CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-112

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-112

Hill Dermaceuticals, Inc.
Attention: Rosario G. Ramirez, M.D.
Director, Medical/Regulatory
2650 South Mellonville Ave.
Sanford, Florida 32773

Dear Dr. Ramirez:

Please refer to your new drug application (NDA) dated March 19, 1999, received March 22, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRI-LUMA (fluocinolone acetonide, 0.01% / hydroquinone, 4% / tretinoin, 0.05%) Cream.

We acknowledge receipt of your submissions dated August 16, 21(two), 22, September 4, 18, 19, 26, October 25, November 1 and 22, December 10, 18, 20, 2001; January 10 and 15, 2002; and facsimile transmissions dated September 17 and 20, and November 16 and 22, 2001; and January 18(two), 2002. Your submission of July 20, 2001, constituted a complete response to our January 21, 2000, action letter.

This new drug application provides for the use of TRI-LUMA ((fluocinolone acetonide, 0.01% / hydroquinone, 4% / tretinoin, 0.05%) Cream for the short-term treatment of moderate to severe melasma of the face, in the presence of measures for sun avoidance, including the use of sunscreens.

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 enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels). 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 the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-112." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your facsimile transmissions dated January 18, 2002. These commitments are listed below:

1. The Applicant commits to the collection of pregnancy outcome data arising from the use of TRI-LUMA Cream in pregnancy, monitor the unintended usage in pregnancy, and provide measures how this can be reduced. The Applicant will submit a protocol for review.

   Protocol Submission: Within 3 months of the date of this letter

2. The Applicant commits to performing dermal carcinogenicity testing of the combination drug product.

   Protocol Submission: Within 4 months of the date of this letter
   Study Start: Within 6 months of the date of the approval of the protocol
   Final Report Submission: Within 12 months after the study completion

In addition, the Applicant will provide to the Agency the complete study reports for Studies 29 as soon as each study is completed, and provide Safety Updates in these submissions.

The Agency reminds the Applicant of their commitment to provide a final report on the 12 months storage stability of tretinoin in human plasma on or before August 2002.

We also acknowledge your agreement on January 18, 2002, to implement changes within six months to revise the container and carton label to show (1) white space between the ingredients listing and the "Storage" condition line; and (2) the established name will be at least ½ the size of the tradename.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

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 as the necessary studies are impossible or highly impractical to conduct because the number of patients is too small.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

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, please call Victoria Lutwak, Project Manager, at 301-828-2073.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL