

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-738

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-738

Connetics Corporation
Attention: Sharon L. Hall
Senior Director, Regulatory Affairs
3290 West Bayshore Road
Palo Alto, CA 94303

Dear Ms. Hall:

Please refer to your new drug application (NDA) dated January 23, 2004, received January 26, 2004, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ketoconazole Foam, 2%.

We acknowledge receipt of your submission dated February 2, 10 (two), 17 and 26, March 23, April 19 (two), 23 and 26, May 28, June 3, 7, and 15, July 9, 15, 19, 22 and 23, August 4 (two), 6 and 27, September 14 and 17, and October 14, 2004.

We completed our review of this application and have concluded that inadequate information has been presented to demonstrate that the drug product is safe and effective for the treatment of seborrheic dermatitis. 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:

The data from study KFD.C.002 do not support the conclusion that ketoconazole foam, 2%, is effective for the treatment of seborrheic dermatitis. Study KFD.C.002 was designed to evaluate whether ketoconazole foam was superior to its vehicle and non-inferior to the active comparator. However, the superiority was not demonstrated for the primary efficacy parameter that was defined prospectively. Because this deficiency cannot be addressed with additional analyses of study KFD.C.002, results from one additional adequate and well-controlled study will need to be submitted demonstrating superiority of ketoconazole foam, 2%, over its vehicle and non-inferiority to the active comparator.

Although not the basis for the Not Approvable action for this application, the following issues should be addressed in the resubmission:

Clinical:

Present plans for a long-term open label safety study as per ICH E1A guidance on the extent of population exposure required to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions.

Chemistry:

b(4)

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 this division 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.

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If you have any questions, contact Felecia Curtis, Regulatory 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

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**This is a representation of an electronic record that was signed electronically and
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/s/

Stanka Kukich
11/23/04 10:52:07 AM
sign off for Dr. Jonathan Wilkin, Division Director

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