CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-497

21-498/S-001

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 21-497
Submission Number	N-000
Submission Code	B2
Letter Date	January 28, 2004
Stamp Date	January 30, 2004
Reviewer Name	Joette M. Meyer, Pharm.D.
Review Completion Date	July 2, 2004
Established Name	Nitazoxanide
(Proposed) Trade Name	Alinia®
Therapeutic Class	Nitrothiazolyl salicylamide
Applicant	Romark Laboratories, L.C.
Priority Designation	Resubmission (6 month review)
Formulation	Oral Tablet
Dosing Regimen	500 mg BID x 3 days
Proposed Indication	
Indication Granted	Treatment of diarrhea caused by *Giardia lamblia* in adults and adolescent patients 12 years of age and older.
Intended Population	

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Approvability

Nitazoxanide (Alinia®) oral suspension was approved by the FDA on November 22, 2002 (NDA 21-498) for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in children aged 1 to 11 years. The tablet formulation of nitazoxanide (NDA 21-497) was given an "Approvable" action on the same date for the treatment of diarrhea caused by *Giardia lamblia* in immunocompetent adults and adolescents 12 years of age and older.

Giardia lamblia

In the Approvable letter for NDA 21-497, an additional study was requested by the Division to support the safety and efficacy of nitazoxanide for the treatment of diarrhea caused by *Giardia lamblia* in non-immunodeficient patients 12 years of age and older. In this resubmission, the applicant has included data from a new clinical trial, Study RM01-3011, to address the safety and efficacy of nitazoxanide tablets and oral suspension for this indication.

The applicant also cites clinical data from Study RM-NTZ-98-001 contained in the original NDA 21-497 submission (dated May 29, 2002) as being supportive of Study RM01-3011. However, there are limited efficacy data on adults and adolescents with *Giardia lamblia* as the sole pathogen treated with nitazoxanide tablets (N=8) versus placebo tablets (N=10) in this study.

Study RM01-3011 was designed to confirm the efficacy of twice daily nitazoxanide administered as a 500 mg tablet versus nitazoxanide 500 mg in suspension form versus placebo tablets in treating giardiasis in non-immunodeficient adults and adolescents. The total number of patients enrolled was 135 (54 randomized to nitazoxanide tablets, 54 randomized to nitazoxanide suspension, and 27 randomized to placebo) enrolled in Peru and Egypt.

The efficacy of nitazoxanide was determined by comparing the clinical and parasitological responses obtained following treatment with nitazoxanide (tablets or suspension) to a placebo response. The clinical response was evaluated on the basis of three definitions: wellness, continuing illness, and clinical treatment failure. The parasitological response was determined on the basis of parasitological examinations conducted on two stool samples collected between 7 and 10 days following the initiation of treatment (i.e., 4 to 7 days following three days of treatment).

Clinical response (i.e., wellness) in the nitazoxanide tablet group (85% [46/54]) was significantly higher than in the placebo treatment group (44% [12/27]) and non-inferior to nitazoxanide suspension [95% confidence interval of the treatment difference (-13.5%, 17.1%)].

Parasitological response, defined as no cysts or trophozoites in either of two stool samples collected between study Days 7 and 10, in the nitazoxanide tablet group (55.5% [30/54]) was significantly higher than in the placebo treatment group (18.5% [5/27]) and non-inferior to nitazoxanide suspension [95% confidence interval of the treatment difference (-12.4%, 26.4%)].

Parasitological response was assessed again at the follow-up visit on Day 14-17 (i.e., 11 to 14 days following the end of treatment), but clinical response was not. An assessment of cyst counts in individual patients between all three time points (i.e., baseline, Day 7-10, and Day 14-17) in the concentrated stool samples showed that parasitological response was not sustained at follow-up and cyst counts tended to rebound to baseline levels, mainly at the Peru study site. Since clinical response was not evaluated along with parasitological response, it is unclear if the patients with increasing cyst counts had a relapse in symptoms.

The nitazoxanide tablet development program contains safety information from 1628 HIV-uninfected adults and adolescent patients 12 years of age and older who received nitazoxanide tablets in controlled and uncontrolled studies, including Studies RM01-3011 and RM-NTZ-98-001. Detailed information was available from 54 HIV-uninfected patients, ages 12 years and older, who received nitazoxanide suspension as a comparator in Study RM01-3011. Adverse events for both the tablet and suspension were mild and most commonly involved the gastrointestinal tract (e.g., abdominal pain, diarrhea, and nausea).

Insufficient data are contained within this submission to provide evidence of the safety and efficacy of nitazoxanide (Alinia®) tablets for the treatment of diarrhea caused by

In summary, nitazoxanide (Alinia®) tablets and oral suspension are safe and effective for the treatment of diarrhea caused by *Giardia lamblia* in adults and adolescent patients 12 years of age and older.

Insufficient data are contained within this submission to provide evidence of the safety and efficacy of nitazoxanide (Alinia®) tablets for the treatment of diarrhea caused by

1.2 Recommendation on Post-marketing Actions

There are no recommendations for risk management activity or required Phase 4 studies at this time.

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

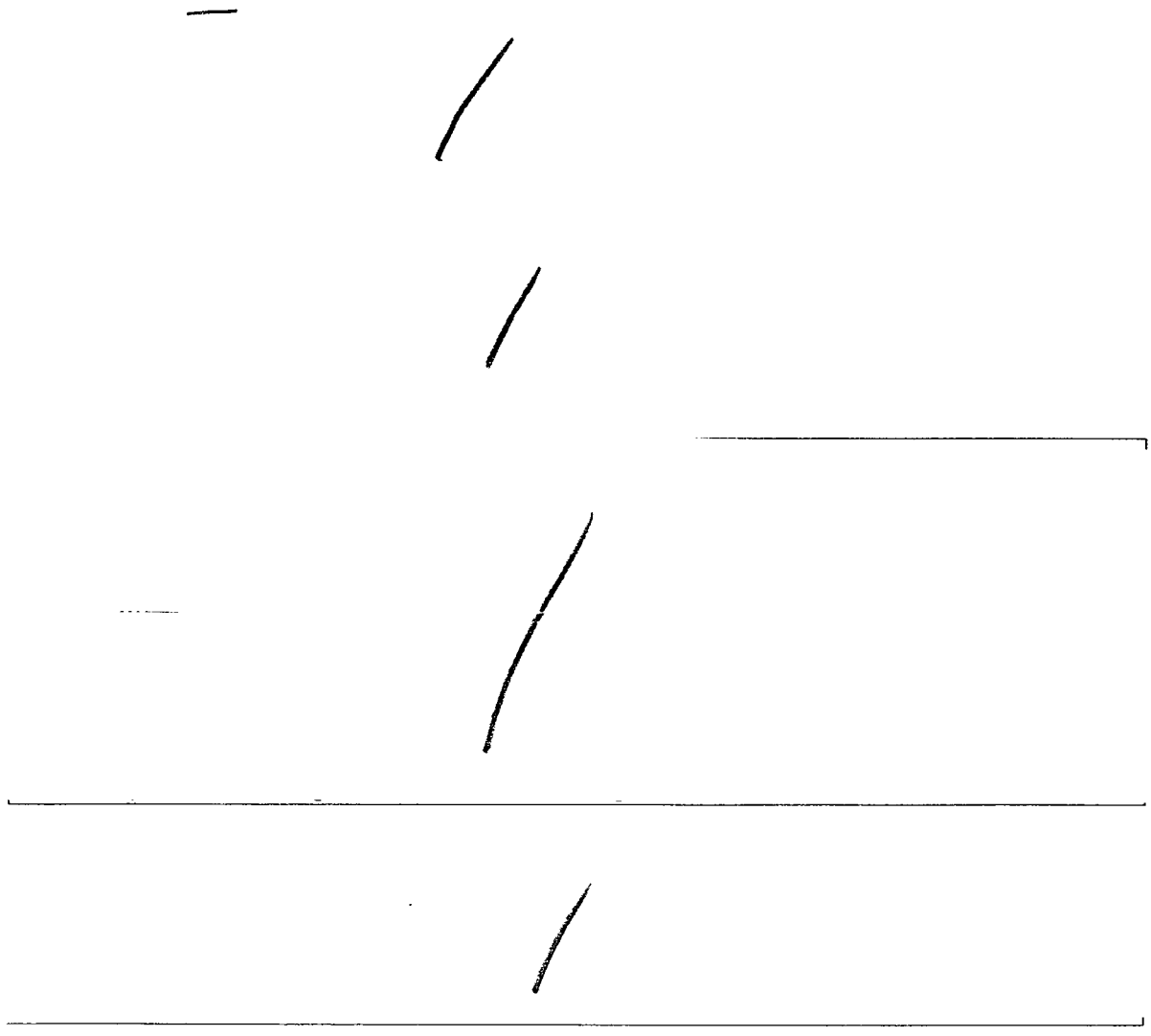
1.3.1 Brief Overview of Clinical Program

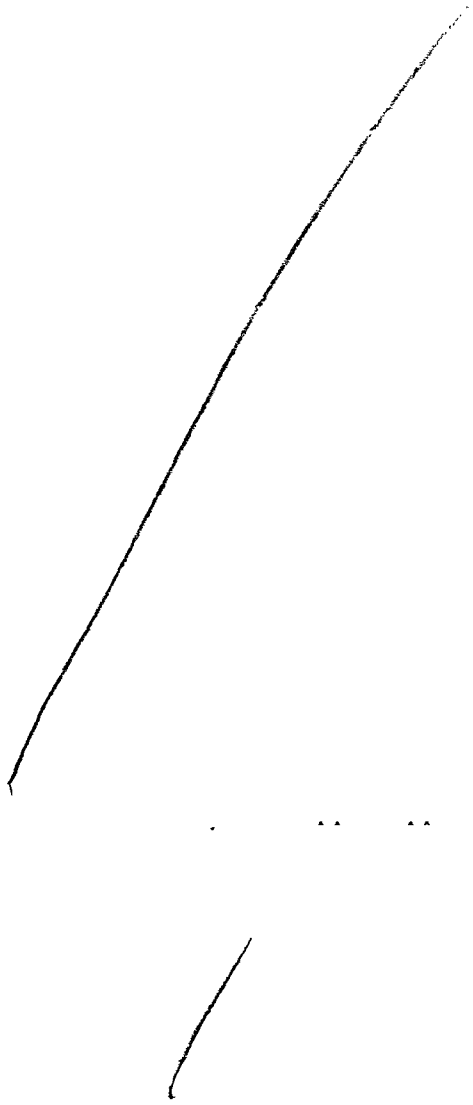
Established Name	Nitazoxanide
(Proposed) Trade Name	Alinia®
Therapeutic Class	Nitrothiazolyl salicylamide
Applicant	Romark Laboratories, L.C.
Priority Designation	Resubmission (6 months)
Formulation	Oral Tablet
Dosing Regimen	500 mg BID x 3 days
Proposed Indication	
Indication Granted	Treatment of diarrhea caused by *Giardia lamblia* in adults and adolescent patients 12 years of age and older. Safety and effectiveness of Alinia® tablets have not been established in patients with immunodeficiency.
Intended Population	

Giardia lamblia:
The applicant has submitted additional information, as requested in the NDA 21-497 Approvable letter, to address the safety and efficacy of nitazoxanide tablets in the

treatment of diarrhea caused by *Giardia lamblia* in non-immunodeficient adults and adolescents. Included in this submission is a clinical trial (Study RM01-3011) designed to confirm the efficacy of twice daily nitazoxanide administered as a 500 mg tablet versus nitazoxanide 500 mg in suspension form versus placebo tablets in treating giardiasis in non-immunodeficient adults and adolescents. The total number of patients enrolled is 135 (54 randomized to nitazoxanide tablets, 54 randomized to nitazoxanide suspension, and 27 randomized to placebo). The study was conducted in Cajamarca, Peru and Benha, Egypt because of the availability of a patient population with diarrhea caused by *Giardia lamblia*. The applicant concluded that this type of study could not be conducted in the United States or Western Europe within an acceptable amount of time.

In the original NDA 21-497 submission there were limited efficacy data (Study RM-NTZ-98-001) on adults and adolescents with *Giardia lamblia* as the sole pathogen treated with nitazoxanide tablets (N=8) when compared infected adults and adolescents treated with placebo tablets (N=10).





1.3.2 Efficacy

Study RM01-3011, a placebo-controlled trial, was designed to evaluate the efficacy and safety of nitazoxanide tablets and oral suspension in the treatment of diarrhea caused by *Giardia lamblia* in non-immunodeficient adults and adolescents aged 12 years of age and older. The study enrolled patients in Peru and Egypt. The primary objective of the study was to demonstrate superiority of clinical and parasitological response rates for nitazoxanide tablets over placebo in patients with diarrhea caused by *Giardia lamblia*. A secondary objective of the study was to demonstrate non-inferiority of nitazoxanide tablets compared to nitazoxanide suspension in the treatment of diarrhea caused by *Giardia lamblia* (i.e., non-inferiority margin of 20%).

A total of 135 patients were enrolled (54 randomized to nitazoxanide tablets, 54 to nitazoxanide suspension, and 27 to placebo). No patients were excluded from the modified intent-to-treat population, and therefore, all patients randomized to the study were included in the statistical analyses.

Clinical response (i.e., wellness) was recorded at the Day 7-10 test of cure visit (i.e., 4 to 7 days following the end of treatment) and was shown to be: 85% (46/54) for the nitazoxanide tablet group, 83% (45/54) of the nitazoxanide suspension group, and 44% (12/27) for the placebo group. The proportion of "well" responses in the active treatment group was significantly higher than in the placebo treatment group ($p = 0.0002$ for tablet versus placebo), the primary statistical comparison for clinical response in the study. The lower bound of the 95% confidence interval of the treatment difference between nitazoxanide tablets and nitazoxanide suspension was above the pre-specified non-inferiority margin of 15% (i.e., -13.5%, 17.1%), indicating that the clinical response rate to the nitazoxanide tablets was non-inferior to the nitazoxanide suspension.

Parasitological response, defined as no cysts or trophozoites observed in either of two stool samples collected between study Days 7 and 10, was 55.5% (30/54) in the nitazoxanide tablet group, 48% (26/54) in the nitazoxanide suspension group, and 18.5% (5/27) in the placebo group. The parasitological response rate in the active treatment group was significantly higher than in the placebo treatment group ($p = 0.0019$ for nitazoxanide tablets versus placebo), the primary statistical comparison for parasitological response in the study. The lower bound of the 95% confidence interval of the treatment difference between nitazoxanide tablets and nitazoxanide suspension was above the pre-specified non-inferiority margin of 15% (i.e., -12.4%, 26.4%), indicating that the parasitological response rate to the nitazoxanide tablets was non-inferior to the nitazoxanide suspension.

The intrapatient correlation of clinical and parasitological response rates at Day 7-10 was calculated using the kappa statistic. The results showed a weak, but positive correlation between the groups (kappa of 0.196 for the nitazoxanide tablet group, 0.313 for the nitazoxanide suspension group, and 0.283 for the placebo group).

Parasitological response was also evaluated at a follow-up visit at Day 14-17 (i.e., 11 to 14 days following the end of therapy). Clinical response was not assessed at this visit. Of the patients who were clinical responders at Day 7-10, the following number of patients were had no cysts detected in the concentrated stool sample at Day 14-17: 49% (22/45) in the nitazoxanide tablet group, 56% (24/43) in the nitazoxanide suspension group, and 25% (3/12) in the placebo group.

Although there was a mean drop in the number of cysts seen in concentrated stool specimens obtained at baseline and the visit at Day 7-10, an assessment of the number of cysts in individual patients between all three time points (i.e., baseline, Day 7-10, and Day 14-17) in the concentrated stool samples showed that the drop in counts at Day 7-10, was not sustained and tended to increase to baseline levels at Day 14-17. Therefore, a

finding of unsustained parasitological response was observed mainly at the Peru study site.

Patients enrolled in Peru had a higher baseline cyst count (mean ± SD) combined across all treatment groups (7.8 ± 11.4) than did the patients in Egypt (1.6 ± 2.2).

The proportion of "well" clinical responses recorded at the Day 7-10 test of cure visit were numerically lower in Peru than in Egypt for both the nitazoxanide treatment groups and higher for the placebo group: 81% (29/36) vs. 94% (17/18) for the nitazoxanide tablet group, 81% (29/36) vs. 89% (16/18) for the nitazoxanide suspension group, and 50% (8/18) vs. 33% (3/9) for the placebo group.

The proportion of patients eradicated at Day 7-10 was lower in Peru than in Egypt for all three treatment groups: 36% (13/36) vs. 94% (17/18) in the nitazoxanide tablet group, 31% (11/36) vs. 83% (15/18) in the nitazoxanide suspension group, and 17% (3/18) vs. 22% (2/9) in the placebo group.

The Peru site compared to the Egypt site also found higher proportions of patients treated with nitazoxanide tablets or suspension who were clinical responders but were still excreting *Giardia* cysts in stool samples at Day 7-10 (i.e., clinically well with parasitological persistence): 47% (17-36) vs. 6% (1/18) for the nitazoxanide tablet group, 50% (18-36) vs. 5.5% (1/18) for the nitazoxanide suspension group, and 33% (6/18) vs. 22% (2/9) for the placebo group.

Clinical responders (as assessed at Day 7-10) in the nitazoxanide tablets and nitazoxanide suspension treatment groups who were enrolled at the study center in Peru were less likely to have negative stool examinations for *Giardia* on Day 14-17 than clinical responders from those treatment groups who were enrolled at the study center in Egypt: 21% (6/29) vs. 100% (16/16) for the nitazoxanide tablet group, 37% (10/27) vs. 87.5% (14/16) for the nitazoxanide suspension group, and 3% (1/29) vs. 67% (2/3) for the placebo group.

The applicant has proposed that the relationship between cyst quantitation in the baseline stool sample and the presence of cysts in stool samples collected after treatment in Peru suggests that in cases of heavy colonization of the intestinal tract by *Giardia* cysts, some cysts may remain sequestered in the small bowel after treatment; and/or patients heavily colonized by *Giardia* at baseline are likely to continue ingesting *Giardia* cysts during treatment and follow-up making it difficult to evaluate parasitological response.

In summary, in Study RM01-3011 clinical response at the test of cure visit (Day 7-10) for the nitazoxanide tablet group was significantly higher than for the placebo treatment group and the clinical response rate for nitazoxanide tablets was non-inferior to nitazoxanide suspension. Parasitological response was weakly correlated with clinical response and was not sustained. Without a clinical assessment at the follow-up visit it is

difficult for an assessment to be made of the significance of this parasitological finding at follow-up.

1.3.3 Safety

The nitazoxanide tablet development program contains safety information from 1628 HIV-uninfected adults and adolescent patients aged 12 years and older who received nitazoxanide tablets in controlled and uncontrolled studies, including Studies RM01-3011 and RM-NTZ-98-001. No deaths were reported. One serious adverse event (appendicitis requiring hospitalization) occurred in 12 year old female patient enrolled in Study RM01-3011 three days after the end of 3 days of treatment with nitazoxanide tablets. The appendicitis, reported as abdominal pain, was considered to be unrelated to treatment. Nine patients discontinued study medication due to adverse events. Adverse events occurring in $\geq$ 1% of patients were: abdominal pain in 6.7% (N=109 patients), diarrhea in 4.3% (N=70), headache in 3.1% (N=51), nausea in 3.1% (N=50), and dizziness in 1% (N=16).

There were 54 HIV-uninfected patients (ages 12 years and older) who received nitazoxanide suspension as a comparator in one controlled clinical study (i.e., Study RM01-3011). No deaths, drop-outs due to adverse events, or other serious or potentially serious adverse events occurred in these patients. Adverse events in patients treated with nitazoxanide suspension were similar to those reported with the tablets.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen in adolescent and adult patients aged 12 years and older with diarrhea caused by *Giardia lamblia* is one tablet (500 mg nitazoxanide) or 25 mL of suspension (500 mg) every 12 hours taken with food for 3 days.

The clinical and parasitological efficacy of a 500 mg nitazoxanide tablet was comparable to 500 mg of the nitazoxanide suspension when administered with food in adolescent and adult patients, although the two formulations are not bioequivalent. (See Section 8.1 "Dosing Regimen and Administration" in this review).

1.3.5 Drug-Drug Interactions

Following oral administration in humans, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide (desacetyl-nitazoxanide). Tizoxanide then undergoes conjugation, primarily by glucuronidation. *In vitro* metabolism studies have demonstrated that tizoxanide has no significant inhibitory effect on cytochrome P450 enzymes. Although no drug-drug interaction studies have been conducted *in vivo*, it is expected that no significant interaction would occur when nitazoxanide is co-administered with drugs that either are metabolized by or inhibit cytochrome P450 enzymes.

Tizoxanide is highly bound to plasma protein (>99.9%). Therefore, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices (e.g., warfarin), as competition for binding sites may occur.

1.3.6 Special Populations

Nitazoxanide suspension was approved for use in pediatrics (children from 1 to 11 years of age) on November 22, 2002 (NDA 21-498). In the current submission, nitazoxanide tablets were studied in adults and adolescents aged 12 years and older (N=84).

Clinical Reviewer's Comment: Based on data obtained from patients 1 to 11 years of age treated with nitazoxanide suspension, [redacted]

Pediatric patients less than 12 years of age, and patients with "serious systemic disorders incompatible with the study", which included patients with renal or hepatic impairment were excluded from the nitazoxanide tablet development program. Pregnant women and those suspected of being pregnant or breast feeding were also excluded. Therefore, it is not possible to comment on the efficacy or adverse event profile of nitazoxanide tablets in these special populations.

In Study RM01-3011 there were no patients aged 65 and over to determine whether or not they respond differently from younger patients. The oldest patient enrolled was 55 years of age. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing nitazoxanide tablets. In addition, the pharmacokinetics in patients with impaired hepatic and/or renal function and geriatric patients has not been studied.

1.3.6.1 Efficacy in Special Populations

Differences, if any, seen in the clinical or parasitological eradication rates between the following patient groups are not considered clinically meaningful: adolescents (12 to < 18 years) and adults (≥ 18 years); males and females; Caucasians, Hispanics, and Blacks. No adjustments to the adult dosing of nitazoxanide tablets or suspension in adolescents are warranted based on age, sex or race.

1.3.6.2 Safety in Special Populations

Differences, if any, seen in adverse events reported for the following patient groups are not considered clinically meaningful: adolescents (12 to < 18 years) and adults (≥ 18 years); males and females; Caucasians and Hispanics. Reporting of adverse events by age, sex, or race is not warranted in the labeling of nitazoxanide tablets.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name:	Nitazoxanide
Trade Name:	(Alinia®)
Dosage Form:	Oral Tablets
Pharmacological Class:	Nitrothiazolyl salicylamide
Spectrum of Activity:	broad spectrum of activity against parasites and anaerobic bacteria
Formulation	Oral Tablet
Dosing Regimen	500 mg BID x 3 days
Proposed Indication	/
Indication Granted	Treatment of diarrhea caused by *Giardia lamblia* in adults and adolescent patients 12 years of age and older.
Intended Population	/

The broad spectrum of activity of nitazoxanide against parasites and anaerobic bacteria has been attributed to the inhibition of pyruvate:ferredoxin oxidoreductase (PFOR), an essential enzyme of central intermediary metabolism in these organisms.

2.2 State of Armamentarium for Indication(s)

Nitazoxanide suspension was approved by the FDA on November 22, 2002 for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in children from 1 to 11 years of age.

Furazolidone is approved at a dose of 100 mg four times a day in adults for the treatment of protozoal diarrhea and enteritis caused by susceptible organisms, including *Giardia lamblia*. Hemolytic anemia can occur patients with G6PD deficiency treated with furazolidone. Until the approval of nitazoxanide suspensions, it was the only drug approved to treat giardiasis available in a liquid formulation.

Metronidazole is approved in US for the treatment of amebiasis, but is not approved for the treatment of giardiasis. However, it is recommended as the drug of choice for giardiasis by *The Medical Letter* at a dose of 250 mg orally three times a day for 5 to 7 days.

Tinidazole (Tindamax®) was approved on May 17, 2004 for the treatment of giardiasis (2 gram and 50 mg/kg single oral dose in adults and children, respectively).

Other agents not approved in the US for *Giardia lamblia* but used elsewhere in the world include quinacrine, paromomycin (sometimes used in pregnant patients) and other nitromidazoles such as ornidazole.

2.3 Availability of Proposed Product in the U.S.

Nitazoxanide suspension was approved by the FDA on November 22, 2002 for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in children aged 1 to 11 years.

Nitazoxanide tablets have been used in the setting of emergency INDs in the US on a case-by-case basis.

2.4 Important Issues with Pharmacologically Related Products

See Section 2.2 ("State of Armamentarium for Indication(s)").

2.5 Pre-submission Regulatory Activity

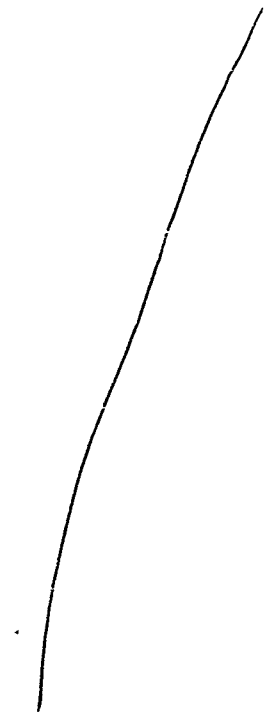
Nitazoxanide suspension (NDA 21-498) was approved by the FDA on November 22, 2002 for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in children aged 1 to 11 years. The applicant agreed to the following Phase 4 commitments:

- *In vivo* study of the effect of food on pharmacokinetics following oral administration of nitazoxanide for Oral Suspension
- *In vitro* study of the effect of nitazoxanide metabolites (tizoxanide and tizoxanide glucuronide) on cytochrome P450 enzymes
- Study of the in vitro transfer of tizoxanide across the epithelial barrier
- 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

Clinical Reviewer's Comment: Final reports for the first 3 commitments were submitted with the current submission. See Clinical Pharmacology and Biopharmaceutics review by Dakshina Chilukuri, Ph.D.

Nitazoxanide tablets (NDA 21-497) were given an "Approvable" action on November 22, 2002 for the treatment of diarrhea caused by —— *Giardia lamblia* in immunocompetent adults and adolescents. The Approvable letter stated:

1.



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 parasitological 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: —

The protocols for Studies RM01-3010 (i.e., RM-NTZ-98-002) and RM01-3011 (i.e., RM-NTZ-98-001), submitted in response to the Approvable letter of NDA 21-497 were submitted for review on December 10, 2002 to IND —. On January 17, 2003 the FDA sent comments to the applicant regarding both protocols.

Clinical Reviewer's Comments:
The final protocol and study report for Study RM01-3011 have adequately addressed the FDA's clinical comments of January 17, 2003.

The applicant has submitted dissolution information for the nitazoxanide tablets in the current NDA submission, as requested above in the Approvable letter of November 22, 2002, which was found to be acceptable by the Clinical Pharmacology/Biopharmaceutics Reviewer, Dakshina Chilukuri, Ph.D. See Clinical Pharmacology and Biopharmaceutics review filed with this NDA submission

2.6 Other Relevant Background Information

Nitazoxanide has been approved in 7 countries. No applications are pending in any country other than the US.

Country	Date Approved for Marketing
Mexico	July 19, 1996
Guatemala	April 3, 1998
Peru	August 19, 1998
Argentina	December 30, 1998
El Salvador	January 6, 1999
Honduras	July 10, 2001
Ecuador	April 16, 2001

The product is marketed by —
under license from Romark Laboratories. Romark Laboratories supplies the active drug substance for these Latin American countries, and pharmaceutical formulations are manufactured in Mexico by —

In each of these countries, nitazoxanide is sold in the following formulations:

- 500 mg film-coated tablets for adults and adolescents

- 200 mg dispersible tablets for children 4 to 11 years of age
- Powder for reconstitution as a 100 mg/5 mL pediatric suspension

The dose used for the product in these Latin American countries for treating protozoal and helminthic infections is 500 mg twice daily in adults, 200 mg twice daily in children aged 4 to 11 years, and 100 mg twice daily in children aged 12 to 47 months. The recommended duration of treatment is 3 days for the intestinal parasites and 7 days for *Fasciola hepatica*. In patients with AIDS and cryptosporidiosis, the recommended dose and duration of treatment is 1000 mg twice daily for 14 days.

More than — courses of the 3-day treatment regimen have been sold in Latin America since 1996 with the majority of these being sold in Mexico. Product sales have been spread among the formulations/packaging as follows:

Formulation/Packaging	Treatment Courses Sold (in millions)
500 mg film-coated tablets for adults (6 tablets)	
200 mg dispersible tablets for children aged 4 to 11 years (6 tablets)	
Powder for oral suspension: 60 mL bottle for children aged 4 to 11 years	
Powder for oral suspension: 30 mL bottle for children aged 12 to 47 months	
TOTAL	

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 Chemistry

From the chemistry, manufacturing and controls standpoint, this application may be approved.

Clinical Reviewer's Comment: The following information was excerpted from the Chemistry Review conducted by Gene Holbert, Ph.D. and filed with this NDA.

For the majority of chemistry, manufacturing and controls information regarding the drug substance, reference is made to DMF — A majority of the information on the drug product is incorporated by cross-reference to NDA 20-871 for Alinia® (nitazoxanide) Tablets. NDA 20-871 was submitted in December 1997 for treatment of cryptosporidial diarrhea in AIDS patients. That application was not approved for reasons of efficacy.

The NDA submissions and the Drug Master File ultimately provided adequate information on the chemistry and manufacturing controls for the production of Alinia® Tablets. During the review, a number of issues, including the following were resolved:

- Containers used for storage of the bulk tablets prior to final packaging were not described
- Acceptance criteria for the drug product were modified to reflect the capabilities of the manufacturer. The proposed limits for desacetyl nitazoxanide were reduced from [redacted] The limit for Total Degradation Products was reduced from not more than [redacted] to not more than [redacted] at expiry.
- No [redacted] data using the current film coating had been provided.
- The original NDA 20-871 contained only [redacted] of stability data for the proposed commercial formulation.

As amended, all acceptance criteria and analytical methods were found adequate to ensure the identity, strength, quality, purity and potency of the drug product.

3.2 Animal Pharmacology/Toxicology

From the pharmacology/toxicology standpoint, this application may be approved.

Clinical Reviewer's Comment: The following information was excerpted from the Pharmacology/Toxicology Review conducted by Steve Kunder, Ph.D. and filed with this NDA.

Nitazoxanide was previously submitted by Unimed Pharmaceuticals Inc. for cryptosporidosis in AIDS patients (NDA 20-871). The application was not approved due to lack of efficacy. A previous developer of the drug, Romark Laboratories, resubmitted NTZ for cryptosporidial diarrhea in children with a three day course of treatment (200 mg, bid, approximately 11 mg/kg/day in an 11 year old child). The previously submitted preclinical studies were used to support this submission, with an additional 28-day oral dog toxicity study. The previous preclinical studies demonstrated support for the safety of NTZ. The lack of toxicity in animal studies at doses greater than human exposure supports the safety of this drug for the short treatment time. There are no other pharmacology/toxicology issues.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

- Report of Study RM01-3011: Volume 10.6
- Literature articles: Volume 10.7
- Medical Officer's Review of NDA 21-497 and 21-498 by Rosemary Johann-Liang, M.D. (DFS date January 1, 2003)
- Electronic datasets for Study RM01-3011: \\CDSESUB1\N21497\N_000\2004-01-28

4.2 Tables of Clinical Studies

Table 1 below summarizes the clinical studies conducted with nitazoxanide tablets in adult and adolescent patients aged 12 years of age and older with diarrhea caused by *Giardia lamblia.*

TABLE 1
Summary of Clinical Studies of Nitazoxanide Tablets to Treat Diarrhea Caused by *Giardia lamblia*

Study	Number of Patients Enrolled	Study Design	Number of Patients Evaluable (MITT)	Clinical Response	Parasitological Response
RM01-3011	134 adults and adolescents aged 12 years and older	Placebo-controlled; 3 treatment arms: NTZ tablets (N=54), NTZ suspension (N=54), and placebo (N=36) Study sites: Peru and Egypt	134 patients	NTZ tablets: 85% (46/54)	NTZ tablets: 55.5% (30/54)
				NTZ suspension: 83% (45/54)	NTZ suspension: 48% (26/54)
				Placebo: 44% (12/27)	Placebo: 18.5% (5/27)
RM-NTZ-98-001	18* adults and adolescents aged 12 years and older	Double-blind, placebo-controlled; NTZ tablets (N=8) versus placebo (N=10)	18	NTZ tablets: 100% (8/8)	NTZ tablets: 75% (6/8)
				Placebo: 30% (3/10)	Placebo: 0% (0/10)

* subset with *Giardia lamblia* as the sole infecting pathogen

4.3 Review Strategy

Study RM01-3011 was considered the pivotal study for the treatment of *Giardia lamblia.* In addition, Study RM-NTZ-98-001 was considered supportive. Study RM-NTZ-98-001 was submitted in the original NDA 21-497 dated May 25, 2002, and reviewed by Dr. Rosemary Johann-Liang (Medical Officer).

4.4 Data Quality and Integrity

DSI inspections were not conducted for this NDA. The two study sites which enrolled adult patients into Study RM01-3011 also enrolled patients into the pediatric studies performed under NDA 21-497 (nitazoxanide tablets in adults and adolescents) and 21-498 (nitazoxanide suspension in children 1 to 11 years). These sites were inspected by DSI in 2002 and no violations were found. The review team felt that reinspection was not necessary at this time.

A summary of the findings from the 2002 inspections are reproduced here from the Medical Officer's review (dated January 7, 2003 by Dr. Rosemary Johann-Liang):

Peru
Investigator:

DSI Reviewer Note (10/23/02)
Re: Protocol RM-NTZ-99-010 titled "Randomized Comparative Study of Nitazoxanide and Metro in the Treatment of *Giardias*is in Children"

- 110 children were enrolled
- Records of 21/1000 patients were reviewed in detail
- No regulatory violations were noted
- All patients underwent an appropriate consent process
- Data appear acceptable

Egypt
Investigator:

DSI Clinical Inspections Summary (11/13/02)
Re: Protocols RM-NTZ-98-001 (A Double-Blind Placebo-Controlled Study in Adults with Diarrhea Caused by *G. lamblia* or *E. histolytica*); and
Protocol RM-NTZ-98-002 (A Double-Blind Placebo-Controlled Study in Adults and Children with Diarrhea Caused by *C. parvum*)

- It appears that the data from this site is acceptable for review
- Screened in excess of 800 patients to randomize a total of 200 patients
- Two contract labs performed the stool examinations — – more modern and — – older lab, —
- The — initially grants a license to a laboratory when it commences operations and does not inspect unless it hears of complaints. Both labs had not had any problems and thus, had not been inspected since its initiation — — is not and has not been accredited by the College of American Pathologists.

A 10% random sample of patients (N=14) enrolled in Study RM01-3011 was generated by the FDA Statistical Reviewer and the applicant was requested to submit the CRFs for

these patients for review. The FDA Clinical Reviewer examined the CRFs for inclusion/exclusion criteria, dates of visits, clinical signs and symptoms, concomitant medications and indications, microbiology findings, and evaluability determinations. The data in the CRFs was compared to the electronic datasets generated by the applicant. The reviewer agreed with the applicant's determinations for the patients in the sample and the applicant's analyses were accepted.

4.5 Compliance with Good Clinical Practices

Study RM 01-3011 was performed in compliance with Good Clinical Practices.

4.6 Financial Disclosures

The applicant obtained certification from each investigator and sub-investigator who enrolled patients in Study RM01-3011. No investigator had any disclosable information to reveal.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Clinical Reviewer's Comment: The following information was taken from the proposed package insert for nitazoxanide tablets and was confirmed by the Clinical Pharmacology/Biopharmaceutics reviewer. Pharmacokinetic information on nitazoxanide oral suspension in children 1 to 11 years of age can be found in the approved package insert.

Absorption: Following oral administration of Alinia® Tablets maximum plasma concentrations of the active metabolites tizoxanide and tizoxanide glucuronide are observed within 1-4 hours. The parent nitazoxanide is not detected in plasma. Pharmacokinetic parameters of tizoxanide and tizoxanide glucuronide are shown in Table 2 below.

TABLE 2
Mean (±SD) Plasma Pharmacokinetic Parameters Following Administration of a Single Dose of one 500 Alinia® Tablet with Food to Subjects ≥ 12 Years of Age

	Tizoxanide			Tizoxanide glucuronide		
Age	C_{max} (µg/mL)	T_{max}* (hr)	AUC_τ (µg•hr/mL)	C_{max} (µg/mL)	T_{max}* (hr)	AUC_τ (µg•hr/mL)
12-17 years	9.1 (6.1)	4.0 (1-4)	39.5 (24.2)	7.3 (1.9)	4.0 (2-8)	46.5 (18.2)
≥ 18 years	10.6 (2.0)	3.0 (2-4)	41.9 (6.0)	10.5 (1.4)	4.5 (4-6)	63.0 (12.3)

* T_{max} is given as a Mean (Range)

Effect of Food: When Alinia® Tablets are administered with food, the AUC_t of tizoxanide and tizoxanide glucuronide in plasma is increased almost two-fold and the C_{max} is increased by almost 50%.

Multiple dosing: Following oral administration of a single Alinia® Tablet every 12 hours for 7 consecutive days, there was no significant accumulation of nitazoxanide metabolites tizoxanide or tizoxanide glucuronide detected in plasma.

Distribution: In plasma, more than 99% of tizoxanide is bound to proteins.

Metabolism: Following oral administration in humans, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide (desacetyl-nitazoxanide). Tizoxanide then undergoes conjugation, primarily by glucuronidation. *In vitro* metabolism studies have demonstrated that tizoxanide has no significant inhibitory effect on cytochrome P450 enzymes.

Elimination: Tizoxanide is excreted in the urine, bile and feces, and tizoxanide glucuronide is excreted in urine and bile. Approximately two-thirds of the oral dose of nitazoxanide is excreted in the feces and one-third in the urine.

Special Populations
Patients with Impaired Hepatic and/or Renal Function: The pharmacokinetics of nitazoxanide in patients with impaired hepatic and/or renal function has not been studied.

Geriatric Patients: The pharmacokinetics of nitazoxanide in geriatric patients has not been studied.

Pediatric Patients: The pharmacokinetics of nitazoxanide following administration of Alinia® Tablets in pediatric patients less than 12 years of age has not been studied (see prescribing information for Alinia® for Oral Suspension).

5.2 Pharmacodynamics

Not applicable.

5.3 Exposure-Response Relationships

Not applicable.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Methods

Study RM01-3011 was considered the pivotal efficacy study for this submission. In addition limited efficacy data from Study RM-NTZ-98-001 in the original submission of NDA 21-497 (submitted May 29, 2002) were also considered.

6.2 General Discussion of Endpoints

Clinical and parasitological response at the test of cure visit (i.e., Day 7-10) should both be evaluated. However, it was determined previously during the study of nitazoxanide suspension in children aged 1 to 11 years, and confirmed in the current submission of nitazoxanide tablets in adults and adolescents aged 12 years and older, that parasitological response may not be associated with clinical response. Therefore, clinical response will be considered the primary endpoint of interest.

6.3 Efficacy Findings

Study RM01-3011: A total of 135 patients were enrolled (54 randomized to nitazoxanide tablets, 54 to nitazoxanide suspension, and 27 to placebo). No patients were excluded from the modified intent-to-treat population, and therefore, all patients randomized to the study were included in the analysis. Two patients (one from the nitazoxanide tablet group and one from the nitazoxanide suspension group) dropped out of the study. These patients were treated as clinical and parasitological failures.

The number of *Giardia* cysts observed per microscopic field after concentration of stool was reported at baseline in 129 of 135 patients. The mean number of cysts was approximately 6 in the nitazoxanide tablet group, 5 in the nitazoxanide suspension group, and 7 in the placebo group. Some patients from the Egyptian site showed no cysts in their stool at baseline by microscopic examination of concentrated stool (6 in the nitazoxanide tablet group, 2 in the nitazoxanide suspension group, and 7 in the placebo group), but had cysts documented by immunofluorescence assay. A sensitivity analysis was performed by the FDA Clinical and Statistical Reviewers excluding these patients, along with an additional patient who was enrolled at the site in Egypt with fewer than 3 stools per day at baseline. The clinical and parasitological response rates were similar whether or not these patients were included in the analysis.

The mean number of cysts in the two concentrated stool samples obtained 24 hours apart between Days 7 and 10 were lower in all three groups (approximately 2 in the

nitazoxanide tablet group, 2 in the nitazoxanide suspension group, and 3 in the placebo group). There were 34, 29, and 5 patients with no cysts detected in both stool samples for the nitazoxanide tablet, nitazoxanide suspension, and placebo groups respectively. However, a drop in the number of cysts between the baseline and Day 7-10 samples (mean ± SD) occurred in all three groups and was reported as: 4.3 ± 9.4 for the nitazoxanide tablet group, 3.7 ± 7.9 nitazoxanide suspension group, and 3.3 ± 5.2 for the placebo group. In addition, the number of cysts in stool samples at baseline and Day 7-10 (using the maximum of two concentrated stool samples at Day 7) was also compared in a categorical analysis (i.e., improved, no change, worsened) and the results showed there was no overall difference between the treatment means (see Appendix 9.1 of this review).

The proportion of "well" clinical responses recorded at the Day 7-10 test of cure visit (i.e., 4 to 7 days following the end of treatment) for the three study groups were: 85% (46/54) for the nitazoxanide tablet group, 83% (45/54) of the nitazoxanide suspension group, and 44% (12/27) for the placebo group. The proportion of "well" clinical responses in the active treatment group was significantly higher than in the placebo treatment group ($p = 0.0002$ for tablet versus placebo), which was the primary statistical comparison. The lower bound of the 95% confidence interval of the treatment difference between nitazoxanide tablets and nitazoxanide suspension was above the pre-specified non-inferiority margin of 15% (i.e., -13.5%, 17.1%), indicating that the clinical response rate to the nitazoxanide tablets was non-inferior to the nitazoxanide suspension by this criterion.

The proportion of patients eradicated (i.e., no cysts or trophozoites observed in two stool samples collected between study Days 7 and 10) was 55.5% (30/54) in the nitazoxanide tablet group, 48% (26/54) in the nitazoxanide suspension group, and 18.5% (5/27) in the placebo group. The parasitological response rate in the active treatment group was significantly higher than in the placebo treatment group ($p = 0.0019$ for nitazoxanide tablets versus placebo), which was the primary statistical comparison. The lower bound of the 95% confidence interval of the treatment difference between nitazoxanide tablets and nitazoxanide suspension was above the pre-specified non-inferiority margin of 15% (i.e., -12.4%, 26.4%), indicating that the parasitological response rate to the nitazoxanide tablets was non-inferior to the nitazoxanide suspension.

The intrapatient correlation of clinical and parasitological response rates at Day 7-10 was calculated using the kappa statistic. The results showed a weak, but positive correlation between the groups (kappa of 0.196 for the nitazoxanide tablet group, 0.313 for the nitazoxanide suspension group, and 0.283 for the placebo group).

The clinical and parasitological response rates, as well as the intrapatient correlation between the two endpoints, were similar whether or not the patients without cysts in the baseline concentrated stool sample were included in the analyses.

Parasitological response was evaluated at a follow-up visit at Day 14-17 (i.e., 11 to 14 days following the end of therapy). Clinical response was not assessed. Of the patients who were clinical responders at Day 7, the following number of patients were had no cysts detected in the concentrated stool sample at Day 14-17: 49% (22/45) in the nitazoxanide tablet group, 56% (24/43) in the nitazoxanide suspension group, and 25% (3/12) in the placebo group. The mean ± SD change in cyst counts between Day 7 and Day 14 was -1.54 ± 4.7 for the nitazoxanide tablet group, -1.53 ± 4.4 for the nitazoxanide suspension group, and -2.2 ± 6.5 for the placebo group. Although there was a mean drop in the number of cysts between the Day 7-10 and Day 14-17 visits, an assessment of cyst counts in individual patients between all three time points (i.e., baseline, Day 7-10, and Day 14-17) revealed some outlier patients who had an initial drop in the number of cysts between baseline and Day 7-10, but then had a rebound in the number of cysts back to baseline levels at Day 14-17. Therefore, nonsustained parasitological response was observed, mainly at the Peru study site.

The patients enrolled in Peru had a higher baseline cyst count (mean ± SD) combined across all treatment groups (7.8 ± 11.4) than did the patients in Egypt (1.6 ± 2.2).

The proportion of "well" clinical responses recorded at the Day 7-10 test of cure visit was numerically lower in Peru than in Egypt for both nitazoxanide treatment groups and higher for the placebo group: 81% (29/36) vs. 94% (17/18) for the nitazoxanide tablet group, 81% (29/36) vs. 89% (16/18) for the nitazoxanide suspension group, and 50% (8/18) vs. 33% (3/9) for the placebo group.

The proportion of patients eradicated at Day 7-10 was lower in Peru than in Egypt for all three treatment groups: 36% (13/36) vs. 94% (17/18) in the nitazoxanide tablet group, 31% (11/36) vs. 83% (15/18) in the nitazoxanide suspension group, and 17% (3/18) vs. 22% (2/9) in the placebo group.

The Peru site compared to the Egypt site also found higher proportions of patients treated with nitazoxanide tablets or suspension who were clinical responders but were still excreting *Giardia* cysts in stool samples at Day 7-10 (i.e., clinically well with parasitological persistence): 47% (17-36) vs. 6% (1/18) for the nitazoxanide tablet group, 50% (18-36) vs. 5.5% (1/18) for the nitazoxanide suspension group, and 33% (6/18) vs. 22% (2/9) for the placebo group.

Clinical responders (as assessed at Day 7) in the nitazoxanide tablets and nitazoxanide suspension treatment groups who were enrolled at the study center in Peru were less likely to have negative stool examinations for *Giardia* on Day 14 than clinical responders from those treatment groups who were enrolled at the study center in Egypt: 21% (6/29) vs. 100% (16/16) for the nitazoxanide tablet group, 37% (10/27) vs. 87.5% (14/16) for the nitazoxanide suspension group, and 3% (1/29) vs. 67% (2/3) for the placebo group.

The applicant has proposed that the relationship between cyst quantitation in the baseline stool sample and the presence of cysts in stool samples collected after treatment in Peru

suggests that in cases of heavy colonization of the intestinal tract by *Giardia* cysts, some cysts may remain sequestered in the small bowel after treatment; and/or patients heavily colonized by *Giardia* at baseline are likely to continue ingesting *Giardia* cysts during treatment and follow-up making it difficult to evaluate parasitological response.

Differences, if any, seen in the parasitological eradication rates between the following patient groups are not considered clinically meaningful: adolescents (12 to < 18 years) and adults (≥ 18 years); males and females; Caucasians and Hispanics. No adjustments to the dosing of nitazoxanide tablets are warranted based on age, sex or race.

Study RM-NTZ-98-001: The following clinical response rates, defined and observed the same as in Study RM01-3011, were obtained from the Medical Officer's review of NDA 21-497 (Dr. Rosemary Johann-Liang): 100% (8/8) for nitazoxanide tablets and 30% (3/10) for placebo in adults and adolescents aged 12 years and older.

6.4 Clinical Microbiology

Biology of *Giardia lamblia*:
Giardia lamblia is a flagellated protozoan found in intestinal tract of humans. *Giardia duodenalis* or *Giardia intestinalis* are alternate names for *G. lamblia*. Infection is caused by ingestion of contaminated food or water containing *G. lamblia* cysts. Following ingestion, the cysts pass through the stomach to the small intestine where they excyst to give rise to trophozoites. The trophozoites attach to the epithelial cells in the duodenum and bile duct of the host, divide by longitudinal fission and encyst on reaching the colon. *G. lamblia* does not invade epithelial cells like *C. parvum*. In cases of severe infection, trophozoites are more commonly observed than cysts in diarrheic stool samples.

Pathogenesis of Giardiasis:
The major clinical manifestations of *Giardia lamblia* infection are diarrhea and malabsorption. Although changes in the villi of the intestine have been observed, the mechanism by which *Giardia* causes diarrhea is not known. The host immune response plays an important role in protection from the infection. In addition to the immune status of the host, the severity and duration of the infection can be affected by the number of cysts ingested and the virulence of the *Giardia* strain.

Preclinical Microbiology:
No new information was included in this submission. Studies describing the mechanism of action, activity of nitazoxanide *in vitro* and *in vivo* against *G. lamblia* were reviewed earlier [please see microbiology reviews dated 06-01-98 (NDA 20-871, N-000), and 11-06-02 (NDA 21-497 and 21-498, N-000)]. Nitazoxanide and its metabolite, tizoxanide, were active *in vitro* in inhibiting the growth of trophozoites of *G. lamblia*.

Clinical Microbiology:
The clinical study (RM01-3011) was conducted in Peru and Egypt to determine the safety and efficacy of nitazoxanide in the treatment of diarrhea due to *G. lamblia* in adults.

Resolution of diarrhea was observed in 85% (46/54) patients treated with nitazoxanide tablets compared to 83% (45/54) patients treated with nitazoxanide suspension, and 44% (12/27) patients treated with placebo.

The sponsor used microscopic examination of unconcentrated stool stained by iodine or immunofluorescence, and concentrated stool samples stained with iodine, to assess presence of *G. lamblia* cysts in stool samples, at baseline and 4 to 7 days after discontinuation of treatment. The processing of the stool samples at the two sites appears to be similar. However, the Peru site determined the actual cyst counts and the Egypt site used a semi-quantitative grading system to determine cyst counts in the stool sample. Based on qualitative data, the percentage of patients that showed absence of *G. lamblia* cysts in the nitazoxanide tablet arm was 55.5% (30/54) compared to 48% (26/54) in the nitazoxanide suspension, and 18.5% (5/27) in the placebo arm. The correlation between the clinical outcome and parasitological outcome was good (Egypt site) when cyst counts were low, and appear to be poor when cyst counts are high (Peru site). The effect of nitazoxanide on eradication or reduction of cysts is difficult to predict, as the cysts counts were reported per high power field rather than per volume or weight of stool. Several factors effect the detection of cysts in stool samples such as specimen collection and transport method, addition of stool preservatives, age of the stool (fresh versus 24 hour old), consistency, number of stools examined, presence of debris, clarity of smears prepared from concentrated stool sediments, presence of background fluorescence, and expertise of the examiner. Additionally, the sensitivities of current assays are 66-70%, when cyst counts are low. Because of these limitations and intermittent shedding of cysts observed in patients with giardiasis, the parasitological outcome of these patients should be interpreted with caution.

At 12 to 14 days after discontinuation of therapy, 14.5% (7/48) of patients treated with nitazoxanide tablets who had eradicated cysts in stool samples collected at 4 to 7 days after discontinuation of therapy were positive again for cysts. Similar observation was made in 12% (6/49) patients treated with nitazoxanide suspension and 12% (3/25) patients treated with placebo. Most of these patients were from the Peru site. The sponsor has stated that Peru being a hyper-endemic area compared to Egypt, the recurrence of cysts was more likely due to re-infection rather than relapse. However, information supporting the basis for higher endemicity of *G. lamblia* in Peru compared to Egypt was not included. The differences in parasitological response in the Egypt and Peru site may also be due to host factors or differences in the *G. lamblia* isolates at these two sites. Overall, the clinical efficacy of nitazoxanide tablets was similar to nitazoxanide suspension and greater than placebo.

6.5 Efficacy Conclusions

In summary, in Study RM01-3011 clinical response at the test of cure visit (Day 7-10) in the nitazoxanide tablet group was significantly higher than in the placebo treatment group and the clinical response rate for nitazoxanide tablets was non-inferior to nitazoxanide suspension. The Clinical Studies section of the nitazoxanide label should include clinical

results for patients at the Day 7-10 visit. Specific parasitological results should not be included since there is only a weak correlation between clinical and parasitological response. The prescriber should also be informed that at the follow-up visit (Day 14-17) cyst counts increased in many patients: without a clinical assessment at the follow-up visit it is difficult for an assessment to be made of the significance of this parasitological finding.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The nitazoxanide tablet development program contains safety information from 1628 HIV-uninfected adults and adolescent patients aged 12 years and older who received nitazoxanide tablets in controlled and uncontrolled studies, as shown in Table 3.

TABLE 3
Summary of Controlled and Uncontrolled Studies of Nitazoxanide Tablets in Patients Aged 12 Years and Older (HIV-uninfected)

Study Number	Indication Studied	Number of Patients	Dosage Regimen
RM01-3011	Diarrhea caused by *Giardia lamblia*	54	500 mg bid x 3 days
RM-NTZ-98-001	Diarrhea caused by *Giardia lamblia* or *Entamoeba histolytica*	47	500 mg bid x 3 days
RM-NTZ-98-002	Diarrhea caused by *Cryptosporidium parvum*	25	500 mg bid x 3 days
CL-NTZ-95-001	Mixed intestinal parasitic infection	121	500 mg bid x 3 days
PRC-94-NTZ03	Mixed intestinal parasitic infection	415	500 mg bid x 3 days
RM-96-401	Mixed intestinal parasitic infection	129	Various doses (500 to 2000 mg qd) and durations (1 to 7 days)
RM-NTZ-99-008	/	40	500 mg bid x 7 days
RM-94-NTZ-04	/	393	500 mg bid x 6 or 7 days
RM-NTZ-96-001	/ /	195	500 mg or 100 mg x 7 or 14 days
RM-NTZ-95-01	/	17	500 mg bid x 10 days
RM-NTZ-99-001	/	68	2000 or 3000 mg x 1 day; and 500 or 1000 mg bid x 3 days

Study Number	Indication Studied	Number of Patients	Dosage Regimen
RM-NTZ-99-002	/	124	2000 or 3000 mg x 1 day; and 500 or 1000 mg bid x 3 or 7 days

There were 54 HIV-negative patients aged 12 years and older who received nitazoxanide suspension as a comparator in controlled clinical trials (i.e., Study RM01-3011). No deaths, drop-outs due to adverse events, or other serious or potentially serious adverse events occurred in these patients.

7.1.1 Deaths

No deaths occurred in patients treated with nitazoxanide tablets. One death was reported in a 38 year old male patient randomized to placebo in Study RM-NTZ-98-001.

Clinical Reviewer's Comment: For more information see Medical Officer's Review for NDA 21-497 dated January 7, 2003, by Rosemary Johann-Liang, M.D.

7.1.2 Other Serious Adverse Events

One serious adverse event (appendicitis requiring hospitalization) occurred in 12 year old female patient enrolled in Study RM01-3011 three days after the end of 3 days of treatment with nitazoxanide tablets. The appendicitis, reported as abdominal pain, was considered to be unrelated to treatment.

7.1.3 Dropouts and Other Significant Adverse Events

Nine patients treated with nitazoxanide tablets and one patient treated with placebo discontinued study medication due to adverse events as shown in Table 4.

TABLE 4
Discontinuations Due to Adverse Events

Study number	Patient age/Sex	Nitazoxanide Dose	Adverse event	Duration (days)	Outcome
RM01-3011	16 F	500 mg BID	Abdominal pain; Study drug discontinued	3	Resolved
RM-NTZ-98-002	30 F	500 mg BID	Dizziness; Study drug discontinued	Unknown	Resolved
RM-NTZ-99-001	40 F	1000 mg BID	Diarrhea; Study drug discontinued	2	Resolved
RM-NTZ-99-002	44 F	1000 mg BID	Nausea; Study drug discontinued	1	Resolved
	48 F	500 mg BID	Stomach pain; Study drug discontinued	2	Resolved
			Vomiting; Study drug discontinued	2	Resolved
	24 F	1000 mg BID	Stomach pain; Study drug discontinued	4	Resolved
	17 F	500 mg BID	Diarrhea; Study drug discontinued	2	Resolved
	24 F	1000 mg BID	Diarrhea; Study drug discontinued	2	Resolved
			Stomach pain; Study drug discontinued	7	Unresolved

7.1.4 Common Adverse Events

Adverse events reported in patients treated with nitazoxanide tablets (N=1628) or placebo (N=129) are shown in Tables 5 and 6, respectively. The rates of occurrence of the adverse events for nitazoxanide tablets do not appear to be different from those of placebo.

Clinical Reviewer's Comment: Tables 5 through 7 were created by the applicant and submitted to the NDA on June 25, 2004.

TABLE 5

Adverse Events: Patients (Aged 12 Years and Older) Who Received Nitazoxanide Tablets in Controlled and Uncontrolled Studies (N=1628)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	109	6.7
HEADACHE	51	3.1
ASTHENIA	10	0.6
FEVER	6	0.4
PAIN	5	0.3
ALLERG REACT	3	0.2
PAIN PELVIC	2	0.1
FLU SYND	1	0.1
CHILLS	1	0.1
CHILLS FEVER	1	0.1
DIG		
DIARRHEA	70	4.3
NAUSEA	50	3.1
VOMIT	7	0.4
NAUSEA/VOMIT	3	0.2
DYSPEPSIA	3	0.2
NAUSEA VOMIT DIAR	2	0.1
ANOREXIA	2	0.1
FLATUL	1	0.1
CONSTIP	1	0.1
THIRST	1	0.1
DRY MOUTH	1	0.1
NER		
DIZZINESS	16	1.0
SOMNOLENCE	10	0.6
HYPESTHESIA	1	0.1
INSOMNIA	1	0.1
TREMOR	1	0.1
UG		
URIN ABNORM	13	0.8
DYSURIA	2	0.1
METRORRHAGIA	1	0.1
PAIN KIDNEY	1	0.1
AMENORRHEA	1	0.1
EDEMA LABIA	1	0.1

TABLE 5 (continued)
Adverse Events: Patients (Aged 12 Years and Older) Who Received Nitazoxanide Tablets in Controlled and Uncontrolled Studies (N=1628)

Body system Adverse event	Patients Reporting AEs Number	%
MAN		
SGPT INC	14	0.9
SKIN		
RASH	3	0.2
PRURITUS	2	0.1
RASH VESIC BULL	1	0.1
SS		
EYE DIS	3	0.2
PAIN EAR	1	0.1
RES		
EPISTAXIS	1	0.1
LUNG DIS	1	0.1
PHARYNGITIS	1	0.1
CV		
SYNCOPE	1	0.1
TACHYCARDIA	1	0.1
MS		
MYALGIA	1	0.1
BONE FRACT SPONTAN	1	0.1
MS/NER		
CRAMPS LEG	1	0.1
CV/NER		
HYPERTENS	1	0.1

TABLE 6
Adverse Events: Patients (Aged 12 and older) in Placebo Control Groups (N=129)

Body system Adverse event	Patients Reporting AEs Number	%
BODY		
PAIN ABDO	11	8.5
HEADACHE	3	2.3
EDEMA FACE	1	0.8
ASTHENIA	1	0.8
DEATH	1	0.8
DIC		
DIARRHEA	4	3.1
DYSPEPSIA	1	0.8
NER		
DIZZINESS	2	1.6
SOMNOLENCE	2	1.6
EMOTION LABIL	1	0.8
UG		
URIN ABNORM	1	0.8
DYSURIA	1	0.8

7.1.5 Laboratory Findings

Laboratory values were not routinely collected in all studies. The values reported for patients with laboratory adverse events are summarized in Table 7. Most of the changes represent only slight deviations from the normal laboratory range.

TABLE 7
Adverse Events Related to Laboratory Abnormalities for Patients (Aged 12 Years and Older) Who Received Nitazoxanide Tablets in Controlled and Uncontrolled Trials

Study no.	Patient no.	Lab parameter	Normal range	Before treatment	After treatment
RM-94-NTZ-04	AM 008	SGPT	< 43	42	45
RM-94-NTZ-04	AM 011	SGPT	< 43	43	46
RM-94-NTZ-04	SMK 189	SGPT	< 43	42	61
RM-94-NTZ-04	HA 264	SGPT	< 43	42	45
RM-94-NTZ-04	HA 265	SGPT	< 43	42	46
RM-94-NTZ-04	HA 266	SGPT	< 43	40	45
RM-94-NTZ-04	HA 267	SGPT	< 43	40	45
RM-94-NTZ-04	HA 285	SGPT	< 43	30	60
RM-94-NTZ-04	HR 056	SGPT	< 43	42	45
RM-94-NTZ-04	HR 079	SGPT	< 43	40	45
RM-94-NTZ-04	HR 082	SGPT	< 43	40	45
RM-94-NTZ-04	HR 117	SGPT	< 43	42	45
RM-NTZ-96-001	007	SGPT	< 43	28	65
RM-NTZ-96-001	235	SGPT	< 43	32	100

Units: SGPT: IU/L

7.1.6 Vital Signs

No clinically significant findings.

7.2 Safety Conclusions

Nitazoxanide tablets and suspension are associated with mild, gastrointestinal adverse events, the most common being abdominal pain which was also reported, although less frequently, in the placebo group.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The 500 mg dose (twice daily) of nitazoxanide and the 3-day duration of treatment selected for this study were based upon prior clinical studies that had demonstrated the safety and efficacy of nitazoxanide in the treatment of *Giardia lamblia.*

The proposed dosing regimen is one tablet (500 mg nitazoxanide) or 25 mL of suspension (500 mg nitazoxanide) every 12 hours taken with food for 3 days.

In the original submission for the nitazoxanide tablet (NDA 21-497), the presence of food was shown to prolong the rate of appearance of tizoxanide (metabolite of nitazoxanide) in plasma and increase the extent of systemic exposure. Administration of nitazoxanide tablets following a high-fat (48% of kcal as fat) meal compared with the fasted state resulted in a 116 ± 83% (range 6% to 289%) increase in AUC and 73 ± 81% (range -26% to 248%) increase in C_{max}. The median T_{max} was greater when nitazoxanide was given with food (3.25 hours versus 2 hours). In summary, administration of nitazoxanide with food results in higher exposure.

Results from the clinical efficacy studies submitted with NDAs 21-497 (nitazoxanide tablet) and 21-498 (nitazoxanide oral suspension), suggest that nitazoxanide oral suspension was effective in treating children (aged 1 to 11 years) with diarrhea when administered as the suspension and taken with food. However, the effectiveness of the tablets administered with food in adolescents and adults (aged ≥ 12 years) was not adequately demonstrated.

The applicant also conducted a bioequivalence study between a 500 mg dose given as suspension or tablet as part of NDA 21-498. The results showed that the bioavailability of the nitazoxanide active metabolite tizoxanide was 41% lower for the suspension formulation compared to the tablet formulation and the bioavailability of tizoxanide glucuronide was 30% lower for the suspension compared to the tablet. The 90% confidence intervals of the test/reference ratios were shifted towards lower values and were outside the acceptable limits of 80% to 125%.

From the pharmacokinetic studies, it can be concluded that food increases the absorption of tizoxanide from the suspension and that the suspension is less bioavailable than the tablets. An increased systemic exposure to tizoxanide with the tablets (taken with or without food) compared to the suspension may result in a decreased efficacy, as concluded from the clinical efficacy studies. Thus, in the Approvable letter for NDA 21-497, the relative contribution of local (i.e., the gastrointestinal tract) versus systemic activity was recommended for further study. The applicant was asked to characterize "the contribution of food-effect (fed-state versus fasting-state) on the clinical efficacy" of the tablets and suspension in adults.

Clinical Reviewer's Comment: The pharmacokinetic results quoted here came from the Clinical Pharmacology/Biopharmaceutics Review by Dakshina Chilukuri, Ph.D. filed with the original submission of NDA 21-497. See also the Approvable letter for NDA 21-497 in Section 2.5 "Pre-Submission Regulatory Activity" of this review.

In the current NDA submission, the applicant submitted a bioavailability study evaluating the rate and extent of absorption of a 500 mg dose of nitazoxanide suspension given in the fed (standard FDA high-fat meal) versus fasted state. The results showed that the AUC of tizoxanide and tizoxanide glucuronide were increased by 39% and 49%, respectively, in the presence of food. The resulting in 90% confidence interval of the AUC test/reference ratio was shifted up and fell outside the acceptable limits of 80% to 125%. The peak plasma concentrations of both tizoxanide and tizoxanide glucuronide were relatively unchanged and the 90% confidence intervals of the C_{max} test/reference ratio were within the acceptable limits of 0.8-1.25. In summary, administration of nitazoxanide suspension with food results in higher exposure, in terms of AUC but not C_{max}.

In Study RM01-3011 the applicant compared the efficacy of nitazoxanide tablets to the nitazoxanide suspension in adult and adolescent patients aged 12 years and older and was able to show that there was no significant effect of dosage form on clinical or parasitological efficacy, as determined by a lower bound of the 95% confidence interval of the treatment difference lying above -15%.

In Study RM01-3011 the applicant was unable to characterize the contribution of food-effect on clinical efficacy due to incomplete reporting of meals in the patients' study diaries. However, since the clinical efficacy of the tablets was comparable to the suspension when administered with food in adults, it can be concluded that an increase in the systemic exposure to tizoxanide does not adversely affect the efficacy of the tablets, although the relative contribution of systemic versus local antimicrobial activity is still unclear.

8.2 Drug-Drug Interactions

Tizoxanide is highly bound to plasma protein (>99.9%). Therefore, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices (e.g., warfarin), as competition for binding sites may occur. *In vitro* metabolism studies have demonstrated that tizoxanide has no significant inhibitory effect on cytochrome P450 enzymes. Although no drug-drug interaction studies have been conducted *in vivo*, it is expected that no significant interaction would occur when nitazoxanide is co-administered with drugs that either are metabolized by or inhibit cytochrome P450 enzymes.

8.3 Special Populations

8.3.1 Efficacy in Special Populations

Clinical and parasitological response rates observed in Study RM01-3011 by sex (males compared to females) and race (Caucasians compared to Hispanics), and can be found in the Review of Study RM01-3011 (Section 10.1 of this document). Differences, if any, seen in the response rates are not considered clinically meaningful. No adjustments to the adult dosing of nitazoxanide tablets or suspension in adolescents are warranted based on sex or race.

8.3.2 Safety in Special Populations

Concentrations of nitazoxanide are not detectable in plasma, although the metabolite tizoxanide is detectable in plasma following oral administration of nitazoxanide and subsequently undergoes glucuronidation in the liver. Nitazoxanide tablets and suspension have not been studied in patients with compromised renal or hepatic function; however, it is not anticipated that patients with hepatic or renal disease will experience drug toxicity, since most of the drug stays intraluminally within the gastrointestinal tract.

There are no adequate and well-controlled studies in pregnant women.

It is not known whether nitazoxanide is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitazoxanide is administered to a nursing woman.

An evaluation of the safety of nitazoxanide tablets by sex and race (Caucasians and Hispanics) in controlled and uncontrolled trials is reported below. The safety data are collected from efficacy trials of various bacterial and parasitic infections. The dosage of nitazoxanide tablets, as well as the duration of treatment, varied across trials (see Table 3 in the Section 7.1 of this document, "Methods and Findings").

Clinical Reviewer's Comment: Tables 8 through 15 were created by the applicant and submitted to the NDA on June 25, 2004.

Males and Females: Adverse events in HIV-uninfected patients who received nitazoxanide tablets or placebo in controlled and uncontrolled studies are shown in Tables 8 and 9 for male and Tables 10 and 11 for female patients, respectively.

TABLE 8
Adverse Events: HIV- Uninfected Patients Who Received Nitazoxanide Tablets in Controlled and Uncontrolled Studies
Males Only (N=849)

Body system Adverse event	Patients Reporting AEs Number	%
BODY		
PAIN ABDO	34	4.0
HEADACHE	10	1.2
ASTHENIA	5	0.6
FEVER	3	0.4
PAIN	1	0.1
CHILLS	1	0.1
DIC		
DIARRHEA	11	1.3
NAUSEA	11	1.3
DYSPEPSIA	2	0.2
VOMIT	1	0.1
NAUSEA VOMIT DIAR	1	0.1
UG		
URIN ABNORM	6	0.7
EDEMA LABIA	1	0.1
MAN		
SGPT INC	6	0.7
NER		
DIZZINESS	2	0.2
SOMNOLENCE	2	0.2
SS		
EYE DIS	1	0.1
PAIN EAR	1	0.1
RES		
EPISTAXIS	1	0.1
LUNG DIS	1	0.1

TABLE 9
Adverse Events: HIV- Uninfected Patients (Ages 12 Years and Older) in Placebo Control Groups
Males Only (N=69)

Body system Adverse event	Patients Reporting AEs Number	%
BODY		
PAIN ABDO	9	13.0
HEADACHE	3	4.3
ASTHENIA	1	1.4
DEATH	1	1.4
DIG		
DIARRHEA	2	2.9
DYSPEPSIA	1	1.4
NER		
DIZZINESS	2	2.9
SOMNOLENCE	1	1.4
EMOTION LABIL	1	1.4
UG		
URIN ABNORM	1	1.4
DYSURIA	1	1.4

TABLE 10
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Tablets in Controlled and Uncontrolled Studies
Females Only (N=779)

Body system Adverse event	Patients Reporting AEs Number	%
BODY		
PAIN ABDO	75	9.6
HEADACHE	41	5.3
ASTHENIA	5	0.6
PAIN	4	0.5
FEVER	3	0.4
ALLERG REACT	3	0.4
PAIN PELVIC	2	0.3
FLU SYND	1	0.1
CHILLS FEVER	1	0.1
DIG		
DIARRHEA	59	7.6
NAUSEA	39	5.0
VOMIT	6	0.8
NAUSEA/VOMIT	3	0.4
ANOREXIA	2	0.3
DYSPEPSIA	1	0.1
NAUSEA VOMIT DIAR	1	0.1
FLATUL	1	0.1
CONSTIP	1	0.1
THIRST	1	0.1
DRY MOUTH	1	0.1
NER		
DIZZINESS	14	1.8
SOMNOLENCE	8	1.0
HYPESTHESIA	1	0.1
INSOMNIA	1	0.1
TREMOR	1	0.1
UG		
URIN ABNORM	7	0.9
DYSURIA	2	0.3
METRORRHAGIA	1	0.1
PAIN KIDNEY	1	0.1
AMENORRHEA	1	0.1

TABLE 10 (continued)
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Tablets in Controlled and Uncontrolled Studies
Females Only (N=779)

Body system Adverse event	Patients Reporting AEs Number	 %
MAN		
SGPT INC	8	1.0
SKIN		
RASH	3	0.4
PRURITUS	2	0.3
RASH VESIC BULL	1	0.1
SS		
EYE DIS	2	0.3
CV		
SYNCOPE	1	0.1
TACHYCARDIA	1	0.1
MS		
MYALGIA	1	0.1
BONE FRACT SPONTAN	1	0.1
RES		
PHARYNGITIS	1	0.1
MS/NER		
CRAMPS LEG	1	0.1
CV/NER		
HYPERTENS	1	0.1

TABLE 11
Adverse Events: HIV- Uninfected Patients (Ages 12 Years and Older) in Placebo Control Groups
Females Only (N=60)

Body system Adverse event	Patients Reporting AEs Number	%
BODY		
PAIN ABDO	2	3.3
EDEMA FACE	1	1.7
DIG		
DIARRHEA	2	3.3
NER		
SOMNOLENCE	1	1.7

Caucasians and Hispanics: Adverse events in HIV-uninfected patients who received nitazoxanide tablets or placebo in controlled and uncontrolled studies are shown in Tables 12 and 13 for Caucasian patients and Tables 14 and 15 for Hispanic patients, respectively.

TABLE 12
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Tablets in Controlled and Uncontrolled Studies
Caucasian Only (N=1,086)

Body system Adverse event	Patients Reporting AEs Number	%
BODY		
PAIN ABDO	34	3.1
ASTHENIA	8	0.7
HEADACHE	7	0.6
FEVER	1	0.1
DIG		
NAUSEA	18	1.7
DIARRHEA	11	1.0
DYSPEPSIA	2	0.2
VOMIT	1	0.1
ANOREXIA	1	0.1
CONSTIP	1	0.1
DRY MOUTH	1	0.1
MAN		
SGPT INC	14	1.3
NER		
DIZZINESS	8	0.7
SOMNOLENCE	3	0.3
UG		
URIN ABNORM	6	0.6
DYSURIA	2	0.2
MS		
BONE FRACT SPONTAN	1	0.1

TABLE 13
Adverse Events: HIV- Uninfected Patients (Ages 12 Years and Older) in Placebo Control Groups
Caucasian Only (N=79)

Body system Adverse event	Patients Reporting AEs Number	%
BODY		
PAIN ABDO	2	2.5
EDEMA FACE	1	1.3
ASTHENIA	1	1.3
DEATH	1	1.3
DIG		
DIARRHEA	1	1.3
DYSPEPSIA	1	1.3
NER		
DIZZINESS	2	2.5
SOMNOLENCE	2	2.5
UG		
URIN ABNORM	1	1.3
DYSURIA	1	1.3

TABLE 14
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Tablets in Controlled and Uncontrolled Studies
Hispanic Only (N=512)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	72	14.1
HEADACHE	44	8.6
FEVER	5	1.0
PAIN	5	1.0
ALLERG REACT	3	0.6
ASTHENIA	2	0.4
PAIN PELVIC	2	0.4
FLU SYND	1	0.2
CHILLS	1	0.2
CHILLS FEVER	1	0.2
DIG		
DIARRHEA	59	11.5
NAUSEA	30	5.9
VOMIT	6	1.2
NAUSEA/VOMIT	3	0.6
NAUSEA VOMIT DIAR	2	0.4
DYSPEPSIA	1	0.2
ANOREXIA	1	0.2
FLATUL	1	0.2
THIRST	1	0.2
NER		
DIZZINESS	8	1.6
SOMNOLENCE	7	1.4
HYPESTHESIA	1	0.2
INSOMNIA	1	0.2
TREMOR	1	0.2
UG		
URIN ABNORM	6	1.2
METRORRHAGIA	1	0.2
PAIN KIDNEY	1	0.2
AMENORRHEA	1	0.2
EDEMA LABIA	1	0.2

TABLE 14 (continued)
Adverse Events: HIV- Uninfected Patients Who Received Nitazoxanide Tablets in Controlled and Uncontrolled Studies
Hispanic Only (N=512)

Body system Adverse event	Patients Reporting AEs Number	%
SKIN		
RASH	2	0.4
PRURITUS	2	0.4
RASH VESIC BULL	1	0.2
SS		
EYE DIS	3	0.6
PAIN EAR	1	0.2
RES		
EPISTAXIS	1	0.2
LUNG DIS	1	0.2
PHARYNGITIS	1	0.2
CV		
TACHYCARDIA	1	0.2
MS		
MYALGIA	1	0.2
MS/NER		
CRAMPS LEG	1	0.2
CV/NER		
HYPERTENS	1	0.2

TABLE 15
Adverse Events: HIV- Uninfected Patients (Ages 12 Years and Older) in Placebo Control Groups
Hispanic Only (N=50)

Body system Adverse event	Patients Reporting AEs Number	%
BODY		
PAIN ABDO	9	18.0
HEADACHE	3	6.0
DIG		
DIARRHEA	3	6.0
NER		
EMOTION LABIL	1	2.0

In the Reviewer's opinion, any differences seen in adverse event rates between male and female patients or Caucasian and Hispanic patients treated with nitazoxanide tablets are not considered clinically meaningful and do not warrant reporting by sex or race in the product labeling.

8.4 Pediatrics

Children (aged 1 to 11 years):
Nitazoxanide suspension has previously been shown to be safe and effective for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in children aged 1 to 11 years. NDA 21-498 for this indication was approved by the FDA on November 22, 2002. See the approved labeling for specific information on efficacy and safety of nitazoxanide suspension in this age group.

Nitazoxanide tablets have not been evaluated for safety and efficacy in children less than 12 years of age.

Adolescents (aged 12 years and older):
Nitazoxanide tablets and suspension were evaluated for safety and efficacy in adolescent patients aged 12 to 17 years for the treatment of diarrhea caused by *Giardia lamblia* in Study RM01-3011. Clinical and parasitological response rates at Day 7-10 for adolescents and adults by treatment group did not reveal any clinically meaningful difference. Similarly, adverse events in adolescents and adults by treatment group were evaluated and no clinically meaningful differences were observed. (See Review of Study RM01-3011 in Section 10.1 of this document).

Nitazoxanide tablets have been evaluated for safety in 197 adolescent patients aged 12 to 17 years and 35 corresponding patients receiving placebo, including patients enrolled in Study RM01-3011. Tables 17 and 18 list the incidence of adverse events in for nitazoxanide tablets and placebo, respectively, in adolescent patients. For comparison, adverse events from 1431 patients $\geq$ 18 years treated with nitazoxanide tablets and 94 corresponding patients receiving placebo are shown in Tables 19 and 20, respectively. Adverse events are similar between nitazoxanide tablets and placebo in both adolescents and adults.

Clinical Reviewer's Comment: Tables 16 through 19 were created by the applicant and submitted to the NDA on June 25, 2004.

TABLE 16
Adverse Events: Patients Treated with Nitazoxanide Tablets
Aged 12 through 17 Years (N=197)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	29	14.7
HEADACHE	13	6.6
FEVER	3	1.5
ASTHENIA	2	1.0
PAIN	1	0.5
CHILLS	1	0.5
DIG		
DIARRHEA	9	4.6
NAUSEA	7	3.6
NAUSEA VOMIT DIAR	1	0.5
NER		
DIZZINESS	5	2.5
SOMNOLENCE	1	0.5
UG		
URIN ABNORM	2	1.0
DYSURIA	1	0.5
EDEMA LABIA	1	0.5
SS		
EYE DIS	2	1.0

TABLE 17
Adverse Events: Patients in Placebo Control Groups
Aged 12 through 17 Years (N=35)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	6	17.1
HEADACHE	2	5.7
NER		
SOMNOLENCE	1	2.9
EMOTION LABIL	1	2.9

TABLE 18
Adverse Events: Patients Treated with Nitazoxanide Tablets
Aged 18 Years and Older (N=1,431)

Body system Adverse event	Patients Reporting AEs Number	 %
BODY		
PAIN ABDO	80	5.6
HEADACHE	38	2.7
ASTHENIA	8	0.6
PAIN	4	0.3
FEVER	3	0.2
ALLERG REACT	3	0.2
PAIN PELVIC	2	0.1
FLU SYND	1	0.1
CHILLS FEVER	1	0.1
DIG		
DIARRHEA	61	4.3
NAUSEA	43	3.0
VOMIT	7	0.5
NAUSEA/VOMIT	3	0.2
DYSPEPSIA	3	0.2
ANOREXIA	2	0.1
NAUSEA VOMIT DIAR	1	0.1
FLATUL	1	0.1
CONSTIP	1	0.1
THIRST	1	0.1
DRY MOUTH	1	0.1
NER		
DIZZINESS	11	0.8
SOMNOLENCE	9	0.6
HYPESTHESIA	1	0.1
INSOMNIA	1	0.1
TREMOR	1	0.1
UG		
URIN ABNORM	11	0.8
DYSURIA	1	0.1
METRORRHAGIA	1	0.1
PAIN KIDNEY	1	0.1
AMENORRHEA	1	0.1

TABLE 18 (continued)
Adverse Events: Patients Treated with Nitazoxanide Tablets
Aged 18 Years and Older (N=1,431)

Body system Adverse event	Patients Reporting AEs Number	%
MAN		
SGPT INC	14	1.0
SKIN		
RASH	3	0.2
PRURITUS	2	0.1
RASH VESIC BULL	1	0.1
RES		
EPISTAXIS	1	0.1
LUNG DIS	1	0.1
PHARYNGITIS	1	0.1
SS		
EYE DIS	1	0.1
PAIN EAR	1	0.1
CV		
SYNCOPE	1	0.1
TACHYCARDIA	1	0.1
MS		
MYALGIA	1	0.1
BONE FRACT SPONTAN	1	0.1
MS/NER		
CRAMPS LEG	1	0.1
CV/NER		
HYPERTENS	1	0.1

TABLE 19
Adverse Events: Patients in Placebo Control Groups
Aged 18 Years and Older (N=94)

Body system Adverse event	Patients Reporting AEs Number	%
BODY		
PAIN ABDO	5	5.3
HEADACHE	1	1.1
EDEMA FACE	1	1.1
ASTHENIA	1	1.1
DEATH	1	1.1
DIC		
DIARRHEA	4	4.3
DYSPEPSIA	1	1.1
NER		
DIZZINESS	2	2.1
SOMNOLENCE	1	1.1
UC		
URIN ABNORM	1	1.1
DYSURIA	1	1.1

In summary, the efficacy and adverse event profile of nitazoxanide tablets and suspension in adolescent patients aged 12 years and older are similar to adults. Therefore, no

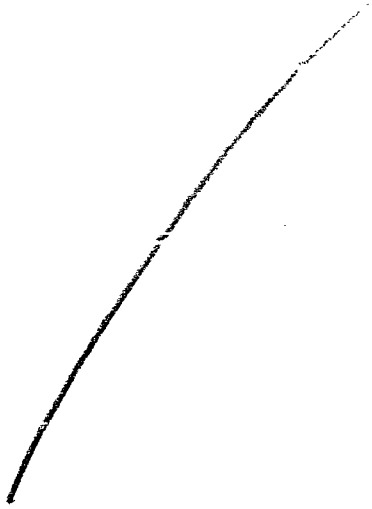
adjustments to the adult dosing of nitazoxanide tablets or suspension in adolescents are warranted based on efficacy. Reporting of adverse events for adolescents separate from adults in the product labeling is also not warranted. Children less than 12 years of age should be dosed with the suspension formulation of nitazoxanide and adverse events for children should be reported separately from adults and adolescents.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

The applicant was asked by the Division on January 28, 2004 to provide additional information to support their request for



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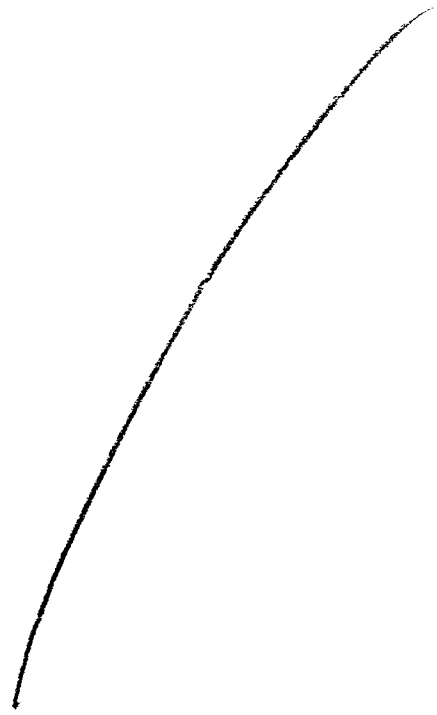

8.7 Other Relevant Materials

None.

9 Overall Assessment

9.1 Conclusions on Available Data

Nitazoxanide (Alinia®) tablets and oral suspension are safe and effective for the treatment of diarrhea caused by *Giardia lamblia* in adults and adolescent patients 12 years of age and older. Nitazoxanide tablets and oral suspension are recommended for approval for this indication.

9.2 Recommendation on Regulatory Action

Nitazoxanide (Alinia®) tablets, as a treatment regimen of one 500 mg tablet taken twice daily for 3 days, should be approved for the treatment of diarrhea caused by *Giardia lamblia* in adults and adolescent patients aged 12 years and older. In addition, nitazoxanide oral suspension, as a treatment regimen of 500 mg (25 mL) taken twice daily for 3 days, should also be approved for the treatment of diarrhea caused by *Giardia lamblia* in adults and adolescent patients aged 12 years and older.

Nitazoxanide (Alinia®) tablets should not be approved for

9.3 Recommendation on Post-Marketing Actions

There are no recommendations for risk management activity or required Phase 4 studies at this time.

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

The label for nitazoxanide oral suspension in pediatrics aged 1 to 11 years (approved previously) and nitazoxanide tablets in adults and adolescents aged 12 years and older (the subject of this submission) were merged in order to help prescribers find all the pertinent information for nitazoxanide in one place, rather than having two separate labels.

A summary of the important changes made to the combined label are discussed below:

CLINICAL PHARMACOLOGY: Pharmacokinetic information on nitazoxanide tablets in patients aged 12 years and older was added. Additional information on the metabolism was also added (i.e., *in vitro* metabolism studies have demonstrated that tizoxanide has no significant inhibitory effect on cytochrome P450 enzymes).

INDICATIONS AND USAGE: This section is formatted by indication, such that diarrhea caused by *Giardia lamblia* is mentioned first followed by *Cryptosporidium parvum.* Both nitazoxanide oral suspension, in patients 1 year of age and older, and nitazoxanide tablets, in patients 12 years and older, are indicated for diarrhea caused by *Giardia lamblia.* Only nitazoxanide oral suspension, in children 1 to 11 years of age, is indicated for diarrhea caused by *Cryptosporidium parvum.* Following the *Cryptosporidium* indication, a sentence has been added which indicates that neither formulation has been shown to be superior to placebo for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients. The prescriber is referred to the **CLINICAL STUDIES** section. The purpose of including this sentence is to alert precribers to the fact that studies have been conducted in the HIV population and the drug was not found to be effective.

It is also indicated in this section that the safety and effectiveness of nitazoxanide tablets and oral suspension have not been established in patients 12 years of age and older for the treatment of diarrhea caused by *Cryptosporidium parvum.*

PRECAUTIONS, Pediatric Use: A statement has been added which says that nitazoxanide oral suspension should be used to dose patients younger than 12 years of age, since a single nitazoxanide tablet contains a greater amount of nitazoxanide than is recommended for pediatric dosing. The prescriber is referred to the **DOSAGE AND ADMINISTRATION** section to obtain information on dosing of nitazoxanide oral suspension in pediatric patients.

PRECAUTIONS, Geriatric Use: This section was worded using the standard text from the geriatric labeling rule (21 CFR 201.57), which states that insufficient numbers of patients aged 65 years of age and older were studied to determine if they respond differently from younger patients and that therapy must be administered with caution to patients with renal or hepatic impairment.

PRECAUTIONS, HIV-Infected or Immunodeficient Patients: This section contains two sentences, the first of which states that nitazoxanide tablets and oral suspension have not been studied for the treatment of diarrhea caused by *Giardia lamblia* in HIV-infected or immunodeficient patients. The second statement is identical to the one in the **INDICATIONS AND USAGE** section which says that nitazoxanide tablets and oral suspension have not been shown to be superior to placebo for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients, and the prescriber is referred to the **CLINICAL STUDIES section.**

ADVERSE REACTIONS: The adverse events reported for nitazoxanide tablets in adults and adolescents are reported separately from the pediatric patients who received nitazoxanide oral suspension. In addition, a statement was added following the section on nitazoxanide oral suspension which states that the adverse events seen in adult patients treated with nitazoxanide oral suspension were similar to those observed in adult patients treated with nitazoxanide tablets.

DOSAGE AND ADMINISTRATION: The recommended dosing for the tablets and oral suspension is represented in a table organized by indication, which follows the format for the **INDICATIONS AND USAGE** section. The indication for the treatment of diarrhea caused by *Giardia lamblia* in ages 1-3, 4-11, and ≥ 12 years is followed by the recommended dosing for diarrhea caused by *Cryptosporidium parvum* in patients 1-3 and 4-11 years. Immediately following the table is a statement that the safety and effectiveness of nitazoxanide tablets and oral suspension have not been established in patients 12 years of age and older. This is followed by a sentence stating that nitazoxanide tablets are not recommended in patients 11 years or younger. This section concludes with two the two identical sentences from the **PRECAUTIONS, HIV-Infected or Immunodeficient Patients** section regarding lack of data in HIV patients with *Giardia lamblia* and the fact that nitazoxanide has not been shown to be superior to placebo in HIV patients with *Cryptosporidium parvum.*

CLINICAL STUDIES: The design of Study RM01-3011 is discussed in the section, including the location where the study was conducted (Peru and Egypt), and the fact that some of the patients with 'well' clinical responses had *Giardia lamblia* cysts in their stool samples 4 to 7 days following the end of treatment. It was added that the relevance of stool examination results in these patients is unknown. A final sentence was added that patients should be managed based upon clinical response to treatment.

The clinical response rates for Study RM-NTZ-98-001 were included in a table with the clinical response rates for Study RM01-3011, using the numbers from the FDA Medical Officer's analysis conducted by Dr. Rosemary Johann-Liang in her review of the original submission of NDA 21-497.

The information regarding patients who were clinically 'well', yet were found to be positive for cysts (or oocysts) following the end of treatment was added to the discussion of each clinical trial in this section, as well as the fact that the relevance of stool examination in these patients is unknown and that they should be managed clinically.

Data on , was not included in this section.

9.5 Comments to Applicant

None.

10 APPENDIX

10.1 Review of Individual Study Report – Protocol RM01-3011

Multicenter, Double-Blind, Placebo-Controlled Study of Nitazoxanide Tablets in the Treatment of Giardiasis in Adults and Adolescents

All of the tables in this review are a reproduction of the applicant's original tables in the NDA submission, except where noted otherwise.

Study Dates: February 2003 to November 2003
Date of Final Report: January 9, 2004

10.1.1 Ethical Conduct of the Study

Prior to initiation of the study, the study protocol and informed consent was approved by the [redacted] for the site in [redacted] Peru and by the ethical committee of the [redacted] for the site in [redacted], Egypt.

Both study medications are approved for marketing in Peru, nitazoxanide as Colufase® and metronidazole as Flagyl®.

The study was performed in accordance with the guidelines set by the World Medical Assembly (Declaration of Helsinki, last amendment in Edinburgh, Scotland, 2000).

10.1.2 Study Objectives

The primary objective of the study was to demonstrate the efficacy of nitazoxanide tablets in the treatment of diarrhea caused by *Giardia lamblia* in non-immunodeficient adults and adolescents.

The secondary objective of the study was to demonstrate non-inferiority of nitazoxanide tablets compared to nitazoxanide suspension in the treatment of diarrhea caused by *Giardia lamblia* (delta of 20%).

10.1.3 Study Design

The study was a multicenter, placebo-controlled study evaluating the efficacy and safety of nitazoxanide tablets and suspension in the treatment of diarrhea caused by *Giardia lamblia*. A total of 135 evaluable patients (≥ 12 years) were to be selected according to the study inclusion and exclusion criteria.

Patients presenting to the hospital with diarrhea were offered the opportunity to participate in the study. The patient was informed of the nature of the study and signed consent was obtained prior to participation in the study.

10.1.4 Microbiologic Procedures

During a screening evaluation, fecal samples from adults and adolescents with diarrhea were subjected to microscopic examination (concentrated and unconcentrated stool) for the detection of cysts of *Giardia lamblia* and for the identification of other parasites. If *Strongyloides stercoralis* was suspected, a Baermann concentration test was carried out.

Stool samples were also subjected to either an immunofluorescence assay — —) or an enzyme immunoassay (— — for the detection of *G. lamblia* and *C. parvum*. Patients were considered positive for cysts of *G. lamblia* if any of the three tests for *G. lamblia* were positive. If a patient was not positive for cysts of *G. lamblia* at baseline, he/she was excluded from the analysis of efficacy.

Clinical Reviewer's Comment: The applicant noted that the — test was recalled from the market and therefore not used in this study. Only the — assay was used.

Stool samples were also cultured to eliminate bacterial causes of diarrhea such as salmonellosis and shigellosis. Patients enrolled with bacterial causes of diarrhea were excluded from the analysis of clinical efficacy.

Patients were evaluated again 7 to 10 days after the start of therapy with collection of two stool samples at least 24 hours apart between Day 7 and Day 10. Stool samples were subjected to examination for cysts of *G. lamblia* using microscopic examination (concentrated and unconcentrated stool), and immunofluorescence assay. If the immunofluorescence assay was not able to be performed, the microscopic examination was relied upon as the sole determination of parasitological response. Patients were considered positive for cysts of *G. lamblia* if any of these three tests were positive.

10.1.5 Inclusion Criteria

- Age ≥ 12 years.
- Patients with diarrhea (≥ 3 bowel movements/day) with one or more enteric symptoms such as abdominal pain or cramps, nausea, vomiting, tenesmus or malabsorption.
- *G. lamblia* cysts detected in a stool specimen obtained 7 days before enrollment

10.1.6 Exclusion Criteria

- Patients with identified causes of diarrhea other than *G. lamblia* (e.g., pathogenic bacteria, *Cryptosporidium parvum*, *Entamoeba histolytica*).
- Use within 2 weeks of enrollment of any drug or therapy with antiprotozoal activity including 5-nitroimidazoles such as metronidazole, tinidazole, ornidazole, secnidazole, hydroxyquinoline derivatives, trimethoprimsulfamethoxazole (trimethoprim-sulfamethoxazole may be used within 2 weeks of enrollment, but may not be used concomitantly during therapy) and acetamide analogues such as diloxanide, paromomycin and nitazoxanide.
- Females who are pregnant, suspected of being pregnant or breast feeding [urine pregnancy tests are required for all women of childbearing potential or who are two years or less post-menopausal].
- Serious systemic disorders incompatible with the study.
- History or hypersensitivity to nitazoxanide.
- Patients in whom the possibility of receiving a placebo and not being able to receive immediately an effective treatment will be incompatible with the severity of the patient's illness according to the Investigator's judgment.
- Patients known or suspected of having AIDS.
- Patients with known immune deficiencies (e.g., cancer chemotherapy patients, patients with hypogammaglobulinemia).

10.1.7 Removal of Patients

Patients may have been removed from the study by the Investigator for any of the following reasons:

- Medical conditions that require study discontinuation.
- Intercurrent illness which would, in the judgment of the Investigator in consultation with the medical monitor, tend to affect the assessment of clinical and mental status to a significant degree.
- Noncompliance with the protocol.
- Patient desire to discontinue participation.

10.1.8 Treatments Administered/Treatment Compliance

Study medications were dispensed during the baseline evaluation. The dose regimens were:

Group 1: One nitazoxanide 500 mg tablet with food each morning and evening for 3 consecutive days.

Group 2: 25 mL of nitazoxanide (100 mg/5 mL) suspension with food each morning and evening for 3 consecutive days.

Group 3: One placebo tablet with food each morning and evening for 3 consecutive days.

Patients were instructed to take the study medication with food.

Patient compliance with the protocol was recorded in the case report form at the Day 7-10 evaluation. Patients were required to return any unused study medication.

At the time of dispensing the medication, each patient was given a diary for recording administration of the medication, adverse events and information related to the number of stools per day and their consistency.

The study medications were provided by The Romark Institute for Medical Research. The active formulations for this study were a tablet (batch 97E07 manufactured by —, containing 500 mg of nitazoxanide plus standard excipients and a strawberry-flavored suspension containing 100 mg/5 mL of nitazoxanide after reconstitution (batch 26726 manufactured by —. The placebo tablets (batch 99I21 manufactured by — had the same appearance and inactive ingredients as the active tablets.

The study medication was packaged and labeled by the Sponsor except that the powder for suspension was packaged in bottles by the manufacturer, —. — The tablets (verum and placebo) were packaged for each patient in an HDPE bottle, each bottle containing six 500 mg nitazoxanide tablets or six placebo tablets according to the treatment regimen. The suspension was packaged for each patient in three small brown glass bottles, each bottle containing 20.4 grams of powder for reconstitution as 60 mL of 100 mg/5 mL nitazoxanide suspension. The bottles were stored at room temperature.

10.1.9 Study Visits

During the baseline visit, the following procedures were carried out:

- confirmation that the patient satisfies all inclusion/exclusion criteria;
- complete medical history;
- physical examination, including body weight;
- urine pregnancy test for all women of child-bearing potential or who were two years or less post-menopausal;
- evaluation of clinical symptoms;
- review concomitant medications; and
- collection of a stool sample to confirm the presence of *G. lamblia* cysts.

Patients were evaluated 7 to 10 days after the start of therapy. Examinations included:

- brief physical examination including body weight;

- review of patient diary and evaluation of clinical symptoms;
- review of adverse events/side effects;
- review of compliance and collection of any unused medications; and
- collection of two stool samples at least 24 hours apart between Day 7 and Day 10.

After they had completed the protocol, and based upon the Investigator's judgment, patients with an unsatisfactory clinical response at the Day 7-10 evaluation were offered a standard course of metronidazole.

All clinical responders at the Day 7-10 evaluation were to return between Days 14 and 17 and submit one fecal sample for examination for *G. lamblia* cysts or trophozoites.

At the time of each return visit, the patients were questioned regarding the occurrence and nature of any adverse events. Any subject affected was examined by the Investigator as deemed necessary to ascertain the course of the event and any residual effects. All patients were instructed to contact the Investigator, Investigator's assistants, or clinical personnel should the subject have any serious adverse experiences.

FIGURE 1
Study Design and Schedule of Assessments

Study Procedure	Study Day			
	Pre-Study/ Screening Evaluation	Baseline (0)	Day 7-10 Follow-up Evaluation	Day 14-17 Confirmation Evaluation
Signed informed consent	X			
Stool sample for parasitological exam	X	X	X*	X
Urine pregnancy test		X		
Review of clinical symptoms		X	X	
Review of inclusion/exclusion criteria		X		
Complete medical history		X		
Physical examination		X	X	
Record concomitant medications		X	X	
Instruct patient on taking study medication/completing patient diary		X		
Record concomitant medications		X	X	
Collection of any unused study medication			X	
Collect patient diary			X	
Review / record AE's			X	
Review / record compliance			X	

* At the day 7-10 evaluation, 2 stool samples were collected at least 24 hours apart

10.1.10 Prior and Concomitant Therapy

The use within 2 weeks of enrollment of any drug or therapy with antiprotozoal activity including 5-nitroimidazoles such as metronidazole, tinidazole, ornidazole, secnidazole, hydroxyquinoline derivatives, trimethoprim-sulfamethoxazole and acetamide analogues such as diloxanide, paromomycin and nitazoxanide was prohibited. Trimethoprim-sulfamethoxazole could be used within 2 weeks of enrollment, but not concomitantly during therapy.

10.1.11 Efficacy and Safety Variables and Assessments

The primary endpoint used to determine efficacy was the clinical response, resolution of clinical symptoms associated with giardiasis.

The secondary endpoints used to determine efficacy were:

- eradication of cysts of *Giardia lamblia* from post-treatment stool samples, and
- time from beginning of treatment to passage of last unformed stool.

On Day 7-10, patients were assessed for clinical and parasitological improvement.

The criteria for evaluating clinical response were:

Well: The patient experienced no symptoms, passed no watery stools and no more than two soft stools, and had no hematochezia within the past 24 hours or the patient experienced no symptoms and passed no unformed stools (i.e., passed either no stools or only formed stools) within the past 24 hours.

Continuing illness: The passage of any number of watery stools, the passage of more than two soft stools per 24 hours, or the documentation of hematochezia or enteric symptoms plus the passage of any number of soft or watery stools during the past 48 hours.

Clinical treatment failure: Clinical deterioration or worsening of symptoms after at least 24 hours of treatment resulting in the patient being removed from the study.

Two fecal samples obtained for each patient between Days 7 and 10 were subjected to parasitological examination. The parasitological response criteria were:

Eradication: No cysts or trophozoites of *G. lamblia* observed in either of the 2 post-treatment parasitological examinations.