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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-498

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-498

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) for Oral Suspension, 100 mg/5 ml.

We acknowledge receipt of your submissions dated September 27, October 23, November 5, and November 12, 2002.

This new drug application provides for the use of nitazoxanide for oral suspension for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia.*

We have completed our review of this application, as amended, and have concluded that the drug is safe and effective for use as recommended in the agreed-upon labeling text (text for the package insert). Therefore, it is approved, effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert submitted November 22, 2002) and the submitted labeling (immediate container label submitted November 22, 2002). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission **"FPL for approved NDA 21-498."** Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated November 12, 2002. These commitments are listed below.

1. In vivo study of the effect of food on pharmacokinetics following oral administration of nitazoxanide for Oral Suspension

Protocol Submission:	Within 4 months of the date of this letter
Study Start:	Within 8 months of the date of this letter
Final Report Submission:	Within 12 months of the date of this letter

2. In vitro study of the effect of nitazoxanide metabolites (tizoxanide and tizoxanide glucuronide) on cytochrome P450 enzymes

Protocol Submission:	Within 4 months of the date of this letter
Study Start:	Within 8 months of the date of this letter
Final Report Submission:	Within 12 months of the date of this letter

3. Study of the in vitro transfer of tizoxanide across the epithelial barrier

Protocol Submission:	Within 4 months of the date of this letter
Study Start:	Within 8 months of the date of this letter
Final Report Submission:	Within 12 months of the date of this letter

4. Three-year study of the use of nitazoxanide for oral suspension (prescribers, diagnoses, dose and duration of treatment) in clinical practice in the United States

Protocol Submission:	Within 1 month of the date of this letter
Study Start:	Upon initiation of marketing
Final Report Submission:	Within 42 months following initiation of marketing with interim reports included in annual reports

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

The text in italics below addresses the application of FDA's Pediatric Rule at 21 CFR 314.55 to this NDA. The Pediatric Rule has been challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. The government has not yet decided whether to seek a stay of the court's order. In addition, the government has not yet decided whether to appeal the decision; an appeal must be filed within 60 days. **Therefore, this letter contains a description of the pediatric studies that would be required under the Pediatric Rule, if the Pediatric Rule remained in effect and/or were upheld on appeal.** Please be aware that whether or not these pediatric studies will be required will depend upon the resolution of

the litigation. FDA will notify you as soon as possible as to whether this application will be subject to the requirements of the Pediatric Rule as described below. In any event, we hope you will decide to conduct these pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Based on information submitted, we conclude the following:

For the treatment of diarrhea caused by Cryptosporidium parvum and Giardia lamblia,

- *We are deferring submission of pediatric studies for patients less than one year of age until November 22, 2007.*
- *We are deferring submission of pediatric studies for patients twelve through sixteen years of age until November 22, 2007.*
- *You have fulfilled the pediatric study requirement at this time for patients one through eleven years of age.*

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, 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 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

Please submit one market package of the drug product when it is available.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville MD 20857

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, call Kristen Miller, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

/S/

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

Mark Goldberger
11/22/02 11:21:41 AM