

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 21-302**

**APPROVAL LETTER**



NDA 21-302

Novartis Pharmaceuticals Corporation  
Attention: James L. DeMartino, Ph.D.  
Associate Director, Drug Regulatory Affairs  
59 Route 10  
East Hanover, New Jersey 07936-1080

Dear Dr. DeMartino:

Please refer to your new drug application (NDA) dated December 15, 2000, received December 15, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elidel (pimecrolimus) Cream, 1%.

This letter amends the letter dated December 13, 2001, to correct administrative issues with this application.

We acknowledge receipt of your submissions dated February 15 and 23, March 8 and 13, April 30, May 21, 23, 24 and 29, June 1, 6, 7, 13 and 19, July 6 and 12, August 7, September 10, 11 and 12, October 8, 9 (2), 10, 11, 22, 29, and 30 (2) and November 1 and 28, December 10 and 13 (2) 2001.

This new drug application provides for the use of Elidel (pimecrolimus) Cream, 1%, for short-term and intermittent long-term therapy in the treatment of *mild to moderate* atopic dermatitis in non-immunocompromised patients 2 years of age and older, in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or intolerant of alternative, conventional therapies.

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 in patients ages 2 and above as recommended in the agreed upon enclosed labeling text, submitted December 13, 2001. Accordingly, the application is approved effective on December 13, 2001.

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 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. Alternatively, 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 21-301." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your post marketing commitments specified in your submission dated December 13, 2001. These commitments, along with any completion dates agreed upon, are listed below.

1. a. The preclinical rodent studies found an increased risk for lymphoma and follicular cell thyroid adenoma in the studies evaluating an oral formulation of pimecrolimus. We agree to conduct a registry study of pediatric patients (aged 2-17, with emphasis on the younger ages) with atopic dermatitis followed through adulthood for those who have long-term intermittent treatment with Elidel (pimecrolimus) 1% Cream to assess the risk of developing systemic malignancies.

Study proposal for review: April 30, 2002

Report: Every 5 years after the division reviews and accepts the proposal and the study is initiated. Data will be submitted with NDA annual report.

- b. A preclinical mouse photocarcinogenicity study showed an accelerated rate of development of cutaneous malignancies. We agree to conduct a registry or case-controlled study of sun-exposed adult patients, aged 40 and above, with atopic dermatitis, who have long-term intermittent treatment with Elidel (pimecrolimus) 1 % Cream to assess the risk of developing cutaneous malignancies.

Study proposal for review: June 30, 2002

Report: Every 5 years after the division reviews and accepts the proposal and the study is initiated. Data will be submitted with NDA annual report.

2. We agree to establish a pregnancy registry to assess the relationship of pimecrolimus cream to spontaneous abortions to determine if the signal in the clinical studies is a valid one. This could be waived by FDA if an acceptable preclinical dermal embryofetal study is performed with continuous dermal drug exposure and found to be negative.

Draft preclinical protocol: April 30, 2002

Study Report: 1 year after the Division reviews and agrees to the protocol (est. June 30, 2003)

Proposal for pregnancy registry: September 30, 2002

Initiation of registry: June 30, 2003 (unless waived by FDA)

**Report:** Yearly, in NDA annual report

3. We agree to study pimecrolimus cream in immunocompromised patients, who have atopic dermatitis, both for efficacy and safety.

**Protocol for review:** April 30, 2002

**Study report:** 2 years after the Division reviews and agrees to the protocol (est. June 30,

2004)

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 note that you have fulfilled the pediatric study requirement at this time.

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.

**APPEARS THIS WAY  
ON ORIGINAL**

NDA 21-302

Page 4

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 Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

Jonca C. Bull, M.D.  
Acting Director  
Office of Drug Evaluation V, HFD 105  
Center for Drug Evaluation and Research

Enclosure

**APPEARS THIS WAY  
ON ORIGINAL**