

10 APPENDICES

10.1 Review of Study RM01-3010

Multicenter, Double-Blind, Placebo-Controlled Study of Nitazoxanide Tablets in the Treatment of Cryptosporidiosis 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.

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10.1.1 Ethical Conduct of the Study

Prior to initiation of the study, the study protocol and informed consent were approved by the medical Ethics Review Board of the ethical committee of the Benha University Hospital of the University of Zagazig for the site in Benha, Egypt and by the Scientific Research Ethical Committee of Alexandria University for the site in Alexandria, Egypt.

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 *Cryptosporidium parvum* in non-immunodeficient adults and adolescents.

The secondary objective of the study was to demonstrate non-inferiority of nitazoxanide tablets compared to nitazoxanide oral suspension in the treatment of diarrhea caused by *Cryptosporidium parvum* in this population.

Clinical Reviewer's Comment: A threshold for noninferiority was not prespecified for the analyses of efficacy for nitazoxanide suspension compared to nitazoxanide tablets.

10.1.3 Study Design

The study was a multicenter, placebo-controlled study evaluating the efficacy and safety of nitazoxanide tablets and oral suspension in the treatment of diarrhea caused by *Cryptosporidium parvum*. A total of 90 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.

Clinical Reviewer's Comment: On June 3, 2005 the Reviewer requested the applicant provide a brief explanation of how patients were recruited for the study at each of the two sites. On June 7, 2005 the applicant responded:

Patients presenting to the outpatient clinics seeking medical care for diarrheal illness were evaluated in accordance with usual standards of care. Patients with suspected enteric protozoal infection were offered the opportunity to participate in the study, signed an informed consent and submitted a stool sample for examination. Patients with positive examinations for *Cryptosporidium* were then subjected to further evaluation for inclusion in the study.

A summary of the number of patients screened and enrolled by study site along with reasons for non-enrollment are discussed in Section 10.1.14 "Disposition of Patients".

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) and a modified Ziehl Neelsen stain for the detection of oocysts of *Cryptosporidium* and for the identification of other parasites. If *Strongyloides stercoralis* was suspected, a Baermann concentration test was carried out. Stool samples were subjected to an immunofluorescence assay () for the detection of *Cryptosporidium* and *Giardia*. Patients were considered positive for oocysts of *Cryptosporidium* if any of the tests for *Cryptosporidium* were positive. If a patient was not positive for oocysts of *Cryptosporidium* or if another enteropathogen was identified, the patient was excluded from the analysis of efficacy.

A bacterial coproculture was carried out to eliminate 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 oocysts of *Cryptosporidium* using microscopic examination (concentrated and unconcentrated stool), a modified Ziehl Neelsen stain, 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 oocysts of *Cryptosporidium* if any of these tests were positive.

All patients were to return between Days 14 and 17 and submit one stool sample for examination for *Cryptosporidium* oocysts or trophozoites.

10.1.5 Inclusion Criteria

- Age \geq 12 years.
- Patients with diarrhea (\geq 3 bowel movements/day) with one or more enteric symptoms such as abdominal pain or cramps, nausea, vomiting, fever or weight loss.
- *Cryptosporidium* oocysts detected in a stool specimen obtained 7 days before enrollment (microscopic examination confirmed by immunofluorescence assay or enzyme immunoassay)

10.1.6 Exclusion Criteria

- Patients with identified causes of diarrhea other than *Cryptosporidium* (e.g., pathogenic bacteria, *Giardia lamblia*, *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, trimethoprim-sulfamethoxazole (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 satisfied 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 *Cryptosporidium* oocysts.

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.

All patients were to return between Days 14 and 17 and submit one fecal sample for examination for *Cryptosporidium* oocysts or trophozoites.

Clinical Reviewer's Comment: During the conduct of the study, the Division requested that a clinical assessment be performed at the Day 14-17 visit, in addition to the parasitological stool assessment, in order to correlate any potential parasitological relapse with symptomatic relapse. As per the action letter to NDA 21-818 on July 21, 2004, the applicant amended the protocol requiring a physical examination at the Day 14-17 visit. Clinical data were collected for 44 of the last 48 patients enrolled in the study. See Results for more information.

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 summarizes the study schedule of assessments.

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	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		
Collection of any unused study medication			X	
Collect patient diary			X	
Review/record AEs			X	
Review/record compliance			X	

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

Source: Figure 1 in the applicant's study report

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 cryptosporidiosis at the Day 7-10 evaluation.

The secondary endpoints used to determine efficacy were:

- eradication of oocysts of *Cryptosporidium* 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 oocysts or trophozoites of *Cryptosporidium* observed in either of the 2 post-treatment parasitological examinations.

Persistence: Oocysts or trophozoites of *Cryptosporidium* observed in at least one of the post-treatment stool examinations performed at the Day 7-10 evaluation.

Clinical Reviewer's Comment: Clinical and microbiological response criteria definitions are similar to the published IDSA guidelines for the evaluation of new anti-infective drugs for the treatment of diarrhea caused by Cryptosporidium.¹ The only difference is that the published guidelines do not mention hematochezia in the definition of continuing illness. Hematochezia is not a common symptom of cryptosporidiosis. Presence or absence of this symptom is not felt by the Reviewer to substantially impact the definition of continuing illness, as long as patients co-infected with other organisms are excluded, as was done in this study. Hematochezia is more commonly seen in patients with giardiasis or amebiasis. For patients living in Egypt, an endemic area where this study was conducted, hematochezia may indicate co-infection with one of these other pathogens. Presence of this symptom at a follow-up visit may indicate a cause of diarrhea other than Cryptosporidium.

Adverse events were reviewed at the Day 7-10 follow-up visit. Adverse events were recorded on the appropriate case report forms (CRF), and the severity of each adverse event was graded on a

¹ Cooperstock M, et al. Clin Infect Dis 1992;15(Suppl 1):S249-53.

four-point scale: mild, moderate, severe and life-threatening. Where applicable, adverse events were classified as Serious or Unexpected, and the relationship to the study drug was always recorded.

10.1.12 Statistical and Analytic Plans

The study analysis was carried out based upon the protocol and a detailed plan designed prior to locking of the database and breaking the blind.

Data for a modified intent-to-treat population was used for the primary efficacy analysis. The modified intent-to-treat population consisted of all patients randomized to the study excluding:

- patients who do not have *Cryptosporidium* oocysts in their stool at baseline, and
- patients who have other identified causes of diarrhea at baseline (e.g., pathogenic bacteria, *Giardia lamblia*, or *E. histolytica*).

A secondary analysis of all patients randomized to the study was also planned by the applicant. In addition, in the event that were a significant number of protocol deviations, the applicant planned to analyze a subset of patients who complete the study according to the protocol.

The primary efficacy analysis was defined by the protocol as a comparison of the proportion of patients with a 'well' clinical response for the nitazoxanide tablet group to that of the placebo group. Planned secondary efficacy analyses included:

- comparison of proportional clinical response rates for nitazoxanide tablets compared to nitazoxanide suspension,
- comparison of proportional clinical response rates for nitazoxanide suspension compared to placebo,
- comparison by treatment group of the median time from initiation of treatment to passage of last unformed stool,

Clinical Reviewer's Comment: The protocol did not specifically state that investigators should obtain the time from initiation of treatment to the passage of last unformed stool. This analysis was to have been a secondary efficacy analysis; however, due to a lack of data, the analysis was not performed by the applicant. The Reviewer feels that an analysis of time to response would be an interesting analysis but not necessary for determining the efficacy of the drug.

- comparison of parasitological response rates for the nitazoxanide tablets and placebo,
- comparison of the proportional parasitological response rates for the nitazoxanide tablets and suspension,
- comparison of the proportional parasitological response rates for the nitazoxanide suspension and placebo,
- inpatient correlation of parasitological outcome with clinical outcome for each treatment group,

- comparison of potential food effect on efficacy for active treatment groups, and

Clinical Reviewer's Comment: Due to the small number of patients with evaluable data, an analysis of efficacy for subgroups based on food consumption was not conducted by the applicant.

- comparison by treatment group of the results of Day 14-17 stool examinations for clinical responders.

Proportional clinical and parasitological response rates, inpatient correlation of parasitological outcome with clinical outcome, and the results of stool examinations at Day 14-17 for clinical responders were compared using Fisher's Exact tests (two-sided).

Two-sided 95% confidence intervals were calculated for the differences in the proportional clinical and parasitological response rates using the preferred method described by Newcombe (1998) with correction for continuity. The comparison by treatment group of the median time from the beginning of treatment to the passage of the last unformed stool was conducted using Kaplan-Meier survival analysis.

Adverse events were summarized for each treatment group, and the proportions of patients in each group experiencing adverse events were compared using chi-square tests.

10.1.13 Determination of Sample Size

Assuming a clinical response rate of 80% for the test drug and a 40% response rate for the placebo (due to the self-limiting nature of the disease) and using the normal approximation to the binomial distribution, a sample size of 30 patients for each of the treatment arms (90 patients total) was deemed by the applicant to be sufficiently powerful (85%) to detect a difference between the response rates of patients treated with nitazoxanide tablets or the nitazoxanide oral suspension and those treated with placebo tablets, at the 5% significance level (two-sided test).

The applicant determined it was not possible to accurately project the number of patients that might be nonevaluable to other identified causes of diarrhea or lack of *Cryptosporidium* oocysts in their stool at baseline. In order to adjust for this uncertainty, the total number of patients planned for enrollment (90) was increased by one for each patient considered non-evaluable due to lack of *Cryptosporidium* oocysts in the baseline stool sample or due to other identified causes of diarrhea at baseline.

Clinical Reviewer's Comment: Four patients did not have Cryptosporidium oocysts in their baseline stool sample. According to the protocol, four additional patients should have been enrolled to replace these patients in the efficacy analysis. Because of the small number of patients involved and the difficulty in recruiting patients, the applicant determined that a sample

size of 86 patients was sufficient and did not replace the 4 patients. The Reviewer agrees with the applicant's approach.

10.1.14 Disposition of Patients

Ninety (90) patients were enrolled and all completed the study.

Clinical Reviewer's Comment: On June 3, 2005 the Reviewer requested the applicant provide the number of patients screened at each of the two study sites and a summary of the reasons for non-eligibility. The applicant replied on June 7, 2005:

Summary of patients screened at Alexandria study site:

Patients screened = 427

Patients enrolled = 38

Patients not enrolled = 389

Reason for not being enrolled:

No Cryptosporidium oocysts in stool sample at screening = 287

Other organisms in stool sample at screening = 98

(44 Blastocystis hominis, 21 Entamoeba histolytica/dispar, 15 Entamoeba coli, 9 Giardia lamblia, 2 B. hominis and E. coli, 1 Cyclospora cayetanensis, 1 Ascaris lumbricoides, 1 Iodamoeba butschlii)

Subjects declined participation in the study prior to enrollment = 4

TOTAL 389

Summary of patients screened at Benha study site:

Patients screened = 3,498

Patients enrolled = 52

Patients not enrolled = 3,446

Reason for not being enrolled

No Cryptosporidium oocysts in stool sample at screening = 3,421

Other organisms in stool sample at screening = 9

(3 Giardia lamblia, 2 Blastocystis hominis, 2 Entamoeba histolytica/dispar, 1 Entamoeba coli, 1 Giardia lamblia and Hymenolepis nana)

Cryptosporidium oocysts in stool sample by immunofluorescence but not by microscopy = 8

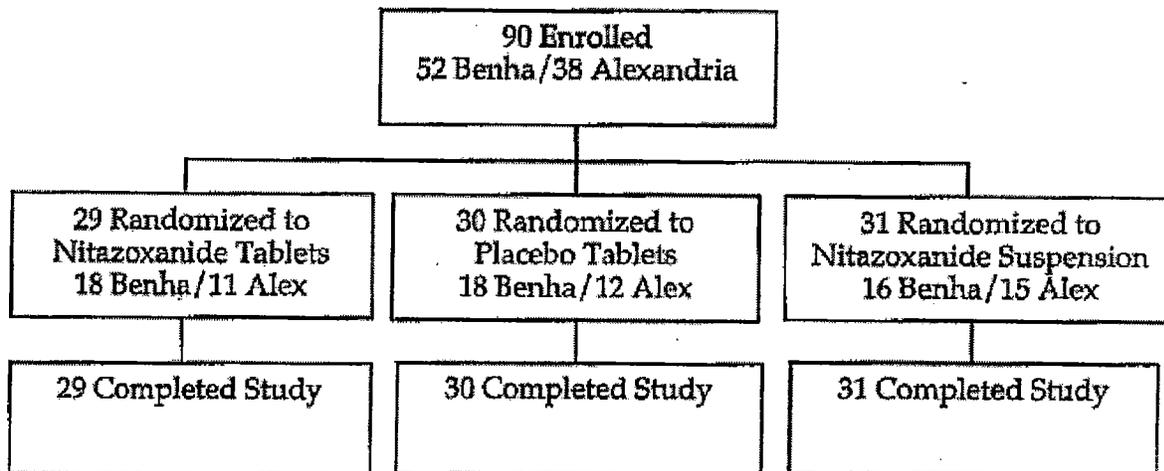
Cryptosporidium oocysts in stool sample by microscopy but not by immunofluorescence = 5

Subjects declined participation in the study prior to enrollment = 3

TOTAL 3,446

A flowchart of patient disposition, for those enrolled into the study, is present in Figure 2.

FIGURE 2
Patient Disposition Flowchart



Source: Figure 2 in the applicant's study report

The protocol called for use of a modified intent-to-treat (MITT) population for the primary efficacy analysis. This population was to consist of all patients randomized excluding

- patients who do not have *Cryptosporidium* oocysts in their stool at baseline, and
- patients who have other identified causes of diarrhea at baseline (e.g., pathogenic bacteria, *Giardia lamblia*, or *E. histolytica*).

Four patients were excluded from the MITT population because they did not have *Cryptosporidium* oocysts in the baseline stool sample (#65, #71, and #110 in the placebo group and #99 in the nitazoxanide tablet group). Patient #65 also did not have symptoms at baseline.

Clinical Reviewer's Comment: A summary of the clinical (Day 7-10) and parasitological (Day 7-10 and Day 14-17) results for these 4 patients excluded from the MITT population are shown below.

<i>Patient Number/Study Site/Age/Sex</i>	<i>Treatment Group</i>	<i>Clinical Response at Day 7-10</i>	<i>Parasitological Response at Day 7-10</i>	<i>Stool Results at Day 14-17</i>
#65/Alexandria/20 yo Male	Placebo	Well	Eradicated	Negative
#71/Benha 43 yo/Male	Placebo	Well	Eradicated	Negative
#99/Alexandria/17 yo/Male	Tablets	Well	Persistence	Negative
#110/Alexandria/40 yo Male	Placebo	Well	Eradicated	Negative

Eight patients enrolled in the study had *H. nana* and/or *Blasocystis hominis* in the baseline stool sample along with *Cryptosporidium*. These patients remained evaluable in the MITT population

Clinical Reviewer's Comment: On June 3, 2005 the Reviewer requested justification why these two organisms are not considered diarrheal pathogens. On June 7, 2005 the applicant provided the following response, which was acceptable to the Reviewer.

Most *Hymenolepis nana* infections are asymptomatic and are probably caused by light or moderate worm numbers. Heavy infections (>15,000 eggs per gram of stool) can cause nonspecific intestinal symptoms, such as abdominal cramps, diarrhea and anorexia.¹ The quantity of *Hymenolepis* eggs identified in the baseline stool sample of two patients (#7 and #27) enrolled in study RM01-3010 were noted as "few". No eggs were identified in the stool sample collected at screening for these two patients.

Blasocystis hominis is not recognized as a pathogen. While there has been some debate about the potential pathogenicity of *B. hominis*, studies have shown that the incidence of gastrointestinal symptoms and pathologic findings on endoscopic examination among persons stool-positive for *B. hominis* is not different than in persons who are not infected with *B. hominis*.²⁻⁵

References:

- Schantz PM. Tapeworms (cestodiasis). *Gastroenterology Clinic of North America*. 1996; 25:637-53.
- Keystone JS, Kozarsky P. *Isospora belli*, *Sarcocystis* Species, *Blasocystis hominis* and *Cyclospora*. Mandell, Douglas & Bennett's Principles and Practice of Infectious Diseases. Eds, Mandell LM, Bennett JE, Dolin R. Vol. II. Philadelphia, Pennsylvania: Churchill Livingstone, 2000; 2915-2920.
- Chen T-L, Chan C-C, Chen H-P, Fung C-P, Lin C-P, Chan W-L, Liu C-Y. Clinical characteristics and endoscopic findings associated with *Blasocystis hominis* in healthy adults. *American Journal of Tropical Medicine and Hygiene*. 2003; 69: 213-16.

4. Shlim DR, Hoge CW, Rajah R, Rabold JG, Echeverria P. Is *Blastocystis hominis* a cause of diarrhea in travelers? A prospective controlled study in Nepal. *Clinical Infectious Diseases*. 1995; 21: 97-101.

5. Udkow MP, Markell EK. *Blastocystis hominis*: prevalence in asymptomatic and symptomatic hosts. *The Journal of Infectious Diseases*. 1993; 168: 242-4.

A summary of the clinical and parasitological results for these 8 patients can be found in the table below:

<i>Patient ID #/Study Site</i>	<i>Age/Sex</i>	<i>Treatment</i>	<i>Clinical Response at Day 7-10</i>	<i>Parasitological Response at Day 7-10</i>	<i>Stool Results at Day 14-17 (Clinical Response at Day 14-17, if available)</i>
#7/Benha	12 F	Placebo	Continuing Illness	Persistence	Positive
#18/Benha	16 M	Placebo	Continuing Illness	Persistence	Negative
#20/Benha	15 M	Placebo	Well	Persistence	Negative
#25/Benha	13 M	Nitazoxanide tablets	Well	Eradicated	Negative
#27/Benha	24 M	Nitazoxanide suspension	Well	Eradicated	Negative
#48/Benha	12 F	Placebo	Continuing Illness	Persistence	Positive
#100/Benha	36 F	Nitazoxanide tablets	Well	Eradicated	Negative (well clinical response)
#102/Benha	45 M	Nitazoxanide suspension	Well	Eradicated	Negative (well clinical response)

10.1.15 Demographic and Other Baseline Characteristics

A summary of demographic data and disease-related characteristics is presented in Table 1.

Other notable symptoms at baseline included mucus in stool (n=13), nausea (n=6), vomiting (n=3), urgency tenesmus (n=3), fever (N=2), abdominal distention (N=2), blood in the stool (n=1), pus in the stool (n=1), anorexia (n=1), flatulence (n=1), and offensive stools (n=1).

TABLE 1
Demographic and Disease-Related Characteristics

	All Subjects	Active Tablets	Placebo Tablets	Suspension	P ¹
Race:					
Caucasian	86	28	27	31	1.0
Gender:					
Male	40	14	14	12	.55
Female	46	14	13	19	
Age (years):					
Mean	30.87	35.68	27.00	29.90	.11
S.D.	15.63	17.01	14.53	14.58	
Range	12-67	12-67	12-55	12-59	
Weight (kgs):					
Mean	65.09	67.29	62.39	65.45	.60
S.D.	18.07	19.88	19.04	15.62	
Range	25-109	26-109	29.5-105	25-100	
Stool Frequency					
3-4/day	44	17	12	15	.45
5-10/day	39	10	15	14	
>10/day	3	1	0	2	
Stool Consistency					
Liquid	61	18	20	23	.64
Soft	25	10	7	8	
Abdominal pain/cramps					
Yes	59	21	20	18	.29
No	27	7	7	13	
Duration of Diarrhea					
Mean	10.98	11.50	8.44	12.71	.41
S.D.	12.27	11.31	1.76	17.30	
Median	8.50	8.00	9.00	9.00	
Range	4-100	4-58	6-12	4-100	

¹ Chi-square test used for comparing proportions, ANOVA for means.

Source: Table 5-1 in the applicant's study report

10.1.16 Assessment of Treatment Compliance

At the Day 7-10 visit, each of the 90 patients reported that they had consumed all of their medication. Completed patient diaries were returned by 85 patients and 75 patients also returned their medication bottles.

The applicant stated that upon review of the returned patient diaries, a majority of the patients indicated that they had taken the study medication with food as instructed. There were no

patients who clearly failed to take at least 4 of their 6 doses with food. Many patients did not complete the section of the diary asking for the type of food administered with the medication. Due to the small number of patients with evaluable data, an analysis of efficacy for subgroups based on food consumption was not conducted by the applicant.

Clinical Reviewer's Comment: The relative importance of systemic versus local (i.e., luminal) drug concentrations for antimicrobial activity is unknown. See discussion of food effect and bioavailability of the tablet versus the suspension in Section 8.1 "Dosing and Administration" of this review.

The Reviewer believes that the clinical data obtained in this study are sufficient to conclude efficacy of nitazoxanide tablets and nitazoxanide suspension for the treatment of diarrhea caused by Cryptosporidium. The subgroup analyses based on food consumption are not necessary.

10.1.17 Efficacy Results

10.1.17.1 Clinical Response

The clinical responses recorded at the Day 7-10 visit for the nitazoxanide tablets, nitazoxanide suspension, and the placebo tablets are summarized in Table 3. The proportion of "well" clinical responses in the active treatment group was significantly higher than in the placebo treatment group ($p < 0.0001$ for tablet versus placebo and $p = 0.0003$ for suspension versus placebo).

Clinical Reviewer's Comments: Table 3 was created by the Reviewer from two tables in the applicant's submission.

This study was not designed to determine compare nitazoxanide tablets and nitazoxanide suspension in a formal non-inferiority analysis and it is not appropriate to conclude from this study that nitazoxanide tablets and suspension are non-inferior to one another. The 95% confidence interval for the difference in clinical response rates between nitazoxanide tablets and nitazoxanide suspension, shown in Table 3 below, is centered at zero. The width of the confidence interval is wide and therefore does not rule out the possibility that a clinically meaningful difference between the tablet and suspension may exist. However, the robust difference in efficacy between the tablet and placebo suggests that the suspension formulation has superior efficacy to placebo.

TABLE 3
Clinical Response Rates by Treatment Group on Days 7-10

Response	Nitazoxanide Tablets N=28	Nitazoxanide Suspension N=31	Placebo N=27
Well	27 (96%)*	27 (87%)**	11 (41%)
	95% CI [-9.5%, 27.5%]		
Continuing Illness	1 (4%)	4 (13%)	16 (59%)

* p < 0.0001 (two-sided Fisher's exact test) for nitazoxanide tablets versus placebo (primary comparison)

** p = 0.0003 (two-sided Fisher's exact test) for nitazoxanide suspension versus placebo (secondary comparison)

Source: Tables 5-2 and 5-3 in the applicant's study report

Clinical Reviewer's Comment: The applicant performed an additional analysis of clinical response rates which included all randomized patients, including the four patients who did not have oocysts present in their baseline stool sample. There was no significant difference in the clinical response rates when these patients were included in the population.

Table 3A
Clinical Response Rates by Treatment Group
All Randomized Patients on Days 7-10

Response	Nitazoxanide Tablets N=29	Nitazoxanide Suspension N=31	Placebo N=30
Well	28 (97%)*	27 (87%)**	14 (47%)
Continuing Illness	1 (3%)	4 (13%)	16 (53%)

p < 0.0001 (Chi Square test)

* p < 0.0001 (two-sided Fisher's exact test) for nitazoxanide tablets versus placebo

** p = 0.001 (two-sided Fisher's exact test) for nitazoxanide suspension versus placebo (secondary comparison)

Source: Tables 28 in the applicant's study report

Clinical Reviewer's Comment: There were 21 patients with continuing illness at the Day 7-10 visit. The majority of patients with continuing illness also had parasitological persistence of Cryptosporidium at this visit. Only two patients with continuing illness eradicated Cryptosporidium. Both were found to have a new infection with Giardia at the Day 7-10 visit. Other organisms were found in addition to Cryptosporidium in some patients. The following table summarizes the results.

Treatment Group	Patient #/Study Site	Age/Sex	Parasitological Response at Day 7-10	Additional Organisms in Concentrated/Unconcentrated Stool at Day 7-10
Nitazoxanide Tablets	#9/Benha	42/F	Persistence	--
Nitazoxanide Suspension	#2/Benha	54/M	Persistence	--
	#72/Benha	12/F	Eradicated	Giardia lamblia
	#92/Alexandria	20/F	Persistence	--
	#109/Alexandria	15/F	Persistence	--
Placebo	#3/Benha	17/M	Eradicated	Giardia
	#7/Benha	12/F	Persistence	H. nana
	#13/Benha	12/M	Persistence	--
	#18/Benha	16/M	Persistence	Blastocystis hominis Entamoeba coli
	#22/Benha	12/M	Persistence	--
	#26/Benha	13/M	Persistence	Blastocystis hominis Entamoeba coli H. nana
	#48/Benha	12/F	Persistence	Blastocystis hominis Entamoeba coli
	#50/Benha	19/F	Persistence	--
	#58/Benha	30/F	Persistence	Blastocystis hominis
	#63/Alexandria	25/F	Persistence	--
	#78/Alexandria	22/F	Eradicated	--
	#95/Alexandria	27/M	Persistence	--
	#101/Alexandria	40/F	Persistence	Entamoeba coli
	#103/Benha	12/F	Persistence	Entamoeba coli
	#108/Alex	18/F	Persistence	--
#112/Benha	23/M	Persistence	Giardia lamblia	

10.1.17.2 Parasitological Response

The parasitological response rates at Day 7-10 for the group receiving nitazoxanide tablets, nitazoxanide suspension, and placebo tablets are summarized in Table 4. The proportion of patients eradicated (i.e., no oocysts or trophozoites observed in two stool samples collected between study Days 7 and 10) in the active treatment group was significantly higher than in the placebo treatment group ($p < 0.001$ for nitazoxanide tablets versus placebo and also for nitazoxanide suspension versus placebo).

Clinical Reviewer's Comment: Table 4 was created by the Reviewer from two tables in the applicant's submission.

This study was not designed to compare nitazoxanide tablets and nitazoxanide suspension in a formal non-inferiority analysis and it is not appropriate to conclude from this study that the nitazoxanide tablets and suspension are non-inferior to one another. The 95% confidence interval for the difference in parasitological response between nitazoxanide tablets and nitazoxanide suspension, shown in Table 4 below, is centered at zero. The width of the confidence interval is wide and therefore does not rule out the possibility that a clinically

meaningful difference between the tablet and suspension may exist. However, the robust difference in efficacy between the tablet and placebo suggests that the suspension formulation has superior efficacy to placebo.

TABLE 4
Parasitological Response Rates by Treatment Group at Day 7-10

Response	Nitazoxanide Tablets N=28	Nitazoxanide Suspension N=31	Placebo N=27
Eradication	26 (93%)*	28 (90%)**	10 (37%)
	95% CI [-16.7%, 20.7%]		
Persistence	2 (7%)	3*** (10%)	17 (100%)

* p < 0.001 (two-sided Fisher's exact test) for nitazoxanide tablets versus placebo (primary comparison)
 ** p < 0.001 (two-sided Fisher's exact test) for nitazoxanide suspension versus placebo (secondary comparison)
 *** one patient (#2) did not submit a stool sample at Day 7-10. This patient was included as a failure (persistence).
 Source: Tables 5-4 and 5-5 in the applicant's study report

Clinical Reviewer's Comment: The applicant performed an additional analysis of parasitological response rates which included all randomized patients, including the four patients who did not have oocysts present in their baseline stool sample. There was no significant difference in the parasitological response rates when these patients were included in the population.

Table 4A
Parasitological Response Rates by Treatment Group
All Randomized Patients on Days 7-10

Response	Nitazoxanide Tablets N=29	Nitazoxanide Suspension N=31	Placebo N=30
Eradicated	26 (90%)*	28 (90%)**	13 (43%)
Persistence	3 (10%)	3 (10%)	17 (57%)

p < 0.0001 (Chi Square test)
 * p = 0.0003 (two-sided Fisher's exact test) for nitazoxanide tablets versus placebo
 ** p = 0.001 (two-sided Fisher's exact test) for nitazoxanide suspension versus placebo (secondary comparison)
 Source: Tables 29 in the applicant's study report

10.1.17.3 Correlation of Clinical and Parasitological Response

The inpatient correlation of clinical and parasitological response rates at Day 7-10 by treatment group was calculated by the applicant using Fisher's exact test. The are presented in Table 5.

Clinical Reviewer's Comment: Table 5 was created by the Reviewer by merging three tables from the applicant's submission.

TABLE 5
Correlation of Clinical and Parasitological Response Rates
by Treatment Group at Day 7-10

Response	Nitazoxanide Tablets* N=28		Nitazoxanide Suspension** N=31		Placebo*** N=27	
	Well	Continuing Illness	Well	Continuing Illness	Well	Continuing Illness
Eradication	26 (93%)	0 (0%)	27 (87%)	1 (3%)	8 (30%)	2 (7%)
Persistence	1 (4%)	1 (4%)	0 (0%)	3 (10%)	3 (11%)	14 (52%)

* p = 0.0714 (two-sided Fisher's exact test)

** p = 0.0009 (two-sided Fisher's exact test)

*** p = 0.0034 (two-sided Fisher's exact test)

Source: Tables 5-6, 5-7, and 5-8 in the applicant's study report

Clinical Reviewer's Comment: The Kappa statistic is a more commonly used measure than Fisher's exact test for measuring correlation between groups. The Clinical and Statistical Reviewers calculated the association between the clinical response and parasitological response using either the Fisher's exact test or Kappa, as shown in Table 6, by treatment group and independent of treatment assignment (to provide a larger sample size in all cells of the cross tabulation). Both Fisher's exact test and the Kappa statistic, in all instances, suggest that clinical and parasitological responses in this study are positively correlated.

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TABLE 6
Association of Clinical and Parasitological Response

Nitazoxanide Tablet Group						
		Clinical Response			Total	Fisher's Exact Test p=0.0714
		"Well"	"Continuing Illness"			
Parasitological Response	Eradication	26	0	26	Kappa=0.65 with 95% C.I. (0.02, 1.0)	
	Persistence	1	1	2		
	Total	27	1	28		
Nitazoxanide Oral Suspension Group						
		Clinical Response			Total	Fisher's Exact Test p=0.0009
		"Well"	"Continuing Illness"			
Parasitological Response	Eradication	27	1	28	Kappa=0.84 with 95% C.I. (0.53, 1.0)	
	Persistence	0	3	3		
	Total	27	4	31		
Placebo Tablet Group						
		Clinical Response			Total	Fisher's Exact Test p=0.0034
		"Well"	"Continuing Illness"			
Parasitological Response	Eradication	8	2	10	Kappa=0.61 with 95% C.I. (0.31, 0.92)	
	Persistence	3	14	17		
	Total	11	16	27		
Pooled Across Treatment Groups						
		Clinical Response			Total	Fisher's Exact Test p<0.0001
		"Well"	"Continuing Illness"			
Parasitological Response	Eradication	61	3	64	Kappa=0.78 with 95% C.I. (0.63, 0.94)	
	Persistence	4	18	22		
	Total	65	21	86		

10.1.17.4 Efficacy at Follow-up (Day 14-17)

The results of stool examinations at Day 14-17 are compared by treatment group for clinical responders (as assessed at Day 7-10) in Table 7.

TABLE 7
Stool Results for Clinical Responders by Treatment Group at Day 14-17

Stool Results	Nitazoxanide Tablets N=27	Nitazoxanide Suspension N=27	Placebo N=11
Negative	27 (100%)	26 (96%)	9 (82%)
Positive	0 (0%)	1 (4%)	2 (18%)

p = 0.509 (Chi Square test)

Source: Table 5-9 in the applicant's study report

Stool examinations were also performed for patients who were clinical failures. The results are presented in Table 8.

TABLE 8
Stool Results for Clinical Failures by Treatment Group at Day 14-17

Stool Results	Nitazoxanide Tablets N=1	Nitazoxanide Suspension ¹ N=3	Placebo ¹ N=15
Negative	0 (0%)	3 (100%)	8 (53%)
Positive	1 (100%)	0 (0%)	7 (47%)

¹ one clinical failure in the active suspension group and one in the placebo group did not submit a Day 14-17 stool sample.

p = 0.1584 (Chi Square test)

Source: Table 5-9 in the applicant's study report

During the study the protocol was amended to include a physical examination on Day 14-17. Data are available for 44 patients (4 of whom were excluded from the efficacy analyses because they had no *Cryptosporidium* oocysts in their baseline stool sample). The clinical responses at Day 14-17 are presented by treatment group in Table 9.

Of the 44 patients, 33 maintained a well response thorough the Day 14-17 visit. Two patients (#72 in the suspension group and #103 in the placebo group) had continuing illness at Day 7-10, but were well at the Day 14-17 visit. All 9 other clinical failures at the Day 14-17 visit also had symptoms at the earlier Day 7-10 visit.

TABLE 9
Clinical Response by Treatment Group at Day 14-17

Response	Nitazoxanide Tablets N=12	Nitazoxanide Suspension N=17	Placebo N=11
Well	12 (100%)	15 (88%)	4 (36%)
Continuing Illness	0 (0%)	2 (12%)	7 (64%)

p < 0.0001 (Chi Square test)

Source: Table 5-11 in the applicant's study report

10.1.17.5 Efficacy Results by Study Site

This trial enrolled patients at two study sites in Egypt – one in Alexandria and one in Benha. A comparison of the demographics and disease-related characteristics of the patients by study site are shown in Table 10.

Patients enrolled at the study center in Alexandria had a higher body weight than patients enrolled at the Benha site ($p = 0.01$). The patients in Alexandria also had more frequent stools ($p < 0.0001$), were more likely to have liquid stools ($p < 0.0001$), but were less likely to report abdominal pain ($p < 0.001$) than patients at the Benha site. The age, race, gender, and duration of diarrhea of the patients enrolled at the two sites were not significantly different.

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TABLE 10
Demographic and Disease-Related Characteristics by Study Center

	All Subjects	Alexandria	Benha	P ¹
Race:				
Caucasian	86	35	51	1.0
Gender:				
Male	40	17	23	.83
Female	46	18	28	
Age (years):				
Mean	30.87	32.57	29.71	.41
S.D.	15.63	13.37	17.03	
Range	12-67	15-67	12-65	
Weight (kgs):				
Mean	65.09	70.97	61.05	.01
S.D.	18.07	7.79	21.75	
Range	25-109	58-85	25-109	
Stool Frequency				
3-4/day	44	5	39	<.0001
5-10/day	39	27	12	
>10/day	3	3	0	
Stool Consistency				
Liquid	61	35	26	<.0001
Soft	25	0	25	
Abdominal pain/cramps				
Yes	59	14	45	<.0001
No	27	21	6	
Duration of Diarrhea				
Mean	10.98	11.43	10.67	.78
S.D.	12.27	7.54	14.73	
Median	8.50	10	8	
Range	4-100	7-42	4-100	

¹ Chi Square or Fisher's Exact test used for comparing proportions, t-test for means.

Source: Table 5-12 in the applicant's study report

Clinical response rates and parasitological response rates at Days 7-10 by study site and treatment group are presented in Tables 13 and 14, respectively.

TABLE 13
Clinical Response Rates (“Well”) by Treatment Group and Study Site at Day 7-10

Treatment Group	Alexandria	Benha	<i>p</i>
Nitazoxanide Tablet	10/10 (100%) (81%)	17/18 (94%)	1.0
Nitazoxanide Suspension	13/15 (87%)	14/16 (86%)	1.0
Placebo Tablet	5/10 (50%)	6/17 (35%)	0.69

Source: Table 5-13 in the applicant’s study report

TABLE 14
Parasitological Response Rates by Treatment Group and Study Site at Day 7-10

Treatment Group	Alexandria	Benha	<i>p</i>
Nitazoxanide Tablet	10/10 (100%)	16/18 (89%)	0.52
Nitazoxanide Suspension	13/15 (87%)	15/16 (94%)	0.60
Placebo Tablet	5/10 (50%)	5/17 (29%)	0.42

Source: Table 5-14 in the applicant’s study report

The inpatient correlation of clinical and parasitological response rates by treatment group are presented in Table 15 for the Alexandria site and in Table 16 for the Benha site.

Clinical Reviewer’s Comment: Tables 17 and 18 were created by the reviewer by merging three of the applicant’s tables.

TABLE 17
Inpatient Correlation of Clinical and Parasitological Response Rates by Treatment Group – Alexandria Site

Response	Nitazoxanide Tablets N=10		Nitazoxanide Suspension** N=15		Placebo** N=10	
	Well	Continuing Illness	Well	Continuing Illness	Well	Continuing Illness
Eradication	10 (100%)	0 (0%)	13 (87%)	0 (0%)	4 (40%)	1 (10%)
Persistence	0 (0%)	0 (0%)	0 (0%)	2 (13%)	1 (10%)	4 (40%)

*p = 0.0095 (two-sided Fisher’s exact test)

**p = 0.2063 (two-sided Fisher’s exact test)

Source: Tables 5-15, 5-17, and 5-19 from the applicant’s study report

TABLE 18
Inpatient Correlation of Clinical and Parasitological Response Rates by Treatment Group – Benha Site

Response	Nitazoxanide Tablets* N=18		Nitazoxanide Suspension** N=18		Placebo*** N=9	
	Well	Continuing Illness	Well	Continuing Illness	Well	Continuing Illness
Eradication	16 (89%)	0 (0%)	14 (88%)	1 (6%)	1 (11.1%)	1 (11.1%)
Persistence	1 (6%)	1 (6%)	4 (33%)	1 (6%)	2 (22.2%)	5 (55.5%)

*p = 0.1111 (two sided Fisher's exact test)

** p = 0.1250 (two-sided Fisher's exact test)

*** p = 0.0276 (two-sided Fisher's exact test)

Source: Tables 5-16, 5-18, and 5-20 from the applicant's study report

The results of stool examinations at Day 14-17 by study site are compared in Table 19 for clinical responders and in Table 20 for clinical failures.

Clinical Reviewer's Comment: Tables 19 and 20 were created by the Reviewer by merging 3 of the applicant's tables.

TABLE 19
Parasitological Response in Stool in Clinical Responders by Treatment Group at Day 14-17

Stool Results	Nitazoxanide Tablets		Nitazoxanide Suspension*		Placebo**	
	Alexandria N=10	Benha N=17	Alexandria N=13	Benha N=14	Alexandria N=5	Benha N=6
Negative	10 (100%)	17 (100%)	13 (100%)	13 (93%)	4 (80%)	5 (83%)
Positive	0 (0%)	0 (0%)	0 (0%)	1 (7%)	1 (20%)	1 (17%)

* p 1.0 (Fisher's exact test)

** p = 1.0 (Fisher's exact test)

Source: Tables 5-21, 5-22, and 5-23 in the applicant's study report

TABLE 20
Parasitological Response in Stool in Clinical Responders by Treatment Group at Day 14-17

Stool Results	Nitazoxanide Tablets		Nitazoxanide Suspension		Placebo*	
	Alexandria N=0	Benha N=1	Alexandria N=2	Benha** N=1	Alexandria N=5	Benha** N=10
Negative	0 (0%)	0 (0%)	2 (100%)	1 (100%)	3 (60%)	5 (50%)
Positive	0 (0%)	1 (100%)	0 (0%)	0 (0%)	2 (40%)	5 (50%)

* p = 1.0 (Fisher's exact test)

** one clinical responder in the suspension group and another in the placebo group did not submit a stool sample on Day 14-17

Source: Tables 5-24, 5-25, and 5-26 in the applicant's study report

10.1.17.6 Efficacy Results by Age, Race, and Sex

Clinical Reviewer's Comment: Tables 21 through 24 were created by the reviewer.

Age: Clinical and parasitological response rates at Day 7 to 10 for adolescents (≥ 12 to < 18 years) and adults (≥ 18 years) by treatment group are shown in Tables 21A and 21B. There were only 3 patients enrolled in the study (all in the nitazoxanide tablet group) who were ≥ 65 years of age, so no analysis of elderly versus younger patients was performed.

Clinical Reviewer's Comment: In the Reviewer's opinion, the study was too small to detect clinically meaningful differences in clinical response and parasitological eradication between adolescent (≥ 12 to < 18 years) and adult (≥ 18 years) patients.

TABLE 21A
Clinical Response Rates (%) by Age and Treatment Group on Days 7-10

Response	Nitazoxanide Tablets		Nitazoxanide Suspension		Placebo	
	Adolescents (≥ 12 to < 18 yrs) N=6	Adults (≥ 18 yrs) N=22	Adolescents (≥ 12 to < 18 yrs) N=8	Adults (≥ 18 yrs) N=23	Adolescents (≥ 12 to < 18 yrs) N=9	Adults (≥ 18 yrs) N=18
Well	6 (100%)	21 (95%)	6 (75%)	21 (91%)	1 (11%)	10 (56%)
Continuing Illness	0 (0%)	1 (5%)	2 (25%)	2 (9%)	8 (89%)	8 (44%)

TABLE 21B
Parasitological Response Rates (%) by Age and Treatment Group at Day 7-10

Response	Nitazoxanide Tablets		Nitazoxanide Suspension		Placebo	
	Adolescents (< 18 yrs) N=6	Adults (≥ 18 yrs) N=22	Adolescents (< 18 yrs) N=8	Adults (≥ 18 yrs) N=23	Adolescents (< 18 yrs) N=9	Adults (≥ 18 yrs) N=18
Eradication	6 (100%)	20 (91%)	7 (87.5%)	21 (91%)	1 (11%)	9 (50%)
Persistence	0 (0%)	2 (9%)	1 (12.5%)	2 (9%)	8 (89%)	9 (50%)

Race: All patients were considered to be of Caucasian race at both study sites, so no additional efficacy analyses by race were performed.

Sex: Clinical and parasitological response rates at Day 7 to 10 for males and females by treatment group are shown in Tables 22A and 22B.

Clinical Reviewer's Comment: In the Reviewer's opinion, any differences seen in clinical response and parasitological eradication between male and female patients is not considered clinically meaningful and no adjustments to the dosing of nitazoxanide are warranted based on sex.

TABLE 22A
Clinical Response Rates (%) by Sex and Treatment Group on Days 7-10

Response	Nitazoxanide Tablets		Nitazoxanide Suspension		Placebo	
	Male N=14	Female N=14	Male N=12	Female N=19	Male N=14	Female N=13
Well	14 (100%)	13 (93%)	11 (92%)	16 (84%)	7 (50%)	4 (31%)
Continuing Illness	0 (0%)	1 (7%)	1 (8%)	3 (16%)	7 (50%)	9 (69%)

TABLE 22B
Parasitological Response Rates (%) by Sex and Treatment Group at Day 7-10

Response	Nitazoxanide Tablets		Nitazoxanide Suspension		Placebo	
	Male N=14	Female N=14	Male N=12	Female N=19	Male N=14	Female N=13
Eradication	13 (93%)	13 (93%)	11 (92%)	17 (89%)	6 (43%)	4 (31%)
Persistence	1 (7%)	1 (7%)	1 (8%)	2 (11%)	8 (57%)	9 (69%)

10.1.18 Safety Results

10.1.18.1 Safety Population

- Twenty-nine (29) patients were exposed to nitazoxanide 500 mg tablets administered as one 500 mg tablet every 12 hours for 3 days.
- Thirty-one (31) patients were exposed to nitazoxanide suspension administered 500 mg nitazoxanide in 25 ml of suspension every 12 hours for 3 days.
- Thirty (30) patients received one placebo tablet every 12 hours for three days.

10.1.18.2 Summary of Adverse Events

There were no deaths, serious adverse events, or discontinuations due to adverse events reported during the study. Sixteen (16) of the 90 patients reported a total of 25 non-serious adverse events of mild to moderate severity.

Nineteen of the 25 adverse events reported were considered possibly or probably related to study drug by the investigator. The other 6 events were considered unlikely or not related to study drug by the investigator.

Table 23 shows adverse events by treatment group.

TABLE 23
Summary of Adverse Events by Treatment Group*

Adverse Event	Active Tablet (n= 29)	Active Suspension (n= 31)	Placebo Tablet (n= 30)
<i>Body as a whole:</i>			
ASTHENIA	2 (7%)	2 (6%)	2 (7%)
HEADACHE	-	1 (3%)	1 (3%)
PAIN ABDO	1 (3%)	1 (3%)	-
ABDO ENLARGE	-	1 (3%)	-
PAIN BACK	1 (3%)	-	-
<i>Nervous:</i>			
SOMNOLENCE	1 (3%)	3 (10%)	2 (7%)
<i>Digestive:</i>			
NAUSEA	-	1 (3%)	1 (3%)
DYSPEPSIA	1 (3%)	1 (3%)	-
<i>U/G:</i>			
URINE ABNORM	1 (3%)	-	1 (3%)
DYSURIA	1 (3%)	-	-

* numbers reflect events and not patients, a patient may have had more than one event
 Source: Table 6-1 in the applicant's study report

Clinical Reviewer's Comment: The term "Urine abnorm" included patients with urine discoloration.

10.1.18.3 Safety Results by Age, Race, and Sex

Clinical Reviewer's Comment: Tables 24 and 25 were created by the Reviewer using the applicant's electronic datasets.

Age: Adverse events in adolescents (≥ 12 to < 18 years) compared to adults (≥ 18 years) are shown in Table 24. There were only 3 patients enrolled in the study (all in the nitazoxanide tablet group) who were ≥ 65 years of age, so no analysis of elderly versus younger patients was performed.

Clinical Reviewer's Comment: In the Reviewer's opinion, the numbers of adolescent (≥ 12 to < 18 years) and adult (≥ 18 years) patients in each treatment group is too small to detect clinically meaningful differences in the incidence of particular adverse events.

TABLE 24
Rates (%) of Adverse Events* by Age and Treatment Group

Adverse Event	Nitazoxanide Tablet		Nitazoxanide Suspension		Placebo	
	Adolescents (≥ 12 to < 18 yrs) N=2	Adults (≥ 18 yrs) N=6	Adolescents (≥ 12 to < 18 yrs) N=2	Adults (≥ 18 yrs) N=8	Adolescents (≥ 12 to < 18 yrs) N=1	Adults (≥ 18 yrs) N=6
Abdo Enlarge	0	0	0	1	0	0
Asthenia	1	1	1	1	1	1
Drowsiness	0	0	0	0	0	0
Dyspepsia	0	1	0	1	0	0
Dysuria	0	1	0	0	0	0
Fatigue	0	0	0	0	0	0
Headache	0	0	0	1	0	1
Nausea	0	0	0	1	0	1
Pain Abdo	0	1	0	1	0	0
Pain Back	0	1	0	0	0	0
Somnolence	1	0	1	2	0	2
Urine Abnorm	0	1	0	0	0	1

* numbers reflect events and not patients, a patient may have had more than one event

Race: All patients were considered to be of Caucasian race at both study sites, so no additional efficacy analyses by race were performed.

Sex: Adverse events in male compared to female patients by treatment group are shown in Table 25.

Clinical Reviewer's Comment: In the Reviewer's opinion, the numbers of adverse events occurring in males and females in each treatment group is too small to detect clinically meaningful differences in the incidence of particular adverse events.

TABLE 25
Rates (%) of Adverse Events* by Sex and Treatment Group

Adverse Event	Nitazoxanide Tablet		Nitazoxanide Suspension		Placebo	
	Male N=4	Female N=4	Male N=8	Female N=2	Male N=7	Female N=0
Abdo Enlarge	0	0	1	0	0	--
Asthenia	0	0	1	1	2	--
Drowsiness	0	1	0	0	0	--
Dyspepsia	1	0	1	0	0	--
Dysuria	1	0	0	0	0	--
Fatigue	0	2	0	0	0	--
Headache	0	0	1	0	1	--
Nausea	0	0	1	0	1	--
Pain Abdo	0	1	1	0	0	--
Pain Back	1	0	0	0	0	--
Somnolence	0	0	2	1	2	--
Urine Abnorm	1	0	0	0	1	--

* numbers reflect events and not patients, a patient may have had more than one event

10.1.18.4 Laboratory Findings

Laboratory tests not routinely collected.

10.1.18.5 Vital Signs

No significant findings.

10.1.19 Conclusions

Nitazoxanide tablets and nitazoxanide oral suspension were shown to be superior to placebo in terms of clinical and parasitological response at the test-of-cure visit (Day 7-10) in Study RM01-3010. Clinical and parasitological response in most patients was maintained at the follow-up visit (Day 14-17). This study was not designed to compare nitazoxanide tablets to nitazoxanide oral suspension in a formal non-inferiority analysis; and therefore, it is not appropriate to conclude that nitazoxanide tablets and suspension are non-inferior to one another.

There were no deaths, serious adverse events, or discontinuations due to adverse events reported during Study RM01-3010. Sixteen (16) of the 90 patients reported a total of 25 non-serious adverse events of mild to moderate severity. The most common events were: asthenia (2 events) in the nitazoxanide tablet group; somnolence (3 events) and asthenia (2 events) in the nitazoxanide suspension group; and asthenia (2 events) and somnolence (2 events) in the placebo group.

The study was too small to detect clinical meaningful differences in efficacy or the incidence of adverse events between adolescent and adults. Differences, if any, seen in the efficacy results between males and females are not considered clinically meaningful. There were too few adverse events in the study to be able to compare differences in the safety profile of nitazoxanide between males and females. All patients were of Caucasian race, so no analyses by race were performed. There were only 3 patients enrolled in the study (all in the nitazoxanide tablet group) who were ≥ 65 years of age, so no efficacy or safety analyses of elderly versus younger patients was performed.

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Eileen Navarro
6/14/05 04:36:52 PM
MEDICAL OFFICER

DIVISION DIRECTOR REVIEW of RESUBMISSION

Applicant: Romark Laboratories, L.C.
Tampa, Florida

Drugs: NDA 21-497 and NDA 21-818,
Alinia™ (nitazoxanide oral tablets) 500 mg
NDA 21-498/S-001
Alinia™ (nitazoxanide for oral suspension) 100 mg/5 mL

Date of Submissions:

Original NDAs: May 29, 2002
(initial User Fee due date November 29, 2002)
Resubmission: January 28, 2004
User Fee Date: July 28, 2004

Proposed Indications:

- NDA 21-497 and NDA 21-498/S-001, Treatment of diarrhea caused by *Giardia lamblia* in patients 12 years and older (adolescent and adult patients)
- NDA 21-818, Treatment of diarrhea caused by *Cryptosporidium parvum* in patients 12 years of age and older (adolescent and adult patients, non-HIV)

Proposed Age Groups and Dosage Regimens:

- Age 12 years and above: 500 mg Tablets or Oral Suspension PO BID for 3 days

Purpose of Review:

The purpose of this review is to provide a brief summary of the Division's recommendations on these applications, including the scientific and regulatory issues surrounding the approval of nitazoxanide tablets.

Recommended Regulatory Actions/ Outstanding Issues:

- NDA 21-497 and NDA 21-498/S-001 should be issued an APPROVAL letter for the treatment of diarrhea caused by *Giardia lamblia* in patients 12 years of age and older, at a dose of 500 mg BID (either tablet or suspension) PO for 3 days
- NDA 21-818 (administratively designated NDA for *C. parvum* indication) should be issued an APPROVABLE letter for the treatment of diarrhea caused by *Cryptosporidium parvum* in patients 12 years and older (non-HIV), citing the deficiencies originally included for this indication in the NDA 21-497 AE letter.

- The proposed Alinia Tablet labeling was combined with the already-approved Alinia for oral suspension labeling to form one package insert. After labeling negotiation with the company, text for this combined labeling was agreed-upon. The joint suspension/tablet labeling should be APPROVED. In addition, per DMETS recommendation, a revised
- The applicant has fulfilled most of the BPCA requirement and studied pediatric patients 1 year and older. The applicant is being asked to study pediatric patients between 0-12 months in age and results from this age group are requested to be submitted by July 21, 2009. In this study, the applicant will be asked that patients be evaluated for both clinical and parasitological outcome at the 4-7 days as well as the 11-14 days post-treatment visits.

Background:

Nitazoxanide was first submitted to the Agency as IND 48,620 on August 10, 1995, and on December 26, 1997, the NDA 20-871 for oral tablets was submitted for the proposed treatment of diarrhea caused by *Cryptosporidium parvum* in HIV positive patients. This application was taken to advisory committee, the committee voted that the studies did not show efficacy of the product in the proposed indication.

On August 31, 1999, IND 58,895 was submitted to the Agency to evaluate nitazoxanide for oral suspension in children.

The applicant obtained orphan drug designation for "treatment of cryptosporidium" on June 1, 2001 and for "intestinal giardiasis" on February 14, 2002.

On May 29, 2002, Romark submitted NDAs 21-497 (tablet) and 21-498 (oral suspension) and requested approval for treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in immunocompetent patients. One study in pediatric patients with AIDS was also submitted. Because the applications contained studies that showed superiority of nitazoxanide over placebo for *C. parvum*, an infection for which there is no currently-approved therapy, the applications were granted priority reviews.

On November 22, 2002, NDA 21-498, Alinia, (nitazoxanide) for Oral Suspension was approved for the treatment of diarrhea due to *C. parvum* and *G. lamblia* in patients 1

through 11 years of age. Two adequate and well-controlled studies demonstrated that nitazoxanide oral suspension was superior to placebo for *C. parvum*. One adequate and well-controlled study was submitted demonstrating efficacy in *G. lamblia*; the results of this study were corroborated by evidence of superiority of nitazoxanide tablets compared to placebo in a limited number of adults treated with diarrhea where *G. lamblia* was the sole pathogen. However, neither rigorous microbiological data nor substantial evidence of the correlation between clinical and microbiological endpoints was shown at this time to warrant the indication “eradication of oocysts or cysts”.

The efficacy results are presented below:

Results of Clinical Studies of *GIARDIA LAMBLIA*
that supported approval and labeling of original NDA for Alinia for oral suspension
for pediatric patients 1 through 11 years of age

Study & Site	Population	NTZ	Control	Statistic
99-010 Peru -ITT -Per protocol	Pediatric patients, sole pathogen (MOR p52)			
		Suspension	Metronidazole	95% C.I.
	Clinical	47/55 (85%)	44/55 (80%)	-9%, +20%
	Microbiology	39/55 (71%)	41/55 (75%)	-20%, +13%
	Clinical	43/48 (90%)	39/47 (83%)	-8%, +21%
	Microbiology	39/47 (83%)	37/46 (80%)	-15%, +17%
98-001 Egypt	Adult patients, sole pathogen (MOR p 49)			
		Tablet	Placebo	P value
	Clinical	8/8 (100%)	3/10 (30%)	< .02
	Microbiology	6/8 (75%)	0/10 (0%)	< .008

The adult study serves as corroborative data for the pediatric study.

Results of Clinical Studies of *CRYPTOSPORIDIUM PARVUM*
that supported approval and labeling of original NDA for Alinia for oral suspension
for patients 1 to 11 years of age

Study & Site	Population	NTZ	Placebo	P value
98-002 Egypt	HIV(-) pediatric patients (MOR p 38)			
	Clinical	21/24 (88%)	9/24 (38%)	.0004
	Parasitological	18/24 (75%)	6/25 (24%)	.0001
	OTLUS*	3.5 days	> 6 days	.0001
3007 Zambia	HIV(-) pediatric patients (MOR p 41)			
	Clinical	14/25 (56%)	5/22 (23%)	.037
	Parasitological	13/25 (52%)	3/22 (14%)	.007
3008 Zambia	HIV(+) pediatric patients treated for 3 days (MOR p 44)			
	Clinical	2/25 (8%)	6/24 (25%)	.14
	Parasitological	4/25 (16%)	5/25 (20%)	1.0
	Mortality	5/25 (20%)	4/24 (17%)	1.0

98-002 Egypt	HIV (-) adult patients with single pathogen (MOR p36)			
	Clinical	15/21 (71%)	9/21 (43%)	.118
	Parasitological	12/21 (57%)	6/21 (29%)	.118

*OTLUS – onset of therapy to time of last unformed stool

Results of Safety Analyses that supported approval of Alinia for oral suspension

		NTZ	Control
Adverse Events	Overall	40/194 (21%)	44/199 (22%)
By age group	Adult patients	14/72 (19%)	11/70 (16%)
	Pediatric patients	26/122 (21%)	33/129 (26%)
Severe adverse events	Pediatric patients	7/122 (6%)	10/129 (8%)
Deaths	Pediatric patients	7/122 (6%)	10/129 (8%)

Severe adverse events and deaths were reported in patients who were HIV positive (study 3008) or in patients on the placebo arm of the studies.

For the overall NTZ program, the applicant indicated that 2,789 patients had been exposed to NTZ, including 2,453 who received at least 3 days of treatment. Safety data has been evaluated from 910 pediatric patients studied in comparative and non-comparative studies for a range of parasitic gastrointestinal infections. Including the pediatric patients studied in the controlled trials summarized above, there were a total of 133 children 1-2 years old, 525 children 4-11 years old and 252 children 12-19 years old enrolled in these trials. Among 2,349 HIV negative patients, there were no serious adverse events reported and no drug-related adverse effects on hematology, chemistry or urinalysis. The adverse events in the NTZ treated patients did not differ significantly from those patients receiving placebo.

Treatment Regimen:

- Age 4-11 years: 10 mL (200 mg nitazoxanide) every 12 hours for 3 days
- Age 1-3 years: 5 mL (100 mg nitazoxanide) every 12 hours for 3 days

On November 22, 2002, NDA 21-497 (nitazoxanide tablets) received an APPROVABLE action, and the applicant was advised that one adequate and well-controlled study be conducted in patients 12 years of age and older for each of the requested indications: treatment of diarrhea due to *C. parvum* and treatment of diarrhea due to *G. lamblia*. In addition, the applicant was asked to develop a dissolution method for nitazoxanide tablets.

Nitazoxanide is currently approved for marketing in multiple Central and South American countries. It has been available since 1996 and approximately 30 courses of therapy have been sold in Latin America, including 10 for patients 1 through 3 years of age.

Content and Review of Resubmission:

On January 28, 2004, Romark submitted a complete response to the November 22, 2002 approvable letter. The resubmission included (1) a clinical study in adults with *G.*

lamblia comparing the tablet, suspension and placebo, (2) a proposal to base approval of *C. parvum* in adults by extrapolating results from *Giardia* studies in adults and pediatric studies of *C parvum* and (3) a dissolution method for the tablet*. The resubmission was accepted for review.

* Per review by the clinical pharmacologist, Dr. Chilukuri, the dissolution method for the tablet, USP Apparatus 2, rotation speed of 75 rpm, dissolution medium of phosphate buffer at pH 7.5 with 6% hexadecyltrimethyl ammonium bromide, is acceptable.

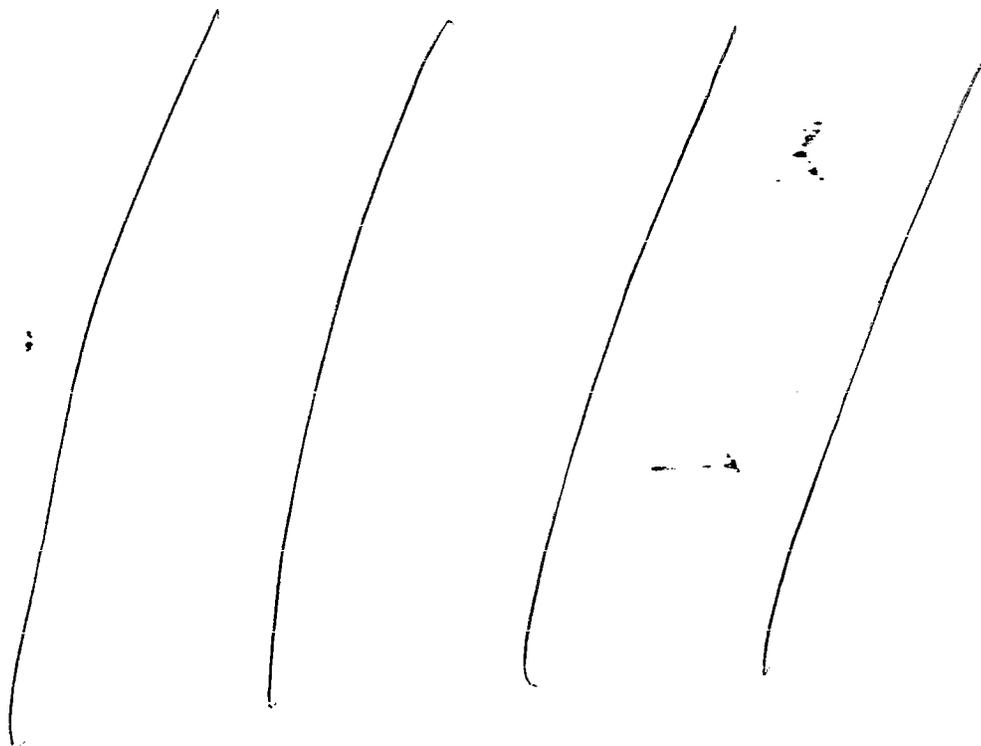
Evaluation of Efficacy and Resulting Labeling:

Giardia lamblia

Data supporting the approval of Alinia tablet in patients 12 years and older are derived from two studies: RM01-3011 was provided in the resubmission and RM-98-001 was included in the original NDA submission.

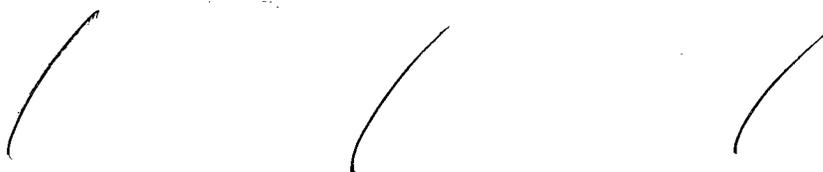
RM01-3011	A three-arm trial in patients 12 years and older randomized to either Alinia tablets 500 mg BID PO x 3 days, Alinia for oral suspension 500 mg BID PO x 3 days or placebo BID x 3 days. (n= 54 / 54 / 27 patients from Peru and Egypt)
RM-98-001	A double-blind placebo-controlled study in adults with diarrhea caused by <i>G. lamblia</i> or <i>E. histolytica</i> (n= 93 adults in Egypt, of whom 8 in the Alinia arm and 10 in the placebo arm had <i>G. lamblia</i> as sole pathogen)

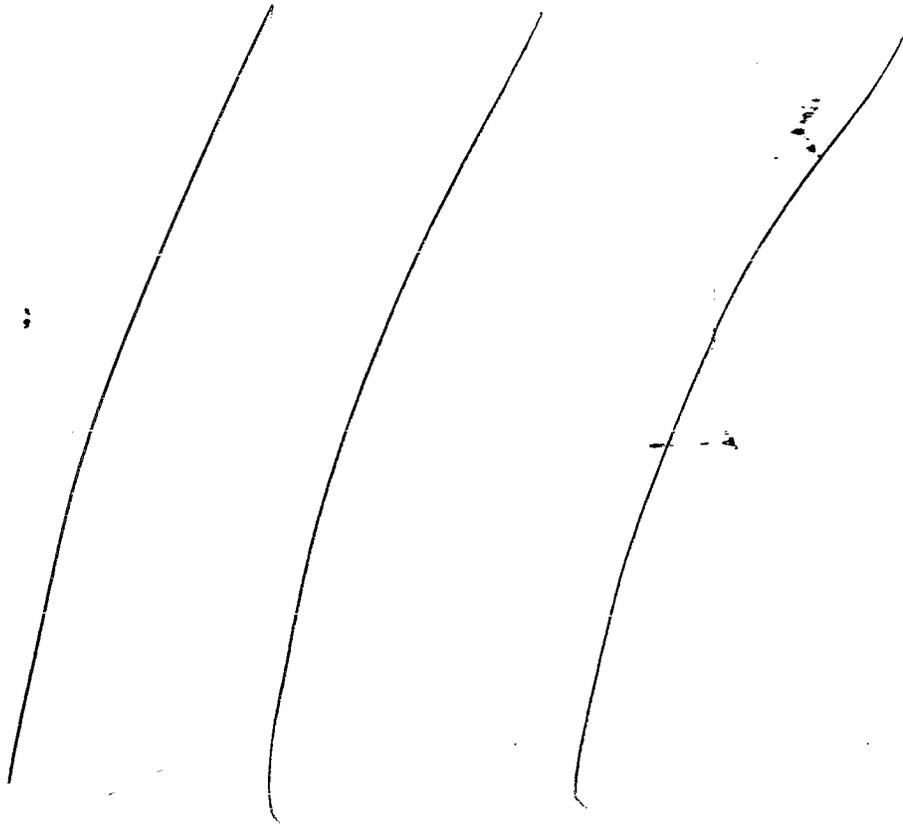
Patients with diarrhea (mean duration = 5 days) were screened for the presence of cysts before enrollment and at enrollment using several procedures (unconcentrated stool stained with iodine or immunofluorescence, concentrated stool stained with iodine). Signs and symptoms were collected and patients were randomized into one of three treatment arms and treated with 500 mg BID PO x 3 days. Follow up clinical and parasitological evaluation was performed 4-7 day after the end of therapy (day 7-10 of study), parasitological outcome was assessed again at 11-14 days after the end of therapy (day 14-17 of study). The clinical outcome was judged as (a) wellness = no symptoms, no watery stools, no more than 2 soft stools, no hematochezia in 24 hours; no symptoms and no unformed stools in 48 hours, (b) continuing illness or (c) clinical treatment failure. Results are presented in the table below. In study 3011, it was noted that in some patients, the cyst count was reduced at the first visit but rebounded at the second, no clinical evaluation was done at that visit. The applicant indicated that Peru is hyperendemic for *Giardia* so patients may have ingested more cysts. While no clinical outcome was formally obtained, the applicant further wrote that investigators did no comment about complaints or relapsed symptoms at the last visit. The question of whether the increased cyst counts may represent persistent shedding or reinfection, and whether patients clinically relapse, will be evaluated post approval



Of note, in study RM01-3011, there was one study site in Peru and one in Egypt. The patients in the Peru site had a higher cyst count at baseline (8 ± 11 cysts) compared to Egypt (2 ± 2 cysts), and the clinical outcome was 81% for both formulations in Peru while it was 89% for the suspension and 94% for the tablet in Egypt. Eradication was in the 30% range in Peru and 80-90% range in Egypt, lending some credence to the idea that there may be an inoculum effect and response correlation. This raises the question whether higher doses or different treatment regimens of nitazoxanide may yield higher rates of eradication. Finally, at the request of the FDA microbiologist regarding number of patients screened, the company reported that 4,278 patients were screened in Peru to identify 90 infected patients who were enrolled in the study and in Egypt, 593 patients were screened and 45 patients were identified and enrolled. The majority of the exclusions were because the patients stool sample did not contain the parasite.

The information submitted supports approval of the indication; the labeling in the INDICATIONS AND USAGE section will read:





Cryptosporidium parvum

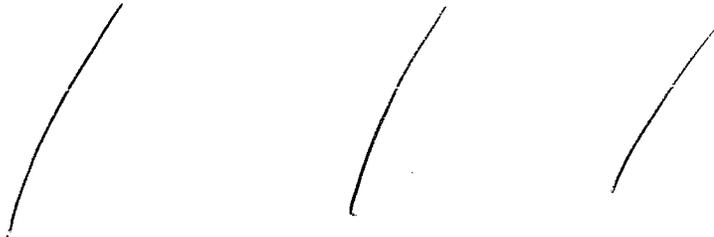
Data from ongoing study RM01-3010 were not submitted. Instead, the applicant asked the FDA to consider (1) results from the *Giardia* studies in adults and (2) pediatric data and approval of NDA 21-498 for patients 1 to 11 years of age and (3) a small study in adults with *Cryptosporidium parvum*, to support the approval of Alinia tablets in patients 12 years and older for the treatment of *Cryptosporidium parvum*.

While it is appropriate to propose supporting an indication with data from other patient populations and indications, in the absence of results from study RM01-3010, in this situation, there is no convincing justification or regulatory precedent for approving an adult indication for one pathogen based on evidence of an adult indication for another pathogen (RM01-3011). The organisms are different, and furthermore, while *G. lamblia* attaches to the duodenum, *C. parvum* can actually invade the villi of the small intestine. The data from pediatric patients, while informative, is not adequate because the dosing is different and the PK properties of the two formulations are different (RM02-3007) and the results of study RM02-3008 in HIV-seropositive patients actually failed to show superiority of Alinia compared to placebo. It is unknown whether there are relevant host differences between pediatric and adult patients for this infection. Study RM-NTZ-98-

002 included both pediatric and adult patients. In pediatric patients, the study results supported approval of the oral suspension. The adult patient results, however, failed to show the regimen to be superior to placebo, with $p=0.118$ (see table) The company currently has study RM02-3010 ongoing, and results of that study will need to be submitted to determine whether the drug works in adults with *C. parvum*.

RM01-3010	Study ongoing – expected completion end of 2004. A double-blind placebo-controlled study of Alinia tablets and oral suspension in HIV-seronegative adult and adolescent patients with diarrhea caused by <i>C. parvum</i>
RM01-3011	See above – adults with <i>Giardia lamblia</i>
RM02-3007	Pediatric HIV-seronegative patients with <i>C. parvum</i>
RM02-3008	Pediatric HIV-seropositive patients with <i>C. parvum</i>
RM-98-002	Pediatric HIV-seronegative patients with <i>C. parvum</i> – data on pediatric patients supported approval of suspension; data in adult patients failed to show efficacy – $p. = .118$

The information presented in the resubmission is not adequate to approve the tablet for the treatment of adults with *C. parvum*. Therefore, at present, in this joint product labeling for the tablet and the oral suspension, the indication will read as follows:



HIV-infected or Immunodeficient Patients

Because there are currently no drugs approved for the treatment of *Cryptosporidium parvum* in HIV-infected patients, investigation of nitazoxanide for this use is important. However, of the pediatric as well as adult studies done to date, none has demonstrated that at the doses and at the regimens tested, nitazoxanide was effective. Therefore, the labeling will reflect this information in the INDICATIONS AND USAGE section (see above), and in the PRECAUTIONS section,

HIV-Infected or Immunodeficient Patients

Alinia Tablets and Alinia for Oral Suspension have not been studied for the treatment of diarrhea caused by *Giardia lamblia* in HIV-infected or immunodeficient patients. Alinia Tablets and Alinia for 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 (see **CLINICAL STUDIES**).

And in the **CLINICAL STUDIES** section, results of the pediatric studies in patients 1 through 11 years of age already include information about one study in HIV-seropositive patients studied with the oral suspension):

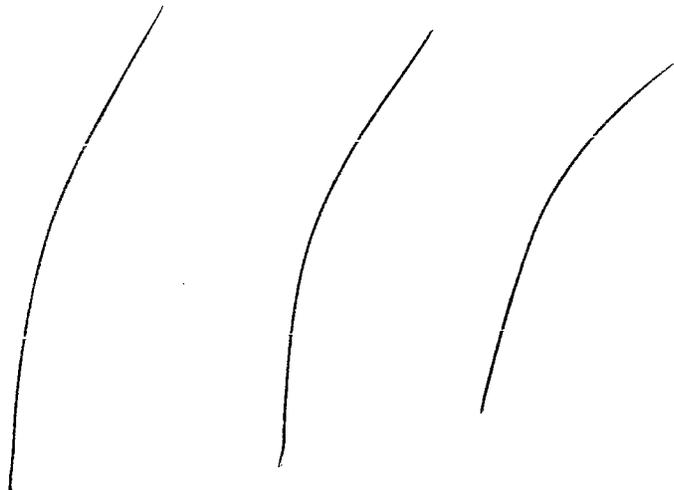
Another double-blind, placebo-controlled study was conducted in hospitalized, severely malnourished pediatric patients with acquired immune deficiency syndrome (AIDS) in Zambia. In this study, a three day course of nitazoxanide suspension (100 mg BID in pediatric patients ages 12-47 months, 200 mg BID in pediatric patients ages 4 through 11 years) did not produce clinical cure rates that were significantly different from the placebo control.

Evaluation of Safety:

Alinia tablets (and Alinia for oral suspension) are minimally absorbed and are associated with mainly mild gastrointestinal adverse events when administered twice daily for 3 days. No deaths occurred on study drug, 1% of patients discontinued treatment and most events were transient. The rate of adverse events was similar for the treatment and placebo arms, and interestingly, the rate of abdominal pain and dizziness was somewhat higher in the placebo than drug arm, perhaps reflecting symptoms of the disease.

The following summary of findings will be included in the **ADVERSE EVENTS** section:

Metai



Recommendations:

NDA 21-497 for Alinia Tablets and NDA 498/S-001 for Alinia for Oral suspension, should be approved for the indication of *G. lamblia* in patients 12 years and older. Labeling text for a joint suspension / tablet package insert has been agreed-upon by the applicant and division.

NDA 21-818 (administrative NDA for the *C. parvum* indication) should be issued an APPROVABLE letter and the deficiencies identified in the original AE letter of November 22, 2003 should be listed.

The applicant has fulfilled most of the BPCA requirement and studied pediatric patients 1 year and older. A study in pediatric patients between 0-12 months in age is being deferred and results should be submitted by July 21, 2009. In this study, the applicant will be asked that patients be evaluated for both clinical and parasitological outcome at the 4-7 days as well as the 11-14 days post-treatment visits.

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic Drug Products

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/s/

Kristen Miller
7/21/04 09:21:48 AM
CSO

Renata Albrecht
7/21/04 10:57:51 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA 21-497 and NDA 21-818
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 Treatment of diarrhea caused by
Cryptosporidium parvum and *Giardia
lamblia* in adults and adolescent
patients greater than 11 years of age.

Indication Granted Treatment of diarrhea caused by
Giardia lamblia in adults and
adolescent patients 12 years of age
and older.

Intended Population Immunocompetent patients 12 years
of age and older

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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* and *Cryptosporidium parvum* 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).

Cryptosporidium parvum

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 *Cryptosporidium parvum* in adults and adolescent patients 12 years of age and older.

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. Safety and effectiveness of Alinia® tablets and suspension have not been established in patients with immunodeficiency.

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 *Cryptosporidium parvum* in adults and adolescent patients greater than 11 years of age. The applicant should request re-consideration of this indication when Study RM01-3010 has been completed.

1.2 Recommendation on Post-marketing Actions

There are no recommendations for risk management activity or required Phase 4 studies at this time. The applicant has indicated that they plan to study parasitological and

clinical response at 2 weeks following the end of treatment with nitazoxanide compared to another FDA-approved drug for *Giardia lamblia*.

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	Treatment of diarrhea caused by <i>Cryptosporidium parvum</i> and <i>Giardia lamblia</i> in adults and adolescent patients greater than 11 years of age. Safety and effectiveness of Alinia® tablets have not been established in patients with immunodeficiency.
Indication Granted	Treatment of diarrhea caused by <i>Giardia lamblia</i> 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	Immunocompetent patients 12 years of age and older.

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).

Cryptosporidium parvum:

With regard to the deficiency in the NDA 21-497 Approvable letter concerning *Cryptosporidium parvum*, the applicant has requested FDA consider the following clinical data as sufficient evidence to support the safety and efficacy of nitazoxanide tablets in non-immunodeficient adults and adolescents with diarrhea due to *Cryptosporidium parvum*.

1. A placebo-controlled study of nitazoxanide tablets demonstrating
 - a. the efficacy of the tablets in treating diarrhea caused by *Giardia lamblia*, and
 - b. non-inferiority of the nitazoxanide tablet compared to the nitazoxanide suspension in treating diarrhea caused by *Giardia lamblia*.

Clinical Reviewer's Comment: The study described is Study RM01-3011, which is discussed above.

2. Two double-blind placebo-controlled studies demonstrating efficacy of the nitazoxanide suspension in treating diarrhea caused by *Cryptosporidium parvum* in pediatric patients.

Clinical Reviewer's Comment: These two pediatric studies were reviewed as part of NDA 21-498 (Studies RM02-3007 and RM02-3008). See Medical Officer's Review by Rosemary Johann-Liang, M.D. dated January 7, 2003.

3. A study providing evidence supporting the efficacy of the nitazoxanide tablet in treating diarrhea caused by *Cryptosporidium parvum* in adult patients.

Clinical Reviewer's Comment: This study was also reviewed as part of NDA 21-498 (Protocol RM-NTZ-98-002).

Based upon the data (items 1-3 above), the Division is not recommending approval at this time of nitazoxanide tablets for the treatment of diarrhea caused by *Cryptosporidium parvum* in adult and adolescent patients for the following reasons:

- Although the pathophysiology of diarrhea caused by *Giardia lamblia* is similar to *Cryptosporidium parvum*, the Division does not consider clinical efficacy data for nitazoxanide tablets in the treatment of *Giardia lamblia* to be supportive of *Cryptosporidium parvum*.
- The Division does not consider pediatric data (obtained in patients 1 to 11 years) demonstrating the efficacy of nitazoxanide suspension in patients with *Cryptosporidium parvum* to be supportive of the efficacy of nitazoxanide tablets in adolescents and adults (≥ 12 years) with *Cryptosporidium parvum*. Nitazoxanide tablets and suspension are not bioequivalent and there are no data establishing a pharmacokinetic link between systemic exposure to the suspension in pediatrics (aged 1 to 11 years) and systemic exposure to the tablets in adolescents and adults (aged ≥ 12 years). In addition, it is not clear if differences, if any, between the pathophysiology of the disease in pediatrics and adults exist.
- Efficacy data of nitazoxanide tablets in treating diarrhea caused by *Cryptosporidium parvum* in adolescent and adult patients from Study RM-NTZ-98-002 was reviewed by the Division with the initial submission of NDA 21-497 and found to be insufficient to support approval.

The applicant is currently conducting a placebo-controlled study of nitazoxanide tablets and suspension in adult and adolescent patients with diarrhea caused by *Cryptosporidium parvum* (Study RM01-3010). Study RM01-3010 was designed by the Division and the applicant to address the deficiencies of NDA 21-497 with regard to *Cryptosporidium parvum*. The applicant expects to complete the study by the end of 2004. The applicant may re-request consideration of the *Cryptosporidium* indication at the time that the data from this study are complete.

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 inpatient 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 \pm 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, the applicant will be granted a pediatric waiver from studying nitazoxanide tablets children below 12 years of age.

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 (\geq 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 (\geq 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	Treatment of diarrhea caused by <i>Cryptosporidium parvum</i> and <i>Giardia lamblia</i> in adults and adolescent patients greater than 11 years of age.
Indication Granted	Treatment of diarrhea caused by <i>Giardia lamblia</i> in adults and adolescent patients 12 years of age and older.
Intended Population	Immunocompetent patients 12 years of age and older.

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 *Cryptosporidium parvum* and *Giardia lamblia* in immunocompetent adults and adolescents. The Approvable letter stated:

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1. The single placebo-controlled study that evaluated the proposed regimen of nitazoxanide tablets, 500 mg PO BID, did not provide sufficient evidence of efficacy in adult patients to support the approval of nitazoxanide tablets for the treatment of *Cryptosporidium parvum* diarrhea in immunocompetent adults. We are not able to determine the contribution of dosage form (systemic vs. luminal exposure) and patient-related factors (host response in children vs. adults) to this finding since you have shown efficacy of nitazoxanide for oral suspension, 100 mg/5 ml, for the treatment of *Cryptosporidium parvum* diarrhea in immunocompetent pediatric patients. In order to address this deficiency, you must submit a second adequate and well-controlled clinical trial using the proposed regimen that confirms the clinical efficacy suggested in Study RM-NTZ-98-002.

Specifically, the following issues need to be addressed. We strongly encourage you to discuss the protocol with the Division of Special Pathogen and Immunologic Drug Products (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
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

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- 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: 900 mL Phosphate Buffer pH 7.5 with 6% hexadecyltrimethyl ammonium bromide
 - Bath temperature: 25 ± 0.5 °C

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 48,620 (Serial No. 060). 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 Grupo Columbia SA de CV of Mexico and its subsidiaries 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 Grupo Columbia.

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:

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- 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 _____ the limit for Total Degradation Products was reduced from not more than _____ to not more than _____ at expiry.
 - No photostability data using the current film coating had been provided.
 - The original NDA 20-871 contained only 6 months 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 cryptosporidiosis 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: Dr. Juan Jave Ortiz
Centro Medico Bautista
Cajamarca, Peru

DSI Reviewer Note (10/23/02)

Re: Protocol RM-NTZ-99-010 titled "Randomized Comparative Study of Nitazoxanide and Metro in the Treatment of *Giardiasis* 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: Dr. Samir Kabil
Department of Hepatology, Gastroenterology and Infectious Diseases
Benha Faculty of Medicine
University of Zagazig
Benha, Egypt

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 Egyptian Ministry of Health 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.

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ON ORIGINAL**

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

Age	Tizoxanide			Tizoxanide glucuronide		
	C _{max} (μ g/mL)	T _{max} [*] (hr)	AUC _t (μ g·hr/mL)	C _{max} (μ g/mL)	T _{max} [*] (hr)	AUC _t (μ g·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)
\geq 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 \pm 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 \pm 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 \pm 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 (\geq 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