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RESEARCH**

APPLICATION NUMBER:

21-406

APPROVABLE LETTER



NDA 21-406

Unigene Laboratories, Inc.
Attention: Heike Maaser, Ph.D.
Director, Regulatory Affairs
83 Fulton Street
Boonton, NJ 07005

Dear Dr. Maaser:

Please refer to your new drug application (NDA) dated and received March 5, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fortical (calcitonin-salmon) Nasal Spray.

We acknowledge receipt of your submissions dated March 12, April 3 and 15, May 12 and 15, July 31, August 12, September 18, October 3, November 2, and December 2, 8, 12, 16(2), and 17, 2003.

We also acknowledge receipt of your submission dated December 16, 2003 which provides a response to microbiology deficiencies. That submission was not reviewed for this action. You may incorporate that submission by specific reference as part of your response to the deficiencies cited in this letter. In addition, in a teleconference dated November 20, 2003, you committed to provide the Division with the address and contact information for the laboratory _____ which is currently doing your bioassay. This was provided in an E-mail dated November 20, 2003. The inspection of this laboratory will be done in the next review cycle.

This new drug application provides for the use of Fortical (calcitonin-salmon) Nasal Spray for the treatment of osteoporosis in women greater than 5 years post menopause with low bone mass relative to healthy premenopausal females. We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Submit data that adequately characterize the human immunogenicity profile of Fortical. We strongly suggest that you seek the Division's agreement with your proposal to characterize Fortical's immunogenetic profile.
2. DMF _____ for the drug substance is deficient. A response to all the deficiencies in the DMF is required for a complete response to this approvable letter.
3. The proposed two separate acceptance criteria for the net content for Fortical Nasal Spray, _____ for average, and _____ for any single container, are not acceptable. Please revise the acceptance criterion for the net content to include a range of values to

better represent the manufacturing data.

4. Provide written commitment regarding reporting any failure in the stability testing to the Division in accordance with 21 CFR 314.81(b)(1)(ii) and FDA guidance on "*Investigating Out of Specification (OOS) Test Results for pharmaceutical Production.*"
5. During recent inspections of _____, _____ manufacturing facilities for this application, our field investigators conveyed deficiencies to the facility representatives. Satisfactory resolution to these deficiencies is required before this application may be approved. In addition, _____ facilities should be withdrawn from the NDA.

Further, The comparability protocol _____ dated September 18, and October 3, 2003, is acceptable. A reduction in the reporting category from CBE-30 to CBE is acceptable, but not acceptable from CBE-30 to annual report.

Also, revision of the draft labeling will be required.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical 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 314.110. In the absence of any such action, FDA may proceed to withdraw the application. 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 the application is approved.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

Eric Colman
12/31/03 02:51:40 PM
Eric Colman for David Orloff