CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022408Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022408 **COMPLETE RESPONSE**

ParaPRO Pharmaceuticals, LLC
Attention: O. Reed Tarwater, Ph.D., RAC
Senior Regulatory Consultant
11460 N. Meridian Street, Suite 150
Carmel, IN 46032

Dear Dr. Tarwater:

Please refer to your new drug application (NDA) dated January 21, 2009 received January 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (spinosad) Suspension, 0.9%.

We acknowledge receipt of your amendments dated February 26, March 10, March 31, May 1, June 29, July 9, July 16, August 24, and September 8, 2009.

We also acknowledge receipt of your amendment dated September 24, 2009, which was not reviewed for this action. You may incorporate applicable sections of the amendment 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.

1. FDA agrees that spinosad, containing spinosyns A and D in a ratio of approximately 5:1, is a single active ingredient. However, we have recently approved a product containing benzyl alcohol (present at 5%) as an active ingredient for the treatment of head lice. This would indicate that your product contains two active ingredients: spinosad and benzyl alcohol (b) (4)

    A. Provide information to support approval of your product according to the regulations for fixed-combination prescription drugs at 21 CFR 300.50.

    B. Provide pharmacokinetic data for benzyl alcohol in lice-infested subjects.

    C. Submit complete CMC information on the drug substance, benzyl alcohol.

    D. Submit complete nonclinical information to support the safety of benzyl alcohol per the ICH M3 (R2) guidance titled “Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals”.

2. Although your maximal usage pharmacokinetic trials detected no systemic exposure of spinosad from the use of TRADENAME (spinosad) Suspension, 0.9%, only 8 healthy subjects under the age of 4 years were evaluated. The youngest subjects with head lice are at greatest risk for systemic exposure due to their greater surface-to-volume ratio and the effects of the infestation itself on the scalp.

(b) (4)

3. Sufficient information has not been submitted to assure the identity, strength, purity and quality of the spinosad drug substance and the drug product.

Drug Substance:

A. In addition to a cross reference to DMF 17795, submit a regulatory specification for acceptance of spinosad to the NDA.

Drug Product:

B. Include ID tests in the excipient specifications for ceteareth-20 and stearalkonium chloride.

C. Submit an updated drug product specification which reflects the revised definition for "active ingredient." The specification should also reflect the revised definitions for "Related Substances," "Impurities," and the Acceptance limit, based on clarifications you provided in the teleconference held on August 28, 2009.

D. Based on the retention time table for the HPLC method used, placebo (b) (4) and spinosyn D (b) (4) very closely. Provide data to demonstrate that the assay value for spinosyn D is not compromised by the placebo peak.

E. Provide more detailed information regarding (b) (4) the drug product when stored under accelerated stability conditions.

F. (b) (4) was observed in the drug product samples provided in May 2009. Provide the following information to address the effects (b) (4) on drug product quality:

1) Data indicating when (b) (4) during storage and whether the storage conditions have any effect (b) (4);

2) Data to demonstrate that content uniformity for the (b) (4) drug product is re-established after shaking; and

3) A description of the physical form of the drug product (e.g., lotion-like, solution-like, etc.) in the Appearance specification for the drug product. This description is needed, in addition to color as proposed, in the Acceptance criteria for the Appearance test.

4. 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

(b) (4)

If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

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/clinical trials 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 trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial 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's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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 Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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

/s/

JULIE G BEITZ
11/18/2009