of LIDAKOL effectiveness in this New Drug Application. Studies 96-06 and 96-07 enrolled patients with early recurrence of oro-facial herpes simplex (prodrome / erythema stages). The primary efficacy endpoint in these studies was time to healing (or time to abortion of recurrence, in the subset of patients who recovered without developing classical recurrent herpes simplex lesions). In study 96-06 and in the combined 96-06/07 analysis, a statistically significant shortening of the time to healing or episode abortion was noted in patients receiving LIDAKOL (median time to healing or episode abortion of 4.1 days for LIDAKOL versus 4.8 days for placebo in the combined analysis, $p<.01$). In study 96-07, the time to healing or episode abortion was not significantly different in the two study groups (median time to healing/episode abortion of 4.3 days for LIDAKOL versus 4.9 days for placebo, $p=.15$). Certain secondary study endpoints were also suggestive of LIDAKOL efficacy in studies 96-06 and 96-07.

Three earlier Phase 3 clinical studies following different protocols, referenced in this New Drug Application (studies 94-04, 94-05, and 95-10), had compared LIDAKOL to a stearic acid-containing placebo, and failed to demonstrate effectiveness of LIDAKOL in treatment of recurrent oro-facial herpes simplex. In fact, the clinical outcomes observed in those studies were no different in the LIDAKOL and placebo groups. However, stearic acid is chemically related to the active ingredient in LIDAKOL, and it was subsequently postulated that the stearic acid "placebo" used in those studies might have been an active treatment.

Following complete review of the data and analyses provided in this New Drug Application, we have determined that additional evidence is needed to substantiate the effectiveness of LIDAKOL in the treatment of recurrent oro-facial herpes simplex. We anticipate that one additional adequate and well controlled trial may be sufficient to substantiate the findings of studies 96-06/07. You are encouraged to discuss with FDA the design of a clinical trial to address this need, before investing resources into additional clinical studies.

Although not the basis for the not approvable action on this application, the following should be addressed in any resubmission.

A. Chemistry

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 should be qualified via a supplement to the NDA.

3. A commitment should be provided 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. Information should be provided 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 following regulatory specifications should be provided 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. Drug product regulatory specifications should be proposed for specified and unspecified impurities, or provide justification for the exclusion of this specification.

6. The decision by the Office of Compliance, regarding the cGMP facilities inspection of additional sites not originally submitted with the application, remains pending at this time.

B. Microbiology

1. To comply with the current USP proposal for microbiological attributes of non-sterile drug products, the total combined yeasts and molds microbial limits specification should be listed as ≤ 10 cfu/g.

2. Although the application states that the preservative effectiveness test has demonstrated that benzyl alcohol is effective as an antimicrobial agent at the lower limit of —%, no supporting data or methodology were included in the submission. Please provide the methodology and supporting data demonstrating the preservative effectiveness of benzyl alcohol in the drug product.

3. Stability of antimicrobial preservative effectiveness should be demonstrated over the product shelf-life. Antimicrobial preservatives are used to inhibit the growth of microorganisms which may be introduced inadvertently during or subsequent to the manufacturing process. Although microbial limits testing results may reflect the antimicrobial effectiveness of the preservative against organisms introduced during the manufacturing process, these results may not necessarily indicate antimicrobial effectiveness against organisms introduced after the manufacturing process. Therefore, microbial limits stability testing and antimicrobial effectiveness testing should be included in the post-approval stability protocol.

   For testing the stability of preservative systems in the drug product, the first three production lots should be tested with a microbial challenge assay at the start and at the end of the stability period, and at one point in the middle of the stability test period if the test period equals or exceeds two years. The first three batches should be assayed for the chemical content of the preservatives at all appropriate test points. Upon demonstration of chemical content commensurate with antimicrobial preservative effectiveness in the first three production batches, chemical assays may be adequate to demonstrate the maintenance of the specified concentrations of preservatives for subsequent lots placed into stability testing.

C. Pharmacology/Toxicology

1. Please calculate and submit the AUC values from data collected on *n*-docosanoic acid concentrations found in rat plasma after a single oral administration of *n*-docosanol suspensions in aqueous ——— prepared by either ——— or Lidak Pharmaceuticals. *n*-Docosanoic acid levels were reported in the addendum: Determination of Docosanoic Acid Using GC/NCI-MS, to study 48BL-20, **A General Pharmacology Study of *n*-Docosanol,** conducted by ———. If the *n*-docosanol levels were measured in these animals please submit that additional information.

2. Please provide an explanation for the *n*-docosanol plasma levels observed in control animals in the four nonclinical studies listed below:

   a) A 4-Week Oral Dose Range-Finding and Preliminary Toxicokinetic Study of *n*-Docosanol Suspensions in CD Rats. Study report no. 94/LAK002/0706. *In life:* 5/4 to 6/8/94, conducted at ——— with toxicokinetic sample analyses performed by ———.

   b) A 26-Week Daily Oral Toxicology Study of *n*-Docosanol Suspensions in Rats including Toxicokinetic Assessments. Study report no. 94/LAK008/0963. *In life:* 12/14/94 to 6/19/95, conducted at ———.

   c) Subacute 28-Day Dermal Tolerance Study With *n*-Docosanol (LIDAKOL) by Daily 6 Hours Administrations to the Intact and Abraded Skin of Rabbits. Study report no. ——— *In life:* 11/9 to 12/10/93, conducted by ———.

   d) [redacted]

3. [redacted]

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the review Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed in the United States until you have been notified in writing that the application is approved.

If you have any questions, contact Kevin Darryl White, Project Manager, at (301) 827-2020.

Sincerely,

Robert J. DeLap 12/22/1998

Robert DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Archival NDA 20-941
HFD-540/Div. Files
HFD-540/Wilkin/12/22/98
HFD-540/Okun/11.18.98
HFD-540/Walker/11.18.98
HFD-540/Reid/11.17.98
HFD-540/Jacobs/11.17.98
HFD-540/Hathaway
HFD-540/DeCamp
HFD-880/Bashaw/11.17.98
HFD-725/Gao/11.17.98
HFD-725/Srinivasan/11.17.98
HFD-530/Biswal
HFD-530Ramsey
HFD-805/Sweeney
HFD-805/Cooney
HFD-540/K.D.White/11.12.98
HFD-540/Kozma-Fornaro/11.17.98
HFD-002/ORM
HFD-105/ADRA
HFD-95/DDMS
HFD-830/Sheinin
DISTRICT OFFICE

final (revised):12/22/98
filename: LIDAK.

NOT APPROVABLE (NA)