DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

K1.1

K1.1

M Casey 1:15
Rec'd
2-13-00

N50777

N50777

DEC 18 2000

Rec'd
12/13/00
1:15PM

Fujisawa Healthcare, Inc.
Attention: Donald E. Baker, JD
Senior Director, Regulatory Affairs
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548

Dear Mr. Baker:

Please refer to your new drug application (NDA) dated September 8, 1999, received September 9, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Protopic (tacrolimus) Ointment, 0.03 and 0.1%.

We acknowledge receipt of your submissions dated October 21, November 9 and December 9, 1999; January 10 and 31, February 11, March 13, 17 and 29, April 7 and 21, May 18, June 2 and 28, August 21, October 2, November 7, 9, 10 (2), 28 and 30 December 2, 4, 7 (2) and 8, 2000.

This new drug application provides for the use of Protopic (tacrolimus) Ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, for short term and intermittent, long term therapy in the treatment of patients with moderate to severe atopic dermatitis 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 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 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 50-777." 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 facsimile dated December 7, 2000. These commitments, along with any completion dates agreed upon, are listed below:

1. A commitment to submit a retrospective analysis of the three pivotal phase 3 studies and the long-term open label study in adults (Study 97-0-035, Study 97-0-036, Study 97-0-037, and Study FG-06-12, respectively) to explore which possible demographic and disease factor(s) might be associated with a patient having persistently detectable whole blood levels of tacrolimus. Such factors may include, but not be limited to, baseline covariates (e.g., gender, age, race, disease severity), response to treatment, nature of use (intermittent versus chronic), or intercurrent events during the study. The analysis plan will be provided to the Division for review by February 28, 2001.

2. A commitment to conduct a registry study of pediatric patients with atopic dermatitis to address the risk of developing cutaneous or systemic malignancies in patients who have long term intermittent treatment with Protopic Ointment 0.03% or 0.01%. The proposal for this study will be provided to the Division for review by June 30, 2001.

3. A commitment to characterize the comparative bioavailability of Protopic Ointment 0.03% and 0.1% in the long term intermittent treatment of atopic dermatitis. The comparative bioavailability can be characterized by conducting a randomized study in adult patients with moderate to severe atopic dermatitis to measure the comparative pharmacokinetics of Protopic Ointment 0.03% and 0.1%. Blood samples should be collected when the subjects' degree of disease and extent of treatment is consistent with that expected during intermittent long term use. The protocol for this study will be provided to the Division for review by February 28, 2001.

4. A commitment to conduct a pharmacokinetic study with the 0.03% Protopic Ointment in the pediatric patient population between the ages of 2-5 years with moderate to severe atopic dermatitis. The study design could be similar to that of Study FG-06-23 with a minimum of 2 weeks duration, where pharmacokinetic parameters could be evaluated on Day 1 and Day 14, with at least 4 blood samples per sampling day. The blood samples could be collected and analyzed by any of the following techniques:

   a. Sparse sampling approach could be taken so that the entire range of plasma concentration time profile is covered with at least 3 samples per time point. If the sparse sampling approach is chosen, standardization of BSA involvement and disease severity would need to be adopted.
   b. Using data from the previous pediatric studies, a pharmacokinetic sampling program could be developed that would have the blood samples drawn at those time points that were identified to have the highest likelihood of positive blood levels of tacrolimus following dosing.

No matter which approach of collecting blood samples is selected information on the body surface area involvement, disease severity and the amount of ointment applied should be reported. The protocol for this study will be provided to the Division for review by February 28, 2001.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your post marketing commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report.

For administrative purposes, all submissions, including labeling supplements, relating to these post marketing commitments must be clearly designated "Post Marketing Commitments."

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). Your application contained pediatric studies supporting the safety and efficacy of Protopic Ointment, 0.03% for ages 2 to 15 years. However, you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27) in ages 3 to 23 months. You have agreed as a Phase 4 commitment to submit a protocol by February 28, 2001 for a pharmacokinetic study with the 0.03% Protopic Ointment in the pediatric patient population between the ages of 2-5 years with moderate to severe atopic dermatitis. We are deferring submission of additional study(ies) in pediatric patients aged 3 to 23 months until submission of this pharmacokinetic study report by June 1, 2002. However, in the interim, please submit your pediatric drug development plans within 120 days of the date of this letter. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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

Sincerely,

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

Enclosures

APPEARS THIS WAY
ON ORIGINAL