

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**050803Orig1s000**

**OTHER ACTION LETTER(s)**



NDA 50-803

Connetics Corporation  
Attn: Darlene O'Banion, Senior Manager, Regulatory Affairs  
3160 Porter Drive  
Palo Alto, California 94304

Dear Ms. O'Banion:

Please refer to your new drug application (NDA) dated August 23, 2004, received August 25, 2004, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME, (clindamycin, 1% - tretinoin, 0.025%) Gel for the treatment of acne vulgaris.

We acknowledge receipt of your submissions dated September 30, October 5, 8, 15, and 28, November 17, 19 and 22, and December 6, 2004; January 7 and 28, February 11, 17, and 22, March 2 (2), 4, 8, 14, 22, and 25, April 5, 8, 14, and 22, May 4, 12, 16 and 17, 2005.

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:

A positive carcinogenicity signal was detected in a Tg.AC mouse dermal carcinogenicity study in the vehicle arm as well as in the arms containing clindamycin phosphate. This suggests that the vehicle or a component of the vehicle of the drug product may be a tumor promoter or may be carcinogenic. This is an unacceptable safety finding for a topical drug product intended for the chronic treatment of a non-life threatening or non-severely debilitating disease for which many alternative therapies exist. Therefore, it was determined that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.

**Information needed to resolve non-approvability issues:**

Reformulate your product so that your choice of vehicle will be safe. Please request a meeting with the Division to discuss the future development of your product and how reformulation will impact the regulatory utility of existing clinical and non-clinical studies.

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.

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 Margo Owens, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

*{See appended electronic signature page}*

Jonathan K. Wilkin, M.D.  
Director  
Division of Dermatology &  
Dental Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Stanka Kukich  
6/10/05 03:21:08 PM  
sign off for Dr. Jonathan Wilkin, Division Director