CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022259Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-259

COMPLETE RESPONSE

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

Dear Dr. Ramirez:

Please refer to your new drug application (NDA) dated August 17, 2007, received August 20, 2007, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tolak (Fluorouracil) Cream, 4% for the treatment of actinic keratosis of the face, scalp, and ears.

We acknowledge receipt of your amendments dated September 10, October 11, November 19, 2007; January 9, February 12 and 25, March 4, April 2, May 5, and 23, June 16, 23 and 24, July 21, and August 4, 2008.

We also acknowledge receipt of your amendments dated January 30, February 4, and March 31, 2009, which were not reviewed for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

You have not assured the identity, strength, purity, and quality of your product as required under CGMP compliance. In addition, acceptable drug product stability has not been established. Reference is made to the September 2008 establishment inspection which revealed major deficiencies in the drug product stability data.

The following information/data is needed to resolve your drug product quality issues:

1. The stability data submitted to date are not adequate to establish a specification for the drug product and an expiration dating period due to the following deficiencies:

    a. Particle size testing, viscosity, homogeneity, and butylated hydroxytoluene assay are not available for the entire stability studies.

b. The validity of data for pH can not be assured.

c. The validity of data for methylparaben and propylparaben assays can not be assured because we have concluded that the chromatograms of the method validation study for (b) (4) provided in the original submission and the February 12, 2008 and April 2, 2008 amendments are not from Tolak Cream. This conclusion is based on the following reasons:

Our facsimile dated, January 14, 2008, stated that the method validation data provided in your original NDA submission were not acceptable because (b) (4) was used in the study. The letter requested that you provide validation data for Tolak Cream.

You responded to our request with a submission of the method validation data, in the February 12 and April 2, 2008 amendments, which included specificity, accuracy/recovery, and precision/repeatability. The method validation protocol was provided only in the April 2, 2008 amendment. (b) (4)

During the September, 2008 establishment inspection:

i) You confirmed that the clinical lot, K050158, was used for evaluation of method precision/repeatability. However, the six chromatograms of the precision/repeatability study (HPLC Bin # 100-105) do not match the release data of Lot K050158 (HPLC Bin # 40-45), but rather they resemble (b) (4), Lot G080139 (HPLC Bin # 36-37 and 41-44).

For instance, a small but distinctive peak with the retention time of (b) (4) minutes is present in all six chromatograms of the release data for (b) (4) Lot G080139. This peak is also present in all of the Tolak Cream chromatograms for the precision/repeatability study, but it is missing in the release data of Tolak Cream, Lot K050158.

ii) You stated that the "placebo cream" contained 5-fluorouracil and was prepared using the same formulation as that of Tolak Cream except for the absence of methylparaben and propylparaben. You also stated that the chromatograms labeled with "Blank 1" (HPLC Bin # 99) and "Blank 2" (HPLC Bin # 100) were those of "vehicle cream without parabens".

However, the chromatograms of "vehicle cream without parabens" looked more like (b) (4) than that of Tolak Cream without parabens. For example, a major peak ((b) (4) minutes) prior to the methylparaben is present in the release data of Tolak Cream, Lot K050158, but it is missing in "Blank 1" or "Blank 2". Since the "vehicle cream without parabens" contains all ingredients in Tolak Cream but the parabens, the chromatograms are expected to resemble that of Tolak Cream except for the absence of the two paraben peaks (retention times at (b) (4) minutes).

iii) You confirmed that four lots of fluorouracil cream varying the amounts of parabens at (b) (4)%, respectively, of the target concentrations in the Tolak formulation, were produced. The differences to make the formula to 100% was added or subtracted (b) (4) in the formula. These four creams were used for evaluation of method accuracy/recovery.

Because the (b) (4) minutes peak is present, the chromatograms of the four creams for the accuracy/recovery study (HPLC Bin # 117-118, 21-22, 58-59, and 63-64) also resemble those of (b) (4), Lot G080139. Furthermore, the HPLC chromatograms of the four creams suggest that they are (b) (4) diluted at four different target concentrations. This is because the area counts of all other peaks (e.g. (b) (4) minutes) increase along with the increase of paraben concentrations. If the four creams had been prepared in the manner you have claimed, the HPLC chromatograms would have shown an increase of only methylparaben and propylparaben area counts at higher paraben concentrations and the area counts of all other peaks would have remained the same.

Therefore, unless you provide a satisfactory explanation for why you apparently repeatedly provided (b) (4) data for the accuracy/recovery and precision/repeatability studies and used (b) (4) data as "placebo cream", the validity of the data for methylparaben and propylparaben assays can not be assured.

You will also need to address the following items in order to provide assurance of the validity of your submitted data for methylparaben and propylparaben assays:

- Provide details to explain why the validation report dated February 8, 2008, (submitted in the February 12, 2008 amendment), differed from the same validation report dated February 8, 2008 (submitted in the April 2, 2008 amendment). The differences include, but are not limited to, table of contents, authorized signatories' signatures, and the contents for the specificity study.
- Provide details to explain why a validation report was provided by you without all authorized signatories' signatures in the February 12, 2008 amendment. The report was signed off only by Sarah Reinartz, Quality Assurance Manager, on February 8, 2008. In addition, the "Report Approval" on page 1 was listed as "Protocol Approval" in the Table of Contents. Pages 5 and 6 of this validation report were missing.
- Provide details to explain why the method specificity study submitted in both amendments was conducted two years prior to the approval of the validation protocol. The validation protocol was signed off on January 17, 2008 by Nancy Puglia, Plant Manager, Sarah Reinartz, Quality Assurance Manager, Kacy McGee, Quality Assurance, and Ingrid Warner, Regulatory CMC. The method specificity study, which included (b) (4) chromatograms of methylparaben and propylparaben standards (HPLC Bin # 92-96) and (b) (4) chromatograms of "placebo cream", was conducted on October 25, 2005.

- Provide details to explain why the deviations from the approved validation protocol were not documented in the validation reports submitted in the February 12, 2008 and April 2, 2008 amendments. The deviations included the date of the specificity study, described above, and missing chromatograms of Tolak Cream for the specificity study as required on page 4 (Actual drug product) of the validation protocol. The validation report submitted in the April 2, 2008 amendment was signed on February 8, 2008, by the same personnel on the validation protocol dated January 17, 2008.
- Provide details to explain why the laboratory preparations of "vehicle cream without parabens" and the four creams used in the method accuracy/recovery study were not documented.

Provided that the above issues are satisfactorily resolved, then stability data from three new primary batches of Tolak Cream should be submitted for review. The data should cover minimum time periods of 12 months for the long-term and 6 months for the accelerated conditions at the time of resubmission. The stability study should follow the drug product stability protocol provided in the March 4, 2008 amendment.

2. The hold time for the bulk drug product (b) (4) should be determined and justified. In-process samples taken at the beginning and end of the hold time should be tested per Tolak Cream In-process Product Specification Form (provided in the February 12, 2008 amendment) to justify the hold time.

3. Regarding the peanut oil, NF specification:

   a. Revise the limit for protein analysis in the peanut oil specification to "for information only". The analytical method, i.e. DSFS D-12 for Protein Analysis Sample Preparation and Amino Acid Analysis Protocol, has not been validated properly.

   b. Change the "Approved Manufacturer" from "(b) (4)" to "(b) (4)".

   c. Several testing facilities are listed as approved testing facilities on your raw material specification forms. For example, Hill Laboratories, Inc., (b) (4) are listed as the approved testing facilities in the peanut oil, NF raw material specification form. Please specify which facilities are currently involved in the testing of the peanut oil and in what capacity.

FACILITY INSPECTIONS

During the September 2008 inspection of the Sanford, Florida manufacturing facility for this application, our field investigator conveyed the deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Based on FDA's findings from its September 2008 inspection of your facility, FDA issued a Warning Letter to you dated April 27, 2009, for significant deviations from CGMP requirements.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

SAFETY UPDATE

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 nonclinical and clinical studies/trials 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 updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

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

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

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

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, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
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/

Susan Walker
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