CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-818 and 21-498/S-003

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-818

Romark Laboratories, L.C.
Attention: Marc Ayers, President
6200 Courtney Campbell Causeway
Suite 880
Tampa, Florida 33607

Dear Mr. Ayers:

Please refer to your new drug application (NDA) dated May 29, 2002, received May 29, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alinia® (nitazoxanide) tablets, 500 mg.

We acknowledge receipt of your submissions dated:

April 2, 2004	June 18, 2004
April 26, 2004	June 25, 2004
June 1, 2004	July 7, 2004

The January 28, 2004 submission constituted a complete response to our November 22, 2002 action letter.

We completed our review of this application, as amended, and it is approvable. The single placebo-controlled study that evaluated the proposed regimen of nitazoxanide tablets, 500 mg PO BID, did not provide sufficient evidence of efficacy in adult patients to support the approval of nitazoxanide tablets for the treatment of *Cryptosporidium parvum* diarrhea in immunocompetent adults. We are not able to determine the contribution of dosage form (systemic vs. luminal exposure) and patient-related factors (host response in children vs. adults) to this finding since you have shown efficacy of nitazoxanide for oral suspension, 100 mg/5 ml, for the treatment of *Cryptosporidium parvum* diarrhea in immunocompetent pediatric patients.

In order to address this deficiency, you must submit a second adequate and well-controlled clinical trial using the proposed regimen that confirms the clinical efficacy suggested in Study RM-NTZ-98-002. Specifically, the following issues need to be addressed:

a. Enrollment of adequate numbers of adult patients with "sole pathogen" as the cause of diarrhea
b. Characterization of the contribution of dosage form effect (the tablet and suspension dosage forms should be compared to each other and to placebo) on clinical efficacy

c. Characterization of the contribution of food-effect (fed-state versus fasting-state) on the clinical efficacy
d. Performing parasitological evaluations using multiple stool samples at different time points such as: at baseline, end of therapy and 3-4 weeks post therapy. Concentration techniques for stool samples in combination with more sensitive immunofluorescence and enzyme immunoassays should be used for detection and quantification of the parasite
e. Clinical evaluation should be performed at each study visit along with parasitological evaluation (see above)
f. Analysis of data to show correlation of intra-patient parasitologic outcome with clinical outcome

In addition, it will be necessary for you to submit draft labeling revised to reflect additional safety or efficacy data submitted.

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 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.

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.

In addition, after you have addressed the deficiencies, please submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. 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 the application is approved.

If you have any questions, please call Kristen Miller, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic
Drug Products
Office of Drug Evaluation IV
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/

Renata Albrecht
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