CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-753

NON-APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-753

Galderma Laboratories
Attn: Christine Shank
Sr. Director, Regulatory Submission
14501 N. Freeway
Fort Worth, Texas 76177

Dear Ms. Shank:

Please refer to your new drug application (NDA) dated March 31, 2004, received April 1, 2004, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (adapalene gel), 0.3%.

We acknowledge receipt of your submissions dated May 25; June 9, 11 and 25; July 13; August 16 and 18; and December 21, 2004.

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

1. The pivotal study failed to demonstrate statistical superiority of the 0.3% adapalene gel over Differin (adapalene) Gel, 0.1%. Therefore, there is insufficient information to support the increased risk of the higher concentration.

2. The higher concentration of adapalene gel, 0.3%, resulted in greater systemic exposure, and consequent teratogenic risk, than with the currently approved Differin Gel, 0.1%.

To address these deficiencies please provide:

1. Adequate evidence that the higher concentration of adapalene gel offers benefit over the currently available concentration of adapalene gel when used in the treatment of acne vulgaris (i.e., a comparative clinical study).

2. A risk management program (e.g., adequate labeling) to address the increased potential for teratogenicity given the systemic levels of adapalene seen in the submitted pharmacokinetic study.

Although not the basis for the Not Approvable action for this application, we remind you of the Agency's December 14, 2004 facsimile in which you were notified that the tradename, Differin XP, was not acceptable.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

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. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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), you may request an informal meeting or telephone conference with the Division of Dermatologic & Dental Drug Products to discuss what 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 this application is approved.

If you have any questions, contact Millie Wright, Project Manager, at (301) 827 2020

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
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24 page(s) of draft labeling has been removed from this portion of the review.