CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-497

21-498/S-001

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-497
NDA 21-498/S-001

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), NDA 21-497, dated May 29, 2002, received May 29, 2002, for Alinia® (nitazoxanide) tablets, 500 mg , and to your supplemental new drug application NDA 21-498/S-001, dated July 16, 2004, received July 19, 2004 for Alinia® (nitazoxanide) for Oral Suspension, 100 mg/5 mL, both submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

We acknowledge receipt of your submissions dated:

April 2, 2004	June 18, 2004	July 16, 2004 (2)
April 26, 2004	June 25, 2004	
June 1, 2004	July 7, 2004	

The January 28, 2004 submission to NDA 21-497 constituted a complete response to our November 22, 2002 action letter.

NDA 21-497 provides for the use of Alinia® (nitazoxanide) tablets, 500 mg for the treatment of diarrhea caused by *Giardia lamblia* in patients 12 years of age and older, and supplemental NDA 21-498/S-001 provides for the use of Alinia® (nitazoxanide) for Oral Suspension, 100 mg/5 mL, for the same indication.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted labeling (immediate container and carton labels submitted July 16, 2004). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling is to be submitted

in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated **"FPL for approved NDA 21-497 and for approved supplements NDA 21-498/S-001."** Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

Based on information submitted, we conclude the following:

For the treatment of diarrhea caused by *Giardia lamblia*,

- We are deferring submission of pediatric studies for patients zero months to twelve months of age until July 22, 2009.
- You have fulfilled the pediatric study requirement at this time for patients one through sixteen years of age.

Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of diarrhea caused by *Giardia lamblia* in pediatric patients zero months to twelve months of age.

   Final Report Submission: July 21, 2009

Submit final study report to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitment**".

In addition, 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

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Enclosure

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
7/21/04 11:22:38 AM

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APPLICATION NUMBER:

21-497

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APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-497

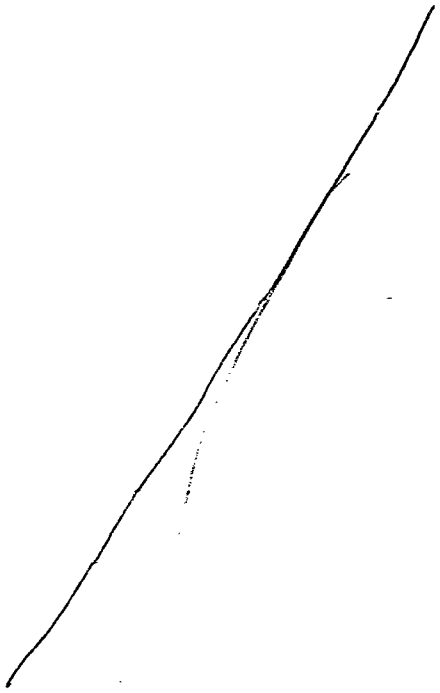
Romark Laboratories, L.C.
Attention: Marc Ayers, President
6200 Courtney Campbell Causeway
Suite 880
Tampa, Florida 33607

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 July 22, July 24, August 30, September 10, September 23, September 27, October 23, and November 22, 2002.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

1.



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2. 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 *Giardia lamblia* 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 *Giardia lamblia* 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-98-001. Specifically, the following issues need to be addressed. We strongly encourage you to discuss the protocol with DSPIDP prior to implementation.

   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. Analysis of data to show correlation of intra-patient parasitologic outcome with clinical outcome

3. Develop a dissolution method for nitazoxanide tablets, 500 mg, by varying the rotation speeds at the following conditions:

   Apparatus: Paddle (USP Apparatus 2)
   Dissolution medium: /
   Bath temperature: /

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 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 death 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.

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 the Division of Special Pathogen and Immunologic Drug Products (DSPIDP) 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 DSPIDP 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, call Kristen Miller, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., M.P.H.
Director
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/

Mark Goldberger
11/22/02 11:20:08 AM